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APPLICATION NUMBER:

125274Orig1s000

OTHER ACTION LETTERS



NDA 22-150

NOT APPROVABLE

Jerini U.S., Inc.
c/o Target Health, Inc.
261 Madison Avenue, 24th Floor
New York, NY 10016

Attention: Glen D. Park, Pharm. D.
Authorized U.S. Agent

Dear Dr. Park:

Please refer to your new drug application (NDA) dated October 22, 2007, received October 26, 2007, submitted on behalf of Jerini U.S., Incorporated, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Firazyr (icatibant) Injection, 30 mg/3mL.

We acknowledge receipt of your submissions dated December 28, 2007, and February 11, 18, 20, 26, and 27, 2008.

We also acknowledge receipt of your submission dated April 1, 2008. This submission has not been reviewed for this action. You may incorporate this submission by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review and find the information presented is inadequate. Therefore, the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies are summarized as follows:

1. The submitted data from your clinical program do not provide substantial evidence that icatibant is sufficiently safe and effective for the proposed indication of the treatment of acute attacks of hereditary angioedema (HAE). The uncertain efficacy of the comparator drug, tranexamic acid, in the treatment of acute attacks of HAE complicates interpretation of the results of Study JE049-2102. Study JE049-2103 failed to demonstrate a statistically significant treatment difference between placebo and icatibant. In addition, there are concerns regarding the validity of the primary endpoint used in both studies (time to onset of symptom relief using the Visual Analog Scale). Without substantial evidence of the efficacy of the proposed dose of icatibant, we cannot evaluate if there is appropriate safety. Before icatibant may be approved, you must submit sufficient evidence of the efficacy of icatibant for the treatment of patients with acute attacks of HAE. This evidence must be generated by using a reliable instrument to assess efficacy and an appropriate control arm. You will need to demonstrate appropriate safety for the dose shown to be efficacious.

2. The completion of nonclinical, chronic, repeat-dose toxicity studies (6-month rat and 9-month dog) via the subcutaneous route of administration is required to support chronic intermittent clinical dosing. The icatibant labeling will reflect a clinical dosing regimen that is supported by the nonclinical toxicology studies in both dose and duration. At this time, you have nonclinical support for subcutaneous clinical dosing for up to 13-weeks duration. We acknowledge your submission stating that chronic toxicity studies have been initiated as of June 2007 (dog study) and July 2007 (rat study) and that the carcinogenicity studies will be initiated April 8, 2008, and July 7, 2008, for mice and rats, respectively.
3. Firazyr injection is likely to be used in settings outside the usual healthcare delivery environment, such as self-injection by patients. Submit data to show that Firazyr can be safely used in such settings.
4. Data from study JE049-1103 indicate that both age and gender have effects on icatibant pharmacokinetics. Address the scientific basis for these large differences in systemic exposure and possible role of proteolytic enzymes. Also provide justification for proposing the same dose regardless of age and gender.
5. Dose selection should be further defined in sufficient patients based on the clinical endpoint or other biomarkers that are validated to be related to the clinical endpoint.
6. Submit revised drug substance specifications to include the following.
 - a. The following impurities in the drug substance and the drug product are not considered to be adequately qualified for safety.



Conduct an adequate qualification study (a 3-month repeat-dose toxicity study in an appropriate species) that provides an appropriate margin of safety (generally 10-

fold) at a NOAEL dose or modify your proposed acceptance criterion to less than

(b) (4)

- b. Tighten the proposed acceptance criteria for the content of residual solvents (b) (4) (b) (4) water, acetic acid, (b) (4) to coincide with batch results and the current manufacturing capabilities.
- c. Upgrade/change the analytical method for heavy metals to include testing for (b) (4) (b) (4)
- d. Tighten the proposed acceptance criteria for amino acid analysis to reflect the test results, (b) (4)

7. The following comments pertain to drug substance stability studies.

- a. Submit the stability protocol for drug substance stability batches 0565984, 0565985, and 0565986. Provide a stability specifications sheet with a complete list of tested attributes, corresponding analytical methods and acceptance criteria, as requested in the comment above. Submit stability results in the same format for each batch across the different time points and for different storage conditions. In addition, provide graphical representation of stability changes with time for each stability-indicating attribute. Explain the observed stability imbalance between the assay and the total impurities (refer to tables 19 and 20 in section 3.2.S.7.3) in the drug substance and revise the analytical methods as needed.
- b. Submit post-approval stability protocols for the drug substance (refer to page 2 of section 3.2.S.7.2) to include a specification sheet with a full list of tested attributes, corresponding analytical methods, and proposed acceptance criteria. Include the testing schedule and storage conditions and provide a stability commitment stating provisions for batch withdrawal from the market.

8. Submit revised drug product specifications to include the following.

- a. Upgrade the proposed impurity specifications by listing each impurity that has been identified or specified, and include provisions for future unidentified impurities/degradants. Each specified but unidentified impurity needs to be described by the corresponding relative retention time (RRT) for the current analytical method. The impurities that are carried over from the drug substance and do not increase during drug product manufacturing and storage do not need to be tested but should be listed for a reference. Attach, to the drug product specifications, a sheet with the chemical names and structures for all identified impurities.
- b. Tighten the proposed acceptance criteria for individual and total impurities and degradation products to reflect the batch results and the current manufacturing capabilities.

- c. Include testing for leachables, (b) (4) until an adequate amount of manufacturing experience and data is accumulated. In view of the manufacturing changes introduced late in the development program (b) (4) (b) (4)), confirm the leachable/extractable profiles obtained on the (b) (4) syringes, for the commercial drug product. Identify the observed leachable/extractable impurities and provide the chemical names and structures.
9. The following comments pertain to the drug product stability studies.
- a. Provide revised a stability protocol with updated stability specifications to include the list of tested attributes, individual method numbers and corresponding acceptance criteria. In addition to revisions requested in comment above, include testing for the (b) (4) to support the recent manufacturing changes.
- b. The submitted stability data do not support the requested expiry period of 18 months for the drug product when stored at the currently proposed label conditions, (b) (4). Given the temperature dependency of the (b) (4) (b) (4), (b) (4) revise the storage conditions for the drug product to (b) (4). Revise the label accordingly.
- c. Submit the 18-month stability update for the primary stability batches in the revised format, as requested in the comment above. Provide a statistical analysis with graphical representation of all instability trends.
10. An Information Request letter dated March 20, 2008, was forwarded to the holder of supporting DMF (b) (4) and a letter dated April 11, 2007, was forwarded to the holder of supporting DMF (b) (4). These comments must be adequately addressed before resubmission of this application.
11. For the carton and container labeling, revise the drug product name to Firazyr (icatibant) Injection, (b) (4). Refer the strength of 10 mg/mL (or the 30 mg per container) to the free icatibant base. (b) (4)

Please refer to the FDA *Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products*, November 1994 (<http://www.fda.gov/cder/guidance/cmc2.pdf>) and provide a response to the following questions:

12. Provide the protocol and data summaries of a container-closure integrity study for the 3 mL (b) (4) syringe system used for the product to demonstrate the integrity of the system following maximum heat exposure during (b) (4).

13. Provide the maximum (b) (4) This (b) (4) should be established and provided in the drug application.
14. Describe the requalification program (number and type of runs, product used) and provide the requalification frequency for the (b) (4)
15. State if there is a program for (b) (4)
16. Provide a description of the environmental monitoring program.
17. There are two reports regarding the validation of the bacterial endotoxins method for the drug product. (b) (4)
(b) (4)
(b) (4)
(b) (4) Please explain this discrepancy in the results between the two reports (b) (4).
18. Provide information on the supplier of the 25G needle to be included in the final packaging with the product. In addition, provide sterility assurance information on the needle (method of sterilization and validation data summaries) or alternatively, the 510k device code.
19. Provide an updated letter of authorization for Type III DMF (b) (4) that specifically identifies the facilities used for (b) (4) components used for the product. The letter should also specify where this information is located in the DMF.
20. Regarding microbiological testing and stability of the drug product:
- a. The current stability protocol for the three registration batches and the post-approval stability protocol state that USP methods are employed for sterility and bacterial endotoxins testing. However, only 1 sample is allocated for testing instead of 20 for the sterility test and 1 sample instead of 3 for the endotoxin test. Please explain this discrepancy.
 - b. Sterility and bacterial endotoxins testing of the product should be performed at expiry. The stability protocols in the submission do not include testing at the proposed expiry of 18 months for the long-term condition.
 - c. Please state if the stability samples are stored with the plunger rod inserted. The stability studies should simulate the manner the product is to be shipped.

We will comment on the labeling when the above deficiencies have been addressed.

We have not yet completed our inspections of your foreign manufacturing facilities. Satisfactory inspection reports for all facilities must be received before this application may be approved.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). You are advised to contact the Division of Pulmonary and Allergy Products regarding the extent and format of your safety update prior to responding to this letter.

We note that the tertiary structure of the peptide is not monitored and the biological activity of the peptide is not assessed either for the drug substance or the drug product. We strongly recommend that you include a test for controlling the biological activity of the peptide in the drug product formulation, during release and stability testing. At the minimum, the standards used for purity evaluation should be tested for the biological activity.

Within 10 days after the date of this letter, you are required to amend the application(s), notify us of your intent to file (an) amendment(s), or follow one of your other options under 21 CFR 314.120. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application(s) 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 a meeting or telephone conference with the Division of Pulmonary and Allergy 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 this application is approved.

If you have any questions, contact Carol Hill, Regulatory Project Manager, at (301) 796-1226.

Sincerely,

{See appended electronic signature page}

Curtis Rosebraugh, M.D., M.P.H.
Acting Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Curtis Rosebraugh
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