

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use INCRELEX® safely and effectively. See full prescribing information for INCRELEX®.

INCRELEX® (mecasermin) injection, for subcutaneous use

Initial U.S. Approval: 2005

INDICATIONS AND USAGE

INCRELEX (mecasermin) injection is indicated for the treatment of growth failure in pediatric patients 2 years of age and older with severe primary IGF-1 deficiency or with growth hormone (GH) gene deletion who have developed neutralizing antibodies to GH. (1)

Limitations of use: INCRELEX is not a substitute to GH for approved GH indications.

DOSAGE AND ADMINISTRATION

- INCRELEX should be administered subcutaneously. (2.2)
- Injection sites should be rotated to avoid lipohypertrophy. (2.2)
- Recommended starting dosage: 0.04 mg/kg to 0.08 mg/kg twice daily. If well-tolerated for at least one week, the dose may be increased by 0.04 mg/kg per dose, to the maximum dose of 0.12 mg/kg given twice daily. (2.1)

DOSAGE FORMS AND STRENGTHS

- Injection: 40 mg/4 mL (10 mg/mL) solution supplied in a multiple-dose glass vial (3)

CONTRAINDICATIONS

- Known Hypersensitivity to mecasermin (4)
- Closed Epiphyses (4)
- Malignant Neoplasia (4)

WARNINGS AND PRECAUTIONS

- Hypoglycemia: Severe hypoglycemia leading to hypoglycemic seizures has been observed with INCRELEX treatment. Administer INCRELEX shortly before or after a meal or snack, because it has insulin-like hypoglycemic effects. (5.1)
- Hypersensitivity and Allergic Reactions, including Anaphylaxis: A low 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. (5.2)

- Intracranial Hypertension: Funduscopy examination is recommended at the initiation and periodically during the course of INCRELEX therapy. (5.3)
- Lymphoid Tissue Hypertrophy (tonsillar/adenoidal hypertrophy): Patients should have periodic examinations to rule out potential complications and receive appropriate treatment if necessary. (5.4)
- Slipped Capital Femoral Epiphysis (SCFE): Evaluate any child with onset of a limp or hip/knee pain for possible SCFE. (5.5)
- Progression of Scoliosis: Monitor any child with scoliosis for progression of the spine curve. (5.6)
- Malignant Neoplasia: Several cases of malignant neoplasia have been observed in pediatric patients treated with INCRELEX. Therapy should be discontinued if evidence of malignant neoplasia develops and appropriate expert medical care sought. (5.7)
- Risk of Serious Adverse Reactions in Infants due to Benzyl Alcohol Preserved Solution: Benzyl alcohol, a preservative in INCRELEX, has been associated with serious adverse reactions, including death, in neonates and infants. Use of INCRELEX in infants is not recommended. (5.8)

ADVERSE REACTIONS

Common INCRELEX-related adverse reactions in clinical trials include: hypoglycemia, local and systemic hypersensitivity, tonsillar hypertrophy (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Eton Pharmaceuticals, Inc. at 1-855-224-0233 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Pediatric Use: Safety and effectiveness has not been established in children less than 2 years of age. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Severe Primary IGF-1 Deficiency (Primary IGFD)

INCRELEX is indicated for the treatment of growth failure in pediatric patients 2 years of age and older with:

- severe primary IGF-1 deficiency or
- growth hormone (GH) gene deletion who have developed neutralizing antibodies to GH.

Severe Primary IGF-1 deficiency (IGFD) is defined by:

- height standard deviation score ≤ -3.0 and
- basal IGF-1 standard deviation score ≤ -3.0 and
- normal or elevated growth hormone (GH).

Limitations of use:

INCRELEX is not a substitute to GH for approved GH indications.

INCRELEX is not indicated for use in patients with secondary forms of IGF-1 deficiency, such as GH deficiency, malnutrition, hypothyroidism, or chronic treatment with pharmacologic doses of anti-inflammatory corticosteroids.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

- Treatment with INCRELEX should be supervised by a physician who is experienced in the diagnosis and management of pediatric patients with short stature associated with severe primary IGF-1 deficiency or with growth hormone gene deletion and who have developed neutralizing antibodies to growth hormone.

- The dosage of INCRELEX should be individualized for each patient. The recommended starting dose of INCRELEX is 0.04 mg/kg to 0.08 mg/kg of body weight twice daily by subcutaneous injection. If well-tolerated for at least one week, the dose may be increased by 0.04 mg/kg of body weight per dose, to the maximum dose of 0.12 mg/kg of body weight given twice daily [*see Warnings and Precautions (5.1 and 5.7)*].
- Preprandial glucose monitoring is recommended at treatment initiation and until a well-tolerated dose is established. If frequent symptoms of hypoglycemia or severe hypoglycemia occur, preprandial glucose monitoring should continue, and glucose monitoring should also occur at the time of event if possible. If hypoglycemia occurs with recommended doses despite adequate food intake, the dose should be reduced. INCRELEX should be administered shortly before or after (\pm 20 minutes) a meal or snack. If the patient is unable to eat shortly before or after a dose for any reason, that dose of INCRELEX should be withheld.
- If one or more doses of INCRELEX is missed, do not increase the subsequent doses to make up for omitted doses.

2.2 Administration Instructions

INCRELEX is administered by subcutaneous injection only. Do not administer intravenously.

INCRELEX injection sites should be rotated to a different site (upper arm, thigh, buttock or abdomen) with each injection to help prevent lipohypertrophy.

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

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if the solution is cloudy or contains particulate matter.

If using syringes that measure dose in units, doses in mg/kg must be converted to units using the following formula: $\text{Weight (kg)} \times \text{Dose (mg/kg)} \times 1 \text{ mL}/10 \text{ mg} \times 100 \text{ units}/1 \text{ mL} = \text{units/injection}$.

3 DOSAGE FORMS AND STRENGTHS

Injection: 40 mg/4 mL (10 mg/mL) clear and colorless solution in a multiple-dose glass vial.

4 CONTRAINDICATIONS

- **Known Hypersensitivity**

INCRELEX should not be used by patients who are allergic to mecaseimerin (rhIGF-1) or any of the inactive ingredients in INCRELEX, or who have experienced a severe hypersensitivity to INCRELEX [see *Warnings and Precautions (5.2) and Adverse Reactions (6.3)*].

- **Closed Epiphyses**

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

- **Malignant Neoplasia**

INCRELEX is contraindicated in pediatric patients with malignant neoplasia or a history of malignancy [see *Warnings and Precautions (5.7) and Adverse Reactions (6.3)*].

5 WARNINGS AND PRECAUTIONS

5.1 Hypoglycemia

Severe hypoglycemia leading to hypoglycemic seizures has been observed with INCRELEX treatment [see *Adverse Reactions (6.1)*]. Because INCRELEX has insulin-like hypoglycemic effects it should be administered shortly before or after (\pm 20 minutes) a meal or snack. Glucose monitoring and INCRELEX dose titration are recommended until a well-tolerated dose is established [see *Dosage and Administration (2.1)*] and subsequently as medically indicated. Special attention should be paid to small children because their oral intake may not be consistent. Patients should avoid engaging in any high-risk activities (e.g., driving, exercise, etc.) within 2 to 3 hours after dosing, particularly during the initiation of INCRELEX treatment until tolerability and a stable dose have been established [see *Adverse Reactions (6.1)*]. INCRELEX should not be administered when the meal or snack is omitted. The dose of INCRELEX should never be increased to make up for one or more omitted doses.

5.2 Hypersensitivity and Allergic Reactions, including Anaphylaxis

Allergic reactions to INCRELEX have been reported post-marketing. They range from localized (injection site) reactions to systemic reactions, including anaphylaxis requiring hospitalization. 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. *[see Contraindications (4) and Adverse Reactions (6.3)]*

5.3 Intracranial Hypertension

Intracranial hypertension (IH) with papilledema, visual changes, headache, nausea and/or vomiting have occurred in patients treated with INCRELEX. IH-associated signs and symptoms resolved after interruption of dosing. Funduscopic examination is recommended at the initiation and periodically during the course of INCRELEX therapy. *[see Adverse Reactions (6.3)]*.

5.4 Lymphoid Tissue Hypertrophy

Lymphoid tissue (e.g., tonsillar and adenoidal) hypertrophy associated with complications, such as snoring, sleep apnea, and chronic middle-ear effusions have been reported with the use of INCRELEX. Patients should have periodic examinations to rule out such potential complications and receive appropriate treatment if necessary *[see Adverse Reactions (6.3)]*.

5.5 Slipped Capital Femoral Epiphysis

Slipped capital femoral epiphysis can occur in patients who experience rapid growth. Any pediatric patient with the onset of a limp or complaints of hip or knee pain during INCRELEX therapy should be carefully evaluated.

5.6 Progression of Preexisting Scoliosis

Progression of scoliosis may occur in patients who experience rapid growth. Because INCRELEX increases growth rate, patients with a history of scoliosis who are treated with INCRELEX should be monitored for progression of scoliosis.

5.7 Malignant Neoplasia

There have been postmarketing reports of malignant neoplasms in pediatric patients who have received treatment with INCRELEX [see *Adverse Reactions (6.3)*]. The cases of malignant neoplasms represented a variety of different malignancies. It is unknown whether there is any relationship between INCRELEX therapy and new occurrence of neoplasia. The occurrence of neoplasia was mostly reported in patients with rare genetic conditions of short stature associated with an increased risk of cancer, or in patients with other cancer predisposing conditions. The tumors were observed also more frequently in patients who received INCRELEX at higher than recommended doses, or at doses that produced serum IGF-1 levels above the normal reference ranges for age and sex. Monitor all patients receiving INCRELEX carefully for development of neoplasms. Advise patients/caregivers to report development of new neoplasms. If malignant neoplasia develops, discontinue INCRELEX treatment [see *Contraindications (4)*].

5.8 Risk of Serious Adverse Reactions in Infants due to Benzyl Alcohol Preserved Solution

Serious and fatal adverse reactions including “gaspings syndrome” can occur in neonates and infants treated with benzyl alcohol-preserved drugs, including INCRELEX. The “gaspings syndrome” is characterized by central nervous system depression, metabolic acidosis, and gasping respirations.

Use of INCRELEX in infants is not recommended [see *Use in Specific Populations 8.4*].

6 ADVERSE REACTIONS

The following serious adverse reactions are described below and elsewhere in the labeling:

- Hypoglycemia [see *Warnings and Precautions (5.1)*].
- Hypersensitivity and Allergic Reactions, including Anaphylaxis [see *Warnings and Precautions (5.2)*]
- Intracranial hypertension (IH) [see *Warnings and Precautions (5.3)*]
- Tonsillar and Adenoidal Hypertrophy and related complications [see *Warnings and Precautions (5.4)*]
- Slipped Capital Femoral Epiphysis [see *Warnings and Precautions (5.5)*]
- Progression of Preexisting Scoliosis [see *Warnings and Precautions (5.6)*]
- *Malignant Neoplasia* [see *Warnings and Precautions (5.7)*]
- Benzyl Alcohol [see *Warnings and Precautions (5.8)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In clinical studies of 71 subjects with Primary IGFD treated for a mean duration of 3.9 years and representing 274 subject-years, no subjects withdrew from any clinical study because of adverse reactions. Adverse reactions to INCRELEX treatment that occurred in 5% or more of these study participants are listed below by organ class.

Metabolism and Nutrition Disorders: hypoglycemia

General Disorders and Administrative Site Conditions: lipohypertrophy, bruising

Infections and Infestations: otitis media, serous otitis media

Respiratory, Thoracic and Mediastinal Disorders: snoring, tonsillar hypertrophy

Nervous System Disorders: headache, dizziness, convulsions

Gastrointestinal Disorders: vomiting

Ear and Labyrinth Disorders: hypoacusis, fluid in middle ear, ear pain, abnormal tympanometry

Investigations: cardiac murmur

Musculoskeletal and Connective Tissue Disorders: arthralgia, pain in extremity

Blood and Lymphatic System Disorders: thymus hypertrophy

Surgical and Medical Procedures: ear tube insertion

Hypoglycemia was reported by 30 subjects (42%) at least once during their course of therapy. Most cases of hypoglycemia were mild or moderate in severity. Five subjects had severe hypoglycemia (requiring assistance and treatment) on one or more occasions and 4 subjects experienced hypoglycemic seizures/loss of consciousness on one or more occasions. Of the 30 subjects reporting hypoglycemia, 14 (47%) had a history of hypoglycemia prior to treatment. The frequency of hypoglycemia was highest in the first month of treatment, and episodes were more frequent in younger children. Symptomatic hypoglycemia was generally avoided when a meal or snack was consumed either shortly (i.e., 20 minutes) before or after the administration of INCRELEX.

Tonsillar hypertrophy was noted in 11 (15%) subjects in the first 1 to 2 years of therapy with lesser tonsillar growth in subsequent years. Tonsillectomy or tonsillectomy/adenoidectomy was performed in 7 subjects; 3 of these had obstructive sleep apnea, which resolved after the procedure in all three cases.

Intracranial hypertension occurred in three subjects. 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.

Mild elevations in the serum AST and LDH were found in a significant proportion of patients before and during treatment. Rise in levels of these serum enzymes did not lead to treatment discontinuation. ALT elevations were occasionally noted during treatment.

Renal and splenic lengths (measured by ultrasound) increased rapidly on INCRELEX treatment during the first years of therapy. This lengthening slowed down subsequently; though in some patients, renal and/or splenic length reached or surpassed the 95th percentile. Renal function (as defined by serum creatinine and calculated creatinine clearance) was normal in all patients, irrespective of renal growth.

Elevations in cholesterol and triglycerides to above the upper limit of normal were observed before and during treatment.

Echocardiographic evidence of cardiomegaly/valvulopathy was observed in a few individuals without associated clinical symptoms. The relation of these cardiac changes to drug treatment cannot be assessed due to underlying disease and the lack of a control group.

Thickening of the soft tissues of the face was observed in several patients and should be monitored during INCRELEX treatment.

6.2 Postmarketing Experience

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 always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Systemic hypersensitivity: *anaphylaxis, generalized urticaria, angioedema, dyspnea*

In the post-marketing setting, the frequency of cases indicative of anaphylaxis was estimated to be 0.3%. Symptoms included hives, angioedema, and dyspnea, and some patients required hospitalization. Upon re-administration, symptoms did not re-occur in all patients.

Local allergic reactions at the injection site: *pruritus, urticaria*

Skin and Subcutaneous Tissue Disorders: *alopecia, hair texture abnormal*

General Disorders and Administrative Site Conditions: *injection site reactions (e.g. erythema, pain, hematoma, hemorrhage, induration, rash, swelling)*

Musculoskeletal and Connective Tissue Disorders: *osteonecrosis/avascular necrosis (occasionally associated with slipped capital femoral epiphysis)*

Neoplasms Benign, Malignant and Unspecified (including cysts and polyps)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on INCRELEX use in pregnant women. Exposure to INCRELEX during pregnancy is unlikely because the drug is not indicated for use after epiphyseal closure. In animal reproduction studies, there were no observed embryo-fetal development abnormalities with intravenous administration of INCRELEX to pregnant rats and rabbits during fetal organogenesis given at exposures up to 11 and 3 times the maximum recommended human dose (MRHD) of 0.24 mg/kg/day based on body surface area (BSA), respectively (*see Data*).

The estimated background risk of birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Studies to assess embryo-fetal toxicity evaluated the effects of INCRELEX during organogenesis in Sprague Dawley rats given 1, 4, and 16 mg/kg/day and in New Zealand White rabbits given 0.125, 0.5, and 2 mg/kg/day, administered intravenously. There were no observed embryo-fetal developmental abnormalities in rats given up to 16 mg/kg/day (11 times the MRHD based on BSA comparison). In the rabbit study, the NOAEL for fetal toxicity was 0.5 mg/kg/day (approximately equivalent to the MRHD based on BSA) due to an increase in fetal death at 2

mg/kg. INCRELEX displayed no teratogenicity or maternal toxicity in rabbits given up to 2 mg/kg (3 times the MRHD based on BSA).

8.2 Lactation

Risk Summary

There is no information available on the presence of mecasermin in human or animal milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for INCRELEX and any potential adverse effects on the breast-fed child from INCRELEX or from the underlying maternal condition.

8.4 Pediatric Use

Toxicity (Gasping Syndrome) with Benzyl Alcohol

Serious adverse reactions including fatal reactions and the “gasping syndrome” occurred in premature neonates and infants in the intensive care unit who received drugs containing benzyl alcohol as a preservative. In these cases, benzyl alcohol dosages of 99 mg/kg/day to 234 mg/kg/day produced high levels of benzyl alcohol and its metabolites in the blood and urine (blood levels of benzyl alcohol were 0.61 mmol/L to 1.378 mmol/L). INCRELEX contains 9 mg/mL benzyl alcohol as a preservative.

Additional adverse reactions included gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse. Preterm, low-birth weight infants may be more likely to develop these reactions because they may be less able to metabolize benzyl alcohol. Use of INCRELEX in infants is not recommended [*see Warnings and Precautions (5.8)*].

Safety and effectiveness in pediatric patients below the age of 2 years of age have not been established.

8.5 Geriatric Use

The safety and effectiveness of INCRELEX in patients aged 65 and over has not been established.

10 OVERDOSAGE

Treatment of acute overdose should be directed at reversing hypoglycemia. 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 hypoglycemic effects.

A small number of overdose cases have been reported in the post-marketing experience. In one case of acute overdose, a 3-year old patient experienced hypoglycemia after receiving one 4 mg dose of INCRELEX (a 10-fold increase beyond the prescribed dose). The event resolved following treatment with IV glucose.

Long term overdosage with INCRELEX may result in signs and symptoms of acromegaly.

11 DESCRIPTION

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 Da. The amino acid sequence of the product is identical to that of endogenous human IGF-1. The rhIGF-1 protein is synthesized in bacteria (*E. coli*) that have been modified by the addition of the gene for human IGF-1.

INCRELEX (mecasermin) injection is a sterile, aqueous, clear and colorless solution intended for subcutaneous injection. Each multiple-dose vial of INCRELEX contains 40 mg of mecasermin in 4 mL solution, and each mL contains 10 mg mecasermin, 9 mg benzyl alcohol, 0.43 mg glacial acetic acid, 2 mg polysorbate 20, 3.51 mg sodium acetate, and 5.84 mg sodium chloride in Water for Injection, USP at a pH of approximately 5.4.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Insulin-like growth factor-1 (IGF-1) is a key hormonal mediator on 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 resulting in 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.

12.2 Pharmacodynamics

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

Tissue Growth – 1) Skeletal growth occurs at the cartilage growth plates of the epiphyses of bones where stem cells divide to produce new cartilage cells or chondrocytes. The growth of chondrocytes is under the control of IGF-1 and GH. The chondrocytes become calcified so that new bone is formed allowing the length of the bones to increase. This results in skeletal growth until the cartilage growth plates fuse at the end of puberty. 2) Cell growth: IGF-1 receptors are present on most types of cells and tissues. IGF-1 has mitogenic activities that lead to an increased number of cells in the body. 3) Organ growth: Treatment of IGF-1 deficient rats with rhIGF-1 results in whole body and organ growth.

Carbohydrate Metabolism –IGF-1 suppresses hepatic glucose production and stimulates peripheral glucose utilization and therefore has a hypoglycemic potential. IGF-1 has inhibitory effects on insulin secretion.

12.3 Pharmacokinetics

Absorption – The absolute bioavailability of rhIGF-1 after subcutaneous administration in healthy subjects is estimated to be close to 100%. However, the absolute bioavailability of INCRELEX given subcutaneously to subjects with primary insulin-like growth factor-1 deficiency (Primary IGFD) has not been determined.

Distribution – In blood, IGF-1 is bound to six IGF binding proteins, with > 80% bound as a complex with IGFBP-3 and an acid-labile subunit. IGFBP-3 is greatly 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 after subcutaneous administration in subjects with severe Primary IGFD is estimated to be 0.257 (\pm 0.073) L/kg at an INCRELEX dose of 0.045 mg/kg and is estimated to increase as the dose of INCRELEX increases.

Elimination – IGF-1 is metabolized by both liver and kidney. The mean terminal $t_{1/2}$ after single subcutaneous administration of 0.12 mg/kg INCRELEX in pediatric subjects with severe Primary IGFD is estimated to be 5.8 hours. Clearance of INCRELEX is inversely proportional to IGF binding protein-3 (IGFBP-3) levels. CL/F is estimated to be 0.04 L/hr/kg at 0.5 micrograms/mL of IGFBP-3, and 0.01 L/hr/kg at 3 micrograms/mL IGFBP-3; the latter is the median IGFBP-3 in subjects with normal IGF-1 serum levels.

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

Race – The effect of race on pharmacokinetics of INCRELEX has not been studied.

Table 1. Summary of INCRELEX Single-Dose Pharmacokinetic Parameters in Children with Severe Primary IGFD (0.12 mg/kg, SC)

	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-8} (hr*ng/mL)	$t_{1/2}$ (hr)	Vd/F (L/kg)	CL/F (L/hr/kg)
n	3	3	3	3	12 ^a	12 ^a
Mean	234	2	2932	5.8	0.257	0.0424
CV%	23	0	50	64	28	38

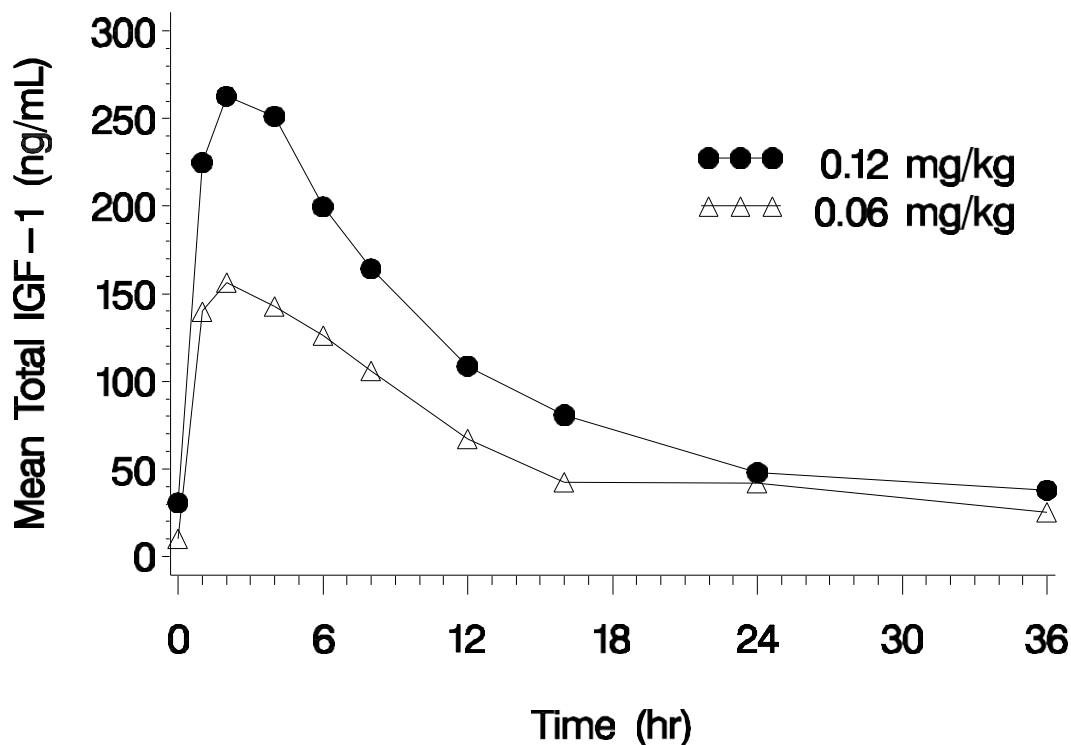
C_{max} = maximum concentration; T_{max} = time of maximum concentration;
 AUC_{0-8} = area under the curve; $t_{1/2}$ = half-life; Vd/F = apparent volume of distribution; CL/F = apparent systemic clearance;
 SC = subcutaneous injection; CV% = coefficient of variation in %.

Male/female data combined, ages 12 to 22 years.

^a Data represents 3 subjects each at doses 0.015, 0.03, 0.06, and 0.12 mg/kg SC.

PK parameters based on baseline adjusted plasma concentrations.

Figure 1. Mean Total IGF-1 Concentration after a Single Subcutaneous Dose of INCRELEX in Children with Severe Primary IGFD (0.06 mg/kg and 0.12 mg/kg, n=3 per group)



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

Hepatic impairment– No studies have been conducted to determine the effect of hepatic impairment on the pharmacokinetics of rhIGF-1 in Primary IGFD children with hepatic impairment.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those of INCRELEX or other growth hormones.

Anti-IGF-1 antibodies were present at one or more of the periodic assessments in 14 of 23 children with Primary IGFD treated for 2 years. However, no clinical consequences of these antibodies were observed (e.g., attenuation of growth).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: INCRELEX was tumorigenic in rats in a study using doses of 0, 0.25, 1, 4, and 10 mg/kg/day by subcutaneous injection for up to 2 years. The incidence of adrenal medullary hyperplasia and pheochromocytoma increased in male rats given ≥ 1 mg/kg/day (below clinical exposure at the maximum recommended human dose [MRHD] based on AUC) and in female rats at all dose levels (below clinical exposure at the MRHD based on AUC). The incidence of keratoacanthoma in the skin increased in male rats given 4 and 10 mg/kg/day (approximately the clinical exposure at the MRHD based on AUC). The incidence of mammary gland carcinoma in male rats increased in animals treated with 10 mg/kg/day (3 times the MRHD based on AUC). Only doses that exceeded the maximum tolerated dose (MTD) (based on excess mortality secondary to IGF-1 induced hypoglycemia) caused skin and mammary tumors.

Mutagenesis: INCRELEX was not clastogenic in the in vitro chromosome aberration assay and the in vivo mouse micronucleus assay.

Impairment of fertility: INCRELEX had no effects on fertility in rats using intravenous doses 0.25, 1, and 4 mg/kg/day (up to 3 times the clinical exposure at the MRHD based on BSA).

14 CLINICAL STUDIES

14.1 Effects of INCRELEX Treatment in Children with Severe Primary Insulin-like Growth Factor-1 Deficiency (Severe Primary IGFD)

Five clinical studies (four open-label and one double-blind, placebo-controlled), with subcutaneous doses of INCRELEX generally ranging from 0.06 to 0.12 mg/kg (60 to 120 micrograms/kg) administered twice daily, were conducted in 71 pediatric subjects with severe Primary IGFD. Patients were enrolled in the trials on the basis of extreme short stature, slow growth rates, low IGF-1 serum concentrations, and normal growth hormone secretion. Data from these 5 clinical studies were pooled for a global efficacy and safety analysis. Baseline characteristics for the patients evaluated in the primary and secondary efficacy analyses were (mean, SD): chronological age (years): 6.7 ± 3.8 ; height (cm): 84.8 ± 15.3 cm; height standard deviation score (SDS): -6.7 ± 1.8 ; height velocity (cm/yr): $2.8 \pm$

1.8; height velocity SDS: -3.3 ± 1.7 ; IGF-1 (ng/mL): 21.6 ± 20.6 ; IGF-1 SDS: -4.3 ± 1.6 ; and bone age (years): 4.2 ± 2.8 . Sixty-one subjects had at least one year of treatment. Fifty-three (87%) had Laron Syndrome; 7 (11%) had GH gene deletion, and 1 (2%) had neutralizing antibodies to GH. Thirty-seven (61%) of the subjects were male; forty-eight (79%) were Caucasian. Fifty-six (92%) of the subjects were pre-pubertal 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 58 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	58	58	48	38	23	21	20	16	13
Mean (SD)	2.8 (1.8)	8.0 (2.2)	5.8 (1.5)	5.5 (1.8)	4.7 (1.6)	4.7 (1.6)	4.8 (1.5)	4.6 (1.5)	4.3 (1.1)
Mean (SD) for change from pre-treatment		+5.2 (2.6)	+2.9 (2.4)	+2.3 (2.4)	+1.5 (2.2)	+1.5 (1.8)	+1.5 (1.7)	+1.0 (2.1)	+0.7 (2.5)
P-value for change from pre-treatment [1]		<0.0001	<0.0001	<0.0001	0.0045	0.0015	0.0009	0.0897	0.3059
Height Velocity SDS									
N	58	58	47	37	22	19	18	15	11
Mean (SD)	-3.3 (1.7)	1.9 (3.0)	-0.2 (1.6)	-0.2 (2.0)	-0.7 (2.1)	-0.6 (2.1)	-0.4 (1.4)	-0.4 (1.9)	-0.4 (1.9)
Mean (SD) for change from pre-treatment		+5.2 (3.1)	+3.1 (2.3)	+2.9 (2.3)	+2.2 (2.2)	+2.5 (2.2)	+2.7 (1.7)	+2.5 (2.1)	+2.7 (2.8)
Height SDS									
N	61	61	51	40	24	21	20	16	13
Mean (SD)	-6.7 (1.8)	-5.9 (1.8)	-5.6 (1.8)	-5.4 (1.8)	-5.5 (1.9)	-5.6 (1.8)	-5.4 (1.8)	-5.2 (2.0)	-5.2 (2.0)
Mean (SD) for change from pre-treatment		+0.8 (0.5)	+1.2 (0.8)	+1.4 (1.1)	+1.3 (1.2)	+1.4 (1.3)	+1.4 (1.2)	+1.4 (1.1)	+1.5 (1.1)

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

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

Forty-nine subjects were included in an analysis of the effects of INCRELEX on bone age advancement. The mean \pm SD change in chronological age was 4.9 ± 3.4 years and the mean \pm SD change in bone age was 5.3 ± 3.4 years.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

INCRELEX injection is supplied as a 40 mg/4 mL (10 mg/mL) sterile, clear, and colorless solution in multiple-dose glass vials (NDC-71863-216-04).

Storage and Handling

Before Opening – Vials of INCRELEX are stable when refrigerated at 2° to 8°C (36° to 46°F). Avoid freezing the vials of INCRELEX. Protect from direct light. Expiration dates are stated on the labels.

After Opening – Vials of INCRELEX are stable for 30 days after initial vial entry when stored refrigerated at 2° to 8°C (36° to 46°F). Avoid freezing the vials of INCRELEX. Protect from direct light.

INCRELEX should not be used after its expiration date. Keep refrigerated and use within 30 days of initial vial entry. Remaining unused material should be discarded.

17 PATIENT COUNSELING INFORMATION

Advise patients and/or caregivers to read the FDA-approved patient labeling (Patient Information) and Instructions for Use.

Counsel patients and/or parents that there have been occurrences of malignant neoplasia observed among pediatric patients who received treatment with INCRELEX. Instruct patients and/or parents to monitor for development of any new growth or symptoms of cancer and to report it immediately.

Instruct patients and/or caregivers in the proper administration of INCRELEX. Give INCRELEX shortly before or after (20 minutes on either side of) a meal or snack. Do not give INCRELEX when the meal or snack is omitted. Do not increase the dose of INCRELEX to make up for one or more omitted doses. INCRELEX therapy will be initiated at a low dose and the dose should be increased only if no

hypoglycemia episodes have occurred after at least 7 days of dosing. Educate patients and caregivers on how to recognize the signs and symptoms of hypoglycemia.

Educate patients and caregivers on the identification of signs and symptoms of serious allergic reactions to INCRELEX and the need to seek prompt medical contact should such a reaction occur. Instruct patients and caregivers to discontinue INCRELEX if a reaction occurs.

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