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:** Insmed 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 assignation 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 product is manufactured by The drug...

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

/s/

Blair Fraser
11/30/2005 02:53:05 PM
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
Table of Contents

Table of Contents ........................................................................................................... 2

Chemistry Review Data Sheet ........................................................................................ 3

The Executive Summary ................................................................................................. 5

I. Recommendations ...................................................................................................... 5
   A. Recommendation and Conclusion on Approvability ........................................... 5
   B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable ...................................................... 5

II. Summary of Chemistry Assessments ........................................................................ 5
   A. Description of the Drug Product(s) and Drug Substance(s) ............................... 5
   B. Description of How the Drug Product is Intended to be Used ............................ 5
   C. Basis for Approvability or Not-Approval Recommendation .............................. 5

III. Administrative .......................................................................................................... 5
   A. Reviewer’s Signature ......................................................................................... 5
   B. Endorsement Block .......................................................................................... 5
   C. CC Block ........................................................................................................... 5

Chemistry Assessment

III. List Of Deficiencies To Be Communicated ............................................................. 14
1. NDA 21-884

2. REVIEW #: 2

3. REVIEW DATE: 18-NOV-2005

4. REVIEWER: Xavier Ysien, PhD

5. PREVIOUS DOCUMENTS:

<table>
<thead>
<tr>
<th>Previous Documents</th>
<th>Document Date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

6. SUBMISSION(S) BEING REVIEWED:

| Submission(s) Reviewed | Document Date | |
|------------------------|---------------|
| Original               | 31-DEC-2004   |
| Amendment              | Rec. 03-JAN-2005 |
|                        | 12-JUL-2005   |
|                        | 12-OCT-2005   |

7. NAME & ADDRESS OF APPLICANT:

<table>
<thead>
<tr>
<th>Name:</th>
<th>Insmed Incorporated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Address:</td>
<td>4831 Lake Brook Drive</td>
</tr>
<tr>
<td></td>
<td>Glen Allen, VA 23060</td>
</tr>
<tr>
<td>Representative</td>
<td>Ronald D. Gunn, Executive Vice President and COO</td>
</tr>
<tr>
<td>Telephone:</td>
<td>(804) 565-3022</td>
</tr>
</tbody>
</table>

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: 1 New Molecular Entity (Claimed)
   · Chem. Type: Priority
   · Submission Priority: 505(b)(1)

9. LEGAL BASIS FOR SUBMISSION:


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

10
Gly Pro Glu Thr Leu Cys Gly Ala Glu Leu Val Asp Ala Leu Glu Phe Val Gln Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly
30
Tyr Gly Ser Ser Ser Arg Arg Ala Pro Glu Thr Gly Ile Val Asp Glu Cys Cys Phe Arg Ser Cys Asp Leu Arg Arg Leu Glu Met Tyr
50
Cys Ala Pro Leu Lys Pro Ala Lys Ser Ala
(1-56, 1-56, Cys18-Cys61, and Cys24-7-Cys52)

70 amino acids \( \text{C}_{238}\text{H}_{384}\text{N}_{66}\text{O}_{78}\text{S}_{6} \)  \( \text{MW} = 7,649 \text{ Da.} \)

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

\[\text{GASSAGGGLGP VVRCEFCDAR ALAQCAPPPA VCAELVREPQ CGCC LICAL SEGQPCGIYT ERCGSGLRCQ}
\]
\[\text{FSPDEARPLQ ALDDGRLCV NASAVSRLRA YLLPAPAPAG NASEDEEDRS AGSVEBPSVS STHRVDPKF}
\]
\[\text{HPLMKSITII KKHAKDSQR YKVDEQSSQT DTQNPSSSESK RETEYGPCR EMEDETLNHLK FLAVLSPRGV}
\]
\[\text{HIPNCDKKGIF YEKKQCRRPSK GRRKFCWCVC DKYQOQLPGY TESKEDVHCR SMQS}
\]

264 amino acids  \( \text{MW} = 28,732 \text{ Da} \)  Disulfide pattern not fully elucidated

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

<table>
<thead>
<tr>
<th>DMF #</th>
<th>Type</th>
<th>Holder</th>
<th>Item Referenced</th>
<th>Code</th>
<th>Status</th>
<th>Date Review Completed</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>III</td>
<td>/</td>
<td>/</td>
<td>4</td>
<td>Adequate</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 – Type 1 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”)
2Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

<table>
<thead>
<tr>
<th>DOCUMENT</th>
<th>APPLICATION NUMBER</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

18. STATUS:

<table>
<thead>
<tr>
<th>CONSULTS/ CMC RELATED REVIEWS</th>
<th>RECOMMENDATION</th>
<th>DATE</th>
<th>REVIEWER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biometrics</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>BES</td>
<td>Acceptable</td>
<td>21-SEP-2005</td>
<td>--</td>
</tr>
<tr>
<td>Pharm/Tox</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Bioparm</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>ODS/DMETs</td>
<td>No objection to the use of the proprietary name “iPlex”</td>
<td>13-AUG-2005</td>
<td>Kimberly Cailey, RPh HFD-420</td>
</tr>
<tr>
<td>Methods Validation</td>
<td>Revalidation by Agency not requested</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>LNC</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>EA</td>
<td>Acceptable (Categorical Exclusion granted)</td>
<td>06-FEB-2004</td>
<td>Xavier Ysem, PhD</td>
</tr>
<tr>
<td>Microbiology</td>
<td>Approval</td>
<td>23-JAN-2004</td>
<td>Bryan S. Riley, PhD</td>
</tr>
</tbody>
</table>

Page 4 of 14
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 °C 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 assignation 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 Yseum, PhD
Pharmaceutical Assessment Lead: Stephen Moore, PhD
ONDQA/DPA I/Branch I Branch Chief: Blair Fraser, PhD

C. CC Block

Rik Losstritto, PhD
Enid Galliers
ONDQA/DPA I/Division Director
Project Manager/HFD-510
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/
------------------
Xavier Ysenn
11/18/2005 04:01:24 PM
CHEMIST

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
# Table of Contents

## Chemistry Review Data Sheet ..................................................... 3

## The Executive Summary ............................................................ 5

I. Recommendations ........................................................................... 5
   A. Recommendation and Conclusion on Approvability .......................... 5
   B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable .............. 5

II. Summary of Chemistry Assessments ............................................. 5
   A. Description of the Drug Product(s) and Drug Substance(s) ................. 5
   B. Description of How the Drug Product is Intended to be Used ............. 8
   C. Basis for Approvability or Not-Approval Recommendation ............... 9

III. Administrative ............................................................................. 9
   A. Reviewer’s Signature .................................................................. 9
   B. Endorsement Block .................................................................. 9
   C. CC Block ............................................................................... 10

## Chemistry Assessment

I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data .................................................... 10
   S. DRUG SUBSTANCE .................................................................. 12
   P. DRUG PRODUCT ..................................................................... 67
   A. APPENDICES ........................................................................ 120
   R. REGIONAL INFORMATION ....................................................... 111

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 ................................................................. 125
   A. Labeling & Package Insert ......................................................... 125
   B. Environmental Assessment Or Claim Of Categorical Exclusion .......... 114
   C. Establishment Inspections ......................................................... 114

III. List Of Deficiencies To Be Communicated .................................. 133
CHEMISTRY REVIEW

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

<table>
<thead>
<tr>
<th>Document Date</th>
<th>Rec. 03-JAN-2005</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original</td>
<td>31-DEC-2004</td>
</tr>
<tr>
<td>Amendment</td>
<td>12-APR-2005</td>
</tr>
<tr>
<td></td>
<td>15-APR-2005</td>
</tr>
<tr>
<td></td>
<td>09-JUN-2005</td>
</tr>
<tr>
<td></td>
<td>08-JUL-2005</td>
</tr>
<tr>
<td></td>
<td>11-JUL-2005</td>
</tr>
<tr>
<td></td>
<td>12-JUL-2005</td>
</tr>
<tr>
<td></td>
<td>19-JUL-2005</td>
</tr>
<tr>
<td></td>
<td>15-SEP-2005 (BL)</td>
</tr>
</tbody>
</table>

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 Rinfaate
c) Code Name: rhIGF-1/IGFBP-3 (or rhIGF-1/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
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 (rIGF-1)

10 Gly Pro Glu Thr Leu Cys Gly Ala Glu Val Asp Ala Leu Val Phe Val Gly Asp Arg Gly Phe Tyr Phe Asn Lys Pro Thr Gly
31 40
30
Tyr Gly Ser Ser Ser Arg Arg Ala Pro Glu 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

(Cys56-Cys48, Cys218-Cys51, and Cys47-Cys52)

70 amino acids C_{235}H_{384}N_{64}O_{78}S_{6} MW = 7,649 Da.

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

GASSAGQLGP VURCEPCDAR ALAQCAPPFA VCAELVREPG CCCCC ITGAL SEQPGCYYT ERGSSGLRCQ PSEPDEARPLQ ALDDQGGLCV NASAVSRLAA YLLPAPPAGC NASESSEEDRS AGSVEFSPVS STHRVSDEPKF

HPLHSKTIII KKGHARDQSR YKDYKESQGQ ITQFPFSRSK RETEGYPCQR EMDTTLNHKL FLVWLSPRGPV HINPCDKKGFF YKKQCQCRPSK GRKGRFCWCV DKGQPLPGY TKGEDVHCY SMQS

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

17. **RELATED/SUPPORTING DOCUMENTS:**

A. DMFs:

<table>
<thead>
<tr>
<th>DMF #</th>
<th>Type</th>
<th>Holder</th>
<th>Item Referenced</th>
<th>Code</th>
<th>Status</th>
<th>Date Review Completed</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>/</td>
<td>III</td>
<td></td>
<td></td>
<td>4</td>
<td>Adequate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td></td>
<td></td>
<td></td>
<td>4</td>
<td>Adequate</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 Action codes for DMF Table:
1 – DMF Reviewed.
2 – Type 1 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")

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

B. Other Documents:

<table>
<thead>
<tr>
<th>DOCUMENT</th>
<th>APPLICATION NUMBER</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

18. **STATUS:**

<table>
<thead>
<tr>
<th>CONSULTS/CMC RELATED REVIEWS</th>
<th>RECOMMENDATION</th>
<th>DATE</th>
<th>REVIEWER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biometrics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EES</td>
<td>Acceptable</td>
<td>21-SEP-2005</td>
<td></td>
</tr>
<tr>
<td>Pharm/Tox</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biopharm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ODS/DMETS</td>
<td>No objection to the use of the proprietary name &quot;iPlex&quot;</td>
<td>13-AUG-2005</td>
<td>Kimberly Culley, RPh HDF-420</td>
</tr>
<tr>
<td>Methods Validation</td>
<td>Pending submission of requested information</td>
<td>--</td>
<td>Xavier Ysern, PhD</td>
</tr>
<tr>
<td>LNC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EA</td>
<td>Acceptable (Categorical Exclusion granted)</td>
<td>06-FEB-2004</td>
<td>Xavier Ysern, PhD</td>
</tr>
<tr>
<td>Microbiology</td>
<td>Approval</td>
<td>23-JAN-2004</td>
<td>Bryan S. Riley, PhD</td>
</tr>
</tbody>
</table>

Page 4 of 133
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 mecamerin rinfahate. 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 Insmed (Santa Clara) in the submission) was closed in September, 1998. Insmed 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 Insmed (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 Insmed 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 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 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 ± 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 AveXia 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 as 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). 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 ≤ -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 ≤ -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) ≤ -3, basal IGF-1 SDS ≤ -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  
DNDCII Director/HFD-820

Blair Fraser, PhD  
DNDCII Deputy Director/HFD-820

Enid Galliers  
Project Manager/HFD-510

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

/s/

Xavier Ysere
9/22/2005 03:19:10 PM
CHEMIST

Stephen Moore
9/22/2005 03:37:35 PM
CHEMIST