

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-884**

**CHEMISTRY REVIEW(S)**

**IPLEX™ (mecasermin rinfabate [rDNA origin] injection)  
NDA 21-884**

**Summary of the Basis for the Recommended Action  
from Chemistry, Manufacturing, and Controls**

**Applicant:** Inmed Incorporated  
4851 Lake Brook Drive  
Glen Allen, VA 23060

**Indication:** Treatment of children with growth failure due to severe growth hormone insensitivity syndrome (GHIS).

**Presentation:** Sterile parenteral solution containing mecasermin rinfabate 60 mg/mL for subcutaneous injection, filled and packaged in 2 mL single-dose glass vials (36 mg/0.6 mL).

**EER Status:** Acceptable 21-SEP-2005

**Consults:** DMETS – Tradename: IPLEX – acceptable 13-AUG-2005  
EA – Categorical exclusion granted under 21 CFR §25.31(b)  
Microbiology – Acceptable 23-JAN-2005  
Methods Validation – Revalidation by Agency not requested

**Original Submission:** 12-DEC-2004

**Post-Approval Agreements:**

An agreement was made to complete the disulfide linkages assignment for rhIGFBP-3.

**Drug Substance**

Mecasermin rinfabate, is a binary protein complex of recombinant human Insulin-like Growth Factor-1 (rhIGF-1) and recombinant human Insulin-like Growth Factor Binding Protein-3 (rhIGFBP-3). rhIGF-1 is a monomeric, non-glycosylated, single chain polypeptide of 70 amino acid residues with three intramolecular disulfide bridges, and a molecular weight of 7649 Daltons. The amino acid sequence of the product is identical to that of endogenous human IGF-1. rhIGFBP-3 is a monomeric, non-glycosylated, single chain polypeptide of 264 amino acid residues with eighteen cysteines, and a molecular weight of 28,732 Daltons. Endogenous IGFBP-3 contains 18 cysteines 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.

The two recombinant DNA origin proteins are synthesized by separate *E. coli* strains that have been modified by the addition of the human gene for hIGF-1 and hIGFBP-3, respectively

The drug substance is manufactured by Insmed Therapeutic Proteins, Boulder, Colorado.

The primary structure (amino acid sequence and disulfide bridge assignments) of rhIGF-1 was confirmed using

Characterization studies confirmed that the amino acid sequence of rhIGFBP-3 is identical to that of endogenous IGFBP-3.

An *in vitro* assay, was developed to measure bioactivity of the rhIGF-1/rhIGFBP-3 complex. Although structural characterization of the drug substance was satisfactory, a post approval agreement was made to complete the disulfide assignment in rhIGFBP-3. Specifications were acceptable.

The drug substance can be stored at -70 °C for 24 months.

**Conclusion:** Drug substance is acceptable.

### Drug Product

IPLEX™ (mecasermin rinfabate [rDNA origin] injection) is a sterile, preservative-free, aqueous solution intended for subcutaneous injection. Each single-dose vial contains 60 ± 6 mg/mL of the active ingredient in 50 mM sodium acetate, 105 mM sodium chloride, pH 5.5 buffer. The product is supplied as a 60 mg/mL sterile solution in 2 mL single dose glass vials (36 mg/0.6 mL per vial). For the manufacture of the drug product, no excipients of human or animal origin are used.

IPLEX™ injection is manufactured by The drug product is manufactured by

Specifications for IPLEX™ drug product include testing for

Stability data included in the original application were mainly supportive. Primary stability data at commercial scale were available for one lot. Based on the available primary data and the supportive stability data, drug product can be stored

at -70 ° for 24 months. For in use purposes, drug product can be stored frozen up to two months at constant temperature (-20°C, -4°F) and up to 2 hours at room temperature (20-25°C, 68-77°F). Due to the high protein concentration of 60 mg of active ingredient per mL, the drug product begins to aggregate and cloud if stored for longer times.

All associated Drug Master Files are acceptable or the pertinent information has been adequately provided in the application.

Labeling has been addressed.

**Conclusion:** Drug product is satisfactory.

**Additional Items:**

- Validation package, describing the test methods and validation procedures, including information supporting the reference standard, is adequately provided. As the analytical methods used in the testing procedures (release, stability and in-process) are well known and widely used by the biopharmaceutical industry, revalidation by Agency laboratories will not be requested

**Overall Conclusion:**

From a CMC perspective, the application is recommended for approval.

Blair A. Fraser, Ph.D.  
Branch Chief, Branch II  
DPA I/ONDQA

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/s/

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Blair Fraser  
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CHEMIST



**NDA 21-884**

**iPlex™**

**[mecasermin rinfabate (rDNA) injection]**

**36 mg/0.6 mL**

**(60 mg/mL, 0.5 mL Vial)**

**(rhIGF-1/rhIGFBP-3)**

**Insmed, Inc.**

**CMC Review # 2**

**Xavier Ysern, PhD**

**HFD-510**



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# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

### Chemistry Review Data Sheet

1. NDA 21-884
2. REVIEW #: 2
3. REVIEW DATE: 18-NOV-2005
4. REVIEWER: Xavier Ysern, PhD
5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original  
Amendment

31-DEC-2004 Rec. 03-JAN-2005  
12-JUL-2005  
12-OCT-2005

7. NAME & ADDRESS OF APPLICANT:

Name: Insmed Incorporated  
 Address: 4851 Lake Brook Drive  
 Glen Allen, VA 23060  
 Representative: Ronald D. Gunn, Executive Vice President and COO  
 Telephone: (804) 565-3022

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: To be determined (TBD)
- b) Non-Proprietary Name: Mecasermin Rinfabate
- c) Code Name: rhIGF-1/IGFBP-3 (or rhIGF-I/IGFBP-3)
- d) Chem. Type/Submission Priority:
  - Chem. Type: 1 New Molecular Entity (Claimed)
  - Submission Priority: Priority

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Protein Hormone. Treatment of children with growth failure due to severe growth hormone insensitivity syndrome (GHIS).

11. DOSAGE FORM: Solution for Injection 36 mg/0.6 mL

12. STRENGTH/POTENCY: 60 mg/mL

13. ROUTE OF ADMINISTRATION: Subcutaneous injection

14. Rx/OTC DISPENSED: Rx

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): SPOTS product – Form Completed

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

*Recombinant human insulin growth factor (rhIGF-1)*



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

1 10 20 30  
 Gly Pro Glu Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Gln Phe Val Cys Gly Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly  
 31 40 50 60  
 Tyr Gly Ser Ser Ser Arg Arg Ala Pro Gln Thr Gly Ile Val Asp Glu Cys Cys Phe Arg Ser Cys Asp Leu Arg Arg Leu Glu Met Tyr  
 61 70  
 Cys Ala Pro Leu Lys Pro Ala Lys Ser Ala (Cys6-Cys48; Cys18-Cys61, and Cys47-Cys52)

70 amino acids  $C_{258}H_{384}N_{64}O_{78}S_6$  MW = 7,649 Da.

### Recombinant human insulin growth factor binding protein-3 (IGFBP-3)

GASSAGLGP VVRCEPCDAR ALAQCAPPPA VCAELVREPG CGCC LTCAL SEGQPCGIYT ERCGSGLRQ  
 PSPDEARPLQ ALLDGRGLCV NASAVSRLRA YLLPAPPAPG NASESEEDRS AGSVESPSVS STHRVSDPKF  
 HPLHSKIIII KKGHAKDSQR YKVDYESQST DTQNFSSSEK RETEYGPCRR EMEDTLNHLK FLNVLSPRGV  
 HIPNCDKKGK YKKKQCRPSK GRKRGFCWCV DKYGQPLPGY TKGKEDVHCY SMQS

264 amino acids MW = 28,732 Da Disulfide pattern not fully elucidated

### 17. RELATED/SUPPORTING DOCUMENTS:

#### A. DMFs:

DMF #	Type	Holder	Item Referenced	Code <sup>1</sup>	Status <sup>2</sup>	Date Review Completed	Comments
/	III	/	/	4	Adequate		
	III			4	Adequate		

<sup>1</sup> Action codes for DMF Table:

1 - DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 - Type I DMF

3 - Reviewed previously and no revision since last review

4 - Sufficient information in application

5 - Authority to reference not granted

6 - DMF not available

7 - Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

#### B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
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### 18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	--	--	--
EES	Acceptable	21-SEP-2005	
Pharm/Tox	--	--	--
Biopharm	--	--	--
ODS/DMETS	No objection to the use of the proprietary name "iPlex"	13-AUG-2005	Kimberly Culley, RPh HFD-420
Methods Validation	Revalidation by Agency not requested	--	
LNC	--	--	--
EA	Acceptable (Categorical Exclusion granted)	06-FEB-2004	Xavier Ysem, PhD
Microbiology	Approval	23-JAN-2004	Bryan S. Riley, PhD



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

### The Chemistry Review for NDA 21-884

#### The Executive Summary

##### **I. Recommendations**

###### **A. Recommendation and Conclusion on Approvability**

The application can be APPROVED (AP) from the CMC point of view.  
Based on the stability data submitted, an expiry of 24 months at -70 ° is granted. In use periods of 2 months at -20 C° and 2 hours at room temperature are also granted.

###### **B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable**

An agreement was made to complete the disulfide linkages assignment for IGFBP-3.

##### **II. Summary of Chemistry Assessments**

###### **A. Description of the Drug Product(s) and Drug Substance(s)**

See CMC Review # 1

###### **B. Description of How the Drug Product is Intended to be Used**

See CMC Review # 1

###### **C. Basis for Approvability or Not-Approval Recommendation**

From a CMC viewpoint this application can be approved (AP) based on the applicant's satisfactory responses to outstanding CMC issues.

##### **III. Administrative**

###### **A. Reviewer's Signature**

See electronic signature page.

###### **B. Endorsement Block**

Chemist Name:	Xavier Ysern, PhD
Pharmaceutical Assessment Lead	Stephen Moore, PhD
ONDQA/DPA I/Branch I Branch Chief	Blair Fraser, PhD

###### **C. CC Block**

Rik Lostritto, PhD	ONDQA/DPA I/Division Director
Enid Galliers	Project Manager/HFD-510

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/s/

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Xavier Ysern  
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Stephen Moore  
11/18/2005 04:08:11 PM  
CHEMIST

Blair Fraser  
11/18/2005 04:36:08 PM  
CHEMIST



**NDA 21-884**

**iPlex™**

**[mecasermin rinfabate (cDNA) injection]**

**36 mg/0.6 mL**

**(60 mg/mL, 0.5 mL Vial)**

**(rhIGF-1/rhIGFBP-3)**

**Insmed, Inc.**

**John Hill, PhD and**

**Xavier Ysern, PhD**

**HFD-510**



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# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

### Chemistry Review Data Sheet

1. NDA 21-884
2. REVIEW #: 1
3. REVIEW DATE: 21-SEP-2005
4. REVIEWER: Xavier Ysern, PhD
5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original  
Amendment

31-DEC-2004	Rec. 03-JAN-2005
12-APR-2005	
15-APR-2005	
09-JUN-2005	
08-JUL-2005	
11-JUL-2005	
12-JUL-2005	
19-JUL-2005	
15-SEP-2005 (BL)	

7. NAME & ADDRESS OF APPLICANT:

Name:	Insmed Incorporated
Address:	4851 Lake Brook Drive Glen Allen, VA 23060
Representative:	Ronald D. Gunn, Executive Vice President and COO
Telephone:	(804) 565-3022

8. DRUG PRODUCT NAME/CODE/TYPE:

- |                                    |                                      |
|------------------------------------|--------------------------------------|
| a) Proprietary Name:               | To be determined (TBD)               |
| b) Non-Proprietary Name:           | Mecasermin Rinfabate                 |
| c) Code Name:                      | rhIGF-1/IGFBP-3 (or rhIGF-I/IGFBP-3) |
| d) Chem. Type/Submission Priority: |                                      |
| - Chem. Type:                      | 1 New Molecular Entity (Claimed)     |
| - Submission Priority:             | Priority                             |

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Protein Hormone. Treatment of children with growth failure due to severe growth hormone insensitivity syndrome (GHIS).

11. DOSAGE FORM: Solution for Injection 2 mL Vial (0.5 ML)

12. STRENGTH/POTENCY: 60 mg/mL

13. ROUTE OF ADMINISTRATION: Subcutaneous injection

14. Rx/OTC DISPENSED: Rx





## The Chemistry Review for NDA 21-629

### The Executive Summary

#### I. Recommendations

##### A. Recommendation and Conclusion on Approvability

The application is APPROVABLE (AE) pending submission of additional CMC information described in List of Deficiencies.

##### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

An agreement is requested regarding disulfide linkages in IGFBP-3 (see List of Deficiencies).

#### II. Summary of Chemistry Assessments

##### A. Description of the Drug Product(s) and Drug Substance(s)

###### Drug Substance

The Drug Substance rhIGF-1/rhIGFBP-3 is a 1:1 non-covalent complex of recombinant human Insulin-like Growth Factor-1 (rhIGF-1) and recombinant human Insulin-like Growth Factor Binding Protein-3 (rhIGFBP-3). The established name is mecasermin rinfabate. Each of the components of the rhIGF-1/rhIGFBP-3 complex is synthesized by recombinant technology in *E. coli* bacteria that have been modified to over express the desired proteins.

rhIGF-1 consists of 70 amino acid residues, including six cysteines. All six cysteines are specifically paired in disulfide bonds to form the biologically active molecule. Characterization studies, which include \_\_\_\_\_ confirmed that the primary structure (amino acid sequence and disulfide linkage) of rhIGF-1 conforms to that of endogenous IGF-1. rhIGFBP-3 consists of 264 amino acid residues, including eighteen cysteines. Endogenous IGFBP-3 contains eighteen cysteines that are all paired in disulfide bonds to form the biologically active molecule. but the pairings are not fully elucidated. Characterization studies, which include \_\_\_\_\_ confirmed that the amino acid sequence of rhIGFBP-3 is identical to that of endogenous IGFBP-3.

\_\_\_\_\_ The complex rhIGF-1/rhIGFBP-3 is characterized by \_\_\_\_\_.

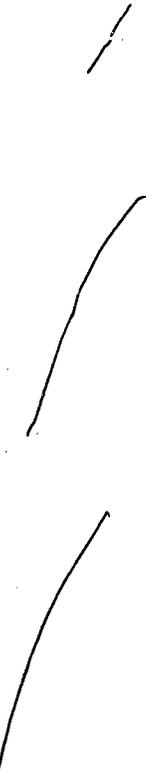
rhIGF-1/rhIGFBP-3 was originally developed by Celtrix Pharmaceuticals, Santa Clara (California). The rhIGF-1/rhIGFBP-3 Drug Substance used in non-clinical, toxicity, and Phase I, II, and III clinical studies (developmental Drug Substance) was manufactured, beginning in 1996, using a process of \_\_\_\_\_.



separate lots of rhIGF-1 and lots of rhIGFBP-3 were used in the manufacture of lots of developmental Drug Substance used in clinical trials starting in 1996. The Drug Substance manufactured in Santa Clara was subsequently used to manufacture development Drug Product (DDP). The Celtrix manufacturing facility in Santa Clara, CA (referred to as Insmmed (Santa Clara) in the submission) was closed in September, 1998. Insmmed Incorporated, Glen Allen (Virginia) acquired Celtrix Pharmaceuticals in February, 2000. The manufacturing process for Drug Substance was subsequently transferred to Avecia Ltd., Billingham, UK (Avecia). In 2004 a bulk Drug Substance manufacturing campaign was conducted at Avecia Ltd. to manufacture additional lots of bulk Drug Substance for the Phase II/III clinical study (INSM-110-303) and commercial Drug Product (CDP). The transfer of manufacturing to Avecia, described in the original submission on January 3, 2005, involved as well as adaptation of the process to a different facility, but the basic manufacturing process was not altered. A comparability study of the Insmmed (Santa Clara) materials and the Avecia produced Drug Substance confirmed the similarity of the Drug Substances used in all the clinical trials.

Transfer of drug substance manufacture from Avecia to Insmmed Therapeutic Proteins (ITP), Boulder (Colorado), as the proposed drug substance commercial site occurred during the review period and required additional approval by the Agency. The manufacturing processes for Avecia and ITP are essentially the same with minor adaptations for the differences in equipment and facilities. The processes use the same starting materials, and equivalent grades of raw materials. To date, the drug substance from two of three batches for the comparability studies have been analyzed.

To manufacture the drug substance, rhIGF-1 and rhIGFBP-3 are





As the formulation of the formulated bulk drug substance does not differ from that of the iPlex™ drug product their specifications are very similar. In addition to the formulated bulk drug substance specifications, iPlex™ drug product specifications incorporate testing for \_\_\_\_\_ and particulate matter and sterility, which are tests expected for pharmaceutical parenteral products. Notably, the applicant has been requested to incorporate an acceptance criterion for the amount of \_\_\_\_\_ the rest of the specifications are common to the drug product.

Drug substance primary stability studies were initiated in 2005 (same year of the NDA submission). Drug substance primary stability studies have been initiated on commercial drug substance lots DS0501 \_\_\_\_\_ stability data available) and DS0503 (release data) produced at Insmed Therapeutic Proteins (ITP). At least one additional lot of drug substance produced at ITP will be placed on stability this year. The limited availability of drug substance made it impractical to run both drug substance and drug product stability studies while supplying clinical requirements. The applicant relied on drug product stability data to judge the stability of the drug substance based on: (1) the similarity of the drug substance and the drug product, which differ only in the \_\_\_\_\_ and the container closure system, and (2) the fact that the drug substance was stored at -70 °C and typically held for just the time needed to release the drug substance and arrange a drug product manufacturing run. The drug substance will be stored at ≤ -70 °C. To date the drug product stability studies have been used as a surrogate for drug substance. At this temperature there are formal drug product studies demonstrating \_\_\_\_\_ of stability. Additional informal studies at ≤ -70 °C show the drug product is stable for more than \_\_\_\_\_ (applicant's claim). This stability data far exceeds the intended drug substance storage period of \_\_\_\_\_

### Drug Product

Orphan drug designation #02-153 was obtained for rhIGF-1/IGFBP-3 by Insmed on May 17, 2002, for the treatment of growth hormone insensitivity syndrome (Laron syndrome).

iPlex™ [mecasermin rinfabate (rDNA origin) injection] is a sterile, preservative-free, aqueous solution intended for subcutaneous injection. Each single-dose vial contains  $60 \pm 6$  mg/mL of the active ingredient in 50 mM sodium acetate, 105 mM sodium chloride, pH 5.5 buffer. All excipients meet compendial requirements. For the manufacture of the drug product, no excipients of human or animal origin are used. Therefore, no contamination risk can be expected with regards to transmissible spongiform encephalopathy (TSE) or other adventitious agents from the excipients.

Development studies carried out by Celtrix Pharmaceutical and Avecia have demonstrated that the primary mechanism of instability are \_\_\_\_\_



## CHEMISTRY REVIEW



During development, several formulations ranging from 10 to 100 mg/mL strength have been used in clinical and non-clinical studies supporting this application. A total delivery volume of \_\_\_\_\_ was preferred in order to minimize injection site pain. Restricted by this delivery volume the 60 mg/mL was chosen based on stability and clinical considerations. Several container/closure were also used during development. The drug product vial selected for commercial manufacture is \_\_\_\_\_ with a 2 mL nominal capacity. The vial is stoppered with a \_\_\_\_\_ Vials are capped with a white, aluminum flip-off seal. The nominal capacity of the vial and the fill volume were chosen for single-entry use because the sterile drug product formulation does not contain a preservative.

iPlex™ injection is manufactured from rhIGF-1/rhIGFBP-3 formulated bulk drug substance by conventional \_\_\_\_\_ processes. The bulk is received at the drug product manufacturing facility in \_\_\_\_\_. \_\_\_\_\_ once only pooling and mixing of the bulk containers is required. The manufacturing procedure is based on conventional techniques such as \_\_\_\_\_ as well as packaging. The drug product is filled by: \_\_\_\_\_. The specified fill weight in each drug product vial is \_\_\_\_\_ for net contents of \_\_\_\_\_. The targeted fill volume of \_\_\_\_\_

Critical manufacturing steps are adequately controlled by in-process controls (IPCs). \_\_\_\_\_ bioburden. \_\_\_\_\_ No new impurities are introduced during the manufacture of the drug product.

Specifications for iPlex™ drug product include testing for \_\_\_\_\_ Purity evaluated by \_\_\_\_\_

iPlex™ is filled into 2 mL glass vials at \_\_\_\_\_ g/vial for a net content of \_\_\_\_\_ /vial. The 2 mL, \_\_\_\_\_ vials are closed with \_\_\_\_\_ Vials are capped with \_\_\_\_\_ seals. The seals consist of \_\_\_\_\_ the surface of the cap is covered by a white, tamper-evident, polypropylene button.

Drug product stability primary data is also brief. At the time of filing, a total of \_\_\_\_\_ of stability data are available for one lot, and release data for a second lot, at the proposed long-term refrigerated storage condition  $\leq -70$  °C. There is supportive stability data demonstrating \_\_\_\_\_ of stability at  $-70$  °C. Although Insmed requested a shelf life period of 24 months, based on the limited stability data provided by the applicant on the proposed commercial drug product a \_\_\_\_\_ expiry dating is granted for the drug product stored at the recommended storage condition of  $\leq -70$  °C.

### B. Description of How the Drug Product is Intended to be Used

In the normal human circulation less than 2 % of total serum IGF-1 exists in free form. Most circulating IGF-1 is found predominantly in association with the growth hormone-dependent IGF binding protein-3 (IGFBP-3), and the binary complex of IGF-1/IGFBP-3 further combines with a third circulating protein, the GH-dependent acid-labile subunit (ALS) to form a ternary complex of ~140-150 kD which represents the natural physiologic reservoir



of IGF-1. The ternary complex, consisting of one mole each of IGF-1, IGFBP-3 and ALS, is non-covalent in nature and the equilibrium constants have been described. Based on this, Insmed proposed the use of rhIGF-1/rhIGFBP-3, as therapeutic alternative to rhIGF-1, to enhance the delivery and improve the safety profile of rhIGF-1 therapy.

iPlex™ [mecasermin rinfabate (rDNA origin) injection] is indicated for the treatment of growth failure in children with to 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 (SDS)  $\leq$  -3, basal IGF-1 SDS  $\leq$  -2, and normal or elevated GH.

iPlex™ [mecasermin rinfabate (rDNA origin) injection] is available in 2 mL clear vials at a strength of 36 mg/0.6 mL. Each box contains 35 vials. After allowing to thaw and equilibrate at room temperature, the product is provided as a ready-to-use liquid formulation, without the need for dilution or mixing prior to injection.

The labeling indicates that iPlex™ [mecasermin rinfabate (rDNA origin) injection] dosage and administration should be individualized for each patient. iPlex™ should be administered via subcutaneous injection at a starting dose of 0.5 mg/kg, given once daily.

iPlex™ (mecasermin rinfabate [rDNA origin] injection) is temperature sensitive and must be stored frozen at -70 °C (-94 °F) while at the manufacturer or distributor. 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. If the medication thaws during transfer or storage, it should be discarded as stability of material may be affected. The medication must remain in the patient's home freezer (-20 °C, -4 °F) until time of use for up to

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. The vial should be swirled in a gentle rotary motion to ensure content uniformity (do not shake). If the solution is cloudy, the contents must not be injected. Unused portion should be discarded.

### C. Basis for Approvability or Not-Approval Recommendation

This application is approvable (AE) from a CMC viewpoint. This recommendation is based upon several CMC issues identified in this review (see List of Deficiencies).

## III. Administrative

### A. Reviewer's Signature

See electronic signature page.

### B. Endorsement Block

Chemist Name:

John Hill, PhD (Stephen Moore for John Hill) and  
Xavier Ysern, PhD

Chemistry Team Leader Name/Date

Stephen Moore, PhD  
(see appended electronic signature page)



**C. CC Block**

Eric Duffy, PhD  
Blair Fraser, PhD  
Enid Galliers

DNDCII Director/HFD-820  
DNDCII Deputy Director/HFD-820  
Project Manager/HFD-510

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