

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-884

APPROVED LABELING

PROPOSED PACKAGE INSERT**IPLEX™ (mecasermin rinfabate [rDNA origin] injection)****DESCRIPTION**

IPLEX™ (mecasermin rinfabate [rDNA origin] injection) is an aqueous solution for injection containing a binary protein complex of human insulin-like growth factor-1 (rhIGF-1) and human insulin-like growth factor-binding protein-3 (rhIGFBP-3), both produced by recombinant DNA technology.

rhIGF-1 and rhIGFBP-3 are produced by two separate *E. coli* strains: one containing the human gene for insulin-like growth factor-1 (IGF-1), the other containing the human gene for insulin-like growth factor-binding protein-3 (IGFBP-3). 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 rhIGF-1 protein is identical to that of endogenous human IGF-1. IGFBP-3 consists of 264 amino acid residues with a molecular weight of 28,732 daltons. The amino acid sequence of the rhIGFBP-3 protein is identical to that of endogenous human IGFBP-3. Endogenous IGFBP-3 contains 18 cysteine residues that are all paired in disulfide bonds to form the biologically active molecule, but the pairings have not been fully elucidated. The rhIGF-1 and rhIGFBP-3 proteins are complexed in a 1:1 molar ratio for formation of mecasermin rinfabate with a molecular weight of 36,381 daltons. IGFBP-3 from human plasma is glycosylated, whereas rhIGFBP-3 produced in *E. coli* is non-glycosylated. Glycosylated and non-glycosylated IGFBP-3 bind IGF-1 with similar affinities.

Primary structures for rhIGF-1/rhIGFBP-3:*Recombinant human insulin growth factor-1 (rhIGF-1)*

1 35
 GlyProGluThrLeuGlyAlaGluLeuValAspAlaLeuGlnPheValCysGlyAspArgGlyPheTyrPheAsnLysProThrGly TyrGlySerSerSer
 ArgArgAlaProGlnThrGlyIleValAsp GluCysCysPheArgSerCysAspLeuArg ArgLeuGluMetTyr CysAlaProLeuLysProAlaLysSerAla
 36 70

Recombinant human insulin growth factor binding protein-3 (rhIGFBP-3)

1 10 11 20
 GlyAlaSerSerAlaGlyLeuGlyProVal ValArgCysGluProCysAspAlaArgAla
 LeuAlaGlnCysAlaProProProAlaVal CysAlaGluLeuValArgGluProGlyCys
 GlyCysCysLeuThrCysAlaLeuSerGlyGlnProCysGlyIleTyrThrGluArg
 CysGlySerGlyLeuArgCysGlnProPro AspGluAlaArgProLeuGlnAlaLeu
 LeuAspGlyArgGlyLeuCysValAsnAla SerAlaValSerArgLeuArgAlaTyrLeu
 LeuProAlaProProAlaProGlyAsnSerGluSerGluGluAspArgSerAlaTyr
 SerValGluSerProSerValSerSerHisArgValSerAspProLysPheHisPro
 LeuHisSerLysIleIleIleIleIleLys GlyHisAlaLysAspSerGlnArgTyrLys
 ValAspTyrGluSerGlnSerThrAspThr GlnAsnPheSerSerGluSerLysArgGln
 ThrGluTyrGlyProCysArgArgGlnAsp GluAspThrLeuAsnHisLeuLysAlaLeu
 AsnValLeuSerProArgGlyValHisAla ProAsnCysAspLysLysGlyPheTyrLys
 LysLysGlnCysArgProSerLysSerArg LysArgGlyPheCysTrpCysValAspLys
 TyrGlyGlnProLeuProGlyTyrSerLys GlyLysGluAspValHisCysTyrSer
 MetGlnSerLys 250 251 260
 261 264

Disulfide bonds not fully elucidated

IPLEX™ is prepared to a final concentration of 36 mg/0.6 mL in 50 mM sodium acetate and 105 mM sodium chloride with a final pH of 5.5. IPLEX™ is for subcutaneous injection only and is a preservative-free, sterile, clear, colorless-to-slightly-yellow liquid.

CLINICAL PHARMACOLOGY

The primary pharmacologic effect of IGF-1 in children is the promotion of linear growth. Secondary pharmacologic actions of IGF-1 include other anabolic effects, insulin sensitization, and insulin-like effects. There are no known direct growth-promoting effects of IGFBP-3. The primary effect of IGFBP-3 in the mecasemin rinfabate complex is the modulation of IGF-1 action.

In normal human circulation, less than 2% of total IGF-1 exists in the free form. Most circulating IGF-1 is found in association with the growth hormone (GH)-dependent binding protein IGFBP-3, and this binary complex further associates with a third serum protein, the GH-dependent acid-labile subunit (ALS), to form a non-covalent ternary complex of ~150 kD, which represents the natural physiologic reservoir of IGF-1. The ternary complex consists of one molecule each of IGF-1, IGFBP-3, and ALS.

The half-life of IGF-1 in the ternary complex is > 12 hr. Proteolytic cleavage of IGFBP-3 and interaction of the ternary complex with proteoglycans have been shown to release IGF-1 from the ternary complex.

Pharmacokinetics

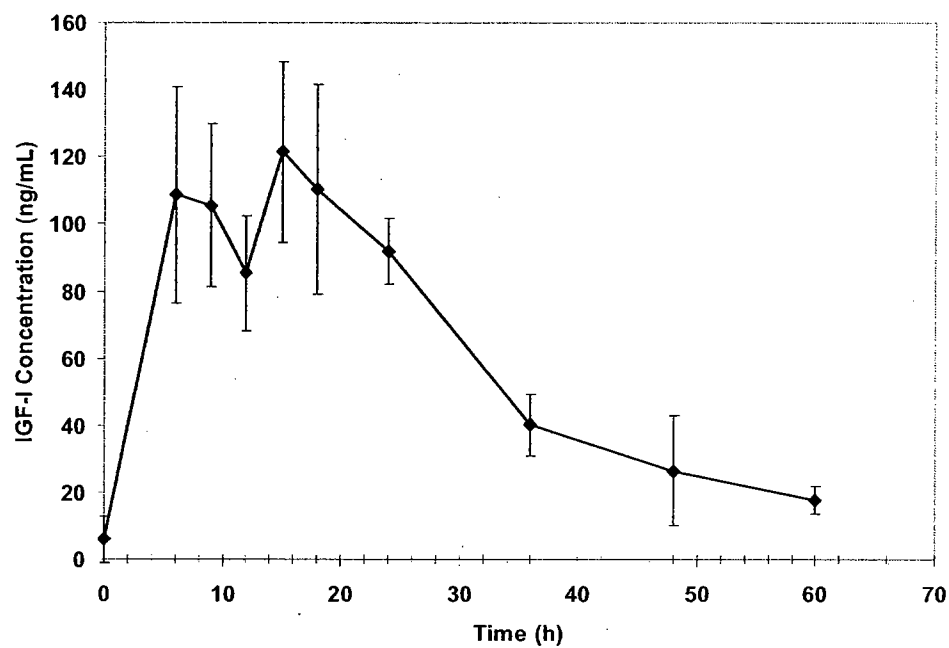
In pediatric patients with severe primary IGF-1 deficiency (Primary IGFD), 1 mg/kg was administered by subcutaneous injection to 4 patients in a pharmacokinetic sub-study of the clinical trial. A summary of the pharmacokinetic parameters for IGF-1 and IGFBP-3, uncorrected for baseline values, is presented in Table 1 and Figure 1. The assays employed do not distinguish between exogenous and endogenous IGF-1 or IGFBP-3.

Table 1. Mean (±SD) Pharmacokinetic Parameters in Patients with Primary IGFD Treated with IPLEX™ 1 mg/kg (n= 4)

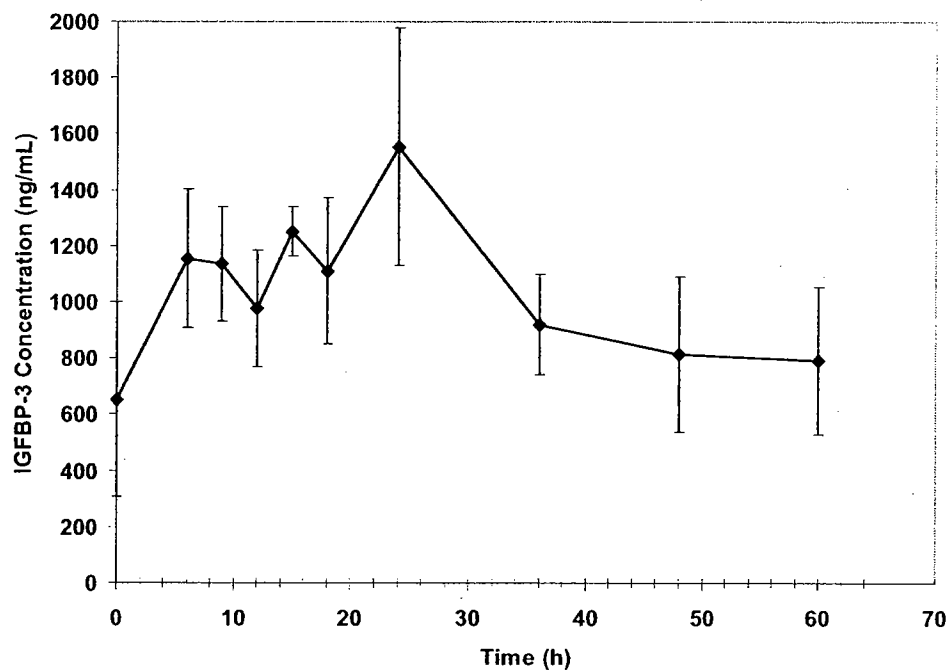
	Cmax (ng/mL)	Tmax (hr)	AUC₀₋₆₀ (ng hr/mL)	Half-life (hr)
IGF-1	133±19	11.3±6.2	3654±237	13.4±2.7
IGFBP-3	1574±401	19.5±9.0	62525±8352	54.1±31.6

Figure 1. Mean ($\pm$ SD) Uncorrected IGF-1 (Panel A) and IGFBP-3 (Panel B) (ng/mL) Concentrations in Patients with Primary IGFD Treated with IPLEXTM 1 mg/kg (n=4)

Panel A.



Panel B.



Special Populations

Geriatric: The pharmacokinetics of IPLEX™ have not been studied in subjects greater than 65 years of age.

Gender: No information is available.

Race: No information is available.

Renal insufficiency: No studies have been conducted to determine the effect of renal impairment on the pharmacokinetics of IPLEX™.

Hepatic insufficiency: No studies have been conducted to determine the effect of hepatic impairment on the pharmacokinetics of IPLEX™.

CLINICAL STUDIES

A prospective, open-label multicenter study was conducted to evaluate the safety and efficacy of IPLEXTM (mecasermin rinfabate [rDNA origin] injection) in children and adolescents with primary IGF-1 deficiency (Primary IGFD). Subjects were enrolled in the clinical trial on the basis of extreme short stature, low IGF-1 and IGFBP-3 serum concentrations, and normal GH secretion. Thirty-six prepubertal subjects received up to 2 mg/kg mecasermin rinfabate administered once daily by subcutaneous injection for a mean duration of 10.4 months (range: 27 days – 22.5 months). Baseline characteristics at enrollment were (mean $\pm$ standard deviation [SD]): chronological age (years): 8.7 ± 3.1 ; bone age (years): 5.9 ± 3.2 (n=27); height standard deviation score (SDS): -6.9 ± 1.7 ; height velocity (cm/yr): 3.0 ± 1.8 . Thirty-two (89%) had Primary IGFD due to GH receptor deficiency (Laron syndrome), 3 (8%) had GH gene deletion with neutralizing antibodies to GH, and one (3%) had Primary IGFD due to unknown etiology. Twenty (56%) of the subjects were male and 28 (78%) were Caucasian. All subjects were prepubertal at baseline.

Subjects were divided into two cohorts treated sequentially: Cohort # 1 (n=19) and Cohort # 2 (n=17). Treatment was initiated at a dose of 0.5 mg/kg daily and titrated upward to a maximum dose of 2 mg/kg/day based on clinical tolerability and serum IGF-1 levels. In Cohort #1, subjects were treated with a dose of up to 1 mg/kg daily for the first 12 months; 16 subjects were evaluable for efficacy at Month 6 and Month 12. Subjects in Cohort # 2 were titrated up to 2 mg/kg daily; 9 subjects were evaluable for efficacy at Month 6. Primary and secondary efficacy endpoints are summarized in Table 2. Efficacy beyond one year of treatment has not been established.

Table 2. Mean ($\pm$ SD) Efficacy Results for Patients with Primary IGFD Treated with Mecasermin Rinfabate

Endpoint	Cohort #1 (≤ 1 mg/kg daily) [1]			Cohort #2 (≤ 2 mg/kg daily) [2]	
	Pre-Tx (n=16)	Month 6 (n=16)	Month 12 (n=16)	Pre-Tx (n=9)	Month 6 (n=9)
Annualized Height Velocity (cm/yr)	3.4 $\pm$ 1.9	7.4 $\pm$ 2.0	6.4 $\pm$ 1.6	2.2 $\pm$ 1.5	8.8 $\pm$ 2.0
Change in Height Velocity from Pre-Tx (cm/yr)		4.0 $\pm$ 1.8	3.0 $\pm$ 1.3		6.6 $\pm$ 2.6
p-value for Change in Height Velocity from Pre-Tx [3]		<0.0001	<0.0001		<0.0001
Height SDS	-6.4 $\pm$ 2.1	-6.1 $\pm$ 2.1	-6.0 $\pm$ 2.2	-7.9 $\pm$ 1.1	-7.5 $\pm$ 1.1
Change in Height SDS from Pre-Tx		0.3 $\pm$ 0.2	0.5 $\pm$ 0.4		0.4 $\pm$ 0.3
p-value for Change in Height SDS from Pre-Tx [3]		<0.0001	<0.002		<0.001

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

[1] Mean Month 0-6 dose: 0.96 mg/kg daily.

[2] Mean Month 0-6 dose: 1.4 mg/kg daily.

[3] Paired t-test or Wilcoxon signed rank test

In the Cohort #1 evaluable population, there were 10 subjects with detectable acid-labile subunit (ALS) levels and 6 subjects with undetectable ALS. The mean height velocity for Months 0-6 was 8.1 $\pm$ 2.2 cm/yr for Cohort #1 subjects with detectable ALS and 6.3 $\pm$ 1.0 cm/yr for Cohort #1 subjects with undetectable ALS levels. In the Cohort #2 evaluable population, 8/9 subjects had undetectable ALS, and had a mean height velocity for Months 0-6 of 9.1 $\pm$ 1.9 cm/yr on the higher dose. In Cohort #1, height velocity correlated with IGF-1 SDS at Month 1 ($r=0.71$, $p=0.005$, $n=14$). The mean height velocity for Month 0-6 was 8.5 $\pm$ 2.1 cm/yr for subjects with IGF-1 SDS at Month 1 ≥ -2 ($n=8$), and 6.7 $\pm$ 1.2 cm/yr for subjects with IGF-1 SDS at Month 1 < -2 ($n=6$).

INDICATIONS AND USAGE

IPLEXTM (mecasermin rinfabate [rDNA origin] injection) is indicated for the treatment of growth failure in children with severe primary IGF-1 deficiency (Primary IGFD) 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 and
- basal IGF-1 standard deviation score ≤ -3 and
- normal or elevated growth hormone

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.

IPLEX™ 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 anti-inflammatory steroids. Thyroid and nutritional deficiencies should be corrected before initiating IPLEX™ treatment.

IPLEX™ is not a substitute for GH treatment.

CONTRAINDICATIONS

IPLEX™ (mecasermin rinfabate [rDNA origin] injection) should not be used for growth promotion in patients with closed epiphyses.

IPLEX™ is contraindicated in the presence of active or suspected neoplasia, and therapy should be discontinued when there is any evidence of active neoplasia.

IPLEX™ is contraindicated in patients allergic to mecasermin rinfabate (rhIGF-1/rhIGFBP-3) or any of the excipients in IPLEX™.

Intravenous administration of IPLEX™ is contraindicated.

WARNINGS

IPLEX™ (mecasermin rinfabate [rDNA origin] injection) is supplied as a single use, preservative-free solution for subcutaneous injection. Aseptic technique must be followed for administration. Discard any unused portion.

If sensitivity to IPLEX™ occurs, treatment should be discontinued.

PRECAUTIONS

General

Therapy with IPLEX™ (mecasermin rinfabate [rDNA origin] injection) should be directed by physicians experienced in the diagnosis and management of patients with growth disorders.

IPLEX™ has not been studied in children less than 3 years of age or adults with Primary IGFD.

IPLEX™ should be administered at approximately the same time every day. Because it has insulin-like hypoglycemic effects, patients should avoid missing meals and should have a balanced diet. IPLEX™ should not be administered on days when the patient cannot or will not eat. Special attention should be paid to small children because their oral intake may be inconsistent. At the time of initiation of IPLEX™ therapy and any upward adjustment of dose patients should avoid engaging in any high-risk activities until tolerability has been established (e.g., 3 – 5 days).

Lymphoid tissue hypertrophy (e.g., tonsillar and adenoidal) has been associated with IPLEX™. Patients should have periodic examinations to detect potential complications

of adenotonsillar enlargement (such as excessive snoring, sleep apnea, chronic middle ear effusions, hearing loss) and receive appropriate treatment if necessary.

The syndrome of intracranial hypertension, with papilledema, visual changes, headache, and nausea and/or vomiting, may occur during treatment with IPLEX™ and has been reported in children with growth failure treated with related products (growth hormone, rhIGF-1). Fundoscopic examination is recommended at the initiation of and periodically during the course of IPLEX™ 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 IPLEX™ treatment.

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

Information for Patients

Patients and/or their caregivers should be instructed in the safe administration of IPLEX™. Because of the possibility of hypoglycemia, patients using IPLEX™ should be on a regular, balanced diet. IPLEX™ should be administered at the same time every day. **IPLEX™ should not be administered if the patient cannot or will not eat or when a meal is omitted.** Therapy should be instituted in accordance with the prescribing physician's instructions. The dose of IPLEX™ should not be increased to make up for a missed dose. If severe or persistent hypoglycemia occurs on treatment despite adequate food intake, IPLEX™ dose reduction should be considered. Providers should educate patients and caregivers on how to recognize the signs and symptoms of adverse reactions, particularly hypoglycemia.

Patients and/or caregivers 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). Needles and syringes must not be reused.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies for the evaluation of carcinogenicity with mecasermin rinfabate (rhIGF-1/rhIGFBP-3) have not been performed.

The genotoxic potential of mecasermin rinfabate has not been assessed. rhIGF-1 tested negative for genotoxic potential in the Ames test and in chromosomal aberration assays conducted with human lymphocytes or rat peripheral lymphocytes.

Animal fertility studies have not been performed with mecasermin rinfabate. Effects of rhIGF-1 on fertility and reproductive performance were assessed in male and female rats administered 0.4, 2, and 10 mg/kg/day subcutaneously (0.2, 1, and 7 times clinical

exposures with the maximum recommended human dose [MRHD] based on body surface area). rhIGF-1 had no effects on mating, fertility, or reproductive performance in rats.

Pregnancy – Pregnancy Category C

Animal reproduction studies have not been conducted with mecasemin rinfabate. Effects of rhIGF-1 on embryofetal development were assessed in rats and rabbits.

Subcutaneous administration of 0.4, 2, or 10 mg/kg/day rhIGF-1 to pregnant rats during organogenesis had no effects on embryofetal development (0.5, 1.5, and 4 times therapeutic exposures with MRHD based on body surface area).

Subcutaneous administration of 0.2, 0.5, or 1.25 mg/kg/day rhIGF-1 to rabbits during organogenesis resulted in an increased incidence of fetal loss but no fetal anomalies. Increased early resorptions were observed in rabbits treated with 1.25 mg/kg and increased preimplantation loss was observed (exposure equivalent to ≥ 0.3 times MRHD based on body surface area).

A second rabbit embryofetal development study was conducted to determine the role of hypoglycemia in rhIGF-1 mediated fetal loss. Rabbits were administered subcutaneous doses of 0, 0.5, and 1.25 mg/kg/day rhIGF-1; 1.25 or 2.5 mg/kg rhIGF-1 plus glucose supplementation; or 2.5 IU/kg/day insulin. A comparable degree of hypoglycemia was observed in rabbits treated with 1.25 mg/kg rhIGF-1 alone or 2.5 IU/kg insulin. Animals treated with 0.5 mg/kg rhIGF-1 or rhIGF-1 plus glucose maintained normal glucose levels.

Similar to the initial rabbit study, an increase in early fetal resorptions was observed in rabbits treated with 1.25 mg/kg/day rhIGF-1 (2 times MRHD based on body surface area). This finding was not observed in insulin-treated rabbits despite a comparable degree of drug-induced hypoglycemia. A dose-related increase in postimplantation loss was observed in all rhIGF-1 treated groups (≥ 0.5 times MRHD based on body surface area). While the incidence of fetal loss was somewhat reduced in glucose-supplemented rabbits, it was not clearly attributable to drug-induced hypoglycemia since significant fetal loss was still observed in normoglycemic rhIGF-1 treated rabbits.

The effects of IPLEXTM 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 secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when IPLEXTM is administered to a nursing woman.

Geriatric Use

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

ADVERSE REACTIONS

Treatment-emergent adverse events were assessed in the clinical study of IPLEX™ (mecasermin rinfabate [rDNA origin] injection) in children with Primary IGFD. In this study, 36 patients had an average exposure of 10.4 months (range: 27 days – 22.5 months), for a total of 374 patient-months. Safety information beyond one year of treatment is limited and safety beyond 21 months of treatment has not been established.

The most common treatment-related adverse events occurring in 2 or more ($\geq 5\%$) subjects were iron deficiency anemia, lymphadenopathy, thyromegaly, injection site conditions, increased transaminases, hyperglycemia, hypoglycemia, arthralgia, bone pain, muscular atrophy, pain in an extremity, headache, papilledema, hematuria, ovarian cysts, and tonsillar hypertrophy.

Common injection site conditions included erythema, lipohypertrophy, and hair growth at the injection sites.

Hypoglycemia was reported in 11/36 (31%) patients in the study generally rated as mild and asymptomatic. Four hypoglycemic episodes were characterized as symptomatic including two cases that required acute intervention.

Headaches were reported in 8/36 (22%) patients in the study. One adverse event of asymptomatic papilledema was reported. An adverse event of increased intracranial pressure and papilledema (possible intracranial hypertension) was also reported, which resolved with revision of a blocked existing ventriculo-peritoneal shunt.

Seven of 36 (19%) patients in the study, reported an adverse event of tonsillar and/or adenoid hypertrophy and 2 patients underwent tonsillectomy and/or adenoidectomy.

Increases in liver, spleen, and kidney size were noted in several patients on abdominal ultrasound assessments; occasional measurements near the upper-limit-of-normal were noted. Renal function (as defined by serum creatinine and calculated creatinine clearance) was normal. Two patients had ovarian cysts on pelvic ultrasound and one patient had sonographic evidence of hepatomegaly.

Mild elevations in the serum AST and LDH were found in a significant proportion of patients before and during treatment without treatment discontinuations. Two patients had AST elevations that required temporary interruption of treatment. Echocardiographic evidence of valvulopathy was observed in a few individuals without associated clinical symptoms. Because of the underlying disease and the lack of a control group, the relationship of the valvular changes to drug treatment cannot be assessed.

Since IGF-1 is the main mediator of GH effects and GH may produce acromegalic changes, such changes should be monitored during IPLEX™ treatment.

By 9 months of treatment, a proportion of patients developed antibodies to the protein complex (90%), rhIGFBP-3 (50%), and/or rhIGF-1 (20%), using assays with varying

degrees of sensitivity. No evidence of neutralization of biological activity, such as reduced height velocity, was noted in antibody-positive patients during the first year of IPLEX™ treatment.

OVERDOSAGE

There were no instances of overdosage with IPLEX™ in the Primary IGFD clinical trial. Based on the known pharmacological effects of IGF-1, acute overdosage could lead to hypoglycemia. Treatment of acute overdosage of IPLEX™ should be directed at reversing hypoglycemia. Mild hypoglycemia can usually be treated with oral glucose or food. If the overdose results in loss of consciousness, treatment with parenteral glucagon or intravenous glucose may be required.

Long-term overdosage could result in signs and/or symptoms of acromegaly.

DOSAGE AND ADMINISTRATION

IPLEX™ dosage and administration should be individualized for each patient. IPLEX™ should be administered via subcutaneous injection at an initial dose of 0.5 mg/kg, to be increased into the therapeutic dose range of 1 to 2 mg/kg, given once daily. IPLEX™ can be given in the morning or in the evening but should be administered at approximately the same time every day and the patient should maintain a regular, balanced diet. IPLEX™ should not be administered if the patient cannot or will not eat or if they skip a meal. Subsequent doses of IPLEX™ should not be increased to make up for a missed dose.

In order to establish tolerability to IPLEX™, glucose monitoring should be considered at treatment initiation or when a dose has been increased. If frequent symptoms of hypoglycemia or severe hypoglycemia occur, preprandial glucose monitoring should continue. Glucose monitoring is also advised for patients with recent occurrences of asymptomatic or symptomatic hypoglycemia. If evidence of hypoglycemia is present at the time of dosing, the dose should be withheld.

Dosage can be titrated up to a maximum of 2 mg/kg daily based on measurement of IGF-1 levels obtained 8-18 hours after the previous dose. Treating physicians should target on-treatment IGF-1 levels of 0 to +2 SD score for age. Dosage should be adjusted downward in the event of adverse effects (including hypoglycemia) and/or IGF-1 levels that are greater than or equal to 3 standard deviations above the normal reference range for IGF-1.

Growth response to IPLEX™ is expected to decrease with time, as seen with other growth-promoting agents. However, failure to increase height velocity during the first year of therapy by at least 2 cm/year suggests the need for assessment of compliance and evaluation of other causes of growth failure, such as hypothyroidism, under-nutrition, and advanced bone age. Patients with undetectable ALS levels at baseline may require higher doses of IPLEX™.

Rotate sites for injection (thigh, abdomen, buttocks, or upper arm). New injections should be given at least one inch from previous injection site(s) and never into areas where the skin is tender, bruised, red, hard, or lipodystrophic.

IPLEX™ 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.

Remove IPLEX™ from the freezer and thaw at room temperature for approximately 45 minutes. After thawing, allow vial to reach room temperature prior to injection (approximately 45 minutes). The vial should be swirled in a gentle rotary motion to ensure content uniformity. **DO NOT SHAKE**. If the solution is cloudy, it may indicate that the drug was previously thawed or exposed to extreme temperatures. If so, it **MUST NOT** be injected. Discard any vial that contains particulate matter, is cloudy or discolored. Use within one hour after the vial reaches room temperature. IPLEX™ **MUST NOT** be injected if it has been exposed to room temperature for more than two hours. After removing the dose of IPLEX™, discard the vial with any unused portion.

STORAGE CONDITIONS

IPLEX™ (mecasermin rinfabate [rDNA origin] injection) is temperature sensitive and must be stored frozen at -70°C (-94°F) while in the distribution chain. The patient must be instructed to keep the medication frozen while transferring it to his/her home freezer (-20°C, -4°F). Frozen (-70°C) IPLEX™ from the distributor can be transported on dry ice to the patient's home freezer. The medication must remain in the patient's home freezer until time of use. Do not store in a home freezer that allows contents to thaw during the defrost cycle. Do not use medication if it thaws during transfer or storage, as stability of material may be affected. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If the solution is cloudy it may indicate that the drug was previously thawed or exposed to extreme temperatures. If so, it **MUST NOT** be injected. Discard any vial that contains particulate matter, is cloudy or discolored.

IPLEX™ can be stored frozen up to two months at constant temperature (-20°C, -4°F). For use, IPLEX™ should be removed from the freezer (-20°C, -4°F) and thawed at room temperature (20-25°C, 68-77°F) for 45 minutes prior to use. After thawing, allow vial to reach room temperature prior to injection (approximately 45 minutes). The vial should be swirled in a gentle rotary motion to ensure content uniformity. **DO NOT SHAKE**. Use within one hour after the vial reaches room temperature. IPLEX™ **MUST NOT** be used if it has been at room temperature for more than two hours. After removing the dose of IPLEX™, discard the vial with any unused portion.

HOW SUPPLIED

IPLEX™ (mecasermin rinfabate [rDNA origin] injection) is supplied as a 36 mg/0.6 mL preservative-free sterile solution in single dose glass vials.. Each box contains 35 vials.

IPLEX™ (mecasermin rinfabate [rDNA origin] injection) is temperature sensitive and must be stored frozen at -70°C (-94°F) while in the distribution chain. The patient must be instructed to keep the medication frozen while transferring it to his/her home freezer (-20°C, -4°F).

NDC-XXXXX-XXXX-X

Rx only

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Boulder, Colorado 80301
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Revision Date:

Version Code:

Patient Information

IPLEX™ (“eye-plex”)

(mecasermin rinfabate [rDNA origin] injection)

Read the Patient Information leaflet that comes with IPLEX™ before starting your child’s IPLEX™ and each time you get a refill. There may be new information. This information does not take the place of talking to your child’s doctor about your child’s condition or treatment.

What is IPLEX™?

IPLEX™ is an injectable medicine that contains man-made insulin-like growth factor-1 (IGF-1) and insulin-like growth factor binding protein-3 (IGFBP-3). IPLEX™ is used to treat children with severe primary IGF-1 deficiency. Children with severe primary IGF-1 deficiency are very short for their age because their bodies do not make enough IGF-1.

IPLEX™ should not be used in place of growth hormone. IPLEX™ is not for other causes of growth failure.

IPLEX™ is not for children less than 3 years old or adults with primary IGF-1 deficiency.

Who should not take IPLEX™?

Your child should not take IPLEX™ if your child:

- has finished growing (bone growth plates are closed)
- has cancer
- is allergic to mecasermin rinfabate or any of the inactive ingredients in IPLEX™. Check with your child’s doctor if you are not sure. See “What are the Ingredients in IPLEX™?”
- Never inject IPLEX™ into a vein.

What should I tell my child’s doctor before my child starts IPLEX™?

Tell your child’s doctor about all of your child’s health conditions, including if your child:

- has diabetes
- has kidney problems
- has liver problems

- has a curved spine (scoliosis)
- is pregnant or breastfeeding

Tell your doctor about all the medicines your child takes, including prescription and nonprescription medicines, vitamins, and herbal supplements. It is especially important to tell your child's doctor if your child takes insulin or other medicines for diabetes. A dose change may be needed for these medicines.

How should my child use IPLEX™?

- IPLEX™ is given as an injection under the skin. See the “**Instructions for Use**” at the end of this leaflet for step-by-step directions. Your child's doctor or nurse should teach you how to inject IPLEX™. Do not give your child IPLEX™ unless you understand all of the instructions.
- Use IPLEX™ exactly as prescribed for your child. Your child's doctor will tell you how much IPLEX™ you should give your child. The doctor may change the dose over time.
- Inject IPLEX™ once a day before a meal at the same time every day, either in the morning or in the evening.
- Inject IPLEX™ just below the skin in your child's upper leg (thigh), stomach area (abdomen), buttocks, or upper arm. Change the injection site for each injection (“rotate the injection site”).
- **Never inject IPLEX™ into a vein.**
- **Skip your child's dose of IPLEX™ if your child cannot or will not eat for any reason at the time of the injection.** Do **not** make up the missed dose by giving two doses the next time. It is important that your child eat well and not skip meals while taking IPLEX™.
- Only use IPLEX™ if the liquid is clear, and either colorless or slightly yellow. Do not inject IPLEX™ if the liquid is cloudy. Contact the national pharmacy who sent you your IPLEX™ for instructions on how to return and obtain replacement of IPLEX™.

What are possible side effects of IPLEX™?

IPLEX™ may cause the following side effects, some of which can be serious.

- **Low blood sugar (hypoglycemia).** IPLEX™ may lower your child's blood sugar levels the way insulin does. Do not give your child IPLEX™ if your child has signs of low blood sugar which include:
 - dizziness
 - headache
 - tiredness
 - restlessness
 - hunger
 - irritability
 - trouble concentrating
 - sweating
 - nausea
 - fast or irregular heartbeat

Severe low blood sugar may cause unconsciousness, convulsions, or death. Your child should not do risky activities until the doctor has found the right dose for your child.

Before beginning treatment with IPLEX™, your doctor or nurse will explain to you how to treat low blood sugar. Make sure your child always has a sugar drink or food with them such as orange juice, hard candy, milk, or glucose gel. These are used to treat symptoms of low blood sugar.

If your child is not alert and cannot drink or eat a sugar-drink or food, you must give an injection of glucagon. Glucagon raises the blood sugar when it is injected. Your child's doctor or nurse will instruct you how to give this injection. It is important that your child have a well-balanced diet including protein and fat such as meat and cheese in addition to sugar-containing foods. Do not give your child IPLEX if your child is sick and cannot eat.

Your child's doctor will tell you if and when you need to check your child's blood-sugar level. Your child's doctor will explain how to do this.

- **Enlarged tonsils.** IPLEX™ may enlarge your child's tonsils. Some signs of enlarged tonsils are snoring, problems breathing or swallowing, earaches, problems hearing, and breathing problems during sleep (sleep apnea, which can also cause excessive daytime sleepiness). Call your child's doctor if your child gets any of these symptoms. Your doctor should do regular exams to check your child's tonsils.
- **Increased pressure in the brain (intracranial hypertension).** Signs of increased pressure in the brain include headache, nausea, vomiting, and vision problems. Call your child's doctor if your child has these symptoms. Your doctor can check to see if increased pressure in the brain is present. If your child has increased pressure in the brain, your child's doctor may reduce or stop IPLEX™ treatment for a time. IPLEX™ treatment may be started again after the pressure is gone.

- **A hip bone problem called slipped capital femoral epiphysis.** This happens when the upper end of the leg bone (femur) slips apart. Get medical attention for your child right away if your child develops a limp, or has hip or knee pain.
- **Worsened curve of the spine (scoliosis).** If your child has scoliosis, your child will need to be checked regularly for an increase in the curve of the spine.
- **Allergic reactions.** Your child may have a mild or serious allergic reaction to IPLEX™. Call your child's doctor right away if your child gets a rash or hives. Get medical help right away if your child has trouble breathing or goes into shock.
- **IPLEX™ can cause reactions at the injection site including:**
 - redness
 - pain
 - increase of fat
 - lumps under the skin
 - slight hair growth

Injection site reactions can be avoided by changing the injection site at each injection ("injection site rotation").

Call your child's doctor if your child has side effects that bother them, or do not go away.

These are not all the side effects of IPLEX™. Ask your child's doctor or pharmacist for more information.

How should I store IPLEX™?

- IPLEX™ should be kept frozen at all times until you are ready to use it.
- IPLEX™ will be shipped by a national pharmacy. The pharmacy will use a national overnight shipping service and deliver IPLEX™ directly to you or to your doctor's office. During the shipment of IPLEX™ to you or your doctor, it will be kept on dry ice so it stays frozen.
- Store IPLEX™ in your freezer at -4°F (-20°C) or colder for no more than 2 months. Do not use IPLEX™ that has been stored in your freezer for longer than 2 months.
- Do not store IPLEX™ in your home freezer if contents thaw during the defrost cycle. The medicine may not work.

- Once IPLEX™ thaws, use it within 1 hour.
- Do not use IPLEX™ if it thaws and stays at room temperature for longer than 1 hour. The medicine may not work.
- If you do not use IPLEX™ within 2 hours after you have removed it from the freezer, discard the vial because it may not work.
- Keep IPLEX™ and all medicines out of reach of children.

General information about IPLEX™

Medicines are sometimes prescribed for conditions other than those described in patient information leaflets. Do not give IPLEX™ to your child for a condition for which it was not prescribed. Do not give your child more IPLEX™ than your doctor prescribed. Do not give IPLEX™ to another person besides your child. It may harm them.

This leaflet summarizes the most important information about IPLEX™. If you would like more information, talk to your child's doctor. You can also ask your child's doctor or pharmacist for information that is written for health professionals. More information about IPLEX™ is available by contacting Insmmed Incorporated.

Insmmed Incorporated
4851 Lake Brook Drive
Glen Allen, VA 23058
804-565-3079

www.insmed.com

What are the Ingredients in IPLEX™?

Active ingredient: mecasemin rinfabate

Inactive ingredients: sodium acetate, sodium chloride

INSTRUCTIONS FOR USE

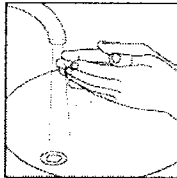
IPLEX™ should be administered using sterile disposable syringes and needles. The syringes should be of small enough volume that the prescribed dose can be withdrawn from the vial with reasonable accuracy.

Preparing IPLEX™ for use:

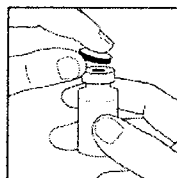
1. When you are ready to use IPLEX™, take it out of the freezer and thaw it at room temperature for 45 minutes.
2. Once IPLEX™ reaches room temperature, use it within 1 hour.
3. Swirl the vial of IPLEX™ in a gentle, circular motion to help mix it.
Do not shake the vial.
4. Make sure IPLEX™ is at room temperature when you give the injection.

Preparing the dose:

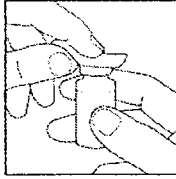
1. Wash your hands with soap and water or a rubbing alcohol-based gel or foam hand sanitizer product.



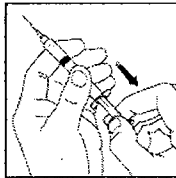
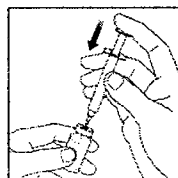
2. Check to make sure the IPLEX™ in the vial is clear and colorless or slightly yellow. Do not use it if it's cloudy or the wrong color. Contact the national pharmacy who sent you your IPLEX™ for instructions on how to return and obtain replacement of IPLEX™.
3. Remove the cap on top of the vial. Do not remove the rubber stopper.



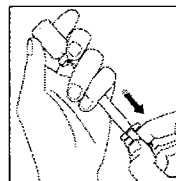
4. Wipe the top of the vial with an alcohol swab.



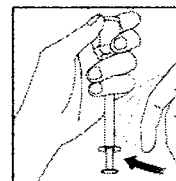
5. Use a new needle and syringe each time you give an injection.
6. Pull out the plunger on the syringe to draw air into the syringe up to the line that matches the prescribed dose of IPLEX™. Put the needle through the rubber top of the vial and push the plunger of the syringe to inject air into the vial.



7. Leave the syringe in the vial and turn both upside down.
8. Hold the syringe and vial tightly in one hand.
9. Make sure the tip of the needle is in the IPLEX™ liquid.
10. With your free hand, pull the plunger back to get the prescribed dose of IPLEX™ into the syringe.

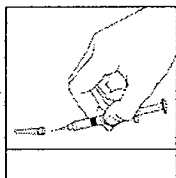


11. Before you take the needle out of the vial, check the syringe for air bubbles. If there are bubbles, hold the vial and syringe with the needle straight up and tap the side of the syringe until the bubbles float to the top. Push the bubbles out with the plunger and if necessary, draw IPLEX™ back in until you have the right amount.



12. Take the needle out of the vial. Do not let the needle touch anything.

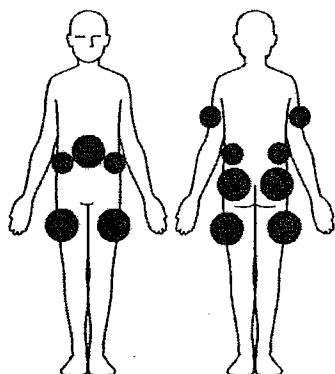
13. Recap the needle as directed by your doctor to help prevent accidental injury while preparing the site for injection.



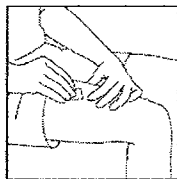
14. You are ready now to inject.

Injecting IPLEX™:

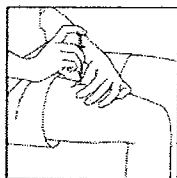
1. Choose a place on your child's body for the injection. Do not inject IPLEX™ into skin areas that are tender, black and blue (bruised), red, hard, or have an increase in fat. Inject IPLEX™ just below the skin on your child's stomach area (abdomen), buttock, upper leg (thigh), or upper arm. **Never inject IPLEX™ into a vein.** Always remember to choose a different site for each injection. You should give the new injection at least 1 inch from the old ones.



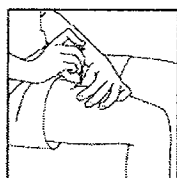
2. Use rubbing alcohol or soap and water to clean the skin where you are going to inject your child. The injection site should be dry before you inject.



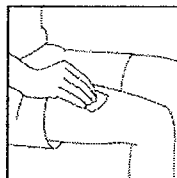
3. Pinch the skin and stick the needle straight in the way your doctor or nurse showed you.



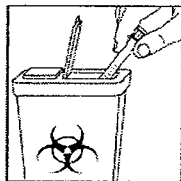
4. Release the skin.
5. Slowly push in the plunger of the syringe all the way. Make sure to inject all the IPLEX™ in the syringe.



6. Leave the needle in the skin for about 10 seconds.
7. Pull the needle straight out and press very lightly on the place of the injection with a cotton ball for a few seconds.



8. Throw away the needle and syringe in the special container your healthcare provider told you to use. Do not put needles and syringes in the trash. Never reuse needles and syringes. Never share needles.



Always throw away any unused IPLEX™.

Identifier no.: xxxxxxxx

Issue/revision date: xxxxxxxx

Carton label

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"printable area"

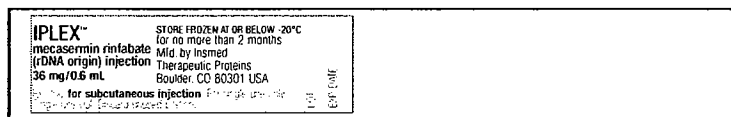
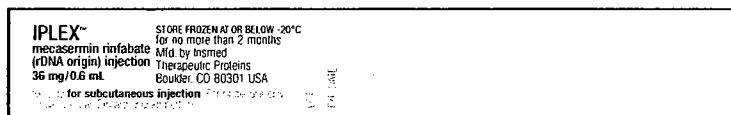
NDC CODE: XXXXX-XXXX-X		INSMED INCORPORATED
IPLEX™ mecasermin rinfabate (rDNA origin) injection 36 mg/0.6 mL	Contents: 35 single-use vials Components: mecasermin rinfabate 36 mg; water for injection q.s. to 0.6 mL; sodium acetate 2.5 mg; sodium chloride 3.7 mg; acetic acid, glacial q.s. to pH 5.5. Lot: xxxxxx Exp. Date: xx/xx/xxxx STORE FROZEN AT OR BELOW -20°C for no more than 2 months Thawed product cannot be refrozen Discard unused portion. See instructions for patient use Manufactured by Insmid Therapeutic Proteins Boulder, CO 80301 USA	
	Rx Only for subcutaneous injection	

NDC CODE: XXXXX-XXXX-X		INSMED INCORPORATED
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	Rx Only for subcutaneous injection	

Vial label

Option A

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"printable area"



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/s/

Robert Meyer
12/12/2005 02:03:59 PM