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RESEARCH**

APPLICATION NUMBER:

21-884

APPROVABLE LETTER(S)



NDA 21-884

Insmmed Incorporated
Attention: Ronald Gunn
Executive Vice President and COO
4851 Lake Brook Drive
Glen Allen, VA 23060

Dear Mr. Gunn:

Please refer to your new drug application (NDA) dated December 31, 2004, received January 3, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for iPlex (mecasermin rinfabate [rDNA origin] injection), 36 mg/0.6 mL.

We acknowledge receipt of your submissions dated January 12, February 4, March 4(2), April 12 and 15, May 4, 17, and 18, June 1, 9, and 17, July 1, 6(2), 8, 11, 12(2), 19, 20, and 27, August 15, 17, 19, and 23(2), and September 2, 13, and 15, 2005.

We have completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to:

1. Provide the chemistry, manufacturing, and controls information as requested below.

A. Drug Substance

- (1) Agree to provide information to support the _____
- (2) Agree to complete the characterization of the disulfide linkages in rhIGFBP-3.
- (3) Provide a drug substance specification for _____
- (4) Tighten the acceptance criterion for _____ in the drug substance or provide a justification for the _____
- (5) Provide information that demonstrates the _____s from your particular *E. coli* strain _____ are satisfactorily recognized by the antibodies in the commercial analytical kit.
- (6) Revise the drug substance stability protocol to include testing _____ for purity, _____
- (7) Provide updated drug substance primary stability data at -70°C, -20°C, _____

B. Drug Product

- (8) Tighten the acceptance criterion of _____ for _____ in the drug product, as determined by _____
- (9) Tighten the acceptance criterion for _____ of the drug product or provide a justification for the range of _____
- (10) Revise the drug product stability protocol to include testing and acceptance criteria for _____
- (11) Provide updated drug product primary stability data at -70°C, -20°C, _____ to support proposed label claims and expiration dating. As part of this submission, provide representative chromatograms from all purity tests.

Incorporate and submit requested changes in specifications in the form of updated, revised drug substance and drug product specification sheets.

2. Submit draft labeling revised as shown in the enclosed package insert (PI) and patient package insert (PPI).
3. Submit vial and carton labels revised as follows:
 - a. Include "For single use only" on vial label.
 - b. Revise "Store frozen at or below -20°C" to "Store frozen at or below -20°C for no more than 2 months" on vial and carton labels.
 - c. Include _____ on the carton label.
 - d. Include "Thawed product cannot be refrozen" on carton label.

These labeling instructions may be revised after receipt of additional stability data.

On August 30, 2005, the FDA approved Tercica's new drug application for Increlex (mecasermin [rDNA origin] injection), which was granted orphan exclusivity for the treatment of severe primary insulin-like growth factor-1 deficiency (Primary IGF1D). The Agency has not yet resolved the issue of whether that exclusivity will block the approval of iPlex. As you are aware, the Agency is still considering this issue.

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

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
 4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
 5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
 6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
 7. Provide English translations of current approved foreign labeling not previously submitted.

While not required for approval, we request additional, longer-term clinical data related to the immunogenicity of the to-be-marketed iPlex™ product, specifically data on the effects of antibody development to the mecasermin rinfabate complex or to its individual components on the long-term growth response to the drug. Should these data not be available prior to the resubmission in response to this letter and/or prior to approval, they can be compiled and submitted post-approval. We encourage you to work with the division as you develop plans for collecting and reporting these data.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with the Division of Metabolism and Endocrinology Products to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

ALL regulatory submissions, whether sent by U.S. Postal Service, overnight mail service, or courier, should be sent to the following address. Processing of submissions sent to other addresses may be delayed.

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

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

Sincerely,

{See appended electronic signature page}

Robert J. Meyer, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures: Package Insert (PI)
Patient Package Insert (PPI)