INCRELEX® (mecasermin [rDNA origin] injection) is an aqueous solution for injection containing 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 intrachain 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 synthesized in bacteria (E. coli) that have been modified by the addition of the gene for human IGF-1.

### Clinical Pharmacology

**General**
Insulin-like growth factor-1 (IGF-1) is the principal hormonal mediator of statal growth. Under normal circumstances, growth hormone (GH) binds to its receptor in the liver, and other tissues, and stimulates the synthesis and 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 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**: 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 deficient rats with rhIGF-1 results in whole body and organ growth.

**Special Populations**

**Geriatric**
- In children with Primary IGF-1 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 Primary IGF1 children with renal impairment.

**Hepatic insufficiency**
- No studies have been conducted to determine the effect of hepatic impairment on the pharmacokinetics of rhIGF-1.

### CLINICAL TRIALS

**Effects of INCRELEX™ Treatment in Children with Severe Primary Insulin-like Growth Factor-1 Deficiency (Primary IGF1)**

Five clinical studies (four open-label and one double-blind, placebo-controlled) with subcutaneous (SC) doses of INCRELEX™ generally ranging from 0.06 to 0.12 mg/kg (60 to 120 mg/kg) administered twice daily (BID), were conducted in pediatric subjects with severe Primary IGF1. 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): chronic age (years): 6.7 ± 3.8; height (cm): 84.8 ± 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; IGF1 (ng/mL): 21.6 ± 20.6; IGF-1 SDS: 4.3 ± 1.6; and bone age (years): 4.2 ± 2.3. 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. Severe Primary IGFD is defined by:

- height standard deviation score ≥ -3.0 and normal or elevated growth hormone (GH) gene deletion who have developed neutralizing antibodies to GH. Severe Primary IGFD is defined by:

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.

INCRELEX™ is not intended for use in subjects with secondary forms of IGF-1 deficiency, such as GH deficiency, malnutrition, hypothyroidism, or chronic treatment with pharmacologic doses of antiandrogenic steroids. Thyroid and nutritional deficiencies should be corrected before initiating INCRELEX™ treatment.

**CONTRAINdications**

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

INCRELEX™ is contraindicated in the presence of active or suspected neoplasia, and therapy should be discontinued if evidence of neoplasia develops.

Intraosseous administration of INCRELEX™ is contraindicated.

INCRELEX™ should not be used by patients who are allergic to mecasermin (IGF-1) or any of the inactive ingredients in INCRELEX™.

### INCRELEX™ is a purified preparation. Biological potency is determined using a bioassay.

INCRELEX™ is a sterile, aqueous, clear and colorless solution intended for subcutaneous injection. Each multi-dose vial of INCRELEX™ contains 10 mg/mL mecasermin, 9 mg/mL benzyl alcohol, 5.84 mg/mL sodium chloride, 2 mg/mL polysorbate 20, and 0.05M acetate at a pH of approximately 5.4.

### Summary of INCRELEX™ Single-Dose Pharmacokinetic Parameters in Children with Severe Primary IGF1 (0.12 mg/kg, SC)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/mL)</td>
<td>0.06 mg/kg: 0.12 mg/kg: 0.06 mg/kg:</td>
</tr>
<tr>
<td>Tmax (hr)</td>
<td>0.12 mg/kg: 0.06 mg/kg:</td>
</tr>
<tr>
<td>AUC0-8 (L/hr)</td>
<td>0.12 mg/kg: 0.06 mg/kg:</td>
</tr>
<tr>
<td>CL/F (L/hr/kg)</td>
<td>0.12 mg/kg: 0.06 mg/kg:</td>
</tr>
<tr>
<td>PK parameters based on baseline adjusted plasma concentrations.</td>
<td></td>
</tr>
</tbody>
</table>

### Table 1: Annual Height Results by Number of Years Treated with INCRELEX™

<table>
<thead>
<tr>
<th>Year</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>58</td>
<td>58</td>
<td>48</td>
<td>38</td>
<td>23</td>
<td>21</td>
<td>20</td>
<td>16</td>
<td>13</td>
</tr>
<tr>
<td>Height Velocity (cm/yr)</td>
<td>Mean (SD)</td>
<td>3.0</td>
<td>3.4</td>
<td>3.4</td>
<td>3.5</td>
<td>3.5</td>
<td>3.5</td>
<td>3.5</td>
<td>3.5</td>
</tr>
<tr>
<td>N</td>
<td>58</td>
<td>58</td>
<td>51</td>
<td>40</td>
<td>23</td>
<td>21</td>
<td>19</td>
<td>19</td>
<td>16</td>
</tr>
<tr>
<td>Height SDS</td>
<td>Mean (SD)</td>
<td>-0.7</td>
<td>-0.9</td>
<td>-0.8</td>
<td>-0.6</td>
<td>-0.6</td>
<td>-0.5</td>
<td>-0.5</td>
<td>-0.5</td>
</tr>
</tbody>
</table>

*P-values for comparison versus pre-Tx values are computed using paired t-tests.

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

### INDICATIONS AND USAGE

INCRELEX™ (mecasermin [rDNA origin] injection) is indicated for the long-term treatment of growth failure in children with severe primary IGF-1 deficiency (Primary IGF1) or with growth hormone (GH) gene deletion who have developed neutralizing antibodies to GH. Severe Primary IGFD is defined by:

- height standard deviation score ≥ -3.0 and normal or elevated growth hormone (GH) gene deletion who have developed neutralizing antibodies to GH. Severe Primary IGFD is defined by:

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.

INCRELEX™ is not intended for use in subjects with secondary forms of IGF-1 deficiency, such as GH deficiency, malnutrition, hypothyroidism, or chronic treatment with pharmacologic doses of antiandrogenic steroids. Thyroid and nutritional deficiencies should be corrected before initiating INCRELEX™ treatment.

INCRELEX™ is not a substitute for GH treatment.
WARNINGS  
INCRELEX™ contains benzyl alcohol as a preservative. Benzyl alcohol has been associated with neurologic toxicity in neonates. If sensitivity to INCRELEX™ occurs, treatment should be discontinued.

PRECAUTIONS  
General: Treatment with INCRELEX™ should be directed by physicians who are experienced in the diagnosis and management of patients with growth disorders. Information for Patients: Patients and/or their parents should be instructed in the safe administration of INCRELEX™. INCRELEX™ should be given only by a trained healthcare provider. 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. INCRELEX™ therapy should be initiated at a low dose and the dose should be increased only if hypoglycemia episodes have occurred after at least 7 days of dosing. If severe hypoglycemia or persistent hypoglycemia occurs on treatment despite adequate food intake, INCRELEX™ dose reductions should educate patients and caregivers on how to recognize the signs and symptoms of hypoglycemia.

Patients and/or parents should be thoroughly instructed in the importance of proper needle disposal. A puncture-resistant container should be used for the disposal of used needles and/or syringes (consistent with applicable state requirements). Injections should not be made into a vein.

INCRELEX™ has not been studied in children less than 2 years of age or in adults.

INCRELEX™ should be administered shortly before or after a meal or snack, because it has insulin-like hypoglycemic effects. 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, etc.) within 3-4 hours after dosing, particularly at the initiation of INCRELEX™ treatment, until a well-tolerated dose of INCRELEX™ has been established.

Lymphoid tissue (e.g., tonsillar) hypertrophy associated with complications, such as snoring, sleep apnea, and chronic middle-ear effusions have been reported with the use of INCRELEX™. Patients should be periodically examined to rule out such potential complications and receive appropriate treatment if necessary. Intracranial hypertension (IH) with papilledema, visual changes, headache, nausea and/or vomiting have been reported in patients treated with INCRELEX™, as they have been reported with therapeutic growth hormone administration. 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. 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.

As with any exogenous protein administration, local or systemic allergic reactions may occur. Parenteral administration of such reactions is possible and that if an allergic reaction occurs, treatment should be interrupted and prompt medical attention should be sought.

Carcinogenesis, mutagenesis, impairment of fertility. INCRELEX™ was administered subcutaneously to Sprague Dawley rats at doses of 0, 0.025, 1, 4, and 10 mg/kg/day for up to 2 years. An increased incidence of adenocarcinoma and pleomorphic osteosarcoma was observed in male rats at doses of 1 mg/kg and above (2-3 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 kidney cancer was observed in male rats at doses of 4 and 10 mg/kg/day (≥ 2 times the MRHD) and in female rats treated with 10 mg/kg/day (7 times 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 MRHD based on AUC). Based on excess mortality secondary to IGF-I induced hyperglycemia, these skin and mammary tumor findings were only observed at doses that exceeded the maximum tolerated dose (MTD).

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

Impairment of fertility: INCRELEX™ was administered intravenously to rats at doses of 0.25, 1, and 4 mg/kg/day to conduct the fertility study. No effects on fertility were observed in male or female rats treated with doses up to 4 mg/kg/day (4 times the clinical exposure with the MRHD based on AUC.)

Pregnancy Category C. Embryo-fetal toxicity studies were conducted in Sprague Dawley rats with doses of 1, 4, and 16 mg/kg/day, and in New Zealand White rabbits with doses of 0.125, 0.5, and 2 mg/kg/day administered intravenously. No embryo-fetal developmental abnormalities were observed in rats with doses up to 16 mg/kg/day (20 times the MRHD based on body surface area (BSA)) comparison. In the rabbit study, the NOAEL for maternal toxicity was 2 mg/kg (8 times the MRHD based on BSA) and the NOAEL for fetal toxicity was 0.5 mg/kg (2 times the MRHD based on BSA). INCRELEX™ displayed no teratogenicity at doses up to 2 mg/kg (8 times the MRHD based on BSA).

The effects of INCRELEX™ on an unborn child have not been studied. Therefore, there is insufficient medical information to determine whether there are significant risks to a fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when INCRELEX™ is administered to a nursing woman.

Geriatric Use: The safety and effectiveness of INCRELEX™ in patients aged 65 and over has not been evaluated in clinical studies.

ADVERSE REACTIONS
At a recommended starting dose of INCRELEX™ of 0.04 to 0.08 mg/kg (40 to 80 µg/kg) twice daily by subcutaneous injection. 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. Doses greater than 0.12 mg/kg given twice daily have not been evaluated in children with Primary IGFD and, due to potential hypoglycemic effects, should not be used. If hypoglycemia occurs with recommended doses, despite adequate food intake, the dose should be reduced. INCRELEX™ should be administered shortly before or after (≤ 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. Subsequent doses of INCRELEX™ should never be increased to make up for one or more omitted dose.

INCRELEX™ injection sites should be rotated to a different site each week..

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

STABILITY AND STORAGE
Before Opening - Vials of INCRELEX™ are stable when refrigerated (2º to 8ºC (35º to 46ºF)). 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 at 2º to 8ºC (35º to 46ºF). Avoid freezing the vials of INCRELEX™. Protect from direct light.

Vial contents should be clear without particulate matter. If the solution is cloudy or contains particulate matter, the contents must not be injected. 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.

HOW SUPPLIED
INCRELEX™ is supplied as a 10 mg/mL sterile solution in multiple dose glass vials (40 mg/mL) NDC 15054-1040-5 Rx only

Manufactured for: Tercica, Inc.  8080 Old Alabama Rd.  Houston, TX 77015
by: Baxter Pharmaceutical Solutions LLC  2000 Baxter Parkway  317-608-5850

Issued: August 2005  3-1015-267

OVERDOSAGE
There is no clinical experience with overdosage of INCRELEX™. Based on known pharmacological effects, acute overdosage would be predicted to lead to hypoglycemia. Long-term overdosage may result in signs and symptoms of acromegaly. Treatment of acute overdose of INCRELEX™ 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.

DOSAGE AND ADMINISTRATION
Preparational glucose monitoring should be considered at treatment initiation and until a well tolerated dose is established. If frequent symptoms of hypoglycemia or severe hypoglycemia occur, preparational glucose monitoring should continue.

The dosage of INCRELEX™ should be individualized for each patient. The recommended starting dose of INCRELEX™ is 0.04 to 0.08 mg/kg (40 to 80 µg/kg) twice daily by subcutaneous injection. 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. Doses greater than 0.12 mg/kg given twice daily have not been evaluated in children with Primary IGFD and, due to potential hypoglycemic effects, should not be used. If hypoglycemia occurs with recommended doses, despite adequate food intake, the dose should be reduced. INCRELEX™ should be administered shortly before or after (≤ 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. Subsequent doses of INCRELEX™ should never be increased to make up for one or more omitted dose.

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