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

Formulated by the UK IGF-1 User's Group
Scope – To guide UK pediatric endocrinologists who are considering the use of rhIGF-1 for SPIGFD.

Version: February 2015 Revision Due Date: February 2018

## 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, have been described. SPIGFD (height <-3 SD, serum IGF-1 <2.5$^{th}$ 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 4$^{th}$ 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.
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 0.04mg/kg bd, aim to increase the dose at regular increments to reach the maintenance dose of 0.12mg/kg bd by around 3 months if tolerated. Doses greater than this have not been evaluated in SPIGFD, thus no information is available on a maximum allowable dose.
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.

| Baseline assessment | Standard | Optional |
|---|---|---|
| Enter patient on IGFD Register | + | |
| Physical examination: height, weight, sitting height, pubertal stage, blood pressure, fundoscopy, tonsils | + | |
| Echocardiography | | + |
| Bone Age | + | |
| Photograph of the face (frontal and lateral) | + | |
| Dietary advice | + | |
| First injection in healthcare setting | + | |
| Fasting cholesterol (HDL, LDL and total), triglycerides | | + |
| DXA – whole body and lumbar spine | | + |
| Arrange home care and nursing support to monitor compliance | + | |

**E. Monitoring 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 necessary 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.This should be managed using standard hypoglycaemia guidelines. The injection should not be given if the blood sugar is low, if the child has not eaten or is unwell for any reason.
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 who have not had a sufficiently long period of treatment with rhIGF-1.
10. Treatment with rhIGF-1 should be reconsidered if after a year of documented good compliance, the patient has an increase in height velocity of less than 30% of baseline or a change in height SDS score of <0.3.
11. The following tests are recommended to be performed at clinic visits and/or annually.

| | Every Clinic Visit | Annually |
|---|---|---|
| Enter data on IGFD Register | + | |
| Physical examination: height, weight, sitting height, pubertal stage, blood pressure, fundoscopy, tonsils | + | |
| Echocardiography, if clinically indicated * | | + |
| Bone Age | | + |
| Examination of injection sites | + | |
| Photograph of the face (frontal and lateral) | | + |
| DXA – whole body and lumbar spine* | | + |
| Audiology* | | + |
| Monitor compliance, enlisting Ipsen nurse support as required | + | |

* These investigations are not considered to be standard but may provide objective data on changes during treatment.

**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 enlarged adenoid or tonsil hypertrophy (snoring, poor feeding pattern, apnoea, reduced hearing) or associated physical examination, a sleep study should be undertaken and 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**

1. Chernausek SD, Backeljauw PF, Frane J, Kuntze J and Underwood LE for the GH Insensitivity Syndrome Collaborative Group. Long-term treatment with recombinant Insulin-like Growth Factor (IGF)-I in children with severe IGF-I deficiency due to growth hormone insensitivity. J Clin Endocrinol Metab 2007;92:902-910

2. Collett-Solberg PF and Misra M on behalf of the Drug and Therapeutics Committee of the Lawson Wilkins Pediatric Endocrine Society. The Role of Recombinant Human Insulin-Like Growth Factor-I in Treating Children with Short Stature. J Clin Endocrinol Metab 2008;93:10-18.

3. Grote FK, van Dommelen P, Oostdijk W, de Muinck Keizer-Schrama, SMPF, Verkerk PH, Wit JM, van Buuren S. Developing an evidence-based guideline for the referral of short stature. Arch Dis Child, 2008;93:212-7.

4. Walenkamp MJE, Wit JM, on behalf of the Leiden Growth Genetics Working Group. Genetic disorders in the growth hormone-IGF-I axis. Minireview. Horm Res. 2006 66:221-230

5. Savage MO, Burren CP, Rosenfeld RG. The continuum of growth hormone-IGF-I axis defects causing short stature: diagnostic and therapeutic challenges. Clin Endocrinol (Oxf). 2010;72:721-8.

6.www.scottishmedicines.org.uk/files/mecasermin__Increlex__FINAL_August_2009.doc_for_website.pdfv

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

8. David A, Hwa V, Metherell LA, Netchine I, Camacho-Hübner C, Clark AJ, Rosenfeld RG, Savage MO. Evidence for a Continuum of Genetic, Phenotypic, and Biochemical Abnormalities in Children with Growth Hormone Insensitivity. Endocr Rev. 2011

9. Backeljauw PF, Kuntze J, Frane J, Calikoglu AS, Chernausek SD. Adult and near-adult height in patients with severe insulin-like growth factor-I deficiency after long-term therapy with recombinant human insulin-like growth factor-I. Horm Res Paediatr. 2013;80(1):47-56.

**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:-
Dr Talat Mushtaq (chair), Leeds, Prof Faisal Ahmed, Glasgow, Dr Rakesh Amin, Dr Caroline Brain, London, Dr Charles Buchanan, London, Dr Louise Denvir, Dr Mohamed Didi, Liverpool, Nottingham, Dr Khalid Hussain, London, Dr Helen Johnstone, Newcastle, Sr Julie Jones, Manchester, , Sr Ethel McNeil, Glasgow, Dr Leena Patel, Manchester, Dr Stephen Rose, Dr Renuka Ramakrishnan, Liverpool, Birmingham, Prof Martin Savage, London, Dr Nick Shaw, Birmingham, London, Sr Amanda Whitehead, Leeds,

Contact details for Chair Of User Group:-
Dr Talat Mushtaq, Consultant in Paediatric Endocrinology, Leeds Teaching Hospitals, Leeds General Infirmary, LS1 3EX, UK. Talat.mushtaq@nhs.net

The group is grateful for the support of Ipsen UK.

**Appendix 1 – Summary of Product Characteristics for Increlex**

## 1. NAME OF THE MEDICINAL PRODUCT

INCRELEX 10mg/mL solution for injection

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains 10mg of mecasermin*.

Each vial contains 40mg 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 9mg 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 $\leq$ –3.0 and
- basal IGF-1 levels below the 2.5$^{th}$ 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 0.04mg/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 0.04mg/kg to the maximum dose of 0.12mg/kg given twice daily. Doses greater than 0.12mg/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 0.04mg/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 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 9mg/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 1mmoL sodium (23mg) 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 fœtus up to 16mg/kg (20 fold the MRHD based on Body surface Area) and in a rabbit teratology with no effects on foetus at dose of 0.5mg/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 4mg/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 1: Adverse reactions**

| ***SYSTEM ORGAN CLASS*** | **Reactions observed in the pivotal clinical trial** | **Reactions observed from the post-marketing environment** |
|---|---|---|
| Infections and infestations | Common: Febrile infection*, upper respiratory tract infection*, otitis media, otitis media serous, chronic otitis media serous *, otitis externa*, pharyngitis*, tonsillitis, ear infection, oral candidiasis* | |
| Blood and lymphatic system disorders | Very common: Thymus hypertrophy<br>Common: Lymphadenopathy* | |
| Immune system disorders | | Not known: Systemic hypersensitivity (anaphylaxis, generalised urticaria, angioedema, dyspnoea) |
| Metabolism and nutrition disorders | Very common: Hypoglycaemia<br>Common: Hypoglycaemic seizure, hyperglycaemia, hyperlipidaemia*, obesity* | |
| Psychiatric disorders | Common: Depression*, sleep terror, nervousness, abnormal behaviour*, disorientation* | |
| Nervous system disorders | Very common: Headache<br>Common: Convulsions, febrile convulsion*, benign intracranial hypertension, loss of consciousness*, sleep apnoea syndrome, dizziness, tremor*, restless leg syndrome* | |

| ***SYSTEM ORGAN CLASS*** | **Reactions observed in the pivotal clinical trial** | **Reactions observed from the post-marketing environment** |
|---|---|---|
| Eye disorders | Common: Papilloedema, reduced visual acuity*, myopia* | |
| Ear and labyrinth disorders | Very common: Hypoacusis<br>Common: Otorrhoea, ear disorder*, middle ear disorder*, tympanic membrane disorder*, ear pain, ear congestion*, fluid in middle ear | |
| Cardiac disorders | Common: Cardiomegaly, ventricular hypertrophy, atrial hypertrophy*, tachycardia, tachycardia paroxysmal*, mitral valve incompetence*, tricuspid valve incompetence* | |
| Respiratory, thoracic and mediastinal disorders | Very common: Tonsillar hypertrophy, snoring<br>Common: Adenoidal hypertrophy, nasal turbinate hypertrophy*, dyspnoea*, nasal mucosal disorder*, obstructive airway disorder*, abnormal respiration*, nasal congestion, mouth breathing | |
| Gastrointestinal disorders | Common: Vomiting, retching*, abdominal pain*, upper abdominal pain*, abdominal distension*, dysphagia* | |
| Skin and subcutaneous tissue disorders | Common: Skin hypertrophy, acrochordons*, abnormal hair texture | Not known: alopecia |
| Musculoskeletal and connective tissue disorders | Common: Arthralgia, pain in extremity, myalgia, scoliosis*, spinal deformity*, soft tissue disorder*, muscle cramp*, flank pain*, | |

| ***SYSTEM ORGAN CLASS*** | **Reactions observed in the pivotal clinical trial** | **Reactions observed from the post-marketing environment** |
|---|---|---|
| | musculoskeletal stiffness* | |
| Renal and urinary disorders | Common: Nephrolithiasis*, hydronephrosis*, renal colic* | |
| Reproductive system and breast disorders | Common: Gynaecomastia, ovarian cyst* | |
| Congenital, familial and genetic disorders | Common: Congenital jaw malformation, pigmented naevus* | |
| General disorders and administration site conditions | Very common: Injection site hypertrophy<br>Common: 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* | Not known: Local allergic reactions at the injection site (pruritus, urticaria) |
| Investigations | Common: Cardiac murmur, abnormal tympanometry, abnormal echocardiogram, increased alanine aminotransferase*, increased aspartate aminotransferase*, increased weight | |
| Surgical and medical procedures | Common: Adenotonsillectomy*, adenoidectomy, ear tube insertion | |

* = occurred in only 1 subject (1%)

Description of selected adverse reactions

Systemic/local hypersensitivity

*Clinical Trial:* During clinical trials in other indications (totaling approximately 300 patients) 8% of patients reported a local and/or systemic hypersensitivity reactions. All cases were mild or moderate in severity and none was serious.

*Post-marketing reports:* Systemic hypersensitivity included symptoms such as anaphylaxis, generalised urticaria, angioedema and dyspnoea. The symptoms in the cases indicative of anaphylaxis included hives, angioedema and dyspnoea. Some patients required hospitalisation. 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.

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

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

Mechanism of action

Insulin-like growth factor-1 (IGF-1) is the principal hormonal mediator of statural growth. Under normal circumstances, growth hormone (GH) binds to its receptor in the liver and other tissues, and stimulates the synthesis/secretion of IGF-1. In target tissues the Type 1 IGF-1 receptor, which is homologous to the insulin receptor, is activated by IGF-1, leading to intracellular signalling which stimulates multiple processes leading to statural growth. The metabolic actions of IGF-1 are in part directed at stimulating the uptake of glucose, fatty acids, and amino acids so that metabolism supports growing tissues.

Pharmacodynamic effects

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

*Tissue Growth*

Skeletal growth is accomplished at the epiphyseal plates at the ends of a growing bone. Growth and metabolism of epiphyseal plate cells are directly stimulated by GH and IGF-1.

Organ growth: treatment of IGF-1 deficient rats with rhIGF-1 results in whole body and organ growth.

Cell growth: IGF-1 receptors are present on most types of cells and tissues. IGF-1 has mitogenic activity that leads to an increased number of cells in the body.

*Carbohydrate Metabolism*

IGF-1 suppresses hepatic glucose production, stimulates peripheral glucose utilisation, 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 120μg/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 neutralising 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**

| | Pre-Tx | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Year 6 | Year 7 | Year 8 |
|---|---|---|---|---|---|---|---|---|---|
| **Height Velocity (cm/yr)** | | | | | | | | | |
| N | 59 | 59 | 54 | 48 | 39 | 21 | 20 | 16 | 14 |
| Mean (SD) | 2.8 (1.8) | 8.0 (2.2) | 5.8 (1.4) | 5.5 (1.9) | 4.7 (1.4) | 4.7 (1.6) | 4.8 (1.5) | 4.6 (1.5) | 4.5 (1.2) |
| Mean (SD) for change from pre-Tx | | +5.2 (2.6) | +3.0 (2.3) | +2.6 (2.3) | +1.6 (2.1) | +1.5 (1.8) | +1.5 (1.7) | +1.0 (2.1) | +0.9 (2.4) |
| P-value for change from pre-Tx [1] | | <0.0001 | <0.0001 | <0.0001 | <0.0001 | 0.0015 | 0.0009 | 0.0897 | 0.2135 |
| **Height Velocity SDS** | | | | | | | | | |
| N | 59 | 59 | 53 | 47 | 38 | 19 | 18 | 15 | 12 |
| Mean (SD) | -3.3 (1.7) | 1.9 (2.9) | -0.2 (1.6) | -0.3 (2.0) | -0.7 (1.9) | -0.6 (2.1) | -0.4 (1.4) | -0.4 (1.9) | -0.3 (1.8) |
| Mean (SD) for change from pre-Tx | | +5.1 (3.1) | +3.2 (2.2) | +3.1 (2.4) | +2.5 (2.1) | +2.5 (2.2) | +2.7 (1.7) | +2.5 (2.1) | +2.8 (2.7) |
| P-value for change from pre-Tx [1] | | <0.0001 | <0.0001 | <0.0001 | <0.0001 | 0.0001 | <0.0001 | 0.0003 | 0.0041 |
| **Height SDS** | | | | | | | | | |
| N | 62 | 62 | 57 | 51 | 41 | 22 | 20 | 16 | 14 |
| Mean (SD) | -6.7 (1.8) | -5.9 (1.7) | -5.6 (1.8) | -5.3 (1.8) | -5.3 (1.8) | -5.5 (1.8) | -5.4 (1.8) | -5.2 (2.0) | -5.2 (1.9) |
| Mean (SD) for change from pre-Tx | | +0.8 (0.5) | +1.1 (0.8) | +1.4 (1.0) | +1.4 (1.1) | +1.4 (1.3) | +1.4 (1.2) | +1.4 (1.1) | +1.6 (1.1) |
| P-value for change from pre-Tx [1] | | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | 0.0001 | <0.0001 |

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

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

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 120µg/kg BID, the mean first year height velocity was approximately 8.7cm/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 0.045mg/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 0.12mg/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 0.04L/hr/kg at 3mg/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 mecasermin was not studied.

*Carcinogenic potential*

Mecasermin was administered subcutaneously to Sprague Dawley rats at doses of 0, 0.25, 1, 4, and 10mg/kg/day for up to 2 years. An increased incidence of adrenal medullary hyperplasia and pheochromocytoma was observed in male rats at doses of 1mg/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 10mg/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 10mg/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

4mL of solution in a 5mL 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

30/08/2012

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