CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21-884/S-001

Trade Name: IPLEX™

Generic Name: mecasermin rinfabate [rDNA origin] injection

Sponsor: Insmed Inc.

Approval Date: February 27, 2007

Indications: 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.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-884/S-001

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-884/S-001

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-884/S-001

Insmed Inc.
Attention: Ronald D. Gunn
Executive VP and COOr
P.O. Box 2400
Glen Allen, VA 23058-2400

Dear Mr. Gunn:

Please refer to your supplemental new drug application dated January 20, 2006, received January 23, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for IPLEX (mecaserman rinfabate [rDNA origin] injection).

We acknowledge receipt of your submissions dated January 24, June 5 and 14, and September 22, 2006.

Your submission of September 22, 2006, constituted a complete response to our May 10, 2006, action letter.

This supplemental new drug application provides for revised storage conditions.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon attached labeling text with the revision listed below.

The storage statement on the carton and vial should state "STORE FROZEN up to 3 months."

The attached carton and container labels are those approved with Supplement -002, approved on September 21, 2006.

Within 21 days of the date of this letter, submit content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical in content to the enclosed labeling text. Upon receipt and verification, we will transmit that version to the National Library of Medicine for public dissemination.

The final printed labeling (FPL) must be identical to the enclosed draft labeling.

Please submit either an electronic version or 20 paper copies of the FPL as soon as it is available (no more than 30 days after it is printed). If paper copies are submitted, individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this

submission **"FPL for approved supplement NDA 21-884/S-001".** Approval of this submission by FDA is not required before the labeling is used.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
5515 Security Lane
HFD-001, Suite 5100
Rockville, MD 20852

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Kati Johnson, Regulatory Project Manager, at (301) 796-1234.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, MD
Director
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: Package Insert
Patient Package Insert (Patient Information and Instructions for Use)
Vial Label
Carton Label

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/s/

Mary Parks

2/27/2007 02:10:44 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-884/S-001

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-884/S-001

INSMED Inc.
Attention: Ron Gunn, M.S., M.B.A.
Executive Vice President and COO
4851 Lake Brook Drive
Glen Allen, VA 23060

Dear Mr. Gunn:

Please refer to your supplemental new drug application dated January 20, 2006, received January 23, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Iplex (mecasermin rinfabate [rDNA origin] injection) 36 mg/0.6 mL.

We acknowledge receipt of your submission dated January 24, 2006.

This supplemental application provides for three stability protocols to support changes in the STORAGE CONDITIONS and HOW SUPPLIED sections of the package insert and in the "How should I store Iplex" section of the patient package insert.

We completed our review of this supplemental new drug application as amended, and it is approvable. Before the application may be approved, however, you must address the following deficiencies:

1. Amend the stability protocols as described below.

   (a) (b) (4)

   (b)

   (c)

2. Upon further consideration, we cannot comment on your proposed labeling changes without reviewing the data from the stability protocol(s).

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

This product may be considered misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes before approval of this supplemental application.

If you have any questions, call Enid Galliers, Chief, Project Management Staff, at (301) 796-1211.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Acting Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Mary Parks

5/10/2006 02:43:03 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-884/S-001

LABELING

PACKAGE INSERT

IPLEX™ (mecasermin rinfabate [rDNA origin] injection)

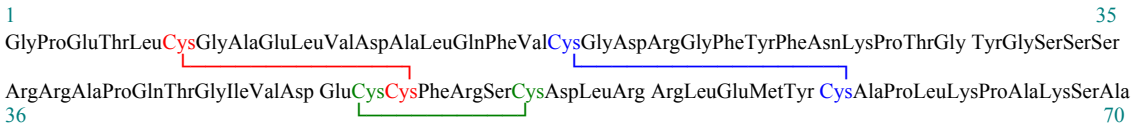
DESCRIPTION

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)



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

```
 1                              10  11                              20
GlyAlaSerSerAlaGlyLeuGlyProVal ValArgCysGluProCysAspAlaArgAla
LeuAlaGlnCysAlaProProProAlaVal CysAlaGluLeuValArgGluProGlyCys
GlyCysCysLeuThrCysAlaLeuSerGlu GlyGlnProCysGlyIleTyrThrGluArg
CysGlySerGlyLeuArgCysGlnProSer ProAspGluAlaArgProLeuGlnAlaLeu
LeuAspGlyArgGlyLeuCysValAsnAla SerAlaValSerArgLeuArgAlaTyrLeu
LeuProAlaProProAlaProGlyAsnAla SerGluSerGluGluAspArgSerAlaGly
SerValGluSerProSerValSerSerThr HisArgValSerAspProLysPheHisPro
LeuHisSerLysIleIleIleIleLysLys GlyHisAlaLysAspSerGlnArgTyrLys
ValAspTyrGluSerGlnSerThrAspThr GlnAsnPheSerSerGluSerLysArgGlu
ThrGluTyrGlyProCysArgArgGluMet GluAspThrLeuAsnHisLeuLysPheLeu
AsnValLeuSerProArgGlyValHisIle ProAsnCysAspLysLysGlyPheTyrLys
LysLysGlnCysArgProSerLysGlyArg LysArgGlyPheCysTrpCysValAspLys
TyrGlyGlnProLeuProGlyTyrThrThr LysGlyLysGluAspValHisCysTyrSer
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 mecasermin 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

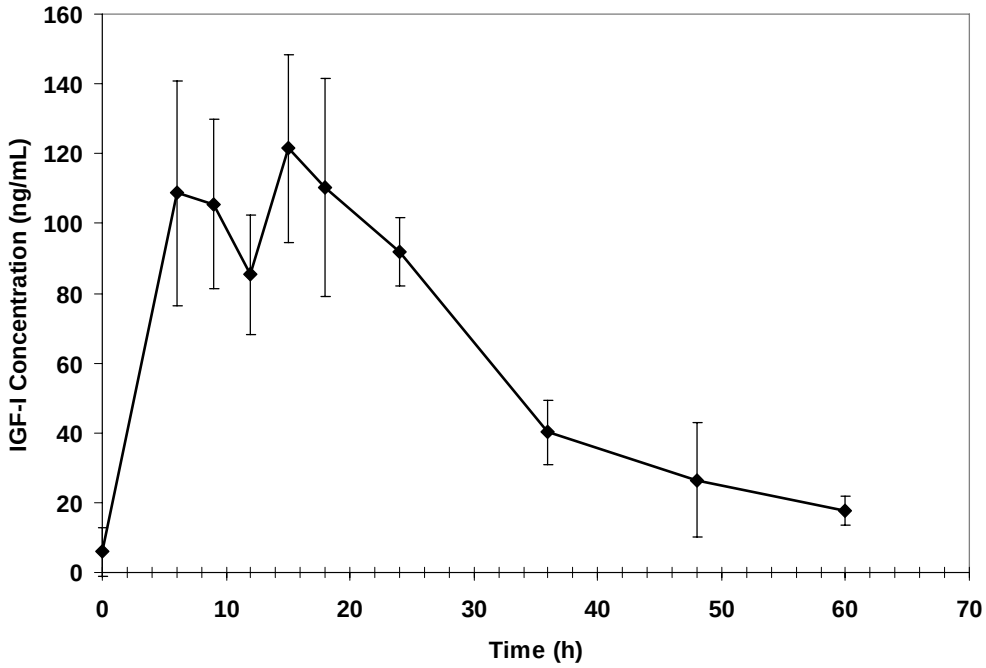
In pediatric patients with severe primary IGF-1 deficiency (Primary IGFD), 1 mg/kg was administered by subcutaneous injection to 4 patients in a pharmacokinetic sub-study of the clinical trial. A summary of the pharmacokinetic parameters for IGF-1 and IGFBP-3, uncorrected for baseline values, is presented 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)

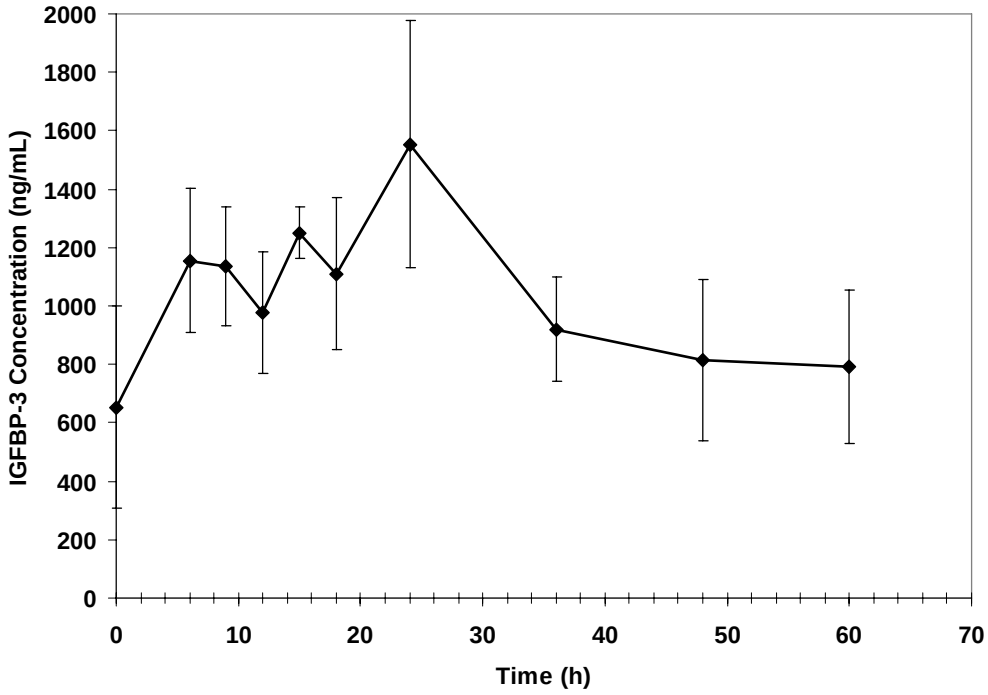
	Cmax (ng/mL)	**Tmax (hr)**	**AUC_{0-60} (ng hr/mL)**	**Half-life (hr)**
IGF-1	133±19	11.3±6.2	3654±237	13.4±2.7
IGFBP-3	1574±401	19.5±9.0	62525±8352	54.1±31.6

Figure 1. Mean (±SD) Uncorrected IGF-1 (Panel A) and IGFBP-3 (Panel B) (ng/mL) Concentrations in Patients with Primary IGFD Treated with IPLEX 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 IPLEX (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 ± 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 (± 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 ± 1.9	7.4 ± 2.0	6.4 ± 1.6	2.2 ± 1.5	8.8 ± 2.0
Change in Height Velocity from Pre-Tx (cm/yr)		4.0 ± 1.8	3.0 ± 1.3		6.6 ± 2.6
p-value for Change in Height Velocity from Pre-Tx [3]		<0.0001	<0.0001		<0.0001
Height SDS	-6.4 ± 2.1	-6.1 ± 2.1	-6.0 ± 2.2	-7.9 ± 1.1	-7.5 ± 1.1
Change in Height SDS from Pre-Tx		0.3 ± 0.2	0.5 ± 0.4		0.4 ± 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 ± 2.2 cm/yr for Cohort #1 subjects with detectable ALS and 6.3 ± 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 ± 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 ± 2.1 cm/yr for subjects with IGF-1 SDS at Month 1 ≥ -2 (n=8), and 6.7 ± 1.2 cm/yr for subjects with IGF-1 SDS at Month 1 < -2 (n=6).

INDICATIONS AND USAGE

IPLEX (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 mecasermin 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 IPLEX 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 IPLEX is administered to a nursing woman.

Geriatric Use

The safety and effectiveness of IPLEX 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 (≥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, upper outer buttock, 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.

For use, remove a vial of IPLEX from the freezer. Thaw the contents by warming the vial in your hand for approximately 2 minutes. When the vial is at room temperature, gently swirl the vial in a rotary motion to ensure content uniformity. DO NOT SHAKE. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. DO NOT inject the contents if the solution is cloudy or discolored; discard the vial. Use IPLEX within 12 hours after the vial is removed from the freezer. 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 should remain frozen at -15. 5 ^{0}C to -1. 5 ^{0}C (4.1 ^{0}F to 29.3 ^{0}F) until time of use. IPLEX can be stored in a home freezer for up to 3 months.

When a freezer is unavailable, a vial of IPLEX (stored for up to 3 months in a home freezer) can be stored at refrigerator temperature for up to 5 days. Use IPLEX within 2 hours after the vial is removed from the refrigerator.

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.

Box containing 35 vials
NDC- 16249-001-01

Single vial
NDC- 16249-001-02

IPLEX (mecasermin rinfabate [rDNA origin] injection) is temperature sensitive and must be transported and stored frozen.

Rx only

Manufactured for: Insmed Incorporated
Glen Allen, Virginia 23058
www.insmed.com

Manufactured by: Insmed Therapeutic Proteins
Boulder, Colorado 80301
www.insmed.com

Identifier no.: IP050
Revision Date: September 19, 2006

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?”

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), upper outer buttock, 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 your child's doctor has found the right dose for your child.

Before beginning treatment with IPLEX, your child's 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 child's 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 child's 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 possible 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 shipment of IPLEX to you or your child's doctor, it will be frozen.

- Store IPLEX in your home freezer at -15. 5 ^{0}C to -1. 5 ^{0}C (4.1 ^{0}F to 29.3 ^{0}F) for no more than 5 months. Do not use IPLEX that has been stored in your freezer for longer than 5 months.

- Use IPLEX within 12 hours after the vial has been removed from the freezer.

- If you do not use IPLEX within 12 hours after you have removed it from the freezer, discard the vial because it may not work.

- When a freezer is unavailable, a dose of IPLEX (stored for up to 3 months in a home freezer) can be stored at refrigerator temperature for up to 5 days. Use IPLEX within 2 hours after the vial is removed from the refrigerator.

- 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 Insmed Incorporated.

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

www.insmed.com

What are the Ingredients in IPLEX?

Active ingredient: mecasermin 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 by warming the vial in your hand for approximately 2 minutes.

2. Use IPLEX within 12 hours after the vial is removed from the freezer.

3. When the vial of IPLEX is at room temperature, swirl the vial 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.

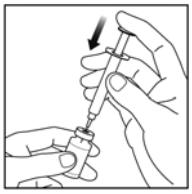
Preparing the dose:

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 protective cap from the top of the vial. Do not touch the rubber vial stopper. The stopper is clean. If the stopper is touched by anything, you must clean it with an antiseptic or alcohol swab before use.

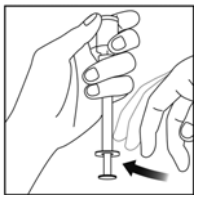
4. Use a new needle and syringe each time you give an injection.

5. 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.

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

10. 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.



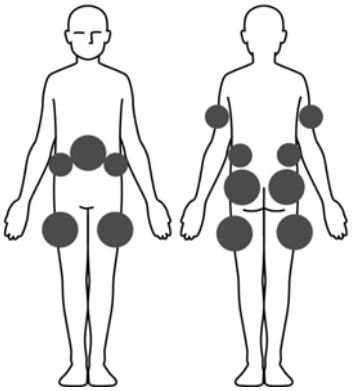
11. Take the needle out of the vial. Do not let the needle touch anything.

12. Recap the needle as directed by your child's doctor to help prevent accidental injury while preparing the site for injection.

13. 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), upper outer 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 child's 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.: IP051
Issue/revision date: September 19, 2006

Carton label

inner grey box indicates "printable area"

NDC 1624900101

INSMED INCORPORATED

IPLEX™
mecasermin rinfabate
(rDNA origin) injection
36 mg/0.6 mL

Rx Only **for subcutaneous injection**

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.
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 Insmed Therapeutic Proteins
Boulder, CO 80301 USA

NDC 1624900101

INSMED INCORPORATED

IPLEX™
mecasermin rinfabate
(rDNA origin) injection
36 mg/0.6 mL

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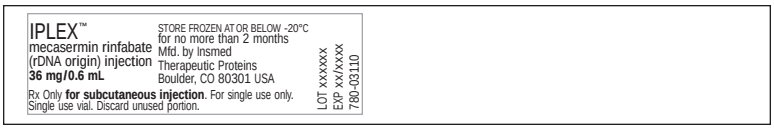
STORE FROZEN AT OR BELOW -20°C
for no more than 2 months
Thawed product cannot be refrozen
Discard unused portion.
See instructions for patient use
Manufactured by Insmed Therapeutic Proteins
Boulder, CO 80301 USA

Revised Vial Label

Vial label

inner grey box indicates
“printable area”



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-884/S-001

CHEMISTRY REVIEW(S)

CHEMISTS REVIEW	1. ORGANIZATION	2. NDA NUMBER
	DMEDP II, HFD-510	21-884
3. NAME AND ADDRESS OF APPLICANT		4. SUPPLEMENT NUMBER, DATE
Insmed Incorporated 4851 Lake Brook Drive Glen Allen, VA 23060		SCS-001, 20-Jan-2006
5. PROPRIETARY NAME	6. NAME OF THE DRUG	7. AMENDMENTS, REPORT, DATE
IPLEX	Mecasermin rinfabate (rDNA) injection	

8. SUPPLEMENT PROVIDES FOR:		
Labeling changes and stability protocol.		
9. PHARMACOLOGICAL CATEGORY	**10. HOW DISPENSED**	**11. RELATED IND, NDA, DMF**
Recombinant Human Insulin-like Growth Factor-1/Recobinant Human Insulin-like Growth Factor Binding Protein-3	RX	
12. DOSAGE FORM	**13. POTENCY**	
Solution for injection	36mg/0.6mL	
14. CHEMICAL NAME AND STRUCTURE		
See Chemistry Review #1		
15. COMMENTS		

This supplement was submitted and filed as a PAS. This supplement should have been submitted as a correspondence to NDA 21-884. The correspondence should have requested comments from the agency for Insmed proposed stability protocol; however it was submitted as a PAS based upon previous discussions with the applicant and the agency. Copies of these e-mail correspondences' were included in the submission.

This supplement includes a marked up version of labeling changes and a stability protocol that includes three different storage conditions. The revised labeling can not be reviewed until adequate CMC data has been submitted and approved to support any labeling changes. The stability protocol includes three proposed studies for patient storage of the drug product (see tables 1-3).

Continued on next page

16. CONCLUSION AND RECOMMENDATION		
There is no data to support labeling changes. Comments to the proposed stability protocol are included in the deficiency and comments to the applicant on the last page of this review. Issue an Approvable Letter.		
17. NAME	**18. REVIEWERS SIGNATURE**	**19. DATE COMPLETED**
Janice T. Brown	See electronic signature	17-Mar-2006
DISTRIBUTION: ORIGINAL JACKET CSO REVIEWER DIVISION FILE		

AE

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Janice Brown
3/17/2006 01:43:47 PM
CHEMIST

Jim Vidra
3/20/2006 10:06:47 AM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-884/S-001

OTHER REVIEW(S)

Division of Metabolism & Endocrinology Products
REGULATORY PROJECT MANAGER REVIEW

Application Number: NDA 21-884/S-001

Name of Drug: IPLEX (mecasermin rinfabate (rDNA origin] injection)
Applicant: INSMED

Material Reviewed:

Submission Dates:
September 22, 2006, containing the following labeling:
- -Package Insert
- -Patient Package Insert (Patient Information on one side and Instructions for Use on the other)

March 21, 2006 submission, upon which Supplement -002 was approved on Sept. 21, 2006:
- -vial label
- -carton label

Background and Summary

IPLEX was approver December 12, 2005 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. It is supplied as a 36 mg/0.6 mL preservative-free sterile solution in single dose glass vials, and requires frozen storage conditions until just prior to administration.
S-001 was initially submitted January 20, 2006 and proposed storage at higher temperatures for longer periods of time. The application was approvable (AE) May 10, 2006 pending revisions to the stability protocols, and a statement was included that comments on labeling could not be provided until the stability date was reviewed. The firm responded to the AE letter on September 22, 2006. The response contained revised labeling.

In a January 26, 2007 review, the chemist is recommending that the applications is AE, pending revised labeling to state storage conditions that are LESS than that being requested by the sponsor.

Review

NOTE: The labeling comments mentioned in the 1/26/07 chemistry review pertains to the labeling submitted on 1/20/06, and NOT that submitted 9/22/06. The proposed labeling in the 9/22/06 was discussed with the reviewer (Janice Brown, PAL).

Package Insert
The firm has revised the package insert, primarily to reflect the proposed revised storage

conditions, but other revisions have been made to clarify and to delete redundancy.
The revision date has been revised to September 19, 2006 and the Identifier to IPO50.

The firm's proposed labeling in the 9/22/06 submission was found acceptable by the chemist with the following exception:
Under STORAGE CONDITIONS, the first sentence was revised to include the underlined information and to delete the text that has been struck out:

> IPLEX…is temperature sensitive and should remain frozen at -15. 5 ^{0}C to -1. 5 ^{0}C (4.1 ^{0}F to 29.3 ^{0}F) until time of use. IPLEX can be stored in a home freezer for up to ~~5~~ 3 months.

Patient Package Insert (Patient Information and Instructions for Use)
The firm has revised the labeling, primarily to reflect the proposed revised storage conditions. The revision date has been revised to September 19, 2006 and the Identifier to IPO51. This identifier and revision date appear only at the end of the Instructions for Use.

The firm's revisions to the Patient Information was found acceptable with the following exceptions:
-The following statement has been revised to include the underlined text:
•Store IPLEX in your home freezer at -15. 5 ^{0}C to -1. 5 ^{0}C (4.1 ^{0}F to 29.3 ^{0}F) for no more than 5 months.
•If you do not use IPLEX within 12 hours after you have removed it from the freezer, discard the vial because it may not work.

Regarding the Instructions for use, the "Preparing IPLEX for use:" section has been revised to include instructions for warming the vial in your hands for 2 minutes after taking it out of the freezer. The timeframe by which the IPLEX must be used after taking out of the freezer has been extended from 1 hour to 12 hours. Other revisions have been made for clarity ("buttock" changed to "upper outer buttock", "doctor" to "child's doctor") which do not affect the meaning of the labeling.

Vial and Carton Labels
The only revision in this supplement is to change the length of storage from 2 months to (b) (4) (b) (4) However, revisions to the vial and carton labels were the subject of Supplement -002, which was approved September 21, 2006. These approved revisions will have to be incorporated into the labeling when the firm submits FPL. The carton and vial labels approved in S-002 will be attached to the AP letter and the sponsor requested to revise the storage statement to read, "Store frozen up to 3 months".

Conclusions

The firm has agreed with the labeling revisions. The submitted labeling (PI, PPI) have been

revised to include these changes.

An approval letter can be drafted.

The approved labeling for this application is as follows:

-PI submitted 9/22/06, revised as requested above
-PPI submitted 9/22/06 revised as requested above
-Vial and carton submitted 3/21/06 and approved 9/21/06 (S-002), revised as requested above.

The firm will be requested to submit SPL and FPL.

Kati Johnson
Project Manager
Division of Metabolism & Endocrinology Products

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Kati Johnson
2/27/2007 12:01:50 PM
CSO