

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-884

ADMINISTRATIVE
DOCUMENTS/CORRESPONDENCE

EXCLUSIVITY SUMMARY

NDA # 21-884

SUPPL #

HFD # 510

Trade Name IPLEX

Generic Name mecaseirin rinfabate (rDNA origin) injection

Applicant Name INSMED INC.

Approval Date, If Known 12/12/2005

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1) NDA

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

7 YEARS' ORPHAN EXCLUSIVITY

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 21-839

INCRELEX (mecasermin [rDNA origin] injection)

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

INSM-110 - 303

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #2	YES <input type="checkbox"/>	NO <input type="checkbox"/>

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #2	YES <input type="checkbox"/>	NO <input type="checkbox"/>

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

INSM-110-303

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1
IND # 50,140 YES ! NO
! Explain:

Investigation #2
IND # YES ! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1
!
!
YES ! NO
Explain: ! Explain:

Investigation #2
!
!
YES ! NO
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

Name of person completing form: Enid Galliers
Title: CPMS, DMEP, ODE II, OND CDER
Date: 12/12/05

Name of Office/Division Director signing form: David Orloff, MD
Title: Director, Division of Metabolism and Endocrinology Products, ODE II

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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this page is the manifestation of the electronic signature.**

/s/

Enid Galliers
12/12/2005 05:13:56 PM

David Orloff
12/14/2005 04:16:59 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21-884 Supplement Type (e.g. SE5): _____ Supplement Number: n/a

Stamp Date: 10/12/05 User Fee Date: 12/12/05

HFD-510 Trade and generic names/dosage form: IPLEX (mecasermin rinfabate [rDNA origin] injection) 36 mg/0.6mL

Applicant: INSMED, INC Therapeutic Class: 1,4 P, V DESIGNATED ORPHAN

Indication(s) previously approved: None.

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application: 1

Indication #1: Treat growth failure in pediatric patients with severe primary IGF-1 deficiency or with growth hormone gene deletion who have developed neutralizing antibodies to growth hormone.

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min x kg _____ mo. 0 yr. _____ Tanner Stage _____
Max x kg _____ mo. _____ yr. 3 Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: Condition is usually not diagnosed before age 2 or 3 yr.

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. 15 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 18 Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: The population is extremely small and the oldest patient treated to date was 14.8 years old. The study is ongoing.

Date studies are due (mm/dd/yy): Dec. 31, 2010

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of "completed" (studies are ongoing) studies:

Min _____ kg _____ mo. _____ yr. 3 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 14.8 Tanner Stage _____

Comments: **This drug should not be used in patients after their epiphyses have closed.**

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by: **Enid Galliers**

{See appended electronic signature page}

Supervisory Project Manager, DMEP (HFD-510)

cc: NDA 21-884
HFD-960/ Grace Carmouze

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.
(revised 12-22-03)**

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this page is the manifestation of the electronic signature.**

/s/

Enid Galliers
12/12/2005 05:22:55 PM

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-884	Efficacy Supplement Type SE-	Supplement Number n/a
Drug: IPLEX (mecasermin rinfabate [rDNA origin] injection)		Applicant: INSMED, Inc.
Review Cycle: # 2		
RPM: Enid Galliers	Date: 11.21.05; 12.12.05	HFD-510 Phone # 301-796-1211
<p>Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</p> <p><input type="checkbox"/> Confirmed and/or corrected</p>		Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):
❖ Application Classifications:		
• Review priority		<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority
• Chem class (NDAs only)		1, 4
• Other (e.g., orphan, OTC)		V (orphan)
❖ User Fee Goal Dates		
		12.12.05
❖ Special programs (indicate all that apply)		
		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2
❖ User Fee Information		
• User Fee		<input type="checkbox"/> Paid UF ID number NONE (orphan)
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other (specify)
• User Fee exception		<input checked="" type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) <input type="checkbox"/> Other (specify)
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.

❖ Exclusivity (approvals only)	
<ul style="list-style-type: none"> Exclusivity summary Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	Draft No
<ul style="list-style-type: none"> Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification. 	<input type="checkbox"/> Maybe, Application # NDA <u>21-839</u> <input checked="" type="checkbox"/> No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	7.17.05;

General Information	
❖ Actions	
• Proposed action	<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA
• Previous actions (specify type and date for each action taken)	None
• Status of advertising (approvals only)	<input type="checkbox"/> Materials requested in AP letter <input type="checkbox"/> Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	<input type="checkbox"/> Yes <input type="checkbox"/> Not applicable
• Indicate what types (if any) of information dissemination are anticipated	<input checked="" type="checkbox"/> None <input type="checkbox"/> Press Release <input type="checkbox"/> Talk Paper <input type="checkbox"/> Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling	12.08.05 PI & PPI; (secure email)
• Original applicant-proposed labeling	12.31.04 PI only
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings)	DMETS: 8.5.05; 9.13.05; 11.8/05; 12.9.05 DDMAC: 9.15.05; 10.28.05 DSRCS: 9.15.05; 10.28.05
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	Increlex NDA 21-839
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	10.12.05; 12.08.05
• Reviews	
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	n/a
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	✓
❖ Memoranda and Telecons	✓
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	6.4.03; 10.8.03; 3.19.04
• Pre-NDA meeting (indicate date)	None
• Pre-Approval Safety Conference (indicate date; approvals only)	Refer to 7/26/05 PASC for N21839
• Other	3.9.05; 7.12.05; 11.04.05; 12.5.05 (internal)
❖ Advisory Committee Meeting	
• Date of Meeting	NONE
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	NONE

Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	DD: 3.9.05; 9.26.05; 11.23.05 OD: 12.12.05
Clinical Information	
❖ Clinical review(s) (indicate date for each review)	9.26.05; 11.15.05
❖ Microbiology (efficacy) review(s) (indicate date for each review)	n/a
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	Included in MOR # 1 & # 2
❖ Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	n/a
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	Draft
❖ Demographic Worksheet (NME approvals only)	n/a
❖ Statistical review(s) (indicate date for each review)	8.20.05; Addendum 8.29.05
❖ Biopharmaceutical review(s) (indicate date for each review)	9.14.05; Addendum 9.14.05
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	n/a
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	None
• Bioequivalence studies	None
CMC Information	
❖ CMC review(s) (indicate date for each review)	9.22.05; 11.18.05; 11.30.05
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	Requested & granted
• Review & FONSI (indicate date of review)	n/a
• Review & Environmental Impact Statement (indicate date of each review)	n/a
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	8.1.05
❖ Facilities inspection (provide EER report)	Date completed: (9.21.05) (✓) Acceptable () Withhold recommendation
❖ Methods validation	() Completed () Requested (✓) Not needed () Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	2.25.05; 9.7.05; 9.12.05; 9.20.05; 12.12.05
❖ Nonclinical inspection review summary	None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	None
❖ CAC/ECAC report	None

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/s/

Enid Galliers

12/12/2005 07:38:52 PM



OFFICE DIRECTOR'S DECISIONAL MEMORANDUM

Date: Monday, December 12, 2005
NDA: 21-844
Sponsor: INSMED
Proprietary Name: IPLEX (mecasermin rinfabate [rDNA origin] injection)
Author: Robert J. Meyer, MD, Director, ODE II

Summary: This is a brief memorandum intended to supplement the previous decisional memos from Dr. David Orloff on IPLEX. This drug is a fixed-dose combination injection product containing the previously approved orphan drug, mecasermin (or recombinant human IGF) along with its specific, cognate binding protein, also recombinant human in derivation – rhIGFBP-3. Mecasermin, marketed by Tercica under the trade name "Increlex " as a single ingredient product without its binding protein, received orphan drug exclusive approval for long term treatment of "severe primary IGF-1 deficiency or with growth hormone gene deletion who have developed neutralizing antibodies to growth hormone" on August 30, 2005. I am in substantial agreement with both Dr. Dragos Roman's medical review and Dr. Orloff's sign off memos for both actions taken on IPLEX. I will not, therefore, reiterate those, including Dr. Orloff's commentary and conclusions summarizing the non-medical aspects of the application and their review.

Rather, the intent of this memo is to document the reasoning behind the Office and Division of Metabolism and Endocrinology Products' (DMEP) finding that IPLEX is a fixed-dose combination drug, which then informs the issue of whether this drug is blocked from approval by Increlex's Orphan Exclusivity, a matter left open in Dr. Orloff's memo. This determination that IPLEX is a fixed-combination prescription drug (under 21 CFR 300.50) means this product is not blocked from approval by the exclusivity granted to Increlex, the rDNA IGF-1 product approved under NDA 21-839, since fixed-combination drug products are not considered "the same drug" as single ingredient products under the Orphan Drug Act and implementing regulations .

First, it is important to state that DMEP, with input from the Office of Drug Evaluation II, has regarded this product as a fixed-dose combination from early on and relayed this to the company at the end-of-phase 2 meeting in June 2003. At that meeting, it was agreed that information relevant to the contribution of the rhIGFBP-3 to the efficacy and/or safety of the combination must be presented to meet the expectations of 21 CFR 300.50. However, considering the difficulties in performing a true factorial design (extremely limited population and ethical considerations), it was acknowledged that this information could be achieved in other ways.

The information the sponsor has presented in their application on this issue is manifold, and only a portion of the most relevant data will be highlighted in this memo.

Firstly, the sponsor has presented both human and animal pharmacokinetic data that shows the presence of this complex (the rhIGFBP-3 and the IGF-1) leads not only to a decrease in peak free IGF-1, but also a prolonged availability of IGF-1 in the circulation. In part, these data are the basis for this drug being recommended for once-daily administration (the Increlex product is recommended to be dosed twice daily). It is clear from the human PK data comparing the kinetics of IGF-1 alone to that of the complex that the presence of rhIGFBP-3 meaningfully changes the pharmacokinetics of the resultant product. While there are no data to show a clinical advantage of this drug dosed by injection once-daily to that of the IGF-1 alone administered twice-daily in terms of adherence or clinical results, this difference in dosing on its face would represent an advantage as there would be fewer injections. It must be reiterated that this does not imply or establish superiority of IPLEX to Increlex when dosed according to labeling, but rather that there is an important difference in dosing instructions based on the established PK differences arising from the presence of the rhIGFBP-3.

The sponsor has also provided animal data to show that equimolar amounts of IGF-1 beta administered either alone or in complex with the rhIGFBP-3 produces less hypoglycemia when administered via the latter formulation. This supports that the pharmacodynamics of the two products are different as a result of the differing pharmacokinetics. This does not, itself, equate to clinical superiority, however, as the products are dosed differently in the clinic. Therefore, these data, which were obtained under controlled conditions in a laboratory (in animals), may not predict what would be seen when the products are dosed in humans according to their respective labeling. In fact, there are no definitive head-to-head studies on which to base comparative clinical claims. The cross-study comparisons done by this sponsor, while they hint at fewer important hypoglycemic episodes with mecaseerin rinfabate, certainly do not establish an important clinical difference, even when the drugs are administered under the conditions of a clinical trial.

One notable difference that does result from the observed differences in PK is that the Increlex product is labeled to be taken in association with meals (since the maximal plasma concentrations of IGF-1 with this product occur early), to protect against hypoglycemia. This advice is not given in the IPLEX labeling as the C_{max} occurs later and the peak exposure curve is broader.

Another difference worth noting, but again without proven clinical consequence, is that the development of antibodies to the rhIGFBP-3/IGF-1 complex is higher than with the IGF-1 alone (approximately 90% for the former compared to about 50% with the latter). These antibodies are not shown to be neutralizing, but because data are certainly less than complete on the long-term consequences of these products, it is possible that this difference in immunogenicity could have clinical implications.

For all these reasons, we believe that the rhIGFBP-3 is active in the formulation, providing a clearly different pharmacokinetic and pharmacodynamic profile for the drug containing the complex compared to the single ingredient product. Again, this does not lead to clear clinical advantages when dosed according to recommendations, even under clinical study conditions (i.e., with attention paid to adherence), but does result in differences in molar dosing, dosing

frequency and the resultant pharmacokinetics/exposures. Therefore, we continue to believe that mecasermin rinfabate is a fixed-dose combination drug under 21 CFR 300.50 that is therefore a different drug under the provisions of the Orphan Drug Act. Therefore, IPLEX (mecasermin rinfabate) may itself be approved during the period of Increlex's orphan exclusivity as an orphan drug with its own exclusivity.

Nomenclature:

The official USAN name for this product is mecasermin rinfabate, which for obvious reasons is very close to that of the single ingredient product – mecasermin. In many similarly constructed USAN names, the second designation is used for salts of the moiety (e.g., fluticasone propionate), where the second name here designates a second moiety, albeit in a complex. This USAN name similarity and the fact that this is not just a “salt” presents the possibility for confusion. Such confusion could be clinically problematic, since the two products are dosed differently and if the IPLEX product were accidentally dosed twice daily, overdosage would result with potential adverse consequences. The sponsor has agreed in writing to ask for a new or modified USAN name. A significant modification (e.g., a very different USAN name altogether) also could present problems, as it may lead to concomitant treatment with both the Tercica and the Inmed products based on disparate established names. This too could lead to serious hypoglycemia. The likelihood of either of the above circumstances seems relatively low given the expert community likely to prescribe these products at present. However, it is possible either company, or both, may expand the proposed uses in the future. Either way, besides prescribing confusion, confusion at the pharmacy level is possible, since these products will distribute through at least one common outlet. The sponsor has been asked for and has submitted plans to limit the possibility of such errors while the USAN name is under review and revision.

The trade names of the Tercica product (Increlex) and this product (IPLEX) have some similarities and both Tercica and DMETS have expressed concern over these similarities, though the dosing range barely overlaps and handwriting of the two does not lead to very similar script results. DMETS' recommendation on the name is a suggestion that the sponsor rename the product. Given where we are on the process and the extent of the differences in the names and dosages (despite some admitted similarity in the “I” and “lex” parts of the names), I believe we can approve the product with the current trade name, given a relatively low likelihood of confusion. One could argue, in fact, that the “plex” portion of this name may be a helpful mnemonic to remember that IPLEX is a complex of two moieties. However, if the trade name indeed becomes an issue in actual medication errors, we will need to have Inmed rename their product in a timely manner in terms of the trade name. They have been informed of such.

Planned Action:

Approval for the treatment of severe primary IGF-1 deficiency (mostly Laron's syndrome) or with growth hormone gene deletion with neutralizing antibodies to growth hormone at a dose of 1 – 2 mg daily (approximately equal to 0.2 to 0.4 mg daily of IGF-1).

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/s/

Robert Meyer
12/12/2005 12:58:37 PM
MEDICAL OFFICER

RPM MEMORANDUM TO THE FILE (LABELING)

DATE: 9 December 2005

APPLICATION NUMBER: NDA 21-884

IPLEX (mecasermin rinfabate [rDNA origin] injection)

SUBJECT: Evaluation of changes to Package Insert (PI), Patient Package Insert (PPI), vial label and carton labels

On November 4, 2005, FDA and Insmed reached agreement on the PI and PPI based on comments from the clinical, preclinical, and chemistry disciplines as well as recommendations from ODS/DSRCS and DDMAC. The firm submitted revised PI and PPI via secure email later that day (November 4, 2005) that incorporated the agreed upon changes.

Subsequently, DMETS completed its review on November 8, 2005, and I notified Insmed that I would send the change requests to the firm on November 18 after returning from vacation. The firm received the requests on November 18 and responded with revised PI, PPI, vial label, and carton label on November 23, 2005. In response to one of DMETS's comments, Insmed changed the drug product name from "iPlex" to "IPLEX." On November 28, 2005, Insmed submitted revised vial and carton labels to correct two errors it had discovered.

The November 23, 2005, PI & PPI and the November 28, 2005, vial and carton labels comply with the changes requested as of November 23.

On November 9, 2005, DMEP submitted another consult request to DMETS based on a letter dated November 2, 2005, from Tercica, Inc. addressing the potential for dispensing/prescribing errors due to the similarity of the (then) proposed trade name, iPlex, to Tercica's approved product's name, INCRELEX. The DMETS reviewer requested information from both companies on the way the drugs would be dispensed and the information was sent to DMETS upon receipt (attached). Subsequently, DMETS requested a meeting with the reviewing medical officer for both drugs, Dr. Dragos Roman.

On November 30, 2005, Kimberly Pedersen Culley and Carol Holquist of DMETS met with Dr. Roman and me to discuss additional issues that had arisen from the most recent consult request. In that meeting DMETS suggested that there might indeed be the possibility of dispensing errors due to the similarity in the trade names between INCRELEX and IPLEX because of the initial "I" and terminal "LEX" in both and because same national pharmacy will dispense both drugs (although Increlex will also be dispensed by three additional national pharmacies). DMETS also stated its concern that prescribing errors could occur because a physician who intended to prescribe "mecasermin rinfabate" might simply write "mecasermin" and INCRELEX would be dispensed instead of IPLEX. Later that day (November 30) I contacted Mr. Gunn of Insmed to relay the suggestion that Insmed consider (1) using a different tradename and (2) proposing procedures to eliminate the possibility of a dispensing error by the national pharmacy. Mr. Gunn

said that Insmmed would change the trade name if FDA required it but requested the opportunity to discuss the issue with the Agency. He also agreed to address the pharmacy procedures issue. Finally, I relayed two small changes to labeling: (1) a new paragraph requested by DMETS (in my November 18, 2005, communication) had been located by Insmmed at the end of the STORAGE CONDITIONS section and needed to be moved to the end of the DOSAGE AND ADMINISTRATION section; (2) the list of ingredients added to the left column of the carton label detracted from the required information in that column/panel and needed to be relocated on the other panel but could be presented in paragraph (running text) format rather than as a list.

On December 1, 2005, Insmmed submitted by secure email a PI that contained the correctly relocated DOSAGE AND ADMINISTRATION paragraph. Insmmed indication that it preferred to postpone sending the revised carton label until it received a decision regarding the need for a trade name change.

On December 2, Dr. Roman and I met with Dr. Robert Meyer to discuss the issues raised by DMETS and the response of Insmmed and its two meeting requests. Dr. Meyer indicated he did not believe that the similarities in the two trade names was likely to result in a dispensing error. He thought it more likely that mistakes could occur because of the similarities of the established names, but that changing the USAN name would not be easily or quickly accomplished. Dr. Meyer wanted the sponsor to submit a description of policies and procedures that the national pharmacy would use for dispensing IPLEX so DMETS could be consulted. Since he was not going to request the firm to change its proposed trade name, there was no need for a meeting. Further, the firm's request to meet after the internal discussion regarding the drug's orphan status vis-à-vis INCRELEX was denied on the grounds that the decision will be made by OOPD.

Subsequently on December 2, I conveyed the meeting denials to Mr. Ron Gunn by phone with the decision not to request a change of trade name and the request to submit pharmacy policy and procedures to prevent prescribing errors.

On December 5, Insmmed emailed a description of the national pharmacy dispensing procedures (also submitted a hard copy) and a text version of changes (cf. a mock-up) to the carton label and asked for DMETS' approval before sending the carton label changes to the contractor for preparation of a new mock-up. Later that morning I emailed DMETS' concurrence with the carton label changes to Insmmed and added DMETS' suggestion to enlarge the strength "36 mg/ 0.6 mL" since the shift of the ingredients to the other panel provided enough room. I also commented that the "Hepatic Insufficiency" section of CLINICAL PHARMACOLOGY in the PI emailed December 1 had a strange font; i.e., bold, upper case characters – although the text itself had not changed. On December 6, Kim Culley (DMETS) indicated that the pharmacy procedures looked pretty good upon her preliminary review. On December 7, Insmmed emailed the revised carton label and the corrected PI, and I requested Insmmed to make a formal submission on electronic media of the agreed upon PI, PPI, vial label, and carton label and to email that submission to me.

On December 8, Insmmed emailed the requested labeling submission. I have compared the

December 9, 2005, Memo to File (LABELING) – NDA 21-884

Page 3

emailed labeling for the PI, PPI, vial label, and carton label with previously agreed upon pieces of various dates and found the December 8, 2005, submission to be acceptable.

It should be noted that this review was completed before receiving a final DMETS review of the trade name, USAN name, and pharmacy dispensing issues.

{See appended signature page.}

Enid Galliers
CPMS, DMEP

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/s/

Enid Galliers
12/9/2005 04:43:48 PM
CSQ

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: November 22, 2005

FROM: David G. Orloff, M.D.
Director, Division of Metabolism and Endocrinology Products

TO: NDA 21-884
IPlex (mecasermin rinfabate)
Insmmed, Inc.
Treatment of primary IGF-1 deficiency due to growth hormone receptor defects leading to GH insensitivity or to growth hormone gene deletions

SUBJECT: NDA review issues and recommended action; complete response to AE letter

Summary of issues

This memo is in follow up to my original division director memo dated September 26, 2005.

As summarized in Dr. Roman's review addendum dated 11/15/05, the response to the AE letter of September 26, 2005, includes information to address the CMC deficiencies that were the basis for the AE action, as well as updated clinical trial data and labeling proposals. The original study cohort of 29 patients continues on therapy with the to-be-marketed product and the submission contains approximately 2 additional months of safety information beyond that contained in the original NDA submission. Additionally, approximately 1 month of safety data from seven patients in a new cohort treated with the to-be-marketed formulation are included in the submission. The total exposure to iPLEX covered in the NDA through this latest submission is 349 subject-months, or approximately 29 subject-years.

Adverse events

Dr. Roman summarizes the adverse event profile of the drug, citing injection site reactions (erythema, pruritis, pain, hair growth) as common events, and hypoglycemia in up to 37% of patients.

The submission also includes an updated comparison of the adverse event profiles and frequencies of iPLEX and rhIGF-1. The data from rhIGF-1 studies was acquired from Pharmacia, Inc. The comparison is of data from independent clinical studies. There are no studies that have directly compared iPLEX and rhIGF-1. The updated comparison includes 6-month safety data from the total of 29 patients treated with iPLEX and from 33 patients treated with rhIGF-1. The overall safety profiles of the two products appear similar based on this comparison of limited trial data derived from independent studies. The sponsor maintains that there is a difference in the frequency of serious adverse events, specifically related to hypoglycemia, though the numbers of such events are small (4 with rhIGF-1 vs. 2 with iPLEX), and given the limitations of such comparisons across studies, we have concluded that there are

no compelling data bearing out the hypothetical lesser risk of hypoglycemia with mecasecmin rinfabate compared to rhIGF-1 alone.

Immunogenicity

Finally, Dr. Roman reviews the updated immunogenicity data (out to 9 months) in cohort #2 treated with the to-be-marketed formulation. The data are essentially unchanged from the 6-month findings previously reviewed. In short, approximately 20% of patients have an anti-IGF-1 antibody titer at any time during the 9 months; approximately 50% have an anti-IGFBP-3 antibody titer at any time; and, the percentage increasing with increasing duration of therapy, approximately 90% have an anti-IGF-1/IGFBP-3 titer at any time. The sponsor has not noted any clinical consequences of these antibodies. Furthermore, the sponsor agrees to provide, post-approval, data out to 2 years from an ongoing clinical trial of iPLEX to further address the antigenicity question.

Labeling

Labeling has been negotiated.

Orphan exclusivity issues related to the approved rhIGF-1 product (Increlex)

The Office of Orphan Product Development has not yet rendered a final opinion on arguments by Insmad that mecasecmin rinfabate and mecasecmin represent different products for the purposes of orphan exclusivity. As above, the division finds no compelling evidence of superior safety of iPLEX relative to Increlex. Additionally, there is no evidence of differences in the efficacy of the two products, specifically of a superior effect of iPLEX on growth promotion in the target population. Assuming blockade of approval by orphan exclusivity of Increlex, at this time, iPLEX will only be tentatively approved.

Nomenclature

A letter has been received from Tercica, Inc., manufacturer of Increlex, citing potential name confusion between Increlex and iPLEX, and delineating the risks of substitution medication errors between these two products. A consult has been sent to DMETS.

CMC

ONDC has completed its review of the CMC package and response to the AE deficiencies. The recommendation is AP with an expiry of 24 months at -70 degrees centigrade, with an in-use expiry of 2 months at -20 degrees C and 2 hours at room temperature.

Recommendation

Tentative approval. Sponsor is to be reminded of their agreement to provide additional immunogenicity data from ongoing trial INSM-110-303, as delineated in their response to the September 26, 2005 AE letter. Consult on the name iPLEX is pending from DMETS.

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/s/

David Orloff
11/22/2005 11:25:12 AM
MEDICAL OFFICER

Robert Meyer
11/23/2005 09:25:03 AM
MEDICAL OFFICER

I substantially agree with this memo and its conclusions

Galliers, Enid M

From: Galliers, Enid M
Sent: Friday, November 18, 2005 7:50 PM
To: 'Ronald Gunn'
Subject: Labeling - NDA 21-884

Dear Ron:

Here are the promised labeling comments on your emailed November 4, 2005, package insert and patient package insert and your emailed November 8, 2005, vial and carton labels.

Our Office of Drug Safety believes the following changes may minimize potential user error. We also include some corrections in storage conditions throughout the labeling.

A. General Comments

DMETS does not recommend the use of the font style proposed for the proprietary name. Using a lower case "i" followed by an upper case "P" makes the name look like Plex, rather than Iplex. Revise the font to be consistent for the proprietary name (Iplex or IPLEX).

B. Container Label

1. Remove the bolding of the "Rx only" statement. At this time, the statement is more prominent and distracts from the more critical route of administration statement.
2. Increase the prominence of "for subcutaneous injection" by bolding or some other means to help draw attention to the route of administration and help alleviate inadvertent intravenous or intramuscular administration.
3. Increase the prominence of the product strength as the current presentation (e.g., font style, lack of bolding) is difficult to read in light of the bolded proprietary name and established name.
4. Include the statement "Single use vial. Discard unused portion." to help prevent patients and providers from using a single vial for multiple injections.

C. Carton Labeling

1. See B1 through B4.
2. Add the quantitative and qualitative ingredients (i.e. sodium acetate and sodium chloride) to the carton label in accordance with 21 CFR 201.10 (i) (2).

Calculate the actual amounts (mass) of all components in the vial, _____, and add:

mecasermin rinfabate	xxx mg
sodium acetate	xxx mg
sodium chloride	xxx mg

3. Revise the placement or remove the sponsor's name from the top of the label as it is distracting from the proprietary name.

D. Package Insert

1. DESCRIPTION

According to USP guidelines, for containers less than 1 mL in volume, the strength per fraction of a milliliter should be the only expression of strength. Thus, for consistency with the carton and the container, please delete the reference to _____ in this section (and the following 'How Supplied' section) as these are common reference sections for practitioners. Only refer to the actual concentration of 36 mg/0.6mL to help alleviate

confusion.

The revised text of the last paragraph of this section is as follows:

"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."

Note: Replace any other references to ' — ' in the labeling with "36 mg/0.6 mL" and make any corrections to the text that are needed.

2. DOSAGE AND ADMINISTRATION

a. Remove trailing zeros as in the therapeutic dose range of "1.0 to 2.0 mg/kg." Trailing zeros often result in error as the decimal is overlooked. The use of trailing zeros could potentially result in a ten-fold medication dose error. Although it is unlikely that a ten-fold medication dosing error would occur since the product is packaged in the required concentration and volume for administration, the use of terminal zeros in the expression of strength or volume is not in accordance with the General Notices (page 12) of 2000 USP, which states, "...to minimize the possibility of errors in the dispensing and administration of the drug . . . the quantity of active ingredient when expressed in whole numbers shall be shown WITHOUT a decimal point that is followed by a terminal zero."

b. We recommend duplicating the sentences from the first and second paragraph under 'Storage Conditions' (as shown below). This would be in accordance with 21 CFR 201.57 (j) that notes the dosage and administration section should "contain specific direction on dilution, preparation" and may aid in preventing administration error.

Add the following paragraph to the end of this section:

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

Note: It is also necessary to revise the second paragraph of the STORAGE CONDITIONS section as shown below.

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

3. HOW SUPPLIED

a. See D1. The revised text follows.

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



E. Patient Package Insert

Patient Information

- a. "How should my child use Iplex?" See comment (b.) below under Instructions for Use.
- b. "How should I store Iplex?" Revise bullets 5 and 6 with the following:
 - Once Iplex thaws, use it within 1 hour.
 - Do not use Iplex if it thaws and stays at room temperature for longer than 1 hour. The medicine may not work.
 - If you do not use Iplex within 2 hours after you have removed it from the freezer, discard the vial because it may not work.

Instructions for Use

"Preparing the dose:"

a. In section 1, we question the addition of "rubbing alcohol" to clean the hands before starting the injection procedure. This is not the standard language (i.e., soap and water) for cleaning instructions. If you intend to provide an alternative for the standard language of soap and water, should this be expanded on to include gel and foam hand sanitizers to broaden the explanation?

b. In section 2, provide further detail about whom to contact for replacement. For example, the patient will likely have to call the distributor for instructions on how to return and get replacement of this drug product. However, if the sponsor must be contacted for product reimbursement, direct the patients/providers accordingly. As is, changing the verbiage to "Contact" from "Return" with the addition of distributor may help alleviate confusion. [Revise the last bullet under "How should my child use Iplex?" in the Patient Information section to be consistent with your decision regarding the use of national pharmacy. terminology. Revise the Patient Package Insert to be consistent in this terminology throughout.]

Contact — for instructions on how to return and obtain replacement of Iplex.

c. In section 10, use the terminology "prescribed dose" as in section 6 and throughout the instructions, consistency in terminology is preferred over the switching to —

d. In section 11, the picture does not match the directions. The patient in the picture is holding the vial, but the directions in the second sentence say "hold the syringe." Perhaps a picture displaying both the vial and syringe being held with revised verbiage would best suit the directions. This, in turn, may aid in the prevention of breaking needles and needle sticks.

You are welcome to contact me with any questions about these changes.

Best regards,

Enid

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/s/

Enid Galliers
11/22/2005 09:46:34 AM
CSO

REQUEST FOR CONSULTATION

TO (Division/Office):

**Director, Division of Medication Errors and
Technical Support (DMETS), HFD-420
WO22, RM 4447**

FROM: Kati Johnson, CPMS, HFD-510

DATE 11/9/05	IND NO.	NDA NO. 21-884	TYPE OF DOCUMENT none	DATE OF DOCUMENT
NAME OF DRUG IPLEX (mecasermin/rinfabate)		PRIORITY CONSIDERATION HIGH	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE 12/1/05

NAME OF FIRM: **Insmed**

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|---|
| <input type="checkbox"/> NEW PROTOCOL
<input type="checkbox"/> PROGRESS REPORT
<input type="checkbox"/> NEW CORRESPONDENCE
<input type="checkbox"/> DRUG ADVERTISING
<input type="checkbox"/> ADVERSE REACTION REPORT
<input type="checkbox"/> MANUFACTURING CHANGE/ADDITION
<input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> PRE-NDA MEETING
<input type="checkbox"/> END OF PHASE II MEETING
<input type="checkbox"/> RESUBMISSION
<input type="checkbox"/> SAFETY/EFFICACY
<input type="checkbox"/> PAPER NDA
<input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER
<input type="checkbox"/> FINAL PRINTED LABELING
<input type="checkbox"/> LABELING REVISION
<input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE
<input type="checkbox"/> FORMULATIVE REVIEW
<input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Trade name review |
|--|--|---|

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):	<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- | | |
|---|--|
| <input type="checkbox"/> DISSOLUTION
<input type="checkbox"/> BIOAVAILABILITY STUDIES
<input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE
<input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS
<input type="checkbox"/> IN-VIVO WAIVER REQUEST |
|---|--|

IV. DRUG EXPERIENCE

- | | |
|--|---|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
<input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
<input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)
<input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
<input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE
<input type="checkbox"/> POISON RISK ANALYSIS |
|--|---|

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> PRECLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS/SPECIAL INSTRUCTIONS: NDA 21-884 was AE on 9/26/05. We had previously submitted the proposed tradename IPLEX for review and it was found acceptable. However, a similar drug for the same population was approved in 8/05 with the tradename INCRELEX (NDA 21-839). The compounds are —, both are injections, but are different concentrations, which could be a potential safety issue if the incorrect product is dispensed. We would like a reassessment of the acceptability of the tradename IPLEX. The proposed PI for IPLEX is in the EDR (9/15/05 submission). The approval letter for INCRELEX is attached.
 PDUFA DATE: 12/16/05

NAME AND PHONE NUMBER OF REQUESTER Kati Johnson, 301-796-1234	METHOD OF DELIVERY (Check one) <input type="checkbox"/> DFS ONLY <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

4 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

MEMORANDUM OF TELECON

DATE: 4 November 2005

APPLICATION NUMBER: NDA 21-884
IPLEX (mecasermin rinfabate [rDNA origin] injection)

BETWEEN:

Ronald D. Gunn, M.S., M.B.A., Executive Vice President & COO
Kenneth Attie, M.D., Vice President, Clinical Development & Medical Affairs &
Chief Medical Officer
Glen Kelley, Ph.D., Senior Director, Pharmaceutical Services
Steven Wallace, Senior Director, Manufacturing

Phone: Conference Call-in Number
Representing: Insmmed, Inc.

AND

FDA:
Robert J. Meyer, MD, Director, Office of Drug Evaluation II (ODE II)
Curtis Rosebraugh, MD, Deputy Director, ODE II
David Orloff, MD, Director, Division of Metabolic and Endocrine Drug Products (DMEDP)
Dragos Roman, MD, Medical Officer, DMEDP
Enid Galliers, CPMS, DMEDP
Xavier Ysern, PhD, Review Chemist, ONDQA
Stephen K. Moore, Ph.D., PAL, ONDQA
Blair Fraser, Ph.D, Deputy Branch Chief, ONDQA

SUBJECT: Discussion of changes to Package Insert (PI) and Patient Package Insert (PPI)

BACKGROUND: On November 2, 2005, FDA sent (by secure email) labeling changes to Insmmed that had been requested by the clinical, preclinical, and chemistry disciplines as well as recommendations from ODS/DSRCS and DDMAC. The Insmmed response had arrived by the morning of November 4, and it incorporated almost every FDA-requested change. In addition, Insmmed proposed a few minor changes.

DISCUSSION:

On November 4, 2005, FDA and Insmmed discussed the changes proposed by the sponsor including the time that the drug product can remain at room temperature. At the conclusion of the telecon, both groups were in agreement.

FDA reminded the firm that the Division was awaiting another labeling consult from DMETS so additional labeling change requests could still be made.

Insmmed agreed to incorporate the changes discussed at the telecon in the PI and PPI and to send the revised labeling to FDA by secure email as soon as available. Because of the possibility of

November 4, 2005, Telecon – NDA 21-884

Page 2

additional changes, FDA told the firm not to make a formal submission with the revised labeling to the NDA until specifically requested to do so.

POSTMEETING NOTE:

The changes were incorporated in the PI and PPI labeling submitted by Insmmed via secure email later that afternoon on November 4, 2005.

{See appended signature page.}

Enid Galliers
CPMS, DMEP

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/s/

Enid Galliers
12/9/2005 04:18:10 PM

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 28, 2005

TO: David Orloff, MD, Director
Division of Metabolic and Endocrine Drug Products
HFD-510

VIA: Enid Galliers, Supervisory Consumer Safety Officer
Division of Metabolic and Endocrine Drug Products
HFD-510

FROM: Catherine Miller, MT(ASCP)
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Gerald Dal Pan, MD, MHS, Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: DSRCS Review of Patient Labeling for iPlex (mecasermin rinfabate [rDNA origin] injection), NDA 21-884

The sponsor submitted revised patient labeling (PPI) for iPlex (mecasermin rinfabate [rDNA origin] injection), NDA 21-884, on October 12, 2005, in response to DSRCS comments sent to the review division (see consult dated September 15, 2005).

We have simplified the wording and made it consistent with the PI to enhance readability and patient comprehension (see attached).

These revisions are based on draft labeling submitted on October 12, 2005. Patient information should always be consistent with the prescribing information. All future relevant changes to the PI should also be reflected in the PPI.

Comments to the review division are bolded, underlined and italicized. We can provide a marked-up and clean copy of the revised document in Word if requested by the review division. Please call us if you have any questions.

9 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling

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/s/

Catherine Miller
10/28/2005 11:11:03 AM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
10/28/2005 02:56:52 PM
DRUG SAFETY OFFICE REVIEWER
for Gerald Dal Pan

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 15, 2005

TO: David Orloff, MD, Director
Division of Metabolic and Endocrine Drug Products
HFD-510

VIA: Enid Galliers, Supervisory Consumer Safety Officer
Division of Metabolic and Endocrine Drug Products
HFD-510

FROM: Catherine Miller, MT(ASCP)
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Gerald Dal Pan, MD, MHS, Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: DSRCS Review of Patient Labeling for iPlex (mecasermin rinfabate [rDNA origin] injection), NDA 21-884

The attached patient labeling (PPI) represents our revisions to the draft patient labeling submitted with the New Drug Application for iPlex (mecasermin rinfabate [rDNA origin] injection), NDA 21-884 and revised by DMEDP on September 12, 2005. We have simplified the wording, made it consistent with the PI, and removed unnecessary information (the purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications). We have put this PPI in the patient-friendly format that we are recommending for all patient information, although this format is not required for voluntary PPIs. Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds.

These revisions are based on draft labeling (PI) submitted on August 24, 2005, and revised by DMEDP on September 13, 2005. Patient information should always be consistent with the prescribing information. All future relevant changes to the PI should also be reflected in the PPI.

There are instructions for use (IFU) in the Patient Information leaflet and we have provided recommendations for some language and organizational changes. We also

recommend the IFU be moved to the end of the PPI to maintain the patient-friendly format of the PPI.

We find the PI to be deficient in information. The PI is missing 3 important subsections under the PRECAUTIONS section: Information for Patients, Drug Interactions, and Pediatric Use. The Information for Patients subsection should include information for healthcare providers to provide to patients in the safe and effective use of the product [see 21 CFR 201.57(f)(2)].

Comments to the review division are bolded, underlined and italicized. We can provide a marked-up and clean copy of the revised document in Word if requested by the review division. Please call us if you have any questions.

**Appears This Way
On Original**

7 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

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this page is the manifestation of the electronic signature.**

/s/

Catherine Miller
9/15/2005 05:18:46 PM
UNKNOWN

Toni Piazza Hepp
9/15/2005 05:22:58 PM
DRUG SAFETY OFFICE REVIEWER
for Gerald Dal Pan



Memorandum

Date: September 12, 2005

From: Dragos Roman M.D., Medical Officer, HFD-510

Through: David Orloff, M.D., Acting Team Leader and Division Director, DMEDP

Subject: Orphan-Drug Designation for INCRELEX (mecasermin)

To: Dr. John McCormick, Deputy Director, Office of Orphan Product Development

Dear Dr. McCormick:

This Memo is in response to the question raised by you and Dr. Henry Startzman to the Division of Metabolic and Endocrine Drug Products regarding whether the terms "Growth Hormone Insensitivity Syndrome" (GHIS) and "Primary IGF-I Deficiency" (primary IGFD) define the same clinical condition. This question is related to the August 1, 2005 submission in which Tercica Inc., the maker of mecasermin (INCRELEX) requests to change the orphan designation for mecasermin from GHIS to Primary IGFD. I concur with Tercica's proposal that the two above-mentioned terms overlap and designate essentially the same patient population (as described in some detail in Tercica's document). Mecasermin has been approved on August 30, 2005 for both Primary IGFD and for an exceedingly rare form of secondary IGF-I deficiency (or growth hormone resistance/insensitivity) characterized by deletion of the growth hormone (GH) gene associated with neutralizing antibodies to GH.

Sincerely,

Dragos Roman M.D.
Medical Officer, HFD-510

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/s/

Dragos Roman
9/12/2005 03:08:21 PM
MEDICAL OFFICER

David Orloff
9/13/2005 01:25:02 PM
MEDICAL OFFICER

From: Galliers, Enid M
Sent: Wednesday, August 31, 2005 2:53 PM
To: Meyer, Robert J; Orloff, David G; Roman, Dragos; Ripper, Leah W
Subject: ODS agrees that PASC is not needed for iPlex NDA 21-884

-----Original Message-----

From: Beam, Sammie
Sent: Wednesday, August 31, 2005 1:50 PM
To: Galliers, Enid M
Subject: FW: DFS Email - Iplex N 021884 N 000 BL 23-Aug-2005 - Forms

See below. Thanks.

-----Original Message-----

From: Green, Lanh
Sent: Wednesday, August 31, 2005 12:10 PM
To: Beam, Sammie; Pamer, Carol; Johann-Liang, Rosemary; Avigan, Mark I
Subject: RE: DFS Email - Iplex N 021884 N 000 BL 23-Aug-2005 - Forms

Sammie,

Thanks for conveying Enid's comments on Iplex. The attached information is adequate and a PASC will not be necessary.

Lanh

-----Original Message-----

From: Beam, Sammie
Sent: Monday, August 29, 2005 8:26 AM
To: Green, Lanh; Pamer, Carol; Johann-Liang, Rosemary; Avigan, Mark I
Subject: FW: DFS Email - Iplex N 021884 N 000 BL 23-Aug-2005 - Forms

Hi,

Please note Enid's remarks below concerning the need for a Pre-Approval Safety Conference for iPlex (mecasermin rinfabate). We just attended the PASC for Increlex (mecasermin). Since they are similar

products the reviewing division wants to know if it is necessary to have a PASC for iPlex. Please let me know if you need additional information to make a decision or if the prior PASC is adequate for both.

Thanks,
Sammie

-----Original Message-----

From: Galliers, Enid M
Sent: Friday, August 26, 2005 8:04 PM
To: Beam, Sammie
Cc: Best, Jeanine A
Subject: FW: DFS Email - N 021884 N 000 BL 23-Aug-2005 - Forms

Sammie:

The DFS email did not indicate that this consult had been sent to the ODS mail box so I'm sending it to you for forwarding. This consult should be for review of the PPI. There will be another consult that I forward for DMETS as well.

Finally, this is a reminder of the conversation we had on Tuesday at 510 DMEDP Admin Rounds. Please ask if DDRE will forgo a PASC for iPlex (mecasermin rinfabate) because it is so similar to the Increlex (mecasermin) (NDA 21-839) product that we discussed on 7/26/05. Also, we don't know that we will recommend approval and even if we do, it looks like orphan exclusivity for Increlex will block approval/marketing of NDA 21-884.

Thanks,

Enid

-----Original Message-----

From: cderdocadmin@cder.fda.gov [mailto:cderdocadmin@cder.fda.gov]
Sent: Friday, August 26, 2005 7:50 PM
To: GALLIERS@cder.fda.gov
Subject: DFS Email - N 021884 N 000 BL 23-Aug-2005 - Forms

Document room update the following:

Decision Date Decision Code

N 021884 N 000 BL 23-Aug-2005 26-Aug-2005 :

Document Type: Forms

Form Group: CONSULT

Form Name: ODS Consult (Except Tradename Reviews)

Submission Description: PPI review requested - iPlex NDA 21-884

Author(s)/Discipline(s)

1. Enid Galliers, CSO

Signer(s)

1. Enid Galliers
26-Aug-2005

Supervisory Signer(s)

1. Enid Galliers
26-Aug-2005

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/s/

Leah Ripper
9/15/2005 05:19:56 PM
CSO

CONSULTATION RESPONSE

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)**

DATE RECEIVED: July 22, 2005	DESIRED COMPLETION DATE: August 19, 2005	ODS CONSULT #: 05-0111-1 05-0111-2
DATE OF DOCUMENT: July 20, 2005	PDUFA DATE: October 03, 2005	

TO: David Orloff, MD
Director, Division of Metabolic and Endocrine Drug Products
HFD-510

THROUGH: Enid Galliers
Chief, Project Management Staff
HFD-510

PRODUCT NAME:
iPlex
(Mecasermin Rinfabate (rDNA origin) Injection)
36 mg/0.6 mL

NDA SPONSOR: INSMED Incorporated

NDA#: 21-884

SAFETY EVALUATOR: Kimberly Culley, RPh

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, iPlex from a safety perspective. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.
2. DMETS recommends implementation of the label and labeling revision outlined in section III of this review to minimize potential errors with the use of this product.
3. DDMAC finds the proprietary names iPlex acceptable from a promotional perspective.

Denise Toyer, PharmD
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety

Carol Holquist, RPh
Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; PKLN Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: August 5, 2005

NDA# 21-884

NAME OF DRUG: iPlex (Mecasermin Rinfabate (rDNA origin) Injection)
36 mg/0.6 mL

NDA HOLDER: INSMED

*****NOTE:** This review contains proprietary and confidential information that should not be released to the public.***

I. INTRODUCTION:

This consult was written in response to a request from the Division of Metabolic and Endocrine Drug Products (HFD-510), for assessment of the proprietary names of iPlex in regard to potential name confusion with other proprietary or established drug names. Container labels and carton labeling were submitted for review and comment. On August 28, 2005, the sponsor submitted revised package insert, carton labels and carton labeling in response to recommendations from a previous DMETS review (see ODS consult 05-0111, August 2005). In addition, the sponsor submitted a patient package insert for review and comment.

PRODUCT INFORMATION

iPlex contains mecaseimerin rinfabate, a binary complex of recombinant human insulin-like growth factor (rhIGF-1) and recombinant human insulin-like growth factor-binding protein (rhIGFBP-3). The pharmacologic action of growth factor is to promote linear growth with a secondary action of anabolic, insulin sensitization and insulin-like effects. iPlex is indicated for the

Recommended starting dosing is 0.5 mg per kilogram subcutaneously daily, which may be increased up to 2 mg/kg daily based on IGF-I levels. iPlex is available as a vial containing a total content of 36 mg in 0.6 mL. Each box contains 35 vials. The drug product must be maintained in the freezer prior to use, thawed at room temperature 45 minutes prior to use. iPlex may be . The vial(s) should reach room temperature prior to injection.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{1,2} as well as several FDA databases³ for existing drug names which sound-alike or look-alike to iPlex to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S.

¹ MICROMEDEX Integrated Index, 2005 MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

² Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

³ AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-05 Drugs@fda.gov, and the electronic online version of the FDA Orange Book.

Patent and Trademark Office's Text and Image Database was also conducted⁴. The Saegis⁵ Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary names Iplex. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary names Iplex acceptable from a promotional perspective.
2. The Expert Panel and independent analysis identified eleven proprietary names that may be potentially confused with Iplex. The products are listed in Table 1 (see below and page 4), along with the dosage forms available and usual dosage.

Table 1: Potential Sound-Alike/Look-alike Names Identified by DMETS Expert Panel and Independent Review

Product Name	Established Name, Strengths, Dosage Form(s)	Usual Dose*	Other**
iPlex	Mescarmerin Rinfabamate (rDNA origin) Injection	0.5 mg per kilogram subcutaneously daily.	
Eprex	Epoetin Alfa Multi-use vial: 20000 IU/mL Single Use pre-filled syringes: 1000 IU/0.5 mL, 2000 IU/0.5 mL, 3000 IU/0.3mL, 4000 IU/0.4mL, 5000 IU/0.5 mL, 6000 IU/0.6 mL, 8000 IU/0.8 mL, 10000 IU/ mL, 40000 IU/ mL	<u>Chronic renal failure</u> : 50-100 IU/kg three times per week for 8 weeks. <u>Cancer</u> : 150 IU/kg SQ three times per week or 40000 IU SQ once per week. <u>Surgery</u> : 600 IU/kg once weekly for 3 weeks. <u>Surgery with ABD</u> : 600 IU/kg twice weekly for 3 weeks	LA
Azelex	Azelaic Acid Cream 20%, 30 grams and 50 grams	Apply to affected areas twice daily, morning and evenings	LA
Epitol	Carbamazepine Tablets, 200 mg	<u>Adults and children over 12</u> : 200 mg BID, then increase up to 800 to 1200 mg per day. <u>Children 6 to 12</u> : 100 mg BID, then increase up to 400 – 800 mg per day. <u>Children under 6</u> : 10 -20 mg/kg/day in two to three divided doses, then increase up to 35 mg/kg/day. <u>Trigeminal neuralgia</u> : 100 mg BID, may increase to 400 to 800 mg per day.	LA
Hiprex	Methenamine Hippurate Tablets, 1 gram	<u>Adults and children > 12 years</u> : 1 gram twice daily. <u>Children 6 to 12 years</u> : 0.5 to 1 gram twice daily	LA/SA
Ifex	Ifosfamide Powder for Injection, 1 gram and 3 gram	Germ Cell Testicular Cancer: IV 1200 mg/m ² /day for 5 days, repeat every three weeks	LA/SA
Iron Plex	Folate 400 mcg, Ferrous Bisglycinate 28 mg, Intrinsic Factor 20 mg,	One capsule daily.	LA/SA

⁴ WWW location <http://www.uspto.gov/tmdb/index.html>.

⁵ Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com

Product Name	Established Name, Strengths, Dosage Form(s)	Usual Dose*	Other**
iPlex	Mescarmerin Rinfabamate (rDNA origin) Injection	0.5 mg per kilogram subcutaneously daily.	
	Dibencozide 250 mcg, 90 capsules		LA
i-STAT	i-STAT is a machine that used cartridges with an applied amount of blood to measure specific laboratory values such as PT/INR, blood gases, creatinine, and blood urea nitrogen	Single drop of blood is applied to a cartridge and this is inserted into a handheld reader that processes the info and reports lab results	LA
Lidex	Fluocinonide 0.05% Cream (15, 30, 60 and 120 grams) Gel (15, 30, 60 and 120 grams), Ointment (15, 30, 60 and 120 grams) Topical Solution (20 and 60 mL)	Apply to affected area twice daily to four times daily.	LA
Lidex-E	Cream 0.05% 15, 30 and 60 grams		
Loprox	Ciclopirox 0.77% Cream: 15, 30 and 90 grams Gel: 30, 45 and 100 grams Topical Suspension: 30 and 60 mL Ciclopirox 1% Shampoo, 120 mL	Cream, gel, suspension: massage into the affected area and surrounding skin twice daily. Shampoo: Wet hair, apply approximately 1 teaspoonful to the scalp. Lather and leave on hair/scalp for 3 minutes. Rinse. Repeat twice weekly for 4 week, with a minimum of 3 days between applications.	LA
Videx	Didanosine Chewable Tablets: 25 mg, 50 mg, 100 mg and 200 mg Powder for Oral Solution: 100 mg and 250 mg, 2 gram and 4 gram Delayed-Release Capsules: 125 mg, 200 mg, 250 mg and 400 mg	≥60kg: Tablets: 400 mg daily or 200 mg twice daily, Capsules: 400 mg daily, Oral Solution: 250 mg twice daily. <60kg: Tablets: 250 mg daily or 125 mg twice daily. Capsules: 250 mg daily, Oral Solution: 167 mg twice daily. Pediatric: 120 mg/m ² twice daily	LA
Videx EC			
*Frequently used, not all-inclusive ** L/A (look-alike), S/A (sound-alike) *** Name pending approval. Not FOI releasable.			

B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

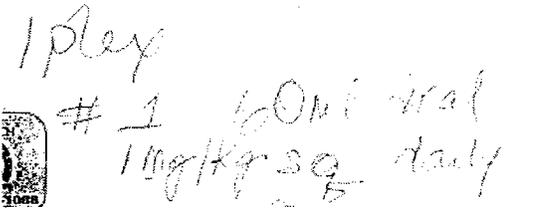
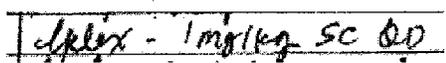
As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to lplex were discussed by the Expert Panel (EPD).

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of lplex with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. Each set of three studies employed a

total of 119 health care professionals (pharmacists, physicians, and nurses) for each. This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescription were written for the proposed name, which consisted of a combination of marketed and unapproved drug products and a prescription for Iplex (see below). The prescriptions were optically scanned and one was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient order was recorded on voice mail, which were sent to a random sample of the participating health professionals for their review and interpretation. After receiving either the written or verbal prescription order, the participants sent their interpretations of the order via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<p data-bbox="300 441 454 472"><u>Outpatient RX:</u></p>  <p data-bbox="300 493 844 714">Iplex # 1 60mL vial 1mg/kg SC daily</p>	<p data-bbox="901 619 1372 735">Iplex 1- 60mL vial 1 mg/kg subcutaneously daily</p>
<p data-bbox="300 735 454 766"><u>Inpatient RX:</u></p>  <p data-bbox="341 808 787 871">Iplex - 1mg/kg SC QD</p>	

2. Result

One participant of the inpatient study identified the proposed name as Exlex, which is similar to the currently marketed Ex-lax. The remaining interpretations were phonetic variations of the proposed name. See appendix A for the complete listing of interpretations from the verbal and written studies.

D. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Iplex, the primary concerns related to look-alike and sound-alike confusion with Eprex, Azelex, Epitol, Hiprex, Ifex, Iron Plex, i-STAT, Lidex, Loprox, and Videx. Upon further review of the names gathered from EPD and independent analysis, the names Iron Plex and i-STAT were not reviewed further due to a lack of convincing look-alike/sound-alike similarities with iPlex. In addition to numerous differentiating product characteristics such as the product strength, indication for use, route of administration and dosage form, Iron Plex is available only on the internet. This product is not available per the 2005 Red Book reference and appears to be unavailable on pharmacy web pages (e.g. Walgreens, CVS). In addition, DMETS can not envision a scenario for the product i-STAT to be confused with Iplex. The products do not overlap in product characteristics, as i-STAT is a handheld device for bedside laboratory testing and Iplex is a drug product. Although post-marketing errors involving names of lab tests and drug names have occurred, the i-STAT product would require the type of lab test requested. Thus, the name would not be alone.

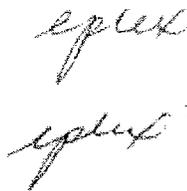
As a whole, due to the small target patient population and storage requirements for Iplex, DMETS suspects confusion with this drug product to be minimal. The need for the drug product to remain frozen and if not maintained so, the resulting concern with stability will limit the number of pharmacies that are capable of maintaining the product. Thus, creating a self-induced limited distribution system. This limitation will help to assure a pharmacy population that

*** Proprietary and confidential information that should not be released to the public

is more aware of the drug product and the patient population; thus, helping to alleviate confusion with knowledge. In addition, growth hormones are typically expensive, which is also another method to alleviate confusion as practitioners will tend to question such orders to prevent burden on their inventory. Furthermore, there is limited concern that a dosage form other than injection will be developed for this drug product given the dosage form availability of currently marketed growth factor hormones. Thus, this further decreases the likelihood for confusion with drug products available in dosage forms other than injectable.

Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with any of the aforementioned names. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Iplex. However, one participant of the inpatient study identified the proposed name as Exlex, which is similar to the currently marketed over-the-counter Ex-lax product. However in light of the numerous differentiating product characteristics such as the product strength, indication for use, route of administration, dosage form, dose, and strength, DMETS will not review this name further.

1. Eprex may look similar to Iplex when scripted. Eprex is not marketed in the United States, but is available in European Union States, Canada, Mexico and multiple other countries. Due to drug importation legislation, DMETS will review the drug name for potential confusion. Eprex contains epoetin alfa to elevate or maintain the red blood cell level and decrease the need for transfusions. Eprex should be used in the treatment of anemia of chronic renal failure, anemia in zidovudine treated HIV infected patients, and anemia in cancer patients. In addition, Eprex is used in surgical procedures to reduce allogeneic blood transfusions. This drug product may also be used to facilitate autologous blood patient with hematocrits of 33 to 39% who are scheduled for major elective surgery that are expected to require more blood than that of autologous blood collection techniques. Dosing is variable depending on condition. Eprex is available in a 20,000 unit per milliliter multi-use vial and multiple pre-filled syringes ranging from 1,000 units per 0.5 mL to 40,000 units per milliliter. The similarities in script stem from the shared "p", concluding "ex" and the likeness of "r" and "l" when incorporated in a word. In addition, the leading "E" and "I" may serve to differentiate the two names when written in upper case; however, when scripted in lower case, these letters lead to a resemblance instead of distinction upon scripting.

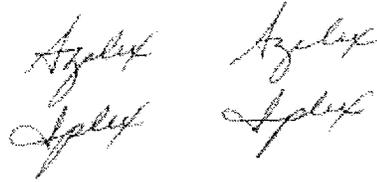


The image shows two lines of handwritten cursive script. The top line reads 'eprex' and the bottom line reads 'lplex'. The letters are slanted and connected, making the two words look very similar when written in a cursive style.

The products share the characteristics of dosage form (injection) and route of administration (subcutaneous use). However, they differ in the three key product characteristics of strength (range of 1,000 to 40,000 international units per vial/pre-filled syringe compared to 36 mg), dose (50 to 600 IU/kg compared to 0.5 mg/kg to 2 mg/kg) and frequency of dosing (once or twice per week/three times per day compared to daily). In addition, the drug products differ in storage as Eprex is maintained in the refrigerator, but Iplex must remain frozen without thawing until use. Their indications of use also differ since Eprex is indicated for anemia and Iplex for growth failure. In addition, the multitude of available strengths for Eprex, differing doses, and the limited use of growth hormone should limit potential confusion. However, DMETS recommends that the sponsor be notified of the availability of this drug product marketed in foreign countries since the names are almost identical when scripted.

2. Azelex may look similar to Iplex when scripted. Azelex contains azelaic acid in a 20% cream formulation for the treatment of acne vulgaris. Recommended dosing is to apply to affected

areas twice daily. Azelex is available in 30 gram and 50 gram tubes. The orthographic similarities stem from the shared concluding "lex" and the possible likeness of capitalized, scripted "A" and "I." In addition, the names share a downstroke "z" compared to "p" in the same position.



The image shows four handwritten examples of drug names in cursive. The top row shows 'Azelex' and 'Iplex' in uppercase. The bottom row shows 'Azelex' and 'Iplex' in lowercase. The letters 'A' and 'I' are particularly stylized, with a downstroke that resembles a 'z' or 'p'.

As these two drug products do not share overlapping strengths (20% compared to 36 mg), dose (thin layer compared to 0.5 mg/kg), dosage forms (cream compared to injectable), route of administration (topical compared with subcutaneous), and dosing frequency (twice daily compared to daily), DMETS has minimal concern with inpatient orders. This is due to JCAHO requirements, which dictate that medication orders must document all the elements required to accurately complete the order, such as frequency and route of administration. Thus, the inclusion of these data on an order would serve to differentiate the two drug products. In regard to outpatient orders, both products are single strength products; therefore, outpatient orders may be completed accurately without notation of the strength of the drug product on the order. In addition, one could suggest that orders could be written with a #1 order amount, indicative of one tube and one box/vial of Azelex and Iplex, respectively. However, it would be unlikely in actuality as Azelex is available in two size tubes, 30 gram and 50 grams and most likely, physicians will order one size or fail to indicate the any reference to amount. Furthermore, physicians will likely order Iplex with a dose and the number of vials or note number of "boxes" on the order to maintain the patient for a month(s). There are other factors that will differentiate the product in an outpatient setting. The storage requirements (remaining frozen) will limit the number of pharmacies that will stock/order Iplex. The indication of use also differs with Azelex, which is used for acne vulgaris/rosacea, whereas Iplex is indicated for growth failure. Due to the lack of overlap in the typical ordering of both drug products and limited use of Iplex, DMETS believes the possibility for confusion to be minimal.

3. Epitol may look similar to Iplex when scripted. Epitol contains carbamazepine in a 200 mg tablet for the treatment of epilepsy and trigeminal neuralgia. Recommended dosing ranges for epilepsy from 100 mg twice daily up to 1600 mg per day. Dosing for trigeminal neuralgia is 100 mg twice daily up to 1200 mg per day. The orthographic similarities stem from the shared "p", similarly placed upstroke ("t" compared to "l") and the possible likeness of the concluding "l" compared to "x" when scripted. In addition, the leading "E" and "I" may serve to differentiate the two names when written in upper case; however, when scripted in lower case, these letters tend to lead to a resemblance.



The image shows two handwritten examples of drug names in lowercase cursive. The top word is 'epitol' and the bottom word is 'Iplex'. The letters 'e' and 'I' are particularly stylized, with a downstroke that resembles a 'p'.

The drug products differ in dosage form (tablet compared to injection), route of administration (oral compared to subcutaneous), and dose (10-20 mg/kg to 600 mg compared to 0.5 to 2 mg/kg). Although the products share single strength status, the narrow therapeutic index for Epitol typically necessitates the practitioner to note the strength on the order to limit confusion. In addition, the practitioner would need to indicate the number of tablets to be dispensed (or one month supply) and the frequency of dosing (two to three

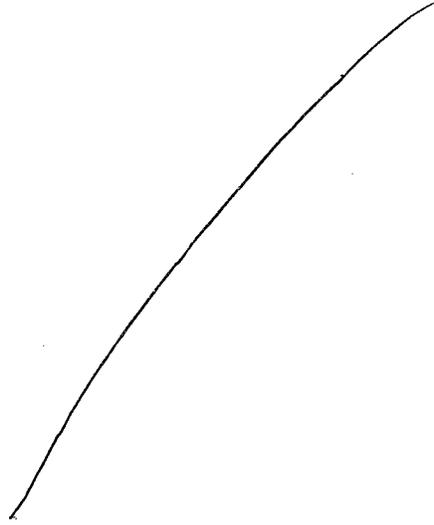
times per day compared to daily). Furthermore, storage differences are unique as Epitol is maintained at room temperature and Iplex is kept frozen and thawed before use. Their indications of use also differ with Epitol used in epilepsy and Iplex in growth failure. Although the names are somewhat orthographically similar, the differences in product characteristics minimize the potential for confusion. DMETS believes the possibility for confusion to be limited.

4. Hiprex may look and sound like Iplex when scripted and spoken. Hiprex contains methenamine hippurate as one gram tablets for the prophylactic or suppressive treatment of frequently occurring urinary tract infections, which is to be used after infection has been eradicated by antimicrobials. Recommended dosing is one gram twice daily for adults and 500 mg to one gram for pediatrics. It is recommended that the patient restrict intake of alkalinizing foods and medications. The orthographic similarities stem from the shared "p" and concluding "ex", with similar, if not identical, placement in the names. This is compounded by the tendency for the central "r" of Hiprex and "l" of Iplex to appear alike when incorporated in a word and the possibility for the leading "l" and "H" to appear similar. The verbal similarities stem from the shared "l" pronounced as in "pie", central "p" and concluding "ex"; however, the leading "H" of Hiprex if given clarity in speech should differentiate the two names.

The differing dosage forms (tablet compared with injectable), routes of administration (oral compared subcutaneous use), dosing frequencies (twice daily compared with daily), storage (room temperature compared to frozen), and indications (prevention of recurrent urinary tract infection compared to growth failure) should extrapolate to limited confusion. In an outpatient setting, orders for both drug products should also indicate the dispensing amount and most likely directions for use. The potential overlap would involve the one gram strength of Hiprex compared to the potential dose of 1 mg/kg for Iplex. However, DMETS was unable to envision where this could result in actual confusion as the order (verbal or written) would need to indicate weight or have the actual dose calculated. Although the names look and sound similar, the potential for medication errors is minimal given the differences in product characteristics.

5. Ifex may look and sound similar to Iplex. Ifex is an antineoplastic agent indicated for the treatment of germ cell testicular cancer. Ifex is available as a 1 gram and 3 gram powder for injection. Ifex is given by intravenous administration at a dose of 1.2 gm/m²/day for five consecutive days. The dose may be repeated every three weeks or after recovery from hematologic toxicity. The innovator, Ifex, was discontinued, but generics are available and the innovator product is marketed in a combination kit with Mesna. The orthographic similarities stem from the shared leading "l" and concluding "x" with the shared downstroke subsequent to the first letter ("f" compared to "p"). The phonetic similarities root in the same shared letters "l" and "x", but the "f" and "pl" serve to distinguish the two in speech.

The drug products could be considered to share a similar dosage form (both injectables, one powder for injection compared to solution for injection) and frequency of dosing (administered daily). The specificity of the drug usage for both products should help alleviate confusion as detailed below. First, Ifex is administered per intravenous infusion for five days, and then repeated in three weeks compared to the continuous, long-term daily subcutaneous injections of Iplex. In addition, the products differ in strength (1 gram/3 gram compared to 36 mg), indication for use (testicular cancer compare to growth failure), and product preparation (Ifex needs to be reconstituted prior to use compared to Iplex being thawed then ready to use). The doses may appear similar since Ifex is dosed at 1.2 gm/m^2 , which is comparable visually to the potential dose of 1 mg/kg for Iplex, but this dose not often appear on prescriptions. The practitioner will likely indicate total daily dose; thus for a 150 pound (68 kg) patient, the dosage range would around 2 grams compared to 68 to 136 mg of Iplex. To further alleviate confusion, the orders for Ifex will likely come from hospital oncologists and will indicate all necessary criteria for order completion (including route of administration); thus, another method to alleviate confusion. In addition, verbal orders would rarely occur with oncology medications, which should only be in emergency situations as most hospital mandate completed written orders. Although the names appear similar when scripted, the lack of overlap in product characteristics and poor phonetic similarities, DMETS believes the possibility for confusion to be minimal.



7. Lidex may look similar to Iplex when scripted. Lidex contains 0.05% fluocinonide in multiple dosage forms for the relief of inflammatory and pruritic manifestations of the skin. Recommended dosing is a thin film two to four times a day. Lidex-E is also available as a 0.05% cream. The orthographic similarities stem from the shared concluding "ex", with the possibility for the leading lower case "L" to resemble the "I" of Iplex. However, the downstroke of the "p" in Iplex should help to differentiate the two names.

Lidex Lidex
Iplex Iplex

One potential overlap would involve the 0.05% strength of Lidex compared to the starting dose of 0.5 mg/kg for Iplex. However, DMETS was unable to envision where this could

*** Proprietary and confidential information that should not be released to the public.

result in actual confusion as the written order would need to indicate weight or have the actual dose calculated for Iplex. In addition, these two drug products do not share overlapping strengths (0.05% compared to 36 mg), dose (thin layer compared to 1 mg/kg), route of administration (topical compared with subcutaneous), and dosing frequency (two to four times daily compared to daily), DMETS has minimal concerns with inpatient orders. This is due to JCAHO requirements, which dictate medication orders must document all the elements required to accurately complete the order, such as frequency and route of administration. Thus, the inclusion of these data on an order would serve to differentiate the two drug products. However, these drug products can be ordered as an outpatient and both products are single strength products; therefore, outpatient orders may be completed accurately without notation of the strength of the drug product on the order. In addition, one could postulate that orders could be written with a "#1" order amount, indicative of one tube and one box/vial of Lidex and Iplex, respectively. However, Lidex is available in multiple dosage forms (cream, gel, ointment, solution), multiple sizes (15 grams to 120 grams), and differing dose (thin layer); all of which should be indicated on prescriptions. Either would help to differentiate the names and serve to limit confusion. Their indications also differ (inflammatory and pruritic manifestations of the skin compared to growth failure) and the storage requirements (remaining frozen) will limit the number of pharmacies that will stock/order Iplex. Due to the poor orthographic similarities and differing product characteristics, DMETS believes the possibility for confusion to be minimal.

8. Loprox may look similar to Iplex when scripted. Loprox contains ciclopirox in four formulations: cream, gel, shampoo and topical suspension. Recommended dosing for the cream, gel, and suspension is to gently massage into the affected and surrounding skin areas twice daily; morning and evening. Dosing for the shampoo is approximately one teaspoonful applied to wet hair, lather and leave on hair/scalp for three minutes. Rinse, then repeat twice weekly for four weeks. The orthographic similarities stem from the similarity of a lower case "L" and "I", shared "p" with similar placement in the name, and concluding, shared "x." However, Loprox contains six letters with two "o's"; thus, lengthening the name when scripted.

Loprox Iplex

As these two drug products do not share overlapping strengths (0.77%/1% compared to 36 mg), dose (apply or shampoo with a small amount compared to 1 mg/kg), route of administration (topical compared with subcutaneous), and dosing frequency (twice daily compared to daily), DMETS has minimal concerns with inpatient orders. This is due to JCAHO requirements, which dictate medication orders must document all the elements required to accurately complete the order, such as frequency and route of administration. Thus, the inclusion of these data on an order would serve to differentiate the two drug products. However, these drug products will also be ordered as outpatients and both products are single strength products; therefore, outpatient orders may be completed accurately without notation of the strength of the drug product on the order. In addition, one could postulate that orders could be written with a #1 order amount, indicative of one tube and one box/vial of Loprox and Iplex, respectively. However, Loprox is available in multiple dosage forms (cream, gel, suspension, shampoo) and multiple sizes (15 gram to 100 grams), and a differing dose (apply or shampoo with a small amount); all of which should be indicated on prescriptions. Either would help to differentiate the names and serve limit confusion. Their indications also differ (tinea pedis/cruris and corporis, seborrheic dermatitis compared to growth failure) and the storage requirements (remaining frozen) will limit the number of pharmacies that will stock/order Iplex. Due to the poor orthographic similarities and differing product characteristics, DMETS believes the possibility for confusion to be minimal.

9. Videx may look similar to Iplex when scripted. Videx contains didanosine for the treatment of human immunodeficiency virus. Videx is available as an antiretroviral agent indicated for the treatment of HIV infection. Videx is available as two dosage forms: chewable tablets (25 mg, 50 mg, 100 mg, and 200 mg) and a powder for oral solution (100 mg buffered, single dose packet, 250 mg buffered, single dose packet, 2 gram-4 ounce bottle, and 4 grams-8 ounce bottle). Videx-EC is also available as delayed-release capsules (125 mg, 200 mg, 250 mg, and 400 mg); however this name will not be discussed further due to the need to document the modifier "EC" for order completion. This addition will alleviate potential look-alike similarities with Iplex. Recommended dosing is based on patient weight. For adult patients weighing greater or equal to 60 kilograms, the dose is 400 mg daily or 200 mg twice daily (tablets) or 250 mg twice daily (oral solution). Adult patients weighing less than 60 kilograms should be dosed as 250 mg daily or 125 mg twice daily (tablets) or 167 mg twice daily (oral solution). Pediatric patients are dosed based on body surface area, as 120 mg/m² twice daily. The orthographic similarities stem from the shared concluding "ex" and the likeness of the leading "v" to resemble the leading "l" of Iplex. However, the downstroke of the "p" in Iplex should help distinguish the two names upon scripting.

Videx
Iplex

The drug products may have an overlap in dose at 125 mg, which is the dose for an adolescent weighing 57 kilograms receiving the higher 2 mg/kg dosing of Iplex; or a 125 kilogram patient receiving the 1 mg/kg of Iplex, but this weight is unlikely for patients considering the indication and duration of therapy. The drug products may also overlap in frequency of dosing, since Videx may be dosed daily. However, the dosage form (tablets/solution compared to injectable solution), route of administration (oral compared to subcutaneous), strength (25 mg to 4 grams compared to 36 mg), indication for use (HIV infection compared to growth failure), and storage (room temperature compared to frozen) differ. Although there is the limited chance of dose overlap, the differing routes of administration, typical dosing regimens and the poor orthographic similarities leads DMETS to believe the possibility for confusion to be minimal.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container labels, carton and insert labeling of Iplex, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified several areas of possible improvement, which might minimize potential user error. These current comments should be taken for consideration in conjunction with the comments from ODS consult 05-0111 dated August 2005, which remain applicable at this time.

A. GENERAL COMMENTS

1. Assure that the storage requirements for this drug product is prominent on all labels and labeling. This insert labeling references stability issues. Additionally, please comment on how patients will be instructed to keep the product frozen until time of use. How will the patient know to bring a cooler to the pharmacy in order to maintain the frozen state until they reach home.
2. Assure the sponsor is complying with the bar code rule per 21 CFR 201.25.

B. CARTON LABELING

1. Add the quantitative and qualitative ingredients to the carton labeling per 201.10 (i) (2).
2. Revise the placement or remove the sponsor's name from the top of the label. This is distracting from the drug product name and gives the label a business card appearance, instead of resembling a typical drug product labeling.
3. Please add "Single-Use Vial. Discard Unused portion." to the label to prevent error is multiple usage.

C. CONTAINER LABEL

Increase the prominence of the total drug content (i.e., 36 mg/0.6 mL), as currently it is the least pronounced data point on the label.

D. INSERT LABELING

1. Dosage and Administration

- a. Reference is made to paragraph three. The last sentence described that the drug product should not be used if it has thawed in transport. If the sponsor is aware of any method to ascertain this on visual appearance (i.e. the color of the solution upon thawing or if the solution is cloudy, etc), please provide this data in this section.
- b. Reference is made to paragraph three and four. As the sponsor notes questionable stability with thawed product ("Do not use medication if it thaws during transfer or storage, as stability of material may be affected. DMETS questions if there is a certain amount of time that the drug product may remain at room temperature before use? If so, please provide this timeline in this section of the insert labeling. We request this because many patients may not come equipped to the pharmacy with a cooler that would maintain the product in a frozen or refrigerated state.

2. How Supplied

Please add reference to the storage of this drug product per 21 CFR 201.57 (k), which noted that any special handling and storage should be referenced in this section. This information is found in the "Description" and "Dosage and Administration" section of the package insert.

D. PATIENT PACKAGE INSERT

1. Reference is made to _____, consider adding the statement of not using the drug product if cloudy to the third paragraph. This will help to reinforce visual inspection of the drug product by the caregiver/patient.
2. Reference is made to "_____ and "Injecting iPlex", in order to make it easier for the patient/caregiver to follow the instructions for the proper use of iPlex, consider the addition of labeled illustrations for key usage points. Such step-by-step illustrations may help the patients/caregivers with proper administration.
3. Reference is made to number 4 under "Injecting iPlex", this direction _____ is vague for the proper way to appropriately inject iPlex. We recommend more specificity in the injection instructions, as patients may not have had adequate education to iPlex usage. Revise accordingly.

IV. RECOMMENDATIONS:

- A. DMETS has no objections to the use of the proprietary name, iPlex from a safety perspective. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.
- B. DMETS recommends implementation of the label and labeling revision outlined in section III of this review to minimize potential errors with the use of this product.
- C. DDMAC finds the proprietary names iPlex acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Diane Smith, project manager, at 301-827-1998.

Kimberly Culley, RPh
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Alina Mahmud, RPh, MS
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

Appendix A. Prescription Study Results

Inpatient	Outpatient	Voice
Yiflex	lplex	lplex
lplex	lplex	lplex
lplex	1 plex	lplex
lplex	lplex	l Flex
lplex	l plex	lplex
Exlex	1 Plex	lplex
lplex	l Plex	lplex
lplex	lplex	lplex
lplex	lplex	lplex
Uplex	1 plex	lprex
lplex	l plex	lplex
lplex	lplex	lprex
lplex	lplex	lplex
lplex	lplex	lplex
lplex	lplex	lprex
lplex	lplex	lplex
lplex	lplex	lpex
lplex	1Plex	
lplex		

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

/s/

Alina Mahmud
9/13/2005 01:19:19 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
9/13/2005 01:40:25 PM
DRUG SAFETY OFFICE REVIEWER

6 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-884 Supplement # N/A SE1 SE2 SE3 SE4 SE5 SE6 SE7 SE8

Trade Name: NONE
Generic Name: mecasermin and rinfabate [rDNA origin] injection
Strengths: 60 mg/mL

Applicant: INSMED Inc.

Date of Application: 12/31/2004
Date of Receipt: 01/03/2005
Date clock started after UN: N/A
Date of Filing Meeting: 02/28/2005 & 03/04/2005
Filing Date: 03/04/2005

Action Goal Date (after extension): **9.23.05**
User Fee Goal Date: 10.03.05 (after extension)

Indication requested:
 treatment of children with growth failure due to severe growth hormone
insensitivity syndrome (hereditary or acquired) resulting in IGF-1 deficiency and presenting with height
standard deviation score less than or equal to -3 and IGF-1 SDS less than or equal to

Type of Original NDA: (b)(1) X (b)(2)
OR
Type of Supplement: (b)(1) (b)(2)

NOTE:

- (1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.
- (2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

NDA is a (b)(1) application OR NDA is a (b)(2) application

Therapeutic Classification: S P
Resubmission after withdrawal? n/a Resubmission after refuse to file? n/a
Chemical Classification: (1,2,3 etc.) 1,4 (2 NME's)
Other (orphan, OTC, etc.) V Designation No. 02-1563

Form 3397 (User Fee Cover Sheet) submitted: YES NO

User Fee Status: Paid Exempt (orphan, government)
Waived (e.g., small business, public health)

NOTE: If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity

or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx to OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES NO

If yes, explain:

- Does another drug have orphan drug exclusivity for the same indication? YES NO

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES NO
 If yes, explain.

- If yes, has OC/DMPQ been notified of the submission? YES NO

- Does the submission contain an accurate comprehensive index? YES NO

- Was form 356h included with an authorized signature? YES NO

If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES NO

If no, explain: Minimal clinical data submitted, no validation for sterility assurance.

- If an electronic NDA, does it follow the Guidance? N/A YES NO

If an electronic NDA, all certifications must be in paper and require a signature.

Which parts of the application were submitted in electronic format?

- PACKAGE INSERT in pdf format (not SPL)
- Case Report Tabluations

Additional comments: Package insert was submitted with a Labeling TOC but without hyperlinks

- If in Common Technical Document format, does it follow the guidance? N/A YES NO

- Is it an electronic CTD? N/A YES NO

If an electronic CTD, all certifications must be in paper and require a signature.

Which parts of the application were submitted in electronic format? Package insert & CRTs

Additional comments:

- Patent information submitted on form FDA 3542a? YES NO
- Exclusivity requested? Orphan exclusivity requested YES, 7 years NO
NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.
- Correctly worded Debarment Certification included with authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge"

- Financial Disclosure forms included with authorized signature? YES NO
(Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)
- Field Copy Certification (that it is a true copy of the CMC technical section)? YES NO

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? YES NO
 If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.
- List referenced IND numbers: IND 50,140
- End-of-Phase 2 Meeting(s)? Date(s) June 4, 2003 mtg NO
 If yes, distribute minutes before filing meeting. Oct. 8, 2003 mtg
 March 19, 2004 (ADV letter)
- Pre-NDA Meeting(s)? Date(s) _____ NO
 If yes, distribute minutes before filing meeting.

Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES NO
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? YES NO
 Trade name was not submitted; however, vial & carton label were consulted to DMETS.
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A YES NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A YES NO
- Has DOTCDP been notified of the OTC switch application? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? N/A YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES NO
If no, did applicant submit a complete environmental assessment? YES NO
If EA submitted, consulted to Florian Zielinski (HFD-357)? YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES NO

Appears This Way
On Original

ATTACHMENT

MEMO OF FILING MEETING

DATE: February 28 and March 4, 2005

BACKGROUND: This product is a combination of two new active chemical moieties, mecasermin (IGF-1) and rinfabate (IGFBP-3) and is proposed for the treatment of pediatric patients with growth hormone insensitivity syndrome. It is a solution for subcutaneous injection.

During development of this product, drug substance (ds) was manufactured at Insmad Santa Clara (California) and was tested in clinical Cohort # 1; subsequently, ds was manufactured with modified methods at Avecia Ltd (UK) and tested in clinical Cohort # 2; finally, ds was manufactured by Insmad at ITP (Boulder, CO) for testing in Cohort #3. The drug product from all three ds sources was to be filled by

At the time of submission, the NDA contained six months' clinical data in Cohort # 1 with the promise to submit 12 months' clinical data in Cohort #1 and six months' clinical data in Cohort # 2 in the 120-day safety update (SU) by June 6, 2005.

ATTENDEES (at one or both meetings): David Orloff, Dragos Roman, Todd Sahlroot, Joy Mele, David Hussong*, Bryan Riley, Jeri El Hage, Herman Rhee, Xavier Ysern, Steve Moore*, Blair Fraser*, Eric Duffy*, Hae Young Ahn, Jim Wei, Jeff Fritsch, Monika Johnson, Enid Galliers (* = only at March 4 meeting)

ASSIGNED REVIEWERS:

<u>Discipline</u>	<u>Reviewer</u>
Medical:	Dragos Roman
Secondary Medical:	n/a
Statistical:	Joy Mele originally, subsequently changed to James Gebert
Pharmacology:	Herman Rhee
Statistical Pharmacology:	n/a
Chemistry:	Xavier Ysern
Environmental Assessment (if needed):	n/a
Biopharmaceutical:	Jim Wei
Microbiology, sterility:	Bryan Riley
Microbiology, clinical (for antimicrobial products only):	n/a
DSI:	Andrea Slavin
Regulatory Project Management:	Enid Galliers
Other Consults:	none

Per reviewers, are all parts in English or English translation? YES NO
If no, explain:

CLINICAL FILE REFUSE TO FILE _____

- Clinical site inspection needed: YES NO
- Advisory Committee Meeting needed? YES, date if known _____ NO

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

N/A YES NO

CLINICAL MICROBIOLOGY N/A FILE _____ REFUSE TO FILE _____

STATISTICS FILE REFUSE TO FILE _____

BIOPHARMACEUTICS FILE REFUSE TO FILE _____

- Biopharm. inspection needed: YES NO

PHARMACOLOGY N/A _____ FILE REFUSE TO FILE _____

- GLP inspection needed: YES NO

CHEMISTRY FILE _____ REFUSE TO FILE

- Establishment(s) ready for inspection? YES NO
- Microbiology FILE _____ REFUSE TO FILE

ELECTRONIC SUBMISSION: Package insert and CRTs only
 Any comments: No hyperlinks

REGULATORY CONCLUSIONS/DEFICIENCIES:

✓ The application is unsuitable for filing. Explain why:
 Refer to March 4, 2005, refuse to file letter.

At the request of Insmmed, the Agency met with the firm and its consultants on March 9, 2005, at which time the firm argued that the Agency can use discretion to file an application that does not meet the minimum requirements. The firm referred to the policy statement titled "New Drug Evaluation Document: Refusal to File," dated July 12, 1993. See the minutes of the referenced meeting and the letter dated March 9, 2005, in which the Division stated that the NDA had been filed. Subsequently, the Division Director decided that this NDA should be considered for priority review and the firm was notified on April 12, 2005.

_____ The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.
 _____ No filing issues have been identified.
 _____ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. If RTF, notify everybody who already received a consult request of the RTF action. Cancel the EER.
2. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. Document filing issues/no filing issues conveyed to applicant by Day 74.

Enid Galliers
 Supervisory 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/

Enid Galliers
7/17/05 09:51:05 PM
CSO

Enid Galliers
7/17/05 09:53:29 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-884

Insmed, Inc.
Attention: Mr. Ronald Gunn
Executive Vice President
P.O. Box 2400
Glen Allen, VA 23058-2400

Dear Mr. Gunn:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for iPlex (mecasermin rinfabate [rDNA origin] injection).

We also refer to the meeting between representatives of your firm and the FDA on July 12, 2005. The purpose of the meeting was to discuss the replacement of your proposed drug substance manufacturer with another during this review cycle.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-6429.

Sincerely,

{See appended electronic signature page}

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug
Products (DMEDP)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: July 12, 2005
TIME: 9:00 – 10:00 AM
LOCATION: Parklawn Building, C/R "C" 3rd floor
APPLICATION: NDA 21-884
DRUG NAME: iPlex (mecasermin rinfabate [rDNA origin] injection)
TYPE OF MEETING: GUIDANCE

MEETING CHAIR: David Orloff

MEETING RECORDER: Enid Galliers

FDA ATTENDEES: (Title and Office/Division)

Robert Meyer, MD, Director, Office of Drug Evaluation II (ODE II), OND, CDER
Lee Ripper, ADRA, ODE II
David Orloff, MD, Director, Division of Metabolic and Endocrine Drug Products (DMEDP), ODE II
Dragos Roman, MD, Medical Officer, DMEDP
Enid Galliers, Chief, Project Management, DMEDP
Xavier Ysern, PhD, Chemistry Reviewer, DNDC II, ONDC
Blair Fraser, PhD, Deputy Director, DNDC II, ONDC
Hae Young Ahn, PhD, Team Leader, DPE II, OCPB
Tan Nguyen, MD, Office of Orphan Product Development (OOPD), OC
Jeff Fritsch, OOPD

EXTERNAL CONSTITUENT ATTENDEES:

INSMED Participants:

Geoffrey Allan, PhD, President & CEO, Insmmed
Ronald Gunn, Executive Vice President, Insmmed
Glen Kelley, Technical Operations, Insmmed
Consultant
Consultant
Consultant

BACKGROUND:

Insmmed initially manufactured drug substance at Insmmed Santa Clara, CA, and patients who received it were designated Cohort #1. At the time of submission of the NDA, Insmmed was using drug substance (ds) manufactured at Avecia Ltd, Billingham, UK. The product made from Avecia ds was administered to Cohort #2.

In late June, Insmmed notified the Agency that Avecia and Insmmed requested this meeting to discuss its proposal to manufacture ds at its own, new facility, Insmmed Therapeutic Proteins (ITP) in Boulder, Colorado. Insmmed planned to start administering drug product made from ITP ds to Cohort #3.

— has conducted the — for drug products made from all three ds manufacturing sites.

MEETING OBJECTIVES:

- To get Agency agreement to the firm's plan to withdraw the second drug substance manufacturing facility, Avecia Ltd, from the NDA and to substitute the third drug substance manufacturing facility, Insmed Therapeutic Proteins (ITP) in Boulder, CO during the first review cycle.
- To obtain Agency agreement to complete its review of this facility during the first review cycle.
- To obtain agreement with the Agency regarding the nature and extent of bridging data that would be required to support this change for the to-be-marketed drug product.

DISCUSSION POINTS:

Insmed described its manufacturing issue (i.e. — and Insmed's need to switch the drug substance manufacturing source for the to-be-marketed product.

The firm also reported the manufacturing process changes and similarities between drug substance manufacturing sites, and it described the comparability (physicochemical, biological, pharmacokinetic, and preclinical) evaluations it had conducted.

Finally, the firm proposed to conduct a single dose, randomized, cross-over pharmacokinetic study in GHIS patients to compare the Avecia- and ITP-sourced products. The proposed sample size was 4 – 6 with 11 serum samples being taken over 60 hr. The firm said the PK study would be completed in August with the study report to be submitted by September 6, 2005.

Drs. Orloff and Ahn inquired whether normal volunteers could be used for the PK study instead of patients. The firm was also questioned about the possibility of inducing neutralizing antibodies in healthy subjects, and it responded that it had not seen neutralizing antibodies develop to date. The Agency expressed a concern that the PK study might not prove adequate if the sample size proved to be too small. Therefore, the Agency suggested a PK study in healthy volunteers with bigger sample size.

Insmed said that it was just starting to administer ITP drug product to Cohort #3 in a safety and efficacy trial, but one month's safety data would be available by September 6, 2005. None of the Cohort #3 patients would be naïve to mecasermin rinfabate since they were all being rolled over from Cohort #1 or Cohort #2. The Agency expressed some concern regarding the large number of patients who have developed antibodies and indicated that the absence of long-term immunogenicity data for the ITP-sourced product could be a concern. The Agency requested submission of 9-month immunogenicity data for patients that had received Avecia-sourced product for 6 months followed by 3 months' ITP product – with the expectation that those data would pick up any immunologic flare by that time.

The Agency requested a clear communication from the firm regarding changes in manufacturing sites as soon as possible because of the changes that would need to be made to the pre-approval establishment inspection requests and the inspectors' travel schedules. Insmmed said the manufacturing process and site changes for ITP had been submitted to the IND and would be submitted to the NDA with a request to withdraw the Avecia site from the NDA within days after the meeting.

DECISIONS (AGREEMENTS) REACHED:

- The Agency noted that it did not object to the change in facilities but asked for a formal amendment to the NDA to clarify which facilities would be doing each manufacturing function and which facilities would be withdrawn from the NDA.
- The Agency did not commit to reviewing all data before taking an action on the NDA. The Agency also noted that it would have to take an action on the NDA in September due to the Division's and Office's move to White Oak and the possibility that the computers might not be operational immediately upon relocation (on the user fee goal date).

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION: None.

ACTION ITEMS: None.

ATTACHMENTS:

SLIDES presented by INSMED

11 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

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/s/

Enid Galliers
8/8/05 01:33:27 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-884

Insmmed Incorporated
Attention: Ronald 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 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TRADENAME (mecasermin and rinfabate [rDNA origin] injection) 60 mg/mL.

We also refer to your June 17, 2005, correspondence, received June 20, 2005, requesting a meeting to discuss your drug substance manufacturing problem at Avecia; your proposal to replace that site with the Insmmed Therapeutic Proteins, Boulder, Colorado site (ITP); evidence of comparability of drug product manufactured at different sites; timeframes for submission of relevant data; and timing of Agency review.

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type A meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000). The meeting is scheduled for:

Date: Tuesday, July 12, 2005

Time: 9:00 - 10:00 AM

Location: C/R "B", 3rd floor, Parklawn Bldg, 5600 Fishers Lane, Rockville, MD 20857

CDER participants:

Robert Meyer, MD, Director, Office of Drug Evaluation II (ODE II), OND, CDER

David Orloff, MD, Director, Division of Metabolic and Endocrine Drug Products
(DMEDP), ODE II

Dragos Roman, MD, Medical Officer, DMEDP

Enid Galliers, Chief, Project Management, DMEDP

Xavier Ysern, PhD, Chemistry Reviewer, DNDC II, ONDC

Stephen Moore, PhD, Chemistry Team Leader, DNDC II, ONDC

Eric Duffy, PhD, Director, DNDC II, ONDC

Please have all attendees bring photo identification and allow 15-30 minutes to complete security clearance. If there are additional attendees, email that information to me at Galliers@cdcr.fda.gov so that I can give the security staff time to prepare temporary badges in

advance. Upon arrival at FDA, give the guards either of the following numbers to request an escort to the conference room: Enid Galliers, 301-827-6429; or the division secretary, 301-827-6428.

Provide the background information for this meeting (two copies to the NDA and **ten** desk copies to me) one week prior to the meeting. If the materials presented in the information package are inadequate to justify holding a meeting, or if we do not receive the package by July 7, we may cancel or reschedule the meeting. **The background package should include the timelines for submission of data, a comparison of the manufacturing process changes, the physicochemical comparison of drug substance manufactured at different sites, an outline of the proposed comparative single dose pharmacokinetics study protocol, and a summary of the comparative preclinical studies.**

If you have any questions, call me at (301) 827-6429.

Sincerely,

{See appended electronic signature page}

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Enid Galliers
6/28/05 10:01:31 AM



PDUFA GOAL DATE EXTENSION

NDA 21-884

Insmed Incorporated
Attention: Ronald 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 December 31, 2004, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for **TRADENAME** (mecasermin and rinfabate [rDNA origin] injection) 60 mg/mL.

On April 13, 2005, we received your April 12, 2005, major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is October 3, 2005.

In addition, we remind you of our request for submission of a proposed proprietary name and color, scale mock-ups of your container and carton labels.

If you have questions, call me at (301) 827-6429.

Sincerely,

{See appended electronic signature page}

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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Enid Galliers

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

FOR SECURE EMAIL TRANSMISSION

DATE: May 26, 2005

To: Ronald Gunn RDGUNN@INSMED.COM	From: Enid Galliers
Company: Insmmed Incorporated	Division of Metabolic and Endocrine Drug Products
Fax number: 804-565-3500	Fax number: 301-443-9282
Phone number: 804-565-3022	Phone number: (301) 827-6429
Subject: Statistics Question	

Total no. of pages including cover: 2

Comments:

This information request is being sent to you only by secure email.

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-6430. Thank you.

NDA 21-884

Dear Mr. Gunn:

Please refer to your 04-MAY-2005 submission containing study **INSM-110-303**. The relevant dataset is **IE.XPT** in folder COHORT 1 that contains inclusion and exclusion responses from the case report forms.

Subjects 105 (SCRNO=7501), 106 (SCRNO=7502), and 107 (SCRNO=7601) in cohort #1 had a No=0 response, and subject 103 (SCRNO=7801) in cohort #1 had a blank response to inclusion question 7 (Peak level of growth hormone > 29.2 mu/L (> 13.3 µg/L) using a GH Provocation test. Yes No).

We have not been able to find any other reference to a GH Provocation test in your submission.

Were GH provocation tests done on all subjects?

If not, explain why they were not done.

If they were done, please identify the location of the information regarding the subject's peak level in your submission.

Please provide your response as an official submission to the pending NDA.

Sincerely,

Enid Galliers
CPMS, DMEDP
301-827-6429

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/s/

Enid Galliers
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CSO



DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF PHARMACOEPIDEMIOLOGY AND STATISTICAL SCIENCES
OFFICE OF BIostatISTICS

Memorandum of Telecon

NDA: 21-884

Drug Name : rhIGF-I/rhIGFBP-3

Indication: _____

Applicant: Insmed

Date: Telecon dated 05/16/2005

Biometrics Division: Division of Biometrics II (HFD-715)

Statistical reviewer: James Gebert, Ph.D.

Medical Division: Division of Allergy and Pulmonary Drug Products
(HFD-570)

Clinical reviewer: Dragos Roman, M.D.

Project manager: Enid Galliers

I talked to Ronald Gunn, Ann Smith, and Kenneth Attie of Insmed on May 16, 2005. My questions involved which values were used in calculating baseline mean values for IGF-I and IGFBP-3 values and IGF-I SDS and IGFBP-3 SDS.

I wanted to know why for cohort 2 in file BLEVEL there were visits labeled 1p, 2p, etc. and why Visit 5p was baseline rather than visit 1. Ann Smith stated that the p visits corresponded to visits in a PK substudy where patients were using the same dose level as that of cohort 1 and the Visit 5p was the first visit that these patients used the higher dose level. She said this was explained in the PK study report.

I asked which visit=1 value was used for baseline in Cohort 1 where for some subjects at the first visit there was PK sampling but also a visit with blank nominal sampling time. [For subjects with no PK sampling the nominal sampling time was always blank.] Ann Smith stated that for patients having both a value without a nominal sampling time and a 0 nominal sampling time. The value with the 0 sampling time was used.

Ann Smith stated that I should be aware that for subject 102 (with screen number=8202) there was no visit 1 value and the visit 0 (screening) value was used.

**APPEARS THIS WAY
ON ORIGINAL**

This memorandum refers to the sponsor's responses to comments sent to the sponsor by facsimile on August 31, 2004. Those comments referred to the Sponsor's Statistical Analysis Plan for Study BY9010/M1-402. Since the sponsor has already unblinded the study on July 15, 2004, those comments can have no effect on the conduct of the study. The sponsor stated that they would perform an analysis suggested by this reviewer. They also explained how missing values would be handled. Since this explanation is after the unblinding of the study, analyses with these missing value assignments may have to be considered post hoc. The adequacy of the sponsor's model and sample size will become a review issue.

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/s/

James Gebert
5/19/05 09:40:54 AM
BIOMETRICS

MEMO

To: David Orloff, MD
Director, Division of Metabolism and Endocrinology Products (HFD-510)

From: Nora Roselle, PharmD
Safety Evaluator, Division of Medication Errors and Technical Support, Office of Drug Safety

Through: Alina Mahmud, MS, RPh, Team Leader
Denise P. Toyer, PharmD, Deputy Director
Carol A. Holquist, RPh, Director
Division of Medication Errors and Technical Support, Office of Drug Safety, HFD-420

Date: June 27, 2005

Re: ODS Consult 05-0111, Mecasermin Rinfabate Injection, 60 mg/mL; NDA 21-884.

This memorandum is in response to a May 9, 2005 request from the Division of Metabolism and Endocrinology Products for a review of container label, carton and insert labeling of Mecasermin Rinfabate. The insert labeling was submitted by the sponsor on May 4, 2005, and the container label and carton labeling were submitted on December 31, 2004.

In the review of the labels and labeling, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

A. GENERAL COMMENTS

1. The container label and carton labeling were difficult to evaluate for all potential safety issues because of the black and white presentation. Please submit color versions when available.
2. The sponsor uses various forms of the abbreviations "rhIGF-1" and "rhIGFBP-3" throughout the container label, carton and insert labeling. In order to avoid confusion among readers, the labels and labeling should be revised to include the established name and/or proprietary name once determined, and the dosage form. The established name should be revised to read "Mecasermin Rinfabate Injection".
3. DMETS notes the use of trailing zeroes when expressing product strengths and volumes (e.g., 2.0 mL and 60.0 mg/mL) throughout the package insert labeling. The use of terminal zeroes may result in error as decimals are often overlooked. As evidenced by our post-marketing surveillance, the use of terminal zeroes could potentially result in a ten-fold medication dose error. The use of terminal zeroes in the expression of strength or volume is not in accordance with the General Notices (page 10) of 2004 USP, which states, "...to help minimize the possibility of error in the dispensing and administration of the drugs...the quantity of active ingredient when expressed in whole numbers shall be shown without a decimal point that is followed by a terminal zero." In addition, the use of trailing zeroes is specifically listed as a dangerous abbreviation, acronym, or symbol in the 2006 National Patient Safety Goals of The Joint Commission for the Accreditation of Hospitals (JCAHO). Lastly, safety groups such as ISMP also list terminal zeroes on their dangerous abbreviations and dose designations list. Revise the labeling so that strengths, volumes, etc. are expressed without the use of a terminal zero (e.g., 2 mL rather than 2.0 mL, and 60 mg rather than 60.0 mg).

4. There is a discrepancy between the insert labeling and the container label and carton labeling. The insert labeling states that the vial contains a delivery volume of \sim mL while the container label and carton labeling state the volume per vial is 0.6 mL. Revise accordingly.
5. According to USP guidelines, for containers less than 1 mL in volume, the strength per fraction of a milliliter should be the only expression of strength. From the information provided, the strength is 60 mg/mL and there is a volume of 0.6 mL per vial. Therefore, the strength should be expressed as "36 mg/0.6 mL". Revise accordingly.
6. According to the description with the photograph (page 2, Section 1.9.4) of the single-dose vial, \sim The actual volume must be listed instead of an approximation in order to provide accurate information to health care providers and patients.
7. According to the description provided by the firm (page 5, Section 1.9.4), each patient box contains " \sim 35 single-dose vials". The labels and labeling should be revised to include the actual net quantity available in each patient box.

B. CONTAINER LABEL (VIAL)

1. From the information provided it is difficult to determine whether the proprietary and established names are the most prominent information on the label. Please ensure that the information is prominent and legible and meets 21 CFR 201.10(g)(2).

2. The "Rx only" statement should be relocated on the principal display panel away from the established name. Currently, the "Rx only" is located:

Relocate so that the statement is distinct from the established name and appears in the lower 1/3 of the label.

3. In order to provide clear and easy to read information to the patient and practitioner, relocate the lot number so that the product strength appears in direct conjunction with the established and proprietary names. We recommend the following format:

Proprietary Name
Established Name
Strength
Storage

4. According to 21 CFR 201.100(b)(3), the route of administration must be included for anything other than oral drug products. In addition, injectable drug products are required to list the quantitative and qualitative inactive ingredients as per 21 CFR 201.100(b)(5). Revise accordingly.
5. Please see 21 CFR 201.1(h)(5) for the proper designation of the manufacturer/distributor statement so that it is consistent between labels and labeling and is not falsely misleading.
6. Relocate the net quantity so that it does not appear in close proximity to the product strength in order to avoid confusion and error between the numerical values.

C. CARTON LABELING

1. See comments A1 - A6.
2. Relocate the statement "Contents: 35 vials" so that it does not appear in close proximity to the product strength and is moved in conjunction with the volume/vial statement.
3. The "Patient Instructions for Use" should also be located on the outside of the carton so health care providers and patients have easy access to the directions without opening the carton.

DMETS would appreciate feedback of the final outcome of this consult. Color labels and labeling in the proposed format need to be submitted for review and comment. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Diane Smith, project manager, at 301-827-3242.

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/s/

Nora L. Roselle
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DRUG SAFETY OFFICE REVIEWER

Alina Mahmud
8/5/05 01:14:23 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
8/5/05 01:21:19 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
8/5/05 03:04:15 PM
DRUG SAFETY OFFICE REVIEWER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-884

Insmmed Incorporated
Attention: Ronald 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 December 31, 2004, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TRADENAME (mecasermin rinfabate injection) 60 mg/mL.

We also refer to our acknowledgment letter dated January 26, 2005, that stated the drug review priority classification for this application would be communicated after the filing meeting.

Our policy regarding determination of priority or standard review status is based on the proposed indication and alternative treatments marketed for the proposed indication. Upon further consideration of your application, we have concluded that this application should receive a priority review. The user fee goal date is July 3, 2005.

If you have any questions, call me at (301) 827-6429.

Sincerely,

{See appended electronic signature page}

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Enid Galliers
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-884

Insmed Incorporated
Attention: Ronald 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 December 31, 2004, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TRADENAME (mecasermin rinfabate injection) 60 mg/mL.

We also refer to our refuse to file letter dated March 4, 2005, and to the March 9, 2005, informal conference between Insmed and the Agency at which we discussed the reason for our decision. At that meeting we also discussed in detail the specific information required for filing that is currently missing from the application, and you indicated the time you would need to supply that information in full. You also presented reasons why you were requesting the Agency to use its discretion to file your application despite the absent data.

We find your proposals to supply the information necessary to complete the application acceptable.

Therefore, this application is hereby filed under section 505(b) of the Act, effective as of March 4, 2005, in accordance with 21 CFR 314.101(a).

In our filing review, we have identified several potential review issues, and we will communicate them to you by March 18, 2005. Those issues only represent a preliminary evaluation of the application and are not indicative of deficiencies that may be identified during our review.

If you have any questions, call Enid Galliers, Chief, Project Management Staff, at (301) 827-6429.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

David Orloff
3/9/05 07:25:56 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-884

Insmed Incorporated
Attention: Ronald 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 December 31, 2004, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TRADENAME (mecasermin rinfabate injection) 60 mg/mL.

We acknowledge receipt on March 7, 2005, of your meeting request dated March 4, 2005.

We also refer to the meeting between representatives of your firm and the FDA on March 9, 2005. The purpose of the meeting was to discuss the possible remedies to the deficiency that was the basis for our March 4, 2005, refusal to file letter.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-6429.

Sincerely,

{See appended electronic signature page}

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: March 9, 2005

FROM: David G. Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products

TO: NDA 21-884
IGF-1/IGFBP-3 (mecasermin rinfabate injection)
Insmmed Incorporated

SUBJECT: Filing memorandum

Summary of issues

This is an "ultra-orphan" drug product for the treatment of growth hormone insensitivity syndrome (GHIS). There are currently no approved products for children with inherited or acquired GHIS, an exceedingly rare form of extreme short stature and developmental delay. In such patients, growth can be promoted and final stature augmented with insulin-like growth factor-1 (IGF-1). This product contains two moieties, the growth factor itself, and its major binding protein, IGF binding protein-3 (IGFBP-3), in stoichiometric amounts. The addition of the binding protein to the active moiety is intended to prolong its activity and, potentially, to mitigate IGF-1 mediated hypoglycemia resulting from its cross-reactivity with the insulin receptor.

NDA 21-884 was submitted on December 31, 2004. On March 3, 2005, the review team was convened for a "filing" meeting that had been postponed from the preceding week due to inclement weather and consequent unavailability of necessary staff. On March 4, 2005, based on preliminary review and discussion with the review team at the meeting on the preceding day, a "refuse to file" letter was issued citing the following facial deficiency in the application:

Chemistry, Manufacturing, and Controls (CMC) information to evaluate sterility assurance was not adequate for review. We acknowledge the summary of this information in CTD section 3.2.P.3.5. However, the experimental methods, data, and acceptance criteria were not provided. For example, there was no discussion of the validation of

Thus, the division refused to file the application under 21 CFR 314.101(d) and consistent with CDER's July 12, 1993, New Drug Evaluation Guidance Document: Refusal to File.

On March 7, 2005, the sponsor requested a meeting to discuss this decision, and the meeting was held on March 9, 2005. At the meeting, with all review disciplines represented, notably chemistry and microbiology, as well as the Office of Orphan Drug Products, the sponsor outlined a proposal to remedy the deficiencies in the information on sterility assurance, which was acceptable to FDA, and committed to a submission of the necessary information in a matter of

weeks. Discussion also ensued regarding the potential fate of the roughly 30 patients currently being treated under IND with this drug with regard to the extreme difficulty in finding other opportunities for therapy with IGF-1, their only therapeutic option. In light of their stated ability to provide, and commitment to expedite submission of, the necessary information to make the application whole, and given the consequences to the patients currently being treated under IND of a potential cessation of studies, the sponsor directly requested a reconsideration and reversal of the division's refuse to file decision.

After the meeting with the sponsor, the FDA participants met to discuss the issues further. The microbiology and chemistry teams were satisfied that the sponsor's proposed remedy was indeed an adequate repair of the application and that the time frame for submission as committed to by the sponsor would allow the necessary time to review. Further discussion, involving the Office of Orphan Drug Products representatives, re-emphasized the risk to patients of a precipitous discontinuation of ongoing studies.

The decision to refuse to file a new drug application is clearly discretionary, according to the 1993 Guidance. Specifically, the guidance states that "the agency may, for particularly critical drugs, not use the RTF procedure, even where it could be invoked..." Furthermore, the Guidance allows that "in general, the deficiencies leading to RTF should be objective and straightforward, not matters of subtle judgment, and should not be quickly reparable." In this instance, based on the meeting with the sponsor, and as is acceptable to the chemistry and microbiology teams, the division feels that this is a potentially important drug product, and that the deficiency cited is fully reparable in an acceptable timeframe. It is furthermore worth noting, had the division and the sponsor had more time to confer leading up to the filing date, it is likely that these issues would have been resolved in advance and the division would not have taken a refuse to file action.

Recommendation

In light of the foregoing, that is after extensive discussion with the sponsor and after subsequent internal consideration of the issues and proposed remedies to this application for an orphan product for a vulnerable population, the division has decided that this application may be filed.

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/s/

David Orloff
3/9/05 07:56:32 PM
MEDICAL OFFICER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-884

Insmed Incorporated
Attention: Ronald 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 December 31, 2004, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TRADENAME (mecasermin rinfabate injection) 60 mg/mL.

After a preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d) for the following reason:

Chemistry, Manufacturing, and Controls (CMC) information to evaluate sterility assurance was not adequate for review. We acknowledge the summary of this information in CTD section 3.2.P.3.5. However, the experimental methods, data, and acceptance criteria were not provided. For example, there was no discussion of the validation of _____
We recommend you refer to FDA's "Guidance for Industry for Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products" -1994. Currently, this guidance can be found on the internet at <<http://www.fda.gov/cder/guidance/cmc2.pdf>>. Guidance for putting this information in CTD format can be found at <<http://www.fda.gov/cder/mapp/5040.1.pdf>>.

Within 30 days of the date of this letter, you may request in writing a meeting about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If, after the informal conference, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you requested the informal conference.

In our preliminary filing review of this application, we also noted a number of deficiencies which are not reasons for this refusal to file action. Deficiencies, comments, and requests for information will be communicated in writing within approximately two weeks.

If you have any questions, call Enid Galliers, Chief, Project Management Staff, at (301) 827-6429.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

David Orloff
3/4/05 05:06:09 PM