

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022150Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

PMR/PMC Description: Impurity Identification

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>Complete</u>
	Study/Trial Completion:	<u>04/30/2012</u>
	Final Report Submission:	<u>08/31/2012</u>
	Other:	<u>None</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

In an information request sent May 24, 2011, the Division requested that the sponsor identify all impurities in the drug product present at levels (b) (4) per ICH Q3B. The sponsor stated that during a pre-NDA meeting held on January 24, 2007 the FDA stated that, given the peptide nature of the drug substance, impurity qualification and identification criteria according to those presented at the 2006 TIDES Conference would be appropriate as opposed to the standard impurity specification criteria per ICH Q3A and ICH Q3B. These alternative standards are as follows: (1) Any peptide-related impurity (b) (4) should be fully identified, characterized and qualified, (2) any peptide-related impurity (b) (4) should be fully identified and characterized, and (3) any peptide-related impurity above (b) (4) should be minimally identified and characterized. However, taking this previous agreement into account, the sponsor still has not identified three HPLC peaks that are present at (b) (4)

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The primary goal of this study is to generate chemical structures that can be assessed for structural alerts and through the use of computational toxicology methods.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Impurity identification study.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/

SALLY M SEYMOUR
08/19/2011

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

PMR/PMC Description: Mouse Carcinogenicity Study

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>Complete</u>
	Study/Trial Completion:	<u>03/31/2014</u>
	Final Report Submission:	<u>12/31/2014</u>
	Other:	<u>None</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

During a pre-NDA meeting held on June 5, 2007 the FDA stated that the sponsor could submit carcinogenicity studies in support of this NDA as "Phase 4 commitments. However, in the intervening time, the Food and Drug Administration Amendments Act of 2007 was signed into law, and under this new law, the proposed carcinogenicity studies are considered post-marketing requirements (PMRs), since they involve patient safety.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The primary goal of this study is to assess the carcinogenic potential of icatibant.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

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- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

104-week carcinogenicity study of icatibant in mice.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
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 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
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- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
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Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
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SALLY M SEYMOUR
08/19/2011

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

PMR/PMC Description: Rat Carcinogenicity Study

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>Complete</u>
	Study/Trial Completion:	<u>08/31/2011</u>
	Final Report Submission:	<u>03/31/2012</u>
	Other:	<u>None</u>

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2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The primary goal of this study is to assess the carcinogenic potential of icatibant.

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/s/

SALLY M SEYMOUR
08/19/2011



DEPARTMENT OF HEALTH AND HUMAN SERVICES

MEMORANDUM

Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
White Oak Building 66
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: August 8, 2011
From: LCDR Nikhil Thakur, Senior Engineering Reviewer, WO66, RM 2562
General Hospital Devices Branch, DAGID, ODE, CDRH
To: Eunice Chung-Davies, Senior Regulatory Health Program Manager, WO22:
RM3343 CDER
Subject: CDRH Consult, (b) (4), prefilled syringes to deliver Firazyr®
(icatibant)

1. Issue

The Center for Drug Evaluation and Research (CDER) has requested a consult from the Center for Devices and Radiological Health (CDRH), regarding the drug delivery device that will deliver the medication known as Firazyr (icatibant) which is being developed as a treatment to Hereditary Angioedema (HAE) in adults. The device constituent of this combination product consists of a prefilled glass syringe and a separate sterile needle (b) (4). On July 29, 2011, the Master File Holder (Device constituent Manufacturer) responded to the questions that CDRH had originally posed regarding mechanical compatibility and interoperability of the various components of the device constituent. The following memorandum assesses the Sponsor's response.

2. Device Description

The device constituent of this combination product consists of a prefilled glass syringe filled with the medication Firazyr (icatibant) 30 mg (10mg/ml). The syringe will be co-packaged with two sterile needles which the patient will assemble prior to use.

3. Documents Reviewed

(b) (4), July 29, 2011, Response to CDRH's deficiencies.

4. Review of Additional Information Submitted and Discussion

In CDRH's original review, we had asked the Sponsor to demonstrate compatibility between the (b) (4) Syringe and the (b) (4) luer locked needle.

In the Sponsor's July 29, 2011, response, the device constituent manufacturer (b) (4) provided a summary of the testing that was performed per ISO (b) (4). The Sponsor states that the needle conforms to the requirements within ISO (b) (4) (b) (4).

(b) (4)) has also performed (b) (4) between the (b) (4) luer locked needle and the (b) (4) Syringe. All of the tests performed demonstrated that the (b) (4) Needle is compatible with the (b) (4) syringe.

However, (b) (4) only provided a descriptive summary of the tests that were performed. There was no discussion of sample size for the tests performed. CDRH had originally recommended that 30 devices be tested to demonstrate that a statistically significant sample size was utilized to demonstrate the safety and effectiveness of the (b) (4) devices. However, it appears that in subsequent conversations between CDRH and the Sponsor, it was agreed that a lesser amount was deemed appropriate. CDRH maintains that the Sponsor should demonstrate that a statistically significant device population was tested to demonstrate the interoperability between the (b) (4) Syringe and the (b) (4) needle. We had recommended 30 samples, but it is the Sponsor's or (b) (4)'s responsibility to justify the sample size. Also, the Sponsor should provide the minimum, maximum, mean, standard deviation, confidence interval, etc. for each test performed.

In CDRH's original review, we had asked the Sponsor to demonstrate that the appropriate Human Factors testing was performed for this combination product. It appears that CDER's Medical Officer has deemed that this testing is unnecessary based on the abundance of clinical data to support the safety and effectiveness of the drug delivered. On July 18, 2011, CDRH has submitted a "Supervisory Level" review from the Director of the Division of Anesthesiology, General Hospital Devices, Infection Control and Dental Devices, concurring with the Lead Medical Device Consultant's request for Human Factors testing. However, we understand that it is ultimately the Lead Center (CDER's) decision on the questions that should be submitted to the Sponsor. In this case, CDER has determined that Human Factors testing is not necessary and that the clinical testing adequately demonstrates the safety and efficacy of the drug (effectiveness of the device). CDRH maintains that clinical testing is not intended to identify use related risks that are typically identified / verified / validated during a Human Factors study. Thus, we believe that the questions regarding Human Factors testing should be asked, especially given that lay users will be self-injecting this drug in a home setting. However, we understand that it is the Lead Center's (CDER) decision to ultimately decide the questions that should be portrayed to the Sponsor for this NDA.

5. **CDRH Recommendation**

Testing Regarding Conformance to ISO (b) (4)

CDRH concurs with (b) (4) response demonstrating the conformance of the (b) (4) needle to the requirements within ISO (b) (4). This testing also appears to demonstrate that the (b) (4) Needle is compatible with the (b) (4) glass prefilled syringe.

We recommend that the following question be sent to (b) (4) (DMF Holder, DMF (b) (4) regarding the ISO (b) (4) performance testing:

We have reviewed your July 29, 2011, supplement to DMF (b) (4) regarding the additional testing that you performed to demonstrate that the (b) (4) Needle and (b) (4) Syringe conform to ISO (b) (4) and to demonstrate interoperability between the luer locked needle and prefilled syringe. Please clarify the sample size that was utilized in performing each test (described in your response), and provide your rationale for selecting this sample size. The FDA's intent for asking this clarification is to ensure that there is a statistically significant sample size to represent the potential for device failure. In the FDA's original request, we had requested that you employ 30 samples for each test that you performed to demonstrate conformance to ISO (b) (4)

Regarding Human Factors Testing:

CDRH maintains that our questions and concerns regarding Human Factors testing should be addressed by the Sponsor (Shire Human Genetic Therapies, Inc.). Our review speaks to the engineering (performance testing) and simulated use (human factors) issues that impact the needle and syringe. However, we understand our role as the "Device Consultant" for this submission, and understand that CDER has the discretion to decide not to request this information. Thus, we defer to CDER as to whether the Human Factors questions should be forwarded to the Sponsor. If CDER decides to submit the Human Factors concerns to Shire Human Genetic Therapies, the following questions should be submitted to the Sponsor:

Provide adequate information to demonstrate that Firazyr in pre-filled syringes can be self-administered safely and effectively by patients from a human factors study in which therapy is delivered by the patient and not a clinical professional. The results from a finished human factors study will be required before approval is granted. The actual final finished product (biologic contained in the finished device) should be used for the human factors/simulated use study to show that patients are able to understand the instructions, calculate the dose, administer the accurate dose, and activate the needle stick prevention mechanism without injury. For guidance on human factors assessments, refer to the following documents:

- *ANSI/AAMI/IEC 62366:2007 Medical devices- Application of usability engineering to medical devices*
- *Guidance for Industry and FDA Premarket and Design Control Reviewers, Medical Device Use Safety: Incorporating Human Factors Engineering into Risk Management (July 2000), available at <http://www.fda.gov/cdrh/humfac/1497.pdf>.*

We recommend that you submit a draft of the test protocol before you implement it for our review and feedback to ensure that your methods will be acceptable. The purpose of a design validation (human factors) study is to demonstrate that the device can be used by representative users under simulated use conditions without producing patterns of failures that could result in negative clinical impact to patients or injury to device users. Tasks included in the study should be those identified through completion of a risk assessment of hazards that may be associated with use-related problems and represent greater than minimal risk to users. The study should collect sufficient and appropriate data to facilitate identification and understanding of the root causes of any use failures or problems that do occur. The causes may be related to the design of the device, the device labeling (including instructions for use), and/or the training of test participants. The test report should present a summary of your test results, data analysis, and conclusions regarding safe and effective use and including whether any modifications are indicated; if they are, these modifications should be described and if significant, the modifications should also be validated.

Your validation study protocol should include the items listed below.

a. Devices and Labeling Used and Training

For design validation, the devices used in your testing should represent the final design, which includes instructions for use, or any other labeling materials.

The training you provide to your test participants should approximate the training that your actual end users will receive. Please describe the training you plan to provide in your validation study and how it corresponds to realistic training levels.

Your participants should assess the clarity of the instructions for use and you should assess the extent to which the instructions support safe and effective use of your device. If any of the other labeling (e.g., packaging, inserts) is critical to

use, include them in your validation testing as well. You may include these assessments in your validation testing or conduct them in a separate study.

If you decide to include the assessment of clarity of instructions for use and training as part of the validation study, the Agency expects that the results demonstrating effectiveness of your training and instructions for use are analyzed separately from the results of use performance.

b. User Tasks and Use-Related Risks Analysis

FDA expects to see a clear description of how you determined which user tasks would be included in the testing and how many trials each participant would complete. In order to adequately assess user performance and safety, the tasks selected for testing should be derived from the results of a comprehensive assessment of use-related hazards and risks that consider all functions of the device. The tasks should be prioritized to reflect the relative magnitude and severity of the potential impact of inadequate task performance on the safety of the device and the user.

Please provide a use-related risk analysis, describe and provide a rationale for the tasks you include in your testing and their relative priority. Please also describe all activities in which your test participants will engage during the test.

c. Use Environment and Conditions

You should conduct your validation testing in an environment that includes or simulates all key aspects of the real-world environments in which you anticipate your device would be used.

Identification of potentially challenging use conditions should be derived through analyses of use hazards prior to conducting validation testing and aspects of use that can be reasonably anticipated, such as use with gloves or wet fingers, dim lighting, noisy situations, etc., should be included in your testing. Please evaluate use of your device under whatever conditions you identify as potentially occurring and hazardous.

Please describe the testing environment and realism of the simulated use in sufficient detail for us and justify how they were appropriate for validation testing.

d. Study Participants

FDA expects you to test a minimum of 15 participants from each major user group for validation of device use. Your test participants should be representative of your intended end-user populations, as described in your indications for use statement. If users with distinctly different characteristics (e.g., age ranges, skill sets, or experience levels, level of disabilities/impairments) will use your device, you should include 15 from each distinct group.

Regardless of the number of groups you test, please provide a rationale that these groups are representative the overall population of users for your device. Note that study participants should not be your own employees, or those that have been exposed to the products prior to the testing.

e. Data Collection

Any data collected and analyzed in a validation study should be described in terms of how it supports the safety case claim that your device can be used safely and effectively by the indicated users. FDA expects you to collect both empirical and qualitative data in a design validation study.

Empirical Data – Your test participants should be given an opportunity to use the device independently and in as realistic a manner as possible, without guidance, coaching, praise or critique from the test facilitator/moderator. Some data, such as successful or failed performance of key tasks or time taken to perform tasks – if time is a safety-critical criterion – should be measured directly rather than soliciting participant opinions. Observing participant behavior during the test is also important, in order to assess participants' adherence to protocol and proper technique and especially to assess and understand the nature of any errors or problems that occur.

Qualitative Data – The Agency expects you to ask open-ended questions of participants at the end of a usability validation, such as, "Did you have any difficulty using this device? [If so] can you tell me about that?" The questions should explore performance of each critical task involved in the use of the device and any problems encountered. Note that since the labeling and instructions for use are considered part of the user interface for your device, the questions should cover those components as well.

Your analysis of performance and subjective data should be directed toward understanding user performance and particularly task failures. The analysis should determine the nature of failures, the causes of failures, and the clinical impact. Every test participant who experiences a "failure" (does something that would have led to harm under actual conditions of use), should be interviewed about that failure to determine the cause of the failure from the perspective of the participant.

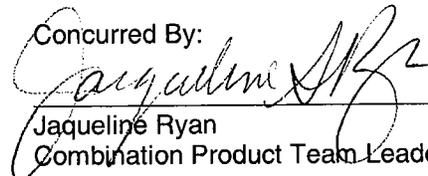
Please describe and provide a rationale for including each type of data you collect. Please provide a proposed protocol for the Agency to review prior to conducting the study.

If you have any questions, please contact LCDR Mary Brooks at (301) 796- 6078 or LCDR Nikhil Thakur at (301) 796-5536.

Sincerely,


LCDR Nikhil Thakur
Senior Engineering Reviewer

Concurred By:


Jaqueline Ryan
Combination Product Team Leader, GHDB

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/s/

EUNICE H CHUNG-DAVIES
08/08/2011
on behalf of CDRH

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

PATIENT LABELING REVIEW

Date: August 1, 2011

To: Badrul Chowdhury, M.D., Director
**Division of Pulmonary, Allergy and Rheumatology
Products (DPARP)**

Through: LaShawn Griffiths, MSHS-PH, BSN
Acting Team Leader, Patient Labeling Reviewer
Division of Risk Management

Melissa Hulett, MSBA, RN
Acting Team Leader, Patient Labeling Reviewer
Division of Risk Management

From: Twanda Scales, RN, MSN
Patient Labeling Reviewer
Division of Risk Management

Subject: DRISK Review of Patient Labeling (Patient Package
Insert and Instructions for Use)

Drug Name: Firazyr (icatibant)

Dosage Form and
Route: Injection

Application
Type/Number: NDA 22150

Applicant: Shire Human Genetic Therapies, Inc.

OSE RCM #: 2010-1049

1 INTRODUCTION

On October 22, 2007 Jerini AG submitted NDA 22-150, Firazyr (icatibant), for the treatment of hereditary angioedema. In November of 2008, Jerini AG became a wholly owned subsidiary of Shire Human Genetic Therapies (HGT) who assumed responsibility for NDA 22-150 under the name Jerini US, Inc.

On April 23, 2008 a Not Approvable action letter was issued for clinical deficiencies. February 25, 2011 Shire Human Genetic Therapies, Inc. submitted a New Drug Application (NDA) for Firazyr (icatibant). The purpose of the Applicant's February 25, 2011 submission was to provide a complete respond to the April 23, 2008 Not Approvable action letter.

On July 19, 2011 The Applicant submitted an Updated Draft Labeling letter which included revised full prescribing information with patient information and packaging components. This review is written in response to a request by the Division of Pulmonary, Allergy and Rheumatology Products (DPARP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Patient Package Insert (PPI), and revised proposed Instructions for Use (IFU) for Firazyr (icatibant).

2 MATERIAL REVIEWED

- Draft Firazyr (icatibant) Injection Patient Package Insert (PPI) and Instructions for Use (IFU) received on July 19, 2011 and received by DRISK on July 20, 2011.
- Draft Firazyr (icatibant) Injection Prescribing Information (PI) received July 19, 2011 and received by DRISK on July 20, 2011.
- DRISK review of Firazyr (icatibant) Injection Instructions for Use (IFU) provided to DPARP on July 15, 2011.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the IFU document using the Verdana font, size 11.

In our review of the PPI and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU is consistent with the prescribing information (PI)
- removed unnecessary or redundant information
- ensured that the PPI and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DRISK on the correspondence.
- Our annotated version of the PPI and IFU is appended to this memo. Consult DRISK regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

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/s/

TWANDA D SCALES
08/01/2011

LASHAWN M GRIFFITHS
08/01/2011

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

*****Pre-decisional Agency Information*****

Memorandum

Date: July 27, 2011

To: Eunice Chung-Davies, Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
(DPARP)

From: Matt Falter, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications
(DDMAC)

CC: Robyn Tyler, Acting DTC Group Leader
Lisa Hubbard, Professional Group Leader
Roberta Szydlo, Regulatory Review Officer
Michael Wade, Regulatory Health Project Manager
Becki Vogt, Regulatory Health Project Manager
(DDMAC)

Subject: NDA # 022150
DDMAC draft labeling comments for FIRAZYR® (icatibant) Injection

DDMAC has reviewed the proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for FIRAZYR® (icatibant) Injection (Firazyr) submitted for consult on July 19, 2011. DDMAC's comments regarding the proposed package insert and proposed carton and container labeling was entered into DARRTS under separate cover on July 15, 2011. DDMAC's comments regarding the first revision of the proposed IFU were entered into DARRTS under separate cover on July 18, 2011.

DDMAC's comments on the PPI and IFU are based on the proposed draft label titled "NDA 22150 Package Insert_sponsor_19JUL2011.doc" sent via e-mail from DPARP to DDMAC on July 20, 2011.

DDMAC has no comments to make on this revision of the proposed IFU at this time. Our comments on the PPI are provided directly in the marked-up document attached (see below).

Thank you for the opportunity to comment on the proposed labeling.

If you have any questions regarding the IFU, please contact Matt Falter at (301) 796-2287 or matthew.falter@fda.hhs.gov.

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/s/

MATTHEW J FALTER
07/27/2011

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

*****Pre-decisional Agency Information*****

Memorandum

Date: July 18, 2011

To: Eunice Chung-Davies, Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
(DPARP)

From: Matt Falter, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications
(DDMAC)

CC: Robyn Tyler, Acting DTC Group Leader
Lisa Hubbard, Professional Group Leader
Roberta Szydlo, Regulatory Review Officer
Michael Wade, Regulatory Health Project Manager
Becki Vogt, Regulatory Health Project Manager
(DDMAC)

Subject: NDA # 022150
DDMAC draft labeling comments for FIRAZYR® (icatibant) Injection

DDMAC has reviewed the proposed Instructions for Use (IFU) for FIRAZYR® (icatibant) Injection (Firazyr) submitted for consult on March 21, 2011. Although a review of IFU was not specifically requested in the consult request form, DDMAC notes that IFU are included in the Patient Counseling Information section of the proposed labeling. DDMAC's comments regarding the proposed package insert and proposed carton and container labeling was entered into DARRTS under separate cover on July 15, 2011.

DDMAC's comments on the IFU are based on the proposed draft marked-up IFU titled "11 0713 NDA 22150 icatibant DRISK IFU (marked).doc" sent via e-mail from DRISK to DPARP and DDMAC on July 7, 2011. Our comments on the IFU are provided directly in the marked-up document attached (see below).

Thank you for the opportunity to comment on the proposed labeling.

If you have any questions regarding the IFU, please contact Matt Falter at (301) 796-2287 or matthew.falter@fda.hhs.gov.

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/s/

MATTHEW J FALTER
07/18/2011

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications**

*****Pre-decisional Agency Information*****

Memorandum

Date: July 15, 2011

To: Eunice Chung-Davies, Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
(DPARP)

From: Roberta Szydlo, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications
(DDMAC)

CC: Lisa Hubbard, Professional Group Leader
Robyn Tyler, Acting DTC Group Leader
Matt Falter, Regulatory Review Officer
Michael Wade, Regulatory Health Project Manager
Becki Vogt, Regulatory Health Project Manager
(DDMAC)

Subject: NDA # 022150
DDMAC labeling comments for FIRAZYR® (icatibant) Injection

DDMAC has reviewed the proposed product package insert (PI) and proposed carton and container labeling for FIRAZYR® (icatibant) Injection (Firazyr) submitted for consult on March 21, 2011. Although a review of Instructions for Use was not specifically requested in the consult request form, DDMAC notes that Instructions for Use are included in the Patient Counseling Information section of the proposed labeling. DDMAC's comments regarding this section of the PI will follow under separate cover.

DDMAC's comments on the PI are based on the proposed draft marked-up labeling titled "SCPI_NDA 22150 draft package insert_8JULY2011.doc" that was modified in the DPARP eRoom on July 8, 2011, at 10:31am. Our comments on the PI are provided directly in the marked-up document attached (see below).

DDMAC has reviewed the proposed carton and container labeling submitted by the applicant on February 25, 2011, available in the EDR at:

- <\\cdsesub5\EVSPROD\NDA022150\0000\m1\us\114-labeling\draft-labeling\draft-carton-container-labels\syringe-label.pdf>
- <\\cdsesub5\EVSPROD\NDA022150\0000\m1\us\114-labeling\draft-labeling\draft-carton-container-labels\blister-label.pdf>
- <\\cdsesub5\EVSPROD\NDA022150\0000\m1\us\114-labeling\draft-labeling\draft-carton-container-labels\blister-tray.pdf>
- <\\cdsesub5\EVSPROD\NDA022150\0000\m1\us\114-labeling\draft-labeling\draft-carton-container-labels\carton-label.pdf>
- <\\cdsesub5\EVSPROD\NDA022150\0018\m1\us\draft-carton-container-labels.pdf>

We have no comments at this time on the proposed carton and container labeling.

Thank you for the opportunity to comment on the proposed labeling.

If you have any questions regarding the PI or carton and container labeling, please contact Roberta Szydlo at (301) 796-5389 or roberta.szydlo@fda.hhs.gov. If you have any questions regarding the Instructions for Use, please contact Matt Falter at (301) 796-2287 or matthew.falter@fda.hhs.gov.

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/s/

ROBERTA T SZYDLO
07/15/2011

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

PATIENT LABELING REVIEW

Date: July 13, 2011

To: Badrul Chowdhury, M.D., Director
**Division of Pulmonary, Allergy and Rheumatology
Products (DPARP)**

Through: LaShawn Griffiths, RN, MSHS-PH, BSN
Acting Team Leader, Patient Labeling Reviewer
Division of Risk Management

Melissa Hulett, MSBA, RN, BSN
Acting Team Leader, Patient Labeling Reviewer
Division of Risk Management

From: Twanda Scales, RN, MSN
Patient Labeling Reviewer
Division of Risk Management

Subject: DRISK Review of Patient Labeling (Instructions for Use)

Drug Name: Firazyr (icatibant)

Dosage Form and Route: Injection

Application Type/Number: NDA 22150

Applicant: Shire Human Genetic Therapies, Inc.

OSE RCM #: 2010-1049

1 INTRODUCTION

On October 22, 2007 Jerini AG submitted NDA 22-150, Firazyr (icatibant), for the treatment of hereditary angioedema. In November of 2008, Jerini AG became a wholly owned subsidiary of Shire Human Genetic Therapies (HGT) who assumed responsibility for NDA 22-150 under the name Jerini US, Inc.

On April 23, 2008 a Not Approvable action letter was issued for clinical deficiencies. February 25, 2011 Shire Human Genetic Therapies, Inc. submitted a New Drug Application (NDA) for Firazyr (icatibant). The purpose of the Applicant's February 25, 2011 submission was to provide a complete respond to the April 23, 2008 Not Approvable action letter.

This review is written in response to a request by the Division of Pulmonary, Allergy and Rheumatology Products (DPARP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Instructions for Use (IFU) for Firazyr (icatibant).

DRISK conferred with DMEPA and DMEPA deferred to DRISK to provide IFU review comments.

2 MATERIAL REVIEWED

- Draft Firazyr (icatibant) Injection Instructions for Use (IFU) received on March 22, 2011 received by DRISK on July 8, 2011.
- Draft Firazyr (icatibant) Injection Prescribing Information (PI) received March 22, 2011, revised by the Review Division throughout the current review cycle and received by DRISK on July 8, 2011.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We have reformatted the IFU document using the Verdana font, size 11.

In our review of the IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the IFU is consistent with the prescribing information (PI)
- removed unnecessary or redundant information

- ensured that the IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The IFU is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DRISK on the correspondence.
- Our annotated version of the IFU is appended to this memo. Consult DRISK regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the IFU.

Please let us know if you have any questions.

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/s/

TWANDA D SCALES
07/13/2011

LASHAWN M GRIFFITHS
07/14/2011

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology**

Date: June 20, 2011

To: Badrul Chowdhury, MD, Director
Division of Pulmonary, Allergy and Rheumatology
Products

Through: Melina Griffis RPh, Team Leader
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis

From: Anne C. Tobenkin, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s) and Strength: Firazyr (Icatibant) Injection, 30 mg/3 mL (10 mg/mL)

Application Type/Number: NDA 022150

Applicant: Shire Human Genetic Therapies, Inc.

OSE RCM #: 2011-1048

1 INTRODUCTION

This review evaluates the proposed container labels, carton and insert labeling for Firazyr (NDA 022150) for areas of vulnerability that could lead to medication errors. The Applicant also submitted the proposed proprietary name, Firazyr, which was found acceptable in 2006 and 2008 (OSE review # 2006-749 and 2007-2386, respectively) and OSE review # 2011-1194.

2 MATERIAL REVIEWED

Using Failure Mode and Effects Analysis, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the product label and labeling submitted on February 25, 2011 to identify vulnerabilities that may lead to medication errors. See Appendix A for samples of the draft container labels and carton labeling.

3 CONCLUSIONS AND RECOMMENDATIONS

Our Label Risk Assessment indicates that the presentation of information on the labels and labeling introduces vulnerability to confusion that could lead to medication errors. The risks we have identified can be addressed and mitigated prior to drug approval. We provide recommendations for the insert labeling in Section 3.1 and recommendations for the container labels and carton labeling in Section 3.2.

Please copy the Division of Medication Error Prevention and Analysis on any communication to Shire Human Genetic Therapies, Inc. with regard to this review. If you have further questions or need clarifications, please contact Nichelle Rashid, OSE Project Manager, at 301-796-3904.

3.1 COMMENTS TO THE DIVISION ON INSERT LABELING

A. *Section 16.2, Storage and Handling*

The storage instructions as stated, Store below 25°C, are too broad and do not indicate if the product should be stored in the refrigerator or at room temperature. Please revise accordingly.

B. (b) (4), *Information for Patient- Preparing the Injection Site Subsection*

This subsection would benefit from the inclusion of a large picture of the midsection which shows areas of the abdomen where injections can occur, instead of just the side of an abdomen that can be misinterpreted for various other parts of the body.

3.2 COMMENTS TO THE APPLICANT ON CONTAINER LABELS AND CARTON LABELING

A. *General Comments for Syringe Labels, Blister and Carton Labeling*

1. Remove or decrease the size of the symbol which appears on the principal display panel so that the proprietary name, established name and strength can be aligned with one another, and presented as follows (note bolding):

Firazyr
Icatibant Injection
30 mg/3 mL
(10 mg/mL)

2. Because the proprietary name and the established name are presented in the same lower case font and color, the two names may be confused as one name. To distinguish the proprietary name from the established name, a parenthesis should be placed around the established name.
3. Remove the trailing zero from the statement of strength, 3.0 mL, so that it reads 3 mL.

B. *Syringe Labels (commercial and sample)*

1. The product name which appears in an orange color on the clear syringe label is difficult to read. Revise the color of the proprietary name and established name so that there is increased color contrast and visibility of this important information.
2. If space permits, include the route of administration on the label.
3. Include the concentration statement, i.e. 10 mg/mL, after the total drug content statement, as presented above in A1.
4. Bold or highlight the total drug content so that it is easily differentiated from the concentration statement, as presented in A1.
5. If space permits, include the 'Rx Only' statement on the label.
6. Decrease the font size of the manufacturer information so that other pertinent information is more prominent.

C. *Blister Label*

1. Remove or decrease the size of the symbol which appears in the principal display paneling to decrease distraction from important information such as name and strength.
2. Increase the prominence and relocate the drug name and strength so that it is more prominently displayed on the principal display panel.
3. Remove the trailing zero in the statement of strength, 3.0 mL, so that it reads, 3 mL.
4. Relocate, increase the prominence and highlight or bold the total drug content statement so that it appears below the established name and include the

concentration, 10 mg/mL, after total drug content statement as described in comment A1.

5. Revise the statement, [REDACTED] ^{(b) (4)} so that it reads 'Injection'.
6. Relocate the statement, 'For subcutaneous use only' so that it appears underneath the 'Injection' statement.
7. Decrease the prominence of the manufacturer information and increase the prominence of important safety information such as 'Single use product. Discard unused portion' so that this vital information is more visible to the patient and practitioner.

D. Carton Labeling

1. Relocate the strength and route of administration statement so that it appears underneath the proprietary name and established name, see A1.
2. Remove or decrease the size of the symbol which appears in the principal display panel, see B3, B4.

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/s/

ANNE C TOBENKIN
06/20/2011

CAROL A HOLQUIST
06/21/2011



Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
White Oak Building 66
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: June 15, 2011

From: LCDR Mary Brooks MS, BSN, RN, Nurse Consultant, WO66, RM G456
General Hospital Devices Branch, DAGID, ODE, CDRH

To: Eunice Chung-Davies, Senior Regulatory Health Program Manager, WO22:
RM3343 CDER

Subject: CDRH Consult, (b) (4) prefilled syringes to deliver Firazry® (icatibant)

1. Issue

The Center for Drug Evaluation and Research (CDER) has requested a consult from the Center for Devices and Radiological Health (CDRH), regarding the drug delivery device that will deliver the medication known as Firazyr (icatibant) which is being developed as a treatment to Hereditary Angioedema (HAE) in adults. The device constituent of this combination product consists of a prefilled glass syringe and a separate sterile needle without an (b) (4). The mid-cycle meeting was held May 24, 2011. Comments to the sponsor are due June 21, 2011. The following CDRH recommendations will be incorporated CDER's response to the manufacturer.

2. Device Description

The device constituent of this combination product consists of a prefilled glass syringe filled with the medication Firazyr (icatibant) 30 mg (10mg/ml). The syringe will be co-packaged with two sterile needles which the patient will assemble prior to use.

3. Documents Reviewed

Image2000, 510(k) Submission (b) (4)
Draft labeling-Available in global summit section 1.14.1
Container closure system information- Available in global summit section:3.2.P.7
Container closure system development information - Available in global summit section:
3.2.P.2
Container closure integrity testing information - Available in global summit section:3.2.P.7
Description and composition of drug product - Available in global summit section: 3.2.P.1

4. Review and Discussion

Shire Human Genetic Therapies identified (b) (4) needle size (b) (4), 25G (b) (4) to be co-packaged with the medication.

Needle Indications for Use: The (b) (4) Needle is intended for use with syringes and injection devices for general purpose fluid injection / aspiration.



The needle manufacturer conducted bench testing demonstrating substantially equivalence to their predicate needle device which was approved under (b) (4). Below is the testing conducted for the (b) (4) needle under (b) (4). This information was also provided to the NDA which is also provided in Container closure system information in section 3.2.



The section 3.2, Container closure system section material specifications for the (b) (4) (b) (4) glass syringe being used in this NDA are provided. The glass syringe and its components are comprised of the following materials; (b) (4)

(b) (4)

(b) (4) However, there is no mention of conformity with ISO (b) (4) (b) (4). CDRH is concerned with (b) (4) glass syringes. Our postmarket data has identified more than 300 adverse events reports to CDRH for failures of (b) (4) (b) (4) glass syringes with the use Risperdal Consta since its approval for market.

CDRH conducted an engineering review of the Drug Master File for Risperdal to review the (b) (4) glass syringe. It was determined the syringe does not comply with ISO (b) (4) (b) (4). These standards are critical for successful needle to syringe connections and therefore the glass needle hub may not remain locked on the needle during injection, which can result in adverse events. Below are relevant sections of the DMF (b) (4) syringe review:

(b) (4)

Given the long history of postmarket issues with the drugs/biologics filled with the (b) (4) glass syringe, the Agency has been asking for performance reviews as well as Human Factors studies for these prefilled products in glass syringes. This testing will assess the safety and effectiveness of the (b) (4) glass syringe with the (b) (4) needle. We recommend a human factor/usability study be conducted due to the likelihood of adverse events in addition to performance bench testing. We have identified general deficiencies to be asked of the NDA sponsor.

The sponsor provided a written protocol test method (Container closure integrity test) to demonstrate the container-closure system can maintain sterility of the drug. The test method has identified a dye penetration test using (b) (4), which has been identified by the Agency as an acceptable test method. However, the sponsor has not provided the bench testing results for review. We have identified general deficiencies to be asked of the NDA sponsor.

5. CDRH Recommendation

CDRH recommends the following additional information from the NDA sponsor:

1. Due to postmarket adverse events with (b) (4) glass syringes please provide bench performance testing demonstrating syringe to needle compatibility.
2. Provide adequate information to demonstrate that Firazyr in pre-filled syringes can be self-administered safely and effectively by patients from a human factors study in which therapy is delivered by the patient and not a clinical professional. The results from a finished human factors study will be required before approval is granted. The actual final finished product (biologic contained in the finished device) should be used for the human factors/simulated use study to show that patients are able to understand the instructions, calculate the dose, administer the accurate dose, and activate the needle stick prevention mechanism without injury. For guidance on human factors assessments, refer to the following documents:
 - ANSI/AAMI/IEC 62366:2007 Medical devices- Application of usability engineering to medical devices
 - *Guidance for Industry and FDA Premarket and Design Control Reviewers, Medical Device Use Safety: Incorporating Human Factors Engineering into Risk Management* (July 2000), available at <http://www.fda.gov/cdrh/humfac/1497.pdf>.

We recommend that you submit a draft of the test protocol before you implement it for our review and feedback to ensure that your methods will be acceptable.

The purpose of a design validation (human factors) study is to demonstrate that the device can be used by representative users under simulated use conditions without producing patterns of failures that could result in negative clinical impact to patients or

injury to device users. Tasks included in the study should be those identified through completion of a risk assessment of hazards that may be associated with use-related problems and represent greater than minimal risk to users. The study should collect sufficient and appropriate data to facilitate identification and understanding of the root causes of any use failures or problems that do occur. The causes may be related to the design of the device, the device labeling (including instructions for use), and/or the training of test participants. The test report should present a summary of your test results, data analysis, and conclusions regarding safe and effective use and including whether any modifications are indicated; if they are, these modifications should be described and if significant, the modifications should also be validated.

Your validation study protocol should include the items listed below.

a. Devices and Labeling Used and Training

For design validation, the devices used in your testing should represent the final design, which includes instructions for use, or any other labeling materials.

The training you provide to your test participants should approximate the training that your actual end users will receive. Please describe the training you plan to provide in your validation study and how it corresponds to realistic training levels.

Your participants should assess the clarity of the instructions for use and you should assess the extent to which the instructions support safe and effective use of your device. If any of the other labeling (e.g., packaging, inserts) is critical to use, include them in your validation testing as well. You may include these assessments in your validation testing or conduct them in a separate study.

If you decide to include the assessment of clarity of instructions for use and training as part of the validation study, the Agency expects that the results demonstrating effectiveness of your training and instructions for use are analyzed separately from the results of use performance.

b. User Tasks and Use-Related Risks Analysis

FDA expects to see a clear description of how you determined which user tasks would be included in the testing and how many trials each participant would complete. In order to adequately assess user performance and safety, the tasks selected for testing should be derived from the results of a comprehensive assessment of use-related hazards and risks that consider all functions of the device. The tasks should be prioritized to reflect the relative magnitude and severity of the potential impact of inadequate task performance on the safety of the device and the user.

Please provide a use-related risk analysis, describe and provide a rationale for the tasks you include in your testing and their relative priority. Please also describe all activities in which your test participants will engage during the test.

c. Use Environment and Conditions

You should conduct your validation testing in an environment that includes or simulates all key aspects of the real-world environments in which you anticipate your device would be used.

Identification of potentially challenging use conditions should be derived through analyses of use hazards prior to conducting validation testing and aspects of use that can be reasonably anticipated, such as use with gloves or wet fingers, dim lighting, noisy situations, etc., should be included in your testing. Please evaluate use of your

device under whatever conditions you identify as potentially occurring and hazardous.

Please describe the testing environment and realism of the simulated use in sufficient detail for us and justify how they were appropriate for validation testing.

d. Study Participants

FDA expects you to test a minimum of 15 participants from each major user group for validation of device use. Your test participants should be representative of your intended end-user populations, as described in your indications for use statement. If users with distinctly different characteristics (e.g., age ranges, skill sets, or experience levels, level of disabilities/impairments) will use your device, you should include 15 from each distinct group.

Regardless of the number of groups you test, please provide a rationale that these groups are representative the overall population of users for your device. Note that study participants should not be your own employees, or those that have been exposed to the products prior to the testing.

e. Data Collection

Any data collected and analyzed in a validation study should be described in terms of how it supports the safety case claim that your device can be used safely and effectively by the indicated users. FDA expects you to collect both empirical and qualitative data in a design validation study.

Empirical Data – Your test participants should be given an opportunity to use the device independently and in as realistic a manner as possible, without guidance, coaching, praise or critique from the test facilitator/moderator. Some data, such as successful or failed performance of key tasks or time taken to perform tasks – if time is a safety-critical criterion – should be measured directly rather than soliciting participant opinions. Observing participant behavior during the test is also important, in order to assess participants' adherence to protocol and proper technique and especially to assess and understand the nature of any errors or problems that occur.

Qualitative Data – The Agency expects you to ask open-ended questions of participants at the end of a usability validation, such as, "Did you have any difficulty using this device? [If so] can you tell me about that?" The questions should explore performance of each critical task involved in the use of the device and any problems encountered. Note that since the labeling and instructions for use are considered part of the user interface for your device, the questions should cover those components as well.

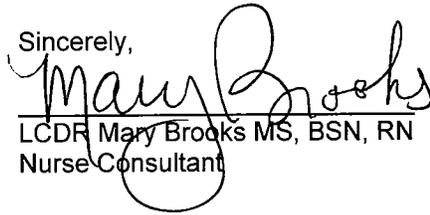
Your analysis of performance and subjective data should be directed toward understanding user performance and particularly task failures. The analysis should determine the nature of failures, the causes of failures, and the clinical impact. Every test participant who experiences a "failure" (does something that would have led to harm under actual conditions of use), should be interviewed about that failure to determine the cause of the failure from the perspective of the participant.

Please describe and provide a rationale for including each type of data you collect. Please provide a proposed protocol for the Agency to review prior to conducting the study.

4. We agree with your container-closure integrity testing protocol however. Please provide the completed test results.

If you have any questions, please contact LCDR Mary Brooks at (301) 796- 6078.

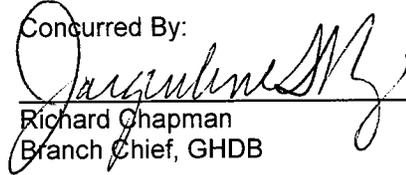
Sincerely,



Handwritten signature of Mary Brooks in cursive script.

LCDR Mary Brooks MS, BSN, RN
Nurse Consultant

Concurred By:



Handwritten signature of Richard Chapman in cursive script.

Richard Chapman
Branch Chief, GHDB

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

/s/

EUNICE H CHUNG-DAVIES
07/27/2011
on behalf of CDRH

**Interdisciplinary Review Team for QT Studies Consultation:
Thorough QT Study Review**

NDA	22150
Brand Name	Firazyr [®]
Generic Name	Icatibant
Sponsor	Jerini US, Inc., Cambridge, MA, USA
Indication	Treatment of acute attacks of hereditary angioedema
Dosage Form	Subcutaneous Injection
Drug Class	Bbradykinin B2 receptor antagonist
Therapeutic Dosing Regimen	30 mg SC
Duration of Therapeutic Use	Acute
Maximum Tolerated Dose	90 mg
Submission Number and Date	SDN 020 /25 Feb., 2010
Review Division	DPAP/ HFD 570

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No significant QTc prolongation effect of icatibant (30 and 90 mg) was detected in this TQT study. The largest upper bounds of the two-sided 90% CI for the mean differences between icatibant (30 and 90 mg) and placebo of QTcI were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the $\Delta\Delta\text{QTcI}$ for moxifloxacin was less than 5 ms, the moxifloxacin profile over time is adequately demonstrated in Figure 5, indicating that assay sensitivity was established.

In this randomized, single-center, placebo- and active-controlled, crossover study, 72 healthy subjects received icatibant 30 mg, icatibant 90 mg, placebo, and moxifloxacin 400 mg. Overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Icatibant (30 mg and 90 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (h)	$\Delta\Delta\text{QTcI}$ (ms)	90% CI (ms)
Icatibant 30 mg	3	0.8	(-2.1, 3.8)
Icatibant 90 mg	2.5	0.1	(-2.7, 3.2)
Moxifloxacin 400 mg*	3	11.2	(8.3, 14.1)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 time points is 7.2 ms.

The suprathreshold dose (90 mg) produces mean C_{max} values of 2.8-fold the mean C_{max} for the therapeutic dose (30 mg). These concentrations are above those for the predicted worst case scenario (26% increase in C_{max} in women) and show that at these concentrations there are no detectable prolongations of the QT-interval. Icatibant is a synthetic decapeptide; therefore regular drug-drug interactions due to metabolic enzyme inhibitions are not anticipated. Hepatic impairment and renal impairment do not alter icatibant clearance, and are not expected to increase icatibant C_{max} or AUC.

2 PROPOSED LABEL

2.1 THE SPONSOR PROPOSED LABEL

The sponsor did not propose any language in the label.

2.2 QT-IRT PROPOSED LABEL

QT-IRT recommends the following label language. Our recommendations are suggestions only. We defer final decisions regarding labeling to the review division.

Section 12.2 Pharmacodynamics

The effect of icatibant 30 and 90 mg following a single subcutaneous injection on QTc interval was evaluated in a randomized, placebo-, and active-controlled (moxifloxacin 400 mg) four-period crossover thorough QT study in 72 healthy subjects. In a study with demonstrated ability to detect small effects, the upper bound of the one-sided 95% confidence interval for the largest placebo adjusted, baseline-corrected QTc based on individual correction method (QTcI) was below 10 ms, the threshold for regulatory concern. The dose of 90 mg is adequate to represent the high exposure clinical scenario.

3 BACKGROUND

3.1 PRODUCT INFORMATION

Icatibant is a competitive antagonist at the bradykinin B2 receptor. Hereditary angioedema (HAE), an autosomal dominant disease, is caused by an absence or dysfunction of C1-esterase-inhibitor. HAE attacks are accompanied by an increased release of bradykinin. The sponsor is seeking approval of icatibant for treatment of acute attacks of HAE.

3.2 MARKET APPROVAL STATUS

Icatibant (under the trade name Firazyr[®]) received Marketing Authorization in the European Union on 11 July 2008. The drug was granted Orphan Drug Status in the United States on 23 November 2003. Regulatory review and/or submission in the United States and other countries are currently ongoing.

3.3 PRECLINICAL INFORMATION

hERG studies per S7B guidelines are unavailable. The sponsor reports no notable ECG effects in the acute and chronic toxicity studies in dogs.

3.4 PREVIOUS CLINICAL EXPERIENCE

Source: Summary of Clinical Safety, eCTD 2.7.4

This Summary includes the data from 3 controlled Phase III studies in which icatibant was administered for the treatment of acute attacks of HAE, one open-label Phase III study in which subjects were able to self-administer icatibant for the treatment of acute attacks of HAE, and data from 13 Phase I and II studies in which IV or SC icatibant was administered to healthy subjects or subjects with HAE.

Overall 2 subjects died, one each in tranexamic acid and placebo groups. No subject who received icatibant died during the study. Post-marketing, there has been 1 serious cardiac AE reported. A 23 year old experienced a life-threatening acute myocardial infarction diagnosed one day after the administration of Firazyr for an acute HAE attack. The patient reportedly had risk factors for coronary artery disease, however, based on the close temporal relationship between Firazyr administration and onset of symptoms and the age of the patient, the company could not exclude a possible causal relationship. Attenuation by icatibant of the protective effect of bradykinin in acute myocardial ischemia remains a theoretical possibility. The sponsor is monitoring for ischemic events in their patient registry. There are no reports of significant ventricular arrhythmias.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of icatibant's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 68,214. The sponsor submitted the study report HGT-FIR-061 for the study drug, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

The Effect of Icatibant on QT and QTc Intervals: A Randomized, Placebo Controlled, Active Comparator, Crossover Study in Healthy Adult Volunteers

4.2.2 Protocol Number

HGT-FIR-061

4.2.3 Study Dates

First subject enrolled: 16 February 2010

Last subject completed: 12 August 2010

4.2.4 Objectives

The primary objective of this study was to assess if administration of a single subcutaneous dose of icatibant (30 or 90 mg) has the potential to cause QT interval prolongation in healthy adults.

The secondary objective of this study was to characterize the pharmacokinetics of icatibant and its metabolites, M1 and M2, after subcutaneous administration of a single 30-mg or 90-mg dose of icatibant.

4.2.5 Study Description

4.2.5.1 Design

This was a Phase 1, single-center, randomized, placebo- and active-controlled, crossover design. Seventy-two subjects (36 males and 36 females) were planned for study participation. Overall, there were 82 subjects who were enrolled in the study and received at least 1 dose of study drug. Of these, 71 subjects completed all 4 treatment periods and 11 subjects received partial dosing.

4.2.5.2 Controls

The sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

The investigator and subjects were not blinded to the treatment administered in each study period, the central electrocardiogram laboratory was blinded to the subject's treatment, sequence, and the time of recording.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

Each treatment period consisted of a check-in day (Day -2 for Period 1, Day -1 for Periods 2, 3 and 4), through the treatment day (Day 1). The Day 1 dose was one of the following:

Treatment A: 1 placebo SC injection

Treatment B: 1 icatibant SC injection (3 mL, 30 mg)

Treatment C: 3 icatibant SC injections (3 mL each, 90 mg total)

Treatment D: 1 moxifloxacin tablet (400 mg orally)

The moxifloxacin tablet (400 mg) was administered orally, as a single dose, with 240 mL water. All SC injections of 3 mL each were administered in the abdominal region. There were at least 2 drug-free washout days (Days 2 and 3) separating each treatment period.

4.2.6.2 Sponsor's Justification for Doses

“Two Phase 3, multicenter, double-blind studies (1 with a placebo control, 1 with an active comparator) had shown that most patients with HAE appeared to benefit from a single 30 mg SC dose of icatibant. Thus, the lower dose selected for this study represents the proposed dose for the treatment of acute attacks of HAE.

“ A previous study of icatibant in healthy male subjects (JE049 #1001) demonstrated that the maximum tolerated dose (MTD) is 1.6 mg/kg/1h when administered by IV infusion over 1 hour. At 3.2 mg/kg/1h, mild or moderate reactions such as malaise, pruritis, flushing, and erythema lasting up to 1.5 hours were noted in all 4 subjects who received this dose. There was also one case of transient hypotension at 3.2 mg/kg, rated as possibly drug related, an event which may actually represent agonist activity of icatibant. The MTD was therefore estimated to be 1.6 mg/kg/1h.

“The formulation used in this study was 10 mg/mL. Icatibant 30 mg was administered as a single 3 mL SC injection. In a 70 kg adult, the MTD of 1.6 mg/kg corresponds to an absolute dose of 112 mg. Also, it is widely accepted that, depending on the viscosity of the injectate, etc., 2.5 to 3 mL is generally the largest volume that can physically be given in any SC injection with reasonable ease. Therefore, the high dose selected for this study (90 mg) divided in 3 SC injections of 3 mL each) represented the highest reasonable dose to be administered SC given, the limitation posed by the MTD and the volume of administration of a single SC injection (3 mL).”

Reviewer's Comments: Acceptable.

4.2.6.3 Instructions with Regard to Meals

“On the treatment day (Day 1) of each treatment period (and on Day -1 of the first treatment period during the first 24-hour ECG recording), subjects were food fasted for 10 hours prior to starting any study related procedures. No fluids were allowed on the treatment day (Day 1) from 2 hours prior to dosing until 2 hours after dosing, other than the 240 mL of water with moxifloxacin administration.

“Subjects were asked to abstain from alcohol and xanthine-containing food and beverages (eg, coffee, tea, chocolate, and cola beverages) during the in-clinic portion of the study. In addition, subjects had to abstain from all alcohol during the entire study.

“Subjects received nutritionally balanced, caffeine-free standard meals throughout the inpatient portions of the study. The nature and timing of all meals and snacks were identical between subjects.”

Reviewer's Comments: Not applicable. Icatibant was administered through subcutaneous injection.

4.2.6.4 ECG and PK Assessments

ECG Measurements:

Individual ECGs were analyzed at the following time points: pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 18, and 23 hours post-dose on Day 1 and corresponding time points on Day -1.

PK Measurements:

Blood samples were collected at pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 18, and 23 hours following study drug administration on Day 1. Plasma concentration of icatibant and metabolites, M1 and M2, were measured for all time points. Moxifloxacin samples were analyzed at the 0, 1, 2, 4, 6, and 12 hour time points.

Reviewer's Comments: Acceptable. The ECG/PK sampling time points are sufficient to cover T_{max} of icatibant and potential delayed effect up to 24 hours post-dose.

4.2.6.5 Baseline

The sponsor used QTc pre-dose values as a QTc baseline values.

4.2.7 ECG Collection

Digital 12-lead resting ECG monitoring using a continuous ECG recorder was started 15 minutes before treatment was administered on the treatment day (Day 1) of each period and continued for 23.25 hours. For Treatment Period 1 only, continuous ECG monitoring was also started in the morning of Day -1 and continued for 23.25 hours.

Individual ECGs were analyzed at time points specified above. Electrocardiogram data collected during treatment were read by an experienced cardiologist in a central laboratory who was blinded to the subjects treatment, sequence, and the time of recording.

Individual ECGs collected on Day -1 of the first treatment period were analyzed and read in the same manner as those collected on Day 1 of each treatment period.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

A total of 82 healthy subjects between the ages of 18 and 50, with a body mass index between 19 and 30 kg/m², inclusive, were eligible for study participation. Of these, 71 subjects received all planned doses of study drug and completed the study per protocol. There were 11 subjects who were prematurely withdrawn from the study, including 3 subjects for AEs, 3 subjects who failed to meet continuing eligibility criteria, 2 subjects who withdrew consent, 2 subjects who became pregnant, and 1 subject who was considered lost to follow-up.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The primary endpoint was the time-matched baseline-adjusted mean differences between icatibant (30 mg and 90 mg) and placebo in QTcI. The sponsor used an analysis of Linear Mixed Effect model and the results for QTcI are presented in Table 2. The model included baseline, treatment, period, sequence, time, with time as a repeated measure within subject. The upper limits of the 2-sided 90% CI for both icatibant 30 mg and 90 mg were below 10 ms, demonstrating that icatibant has no effect on QTcI at clinically relevant doses.

Table 2: Sponsor's results for $\Delta\Delta$ QTcI for Icatibant 30 mg BID

Time point (h)	Placebo		Icatibant 30 mg		Difference ($\Delta\Delta$ QTcI)	Two-sided 90% CI
	n	LS Mean	n	LS Mean		
0.25	70	1.3	69	1.8	0.5	(-1.7, 2.7)
0.5	70	0.9	69	0.2	-0.7	(-2.9, 1.5)
0.75	70	1.0	69	2.1	1.1	(-1.1, 3.4)
1	70	0.3	69	0.6	0.3	(-1.9, 2.5)
1.5	70	1.6	69	2.7	1.1	(-1.1, 3.3)
2	70	0.3	69	0.9	0.6	(-1.6, 2.8)
2.5	70	1.1	69	2.2	1.0	(-1.2, 3.2)
3	69	-3.5	69	-1.9	1.6	(-0.6, 3.8)
4	70	-5.8	69	-5.7	0.1	(-2.1, 2.3)
5	70	-6.4	68	-5.0	1.3	(-0.9, 3.5)
6	70	-4.1	68	-3.3	0.8	(-1.4, 3.0)
8	69	-3.6	68	-3.7	-0.1	(-2.4, 2.1)
12	69	-3.5	67	-2.9	0.5	(-1.7, 2.8)
18	69	5.2	68	5.4	0.2	(-2.0, 2.4)
23	68	2.0	67	2.8	0.8	(-1.4, 3.1)

Note(s): CI=confidence interval; LS Mean=least-squares mean.

Source: Table 7-11, page 63/505

Table 3: Sponsor's results for $\Delta\Delta$ QTcI for Icatibant 90 mg BID

Time point (h)	Placebo		Icatibant 90 mg		Difference ($\Delta\Delta$ QTcI)	Two-sided 90% CI
	n	LS Mean	n	LS Mean		
0.25	70	1.3	70	0.9	-0.3	(-2.5, 1.9)
0.5	70	0.9	70	1.1	0.1	(-2.1, 2.3)
0.75	70	1.0	70	1.8	0.8	(-1.4, 3.0)
1	70	0.3	70	0.9	0.5	(-1.7, 2.7)
1.5	70	1.6	69	2.1	0.5	(-1.7, 2.7)
2	70	0.3	69	0.2	-0.1	(-2.3, 2.1)
2.5	70	1.1	69	2.2	1.1	(-1.1, 3.3)
3	69	-3.5	69	-2.3	1.2	(-1.0, 3.4)
4	70	-5.8	69	-7.8	-1.9	(-4.2, 0.3)
5	70	-6.4	68	-5.3	1.0	(-1.2, 3.2)
6	70	-4.1	69	-4.3	-0.1	(-2.3, 2.1)
8	69	-3.6	70	-2.9	0.7	(-1.5, 2.9)
12	69	-3.5	70	-3.0	0.5	(-1.7, 2.7)
18	69	5.2	67	5.7	0.5	(-1.8, 2.7)
23	68	2.0	67	1.1	-0.9	(-3.1, 1.3)

Note(s): CI=confidence interval; LS Mean=least-squares mean.

Source: Table 7-11, page 64/505

4.2.8.2.2 Assay Sensitivity

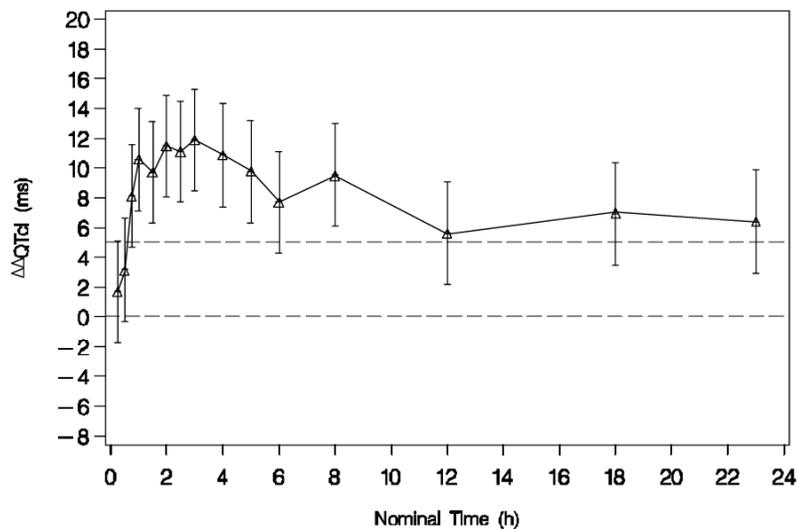
The sponsor used the same mixed model to analyze the Δ QTcI effect for moxifloxacin. The analysis results were presented in Table 4 and Figure 1. The lower limit of the two-sided 99% confidence interval for each placebo-corrected, change-from-baseline LS mean QTcI value was greater than 5 ms from 1 to 3 hours post-dose. Thus, assay sensitivity in this thorough QTc study was established.

Table 4: Sponsor’s results for $\Delta\Delta\text{QTcI}$ for Moxifloxacin 400 mg

Time point (h)	Placebo		Moxifloxacin		Difference ($\Delta\Delta\text{QTcI}$)	Two-sided 99% CI
	n	LS Mean	n	LS Mean		
1.0	70	0.3	71	10.9	10.6	(7.1, 14.0)
1.5	70	1.6	71	11.3	9.7	(6.3, 13.1)
2.0	70	0.3	71	11.8	11.5	(8.1, 14.9)
2.5	70	1.1	71	12.2	11.1	(7.7, 14.5)
3.0	69	-3.5	71	8.4	11.9	(8.5, 15.3)

Note(s): CI = confidence interval; LS Mean = least-squares mean.
Source: Table 7-10, page 62/505

Figure 1: Sponsor’s mean and 90% CI $\Delta\Delta\text{QTcI}$ Time Course for Moxifloxacin 400 mg



Reviewer’s Comments: We will provide our independent analysis result in Section 5.2.

4.2.8.2.3 Categorical Analysis

Categorical analysis was used to summarize in the categories of QTc ≤ 450 ms, between 450-480 ms, between 480-500 ms, and >500 ms, and changes from baseline QTc ≤ 30 ms, between 30-60 ms, and >60 ms. No subject’s absolute QTc above 480 ms and ΔQTc above 60 ms.

4.2.8.3 Safety Analysis

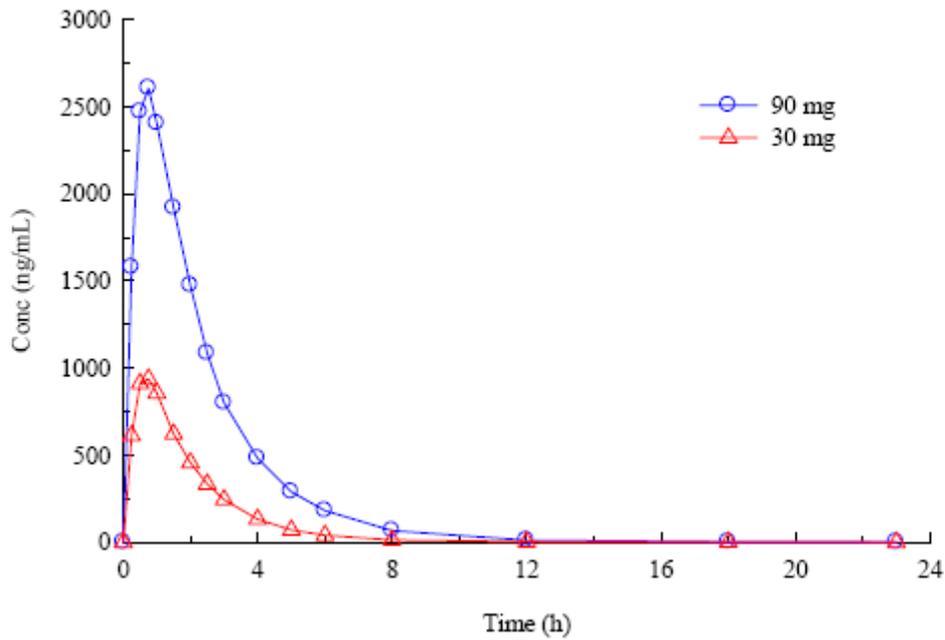
There were no deaths or SAEs in the study. As mentioned earlier 3 subjects discontinued due to AEs of increased ALT (occurred during moxifloxacin treatment period), chlamydial urethritis (began prior to dosing) and vomiting (occurred during 30 mg icatibant treatment period). Additionally, 2 subjects were withdrawn from the study for pregnancy.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The PK results of icatibant are presented in Figure 2 and summarized in Table 5. C_{max} and AUC values for 90 mg were 2.8-fold and 3.1-fold higher values obtained with the 30-mg therapeutic dose.

Figure 2: Mean Plasma Concentration of Icatibant After Subcutaneous Administration of Single 30-mg and 90-mg Doses of Icatibant to Healthy Subjects



Source: Table 7-1 page 51/505

Table 5: Summary of Pharmacokinetic Parameter Estimates for Icatibant After Subcutaneous Administration of Single 30-mg and 90-mg Doses of Icatibant to Healthy Subjects

Parameter (unit)	Icatibant Dose	
	30 mg SC (n)	90 mg SC (n)
C _{max} (ng/mL)	979 ± 262 (76)	2719 ± 666 (72)
T _{max} (h)	0.75 (76) [0.25 - 1.04]	0.75 (72) [0.49 - 1.57]
AUC _(0-t) (h·ng/mL)	2178 ± 565 (76)	6734 ± 1221 (72)
AUC _(inf) (h·ng/mL)	2191 ± 565 (75)	6736 ± 1230 (71)
λ _z (h ⁻¹)	0.4885 ± 0.0960 (75)	0.3686 ± 0.0868 (71)
t _{1/2} (h)	1.48 ± 0.35 (75)	2.00 ± 0.57 (71)
CL/F (mL/min)	241 ± 54.8 (75)	230 ± 42.3 (71)
V _z /F (L)	30.5 ± 8.08 (75)	39.3 ± 10.9 (71)
V _{ss} /F (L)	28.6 ± 8.24 (75)	31.4 ± 7.45 (71)

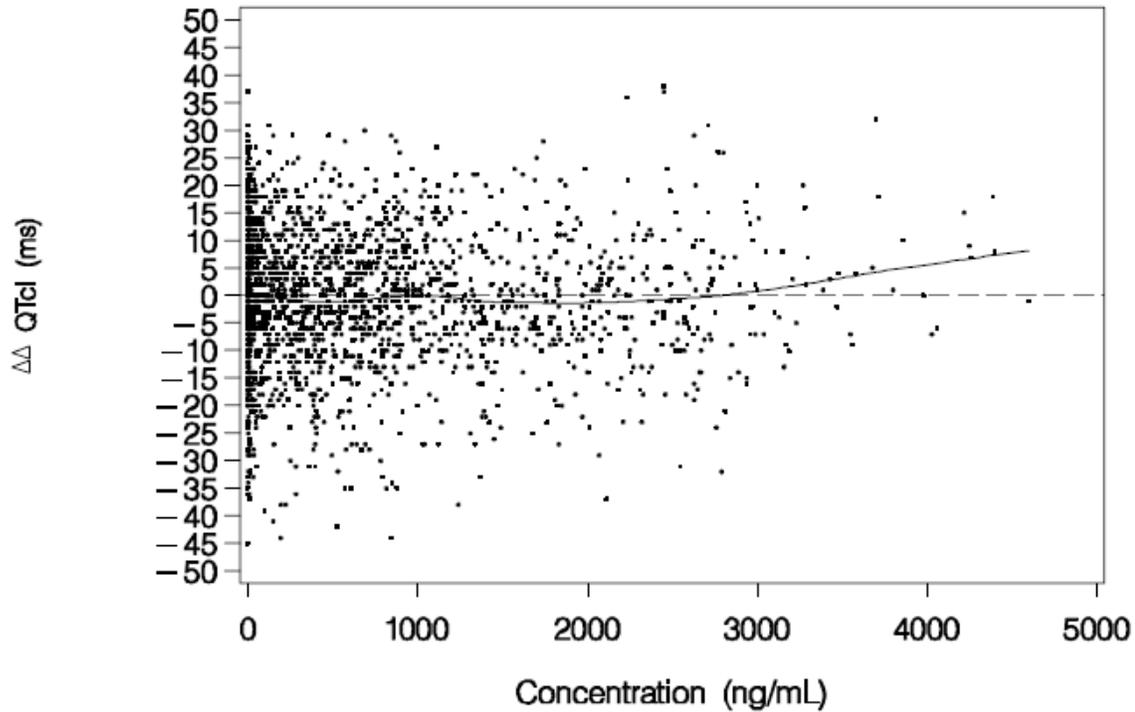
Note(s): SC = subcutaneous. Arithmetic mean ± standard deviation (n), except T_{max} for which the median (n) [range] is reported.

Source: Table 7-3 page 52/505

4.2.8.4.2 Exposure-Response Analysis

Exposure-response analysis was conducted. A plot of ΔΔQTcI vs. Icatibant demonstrated below indicated no evident exposure-response relationship.

Figure 3: Placebo-Corrected Change from Baseline QTcI versus Icatiant Concentration in Plasma.



The solid line represents a cubic spline estimate of the mean effect for a given concentration.

Source: Figure 10.2.4.4, page 218/505

Reviewer's Analysis: The reviewer independently conducted the exposure-response analysis. The results are demonstrated in 5.3.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

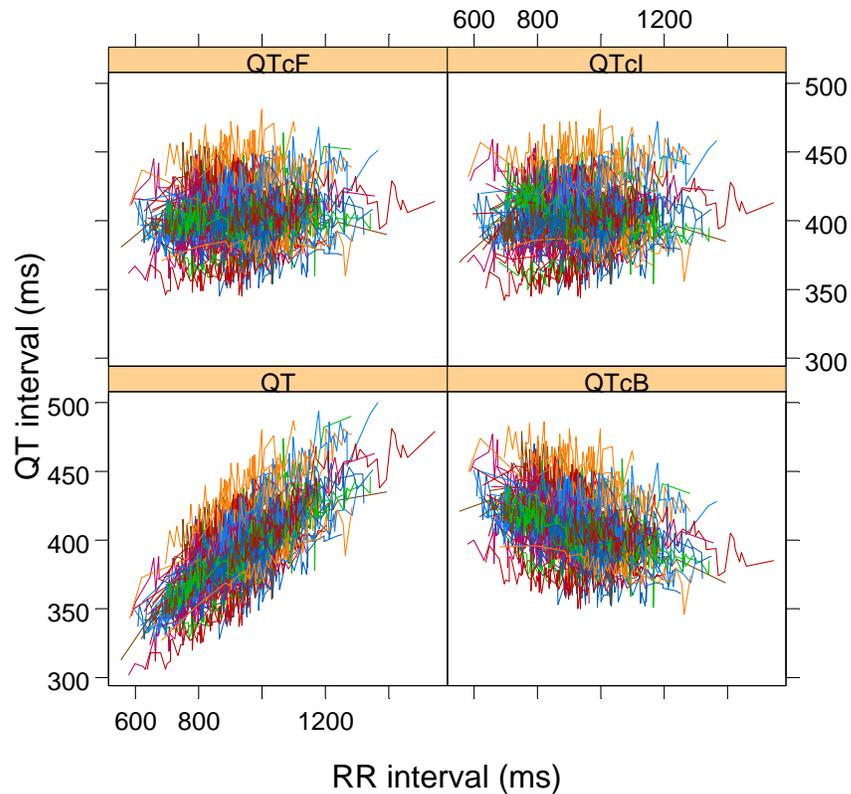
We used the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 6, it appears that QTcF and QTcI are equally better than QTcB. Therefore, this statistical reviewer used QTcI for the primary statistical analysis. This is consistent with the sponsor's choice of QTcI for their primary analysis.

Table 6: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

Treatment Group	Correction Method					
	QTcB		QTcF		QTcI	
	N	MSSS	N	MSSS	N	MSSS
Icatibant 30 mg	71	0.0051	71	0.0016	71	0.0016
Icatibant 90 mg	71	0.0042	71	0.0013	71	0.0016
Moxifloxacin 400 mg	71	0.0060	71	0.0017	71	0.0016
Placebo	71	0.0038	71	0.0017	71	0.0018
All	71	0.0038	71	0.0011	71	0.0010

The QT-RR interval relationship is presented in Figure 4 together with the Bazett's (QTcB), Fridericia (QTcF), and individual correction (QTcI).

Figure 4: QT, QTcB, QTcF, and QTcI, vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for the Study Drug

The statistical reviewer used mixed model to analyze the Δ QTcI effect. The model includes treatment as fixed effects and baseline values as a covariate. The analysis results are listed in Table 7. The largest upper bounds of the two-sided 90% CI for the mean differences between icatibant 30 mg and placebo, and between icatibant 90 mg and placebo are 3.8 ms and 3.2 ms, respectively.

Table 7: Analysis Results of Δ QTcI and $\Delta\Delta$ QTcI for Icatibant (30 mg and 90 mg) and Moxifloxacin 400 mg

Time (h)	Treatment Group														
	Placebo		Icatibant 30 mg				Icatibant 90 mg				Moxifloxacin 400 mg				
	Δ QTc		Δ QTc		$\Delta\Delta$ QTc		Δ QTc		$\Delta\Delta$ QTc		Δ QTc		$\Delta\Delta$ QTc		
	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	Adj. 90% CI	
0.25	1.9	70	1.6	-0.3	(-2.7, 2.2)	70	0.6	-1.3	(-3.7, 1.2)	71	2.9	1.0	(-1.4, 3.4)	(-2.3, 4.3)	
0.5	1.6	70	0.1	-1.5	(-4.4, 1.3)	70	0.7	-0.8	(-3.7, 2.0)	71	4.0	2.4	(-0.4, 5.3)	(-1.4, 6.3)	
0.75	1.6	70	2.0	0.3	(-2.4, 3.1)	70	1.5	-0.1	(-2.9, 2.6)	71	9.1	7.4	(4.7, 10.1)	(3.7, 11.1)	
1	1.0	70	0.5	-0.5	(-3.3, 2.3)	70	0.5	-0.4	(-3.2, 2.4)	71	10.8	9.9	(7.1, 12.7)	(6.0, 13.7)	
1.5	2.3	70	2.5	0.2	(-2.3, 2.8)	69	1.7	-0.5	(-3.1, 2.1)	71	11.2	9.0	(6.4, 11.5)	(5.5, 12.5)	
2	1.0	70	0.8	-0.2	(-2.9, 2.5)	70	-0.1	-1.1	(-3.7, 1.6)	71	11.7	10.8	(8.1, 13.4)	(7.2, 14.4)	
2.5	1.8	69	2.0	0.3	(-2.6, 3.1)	70	1.9	0.1	(-2.7, 2.9)	71	12.1	10.4	(7.6, 13.1)	(6.6, 14.2)	
3	-2.8	70	-2.0	0.8	(-2.1, 3.8)	70	-2.6	0.2	(-2.7, 3.2)	71	8.4	11.2	(8.3, 14.1)	(7.2, 15.2)	
4	-5.2	70	-5.8	-0.6	(-3.4, 2.2)	70	-8.1	-2.8	(-5.6, 0.0)	70	5.0	10.3	(7.5, 13.1)	(6.5, 14.1)	
5	-5.9	69	-5.1	0.8	(-1.9, 3.5)	69	-5.5	0.4	(-2.3, 3.1)	70	3.4	9.3	(6.6, 12.0)	(5.6, 13.0)	
6	-3.6	69	-3.4	0.2	(-2.6, 3.0)	70	-4.6	-1.0	(-3.7, 1.8)	71	3.5	7.1	(4.3, 9.9)	(3.3, 10.9)	
8	-3.1	69	-3.8	-0.7	(-3.5, 2.1)	71	-3.2	-0.1	(-2.8, 2.7)	69	6.0	9.2	(6.4, 12.0)	(5.4, 13.0)	
12	-3.0	69	-3.0	0.0	(-2.9, 2.9)	71	-3.3	-0.3	(-3.2, 2.5)	71	2.0	5.0	(2.2, 7.9)	(1.2, 8.9)	
18	5.8	70	5.2	-0.6	(-3.7, 2.6)	68	5.1	-0.7	(-3.8, 2.5)	70	12.0	6.2	(3.1, 9.3)	(2.0, 10.5)	
23	2.6	69	2.6	0.1	(-2.9, 3.0)	68	0.7	-1.9	(-4.8, 1.0)	68	8.5	5.9	(3.0, 8.8)	(1.9, 9.9)	

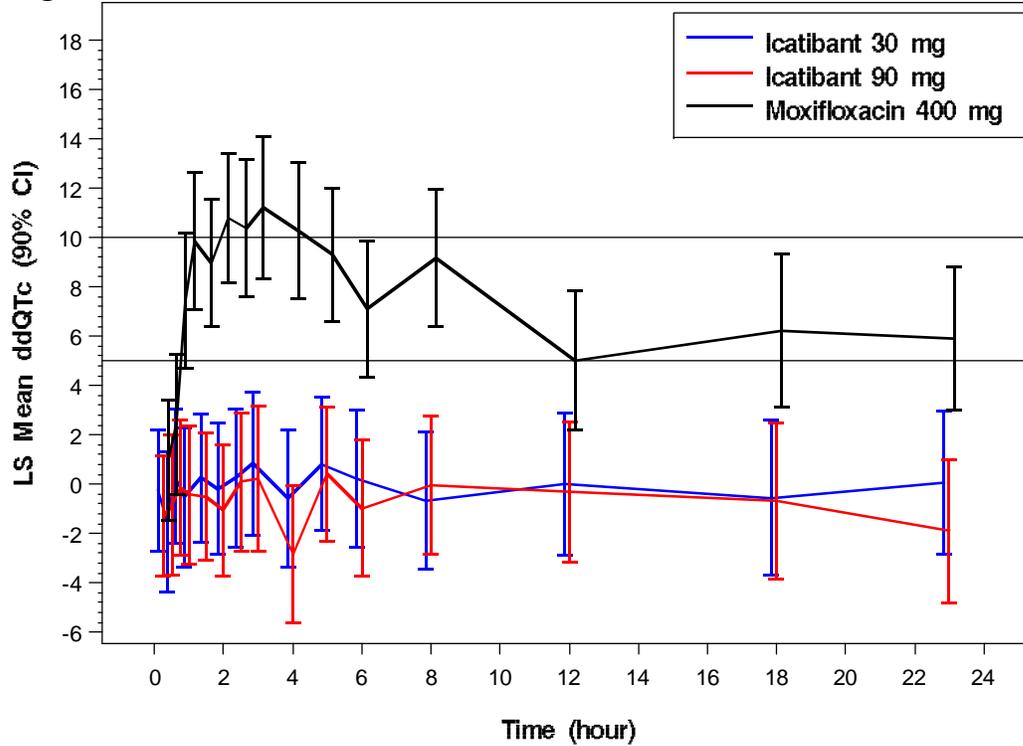
5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 7. The largest unadjusted 90% lower confidence interval is 8.3 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval is 7.2 ms, which indicates that an at least 5 ms QTcI effect due to moxifloxacin can be detected from the study.

5.2.1.3 Graph of $\Delta\Delta QTcI$ Over Time

Figure 5 displays the time profile of $\Delta\Delta QTcI$ for icatibant treatment groups and moxifloxacin 400 mg.

Figure 5: Mean and 90% CI $\Delta\Delta QTcI$ Time Course for Icatibant and Moxifloxacin



5.2.1.4 Categorical Analysis

Table 8 lists the number of subjects as well as the number of observations whose QTcI values are ≤ 450 ms, between 450 ms and 480 ms and between 480 ms and 500 ms. No subject's QTcI is above 500 ms.

Table 8: Categorical Analysis for QTcI

Treatment Group	Total N	Value ≤ 450 ms	450 ms < Value ≤ 480 ms	480 ms < Value ≤ 500 ms
Icatibant 30 mg	71	68 (95.8%)	3 (4.2%)	0 (0.0%)
Icatibant 90 mg	71	67 (94.4%)	4 (5.6%)	0 (0.0%)
Moxifloxacin 400 mg	71	64 (90.1%)	7 (9.9%)	0 (0.0%)
Placebo	71	69 (97.2%)	1 (1.4%)	1 (1.4%)

Table 9 lists the categorical analysis for $\Delta QTcI$. No subject's change from baseline is above 60 ms.

Table 9: Categorical Analysis of $\Delta QTcI$

Treatment Group	Total N	Value \leq 30 ms	30 ms<Value \leq 60 ms
Icatibant 30 mg	69	68 (98.6%)	1 (1.4%)
Icatibant 90 mg	70	68 (97.1%)	2 (2.9%)
Moxifloxacin 400 mg	71	62 (87.3%)	9 (12.7%)
Placebo	70	67 (95.7%)	3 (4.3%)

5.2.2 HR Analysis

The same statistical analysis was performed based on HR interval. The point estimates and the 90% confidence intervals are presented in Table 10. The largest upper bounds of the two-sided 90% CI for the HR mean differences between icatibant 30 mg and placebo, and between icatibant 90 mg and placebo are 4.9 bpm and 3.9 bpm, respectively. Table 11 presents the categorical analysis of HR. One subject who experienced HR interval greater than 100 bpm in icatibant 90-mg group. Table 12 presents the list of individual subjects with HR \geq 100 bpm in treatment groups.

Table 10: Analysis Results of ΔHR and $\Delta\Delta HR$ for Icatibant (30 mg and 90 mg) and Moxifloxacin 400 mg

Time (hrs.)	Treatment Group												
	Placebo	Icatibant 30 mg				Icatibant 90 mg				Moxifloxacin 400 mg			
		LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean
0.25	-2.5	70	-2.1	0.4	(-1.5, 2.3)	70	-2.6	-0.1	(-2.0, 1.8)	71	-4.4	-1.9	(-3.8, -0.0)
0.5	-2.3	70	-2.1	0.2	(-1.7, 2.2)	70	-2.9	-0.6	(-2.5, 1.3)	71	-3.7	-1.4	(-3.3, 0.5)
0.75	-3.5	70	-2.6	0.8	(-1.1, 2.7)	70	-2.2	1.2	(-0.6, 3.1)	71	-2.6	0.9	(-1.0, 2.8)
1	-3.0	70	-2.8	0.2	(-2.1, 2.5)	70	-1.4	1.6	(-0.7, 3.9)	71	-0.5	2.5	(0.2, 4.7)
1.5	-3.8	70	-3.4	0.4	(-1.7, 2.5)	69	-3.2	0.6	(-1.5, 2.8)	71	-2.5	1.3	(-0.8, 3.5)
2	-2.3	70	-2.8	-0.5	(-2.5, 1.6)	70	-2.9	-0.6	(-2.6, 1.5)	71	-1.7	0.6	(-1.5, 2.6)
2.5	-0.6	69	0.0	0.6	(-1.7, 2.9)	70	-1.2	-0.6	(-2.9, 1.7)	71	-1.4	-0.8	(-3.0, 1.5)
3	1.3	70	1.8	0.5	(-1.8, 2.9)	70	0.6	-0.7	(-3.1, 1.6)	71	0.2	-1.1	(-3.4, 1.3)
4	1.7	70	2.2	0.4	(-1.8, 2.7)	70	1.8	0.0	(-2.2, 2.3)	70	1.7	0.0	(-2.2, 2.2)
5	4.1	69	4.5	0.4	(-1.8, 2.7)	69	3.4	-0.7	(-2.9, 1.6)	70	5.2	1.1	(-1.1, 3.4)
6	4.3	69	4.7	0.4	(-1.8, 2.6)	70	4.2	-0.1	(-2.3, 2.1)	71	5.9	1.6	(-0.6, 3.8)
8	1.4	69	2.3	0.9	(-1.3, 3.1)	71	1.6	0.2	(-1.9, 2.4)	69	3.3	1.9	(-0.2, 4.1)
12	5.9	69	7.4	1.5	(-0.9, 3.9)	71	6.1	0.2	(-2.2, 2.6)	71	6.6	0.7	(-1.7, 3.1)
18	-3.9	70	-2.7	1.2	(-1.1, 3.6)	68	-4.0	-0.1	(-2.4, 2.3)	70	-3.4	0.5	(-1.8, 2.9)
23	-1.7	69	1.0	2.7	(0.6, 4.9)	68	-1.2	0.5	(-1.7, 2.6)	68	-0.6	1.1	(-1.0, 3.3)

Table 11: Categorical Analysis for HR

Treatment Group	Total N	HR < 100 bpm	HR >=100 bpm
Icatibant 30 mg	71	71 (100%)	0 (0.0%)
Icatibant 90 mg	71	70 (98.6%)	1 (1.4%)
Moxifloxacin 400 mg	71	70 (98.6%)	1 (1.4%)
Placebo	71	70 (98.6%)	1 (1.4%)

Table 12: List of Subjects with HR > 100 bpm

Subject ID	Treatment	Day	Time (hr)	HR at Baseline	HR at Post-Dose	HR Change
HGT-FIR-061-001-062	Icatibant 90 mg	1	1	80.0	109.0	29.0

5.2.3 PR Analysis

The same statistical analysis was performed based on PR interval. The point estimates and the 90% confidence intervals are presented in Table 13. The largest upper bounds of the two-sided 90% CI for the PR mean differences between icatibant 30 mg and placebo, and between icatibant 90 mg and placebo are 4.3 ms and 4.7 ms, respectively. Table 14 presents the categorical analysis of PR. Eight subjects who experienced PR interval greater than 200 ms in icatibant treatment groups. Table 15 presents the list of individual subjects with PR \geq 200 ms in treatment groups.

Table 13: Analysis Results of Δ PR and $\Delta\Delta$ PR for Icatibant (30 mg and 90 mg) and Moxifloxacin 400 mg

		Treatment Group											
		Icatibant 30 mg				Icatibant 90 mg				Moxifloxacin 400 mg			
Placebo		Δ PR		$\Delta\Delta$ PR		Δ PR		$\Delta\Delta$ PR		Δ PR		$\Delta\Delta$ PR	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
0.25	2.1	70	2.0	-0.2	(-2.4, 2.0)	70	2.9	0.7	(-1.5, 3.0)	71	3.0	0.8	(-1.4, 3.0)
0.5	2.8	70	2.1	-0.7	(-3.1, 1.8)	70	4.0	1.2	(-1.2, 3.7)	71	2.9	0.2	(-2.3, 2.6)
0.75	3.7	70	2.5	-1.1	(-3.6, 1.4)	70	4.5	0.8	(-1.7, 3.3)	71	1.9	-1.8	(-4.3, 0.7)
1	2.8	70	1.7	-1.0	(-3.4, 1.4)	70	3.4	0.6	(-1.8, 3.0)	71	2.2	-0.6	(-2.9, 1.8)
1.5	2.8	70	2.3	-0.5	(-2.9, 1.8)	69	3.5	0.7	(-1.7, 3.0)	71	2.1	-0.7	(-3.1, 1.6)
2	1.5	70	3.3	1.9	(-0.6, 4.3)	70	3.7	2.3	(-0.2, 4.7)	71	1.3	-0.1	(-2.6, 2.3)
2.5	-0.1	69	0.5	0.5	(-2.2, 3.3)	70	2.5	2.5	(-0.2, 5.3)	71	0.1	0.2	(-2.5, 2.9)
3	1.4	70	0.9	-0.5	(-3.0, 1.9)	70	3.3	1.9	(-0.6, 4.3)	71	-0.2	-1.6	(-4.1, 0.8)
4	-0.9	70	0.3	1.2	(-1.3, 3.7)	70	0.7	1.6	(-0.9, 4.2)	70	-1.8	-0.9	(-3.4, 1.7)
5	-2.9	69	-1.7	1.2	(-1.2, 3.7)	69	-0.8	2.1	(-0.3, 4.6)	70	-4.1	-1.2	(-3.7, 1.2)
6	-3.7	69	-2.6	1.1	(-1.5, 3.7)	70	-2.3	1.3	(-1.2, 3.9)	71	-5.3	-1.7	(-4.2, 0.9)
8	-2.4	69	-2.2	0.1	(-2.4, 2.6)	71	-2.1	0.2	(-2.3, 2.7)	69	-4.1	-1.8	(-4.2, 0.7)
12	-1.4	69	-1.4	-0.0	(-2.9, 2.8)	71	-0.8	0.6	(-2.2, 3.4)	71	-1.1	0.3	(-2.5, 3.1)
18	5.2	70	5.3	0.2	(-2.9, 3.2)	68	4.8	-0.4	(-3.5, 2.7)	70	5.7	0.6	(-2.5, 3.6)
23	2.4	69	2.1	-0.3	(-2.7, 2.2)	68	3.6	1.2	(-1.3, 3.7)	68	2.3	-0.1	(-2.6, 2.3)

Table 14: Categorical Analysis of PR

Treatment Group	Total	PR <200 ms	PR \geq 200 ms
	N		
Icatibant 30 mg	71	66 (93.0%)	5 (7.0%)
Icatibant 90 mg	71	64 (90.1%)	7 (9.9%)
Moxifloxacin 400 mg	71	68 (95.8%)	3 (4.2%)
Placebo	71	64 (90.1%)	7 (9.9%)

Table 15: List of Subjects with PR > 200 ms

Subject ID	Treatment	Day	Time (h)	PR at Baseline	PR at Post-Dose	PR Change
HGT-FIR-061-001-003	Icatibant 30 mg	1	18	187.0	203.0	16.0
HGT-FIR-061-001-008	Icatibant 90 mg	1	0.75	195.0	201.0	6.0
HGT-FIR-061-001-018	Icatibant 30 mg	1	0.25	220.0	219.0	-1.0
	Icatibant 30 mg	1	0.5	220.0	216.0	-4.0
	Icatibant 30 mg	1	0.75	220.0	214.0	-6.0
	Icatibant 30 mg	1	1	220.0	201.0	-19.0
	Icatibant 30 mg	1	1.5	220.0	220.0	0.0
	Icatibant 30 mg	1	2	220.0	217.0	-3.0
	Icatibant 30 mg	1	2.5	220.0	203.0	-17.0
	Icatibant 30 mg	1	3	220.0	201.0	-19.0
	Icatibant 30 mg	1	4	220.0	202.0	-18.0
	Icatibant 90 mg	1	0.25	187.0	214.0	27.0
	Icatibant 90 mg	1	0.75	187.0	204.0	17.0
	Icatibant 90 mg	1	1	187.0	200.0	13.0
	Icatibant 90 mg	1	1.5	187.0	216.0	29.0
	Icatibant 90 mg	1	2	187.0	214.0	27.0
	Icatibant 90 mg	1	2.5	187.0	212.0	25.0
	Icatibant 90 mg	1	3	187.0	208.0	21.0
HGT-FIR-061-001-041	Icatibant 30 mg	1	0.25	197.0	207.0	10.0
	Icatibant 30 mg	1	0.5	197.0	212.0	15.0
	Icatibant 30 mg	1	0.75	197.0	205.0	8.0
	Icatibant 30 mg	1	1	197.0	208.0	11.0
	Icatibant 30 mg	1	1.5	197.0	208.0	11.0
	Icatibant 30 mg	1	2	197.0	206.0	9.0
	Icatibant 30 mg	1	2.5	197.0	207.0	10.0
	Icatibant 30 mg	1	3	197.0	212.0	15.0
	Icatibant 30 mg	1	4	197.0	208.0	11.0
	Icatibant 30 mg	1	5	197.0	206.0	9.0
	Icatibant 30 mg	1	6	197.0	212.0	15.0
	Icatibant 30 mg	1	8	197.0	203.0	6.0
	Icatibant 30 mg	1	12	197.0	213.0	16.0

Subject ID	Treatment	Day	Time (h)	PR at Baseline	PR at Post-Dose	PR Change
	Icatibant 30 mg	1	18	197.0	205.0	8.0
	Icatibant 90 mg	1	0.25	209.0	206.0	-3.0
	Icatibant 90 mg	1	0.5	209.0	206.0	-3.0
	Icatibant 90 mg	1	0.75	209.0	210.0	1.0
	Icatibant 90 mg	1	1	209.0	213.0	4.0
	Icatibant 90 mg	1	1.5	209.0	206.0	-3.0
	Icatibant 90 mg	1	2	209.0	206.0	-3.0
	Icatibant 90 mg	1	2.5	209.0	206.0	-3.0
	Icatibant 90 mg	1	3	209.0	211.0	2.0
	Icatibant 90 mg	1	4	209.0	207.0	-2.0
	Icatibant 90 mg	1	5	209.0	206.0	-3.0
	Icatibant 90 mg	1	6	209.0	202.0	-7.0
	Icatibant 90 mg	1	8	209.0	205.0	-4.0
	Icatibant 90 mg	1	12	209.0	206.0	-3.0
	Icatibant 90 mg	1	18	209.0	208.0	-1.0
	Icatibant 90 mg	1	23	209.0	202.0	-7.0
HGT-FIR-061-001-047	Icatibant 90 mg	1	23	193.0	207.0	14.0
HGT-FIR-061-001-070	Icatibant 30 mg	1	18	200.0	205.0	5.0
	Icatibant 90 mg	1	12	182.0	205.0	23.0
HGT-FIR-061-001-125	Icatibant 30 mg	1	18	186.0	206.0	20.0
	Icatibant 90 mg	1	18	171.0	206.0	35.0
HGT-FIR-061-001-127	Icatibant 90 mg	1	0.75	182.0	201.0	19.0

5.2.4 QRS Analysis

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in Table 16. The largest upper bounds of the two-sided 90% CI for the QRS mean differences between icatibant 30 mg and placebo, and between icatibant 90 mg placebo are 1.6 ms and 1.6 ms, respectively. No subject who experienced QRS interval greater than 110 ms in icatibant treatment groups.

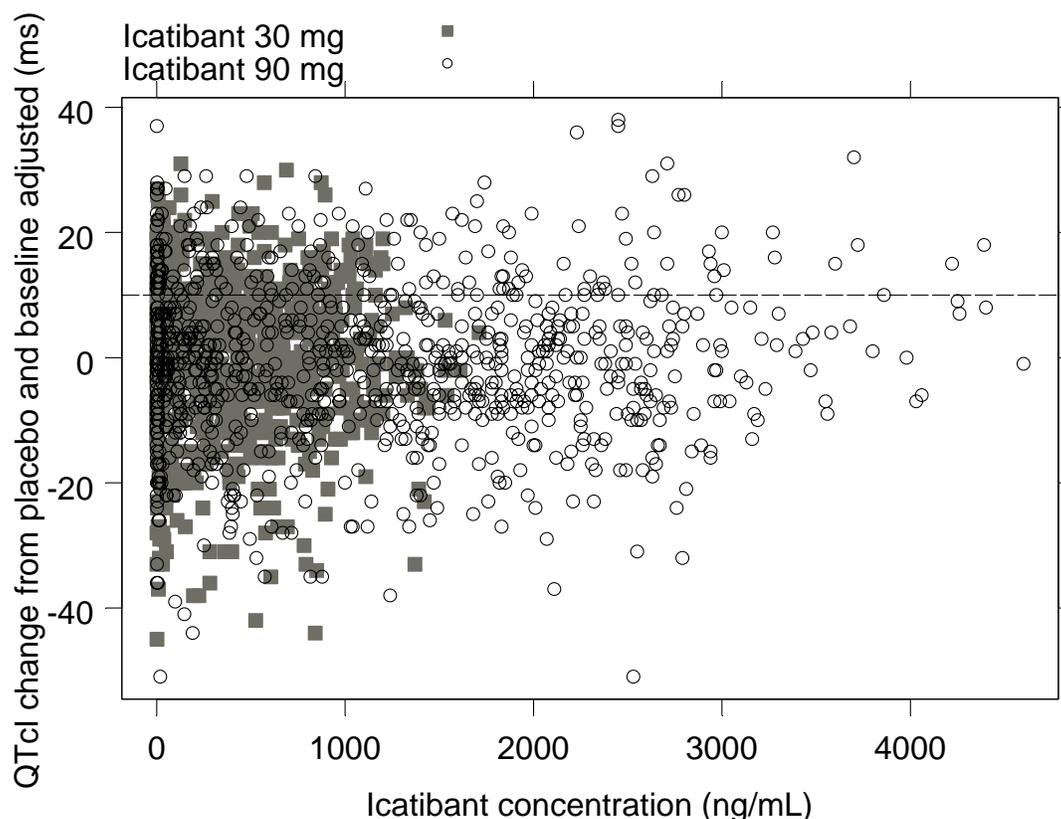
Table 16: Analysis Results of Δ QRS and $\Delta\Delta$ QRS for Icatibant (30 mg and 90 mg) and Moxifloxacin 400 mg

		Treatment Group													
		Icatibant 30 mg				Icatibant 90 mg				Moxifloxacin 400 mg					
		Placebo		Δ QRS		$\Delta\Delta$ QRS		Δ QRS		$\Delta\Delta$ QRS		Δ QRS		$\Delta\Delta$ QRS	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI		
0.25	0.4	70	0.7	0.3	(-0.5, 1.1)	70	1.0	0.6	(-0.3, 1.4)	71	1.0	0.6	(-0.3, 1.4)		
0.5	0.8	70	0.5	-0.2	(-1.1, 0.6)	70	1.0	0.2	(-0.6, 1.0)	71	0.6	-0.1	(-1.0, 0.7)		
0.75	0.4	70	0.9	0.5	(-0.4, 1.3)	70	0.7	0.2	(-0.6, 1.1)	71	0.6	0.2	(-0.7, 1.1)		
1	0.5	70	1.2	0.6	(-0.3, 1.5)	70	0.8	0.2	(-0.7, 1.2)	71	0.9	0.3	(-0.6, 1.2)		
1.5	0.3	70	0.9	0.6	(-0.2, 1.5)	69	0.6	0.3	(-0.6, 1.1)	71	0.7	0.4	(-0.4, 1.3)		
2	0.5	70	0.7	0.2	(-0.7, 1.1)	70	0.6	0.1	(-0.7, 1.0)	71	0.5	0.0	(-0.8, 0.9)		
2.5	1.0	69	0.9	-0.0	(-1.0, 0.9)	70	1.1	0.2	(-0.8, 1.1)	71	0.7	-0.2	(-1.2, 0.7)		
3	1.1	70	1.1	0.0	(-0.9, 1.0)	70	1.0	-0.1	(-1.1, 0.8)	71	1.0	-0.1	(-1.0, 0.9)		
4	0.2	70	0.3	0.1	(-0.8, 1.1)	70	0.2	0.0	(-0.9, 1.0)	70	0.2	0.0	(-0.9, 1.0)		
5	0.7	69	1.2	0.5	(-0.5, 1.6)	69	1.3	0.6	(-0.4, 1.6)	70	0.5	-0.2	(-1.2, 0.8)		
6	0.1	69	0.2	0.1	(-0.8, 1.1)	70	0.3	0.2	(-0.7, 1.2)	71	0.0	-0.1	(-1.1, 0.9)		
8	-0.4	69	-0.0	0.4	(-0.5, 1.3)	71	-0.0	0.4	(-0.5, 1.3)	69	-0.1	0.3	(-0.6, 1.2)		
12	0.5	69	0.3	-0.2	(-1.2, 0.8)	71	0.1	-0.5	(-1.4, 0.5)	71	-0.2	-0.7	(-1.7, 0.3)		
18	1.6	70	1.8	0.2	(-0.9, 1.3)	68	1.7	0.1	(-1.0, 1.2)	70	1.4	-0.2	(-1.3, 0.9)		
23	0.6	69	0.6	0.0	(-1.0, 1.0)	68	1.0	0.4	(-0.6, 1.4)	68	0.8	0.2	(-0.8, 1.2)		

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The relationship between $\Delta\Delta$ QTcI and icatibant concentrations is visualized in Figure 6 with no evident exposure-response relationship.

Figure 6: $\Delta\Delta\text{QTcI}$ vs. Icatibant Concentration



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

5.4.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. According to ECG warehouse statistics over 94% of the ECGs were annotated in the primary lead II with V5 being the usual back-up lead. Less than 0.05% of ECGs were reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

There were no clinically relevant effects on the PR and QRS intervals. Subjects with a post-treatment PR interval of over 200 ms had a change from baseline that was less than 25%.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

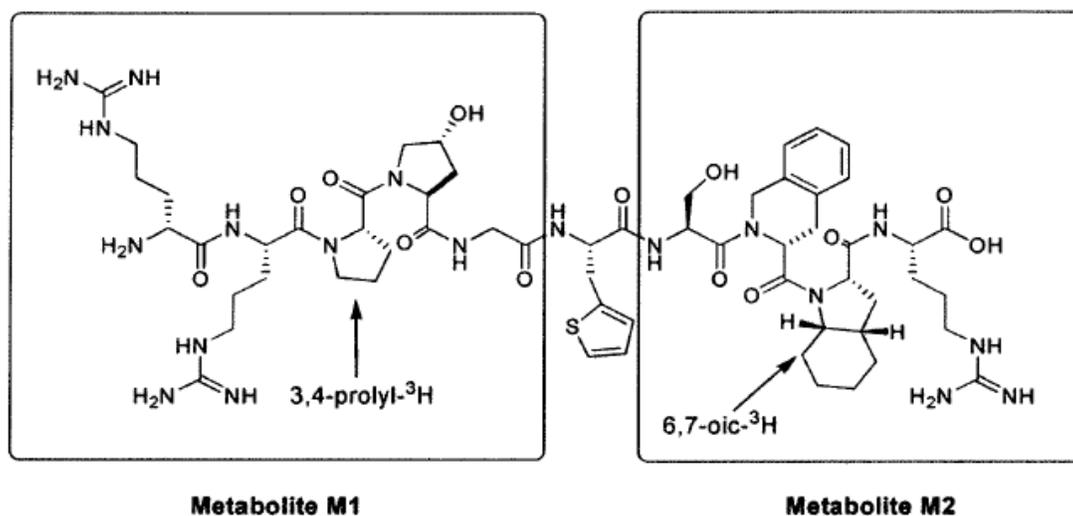
Therapeutic dose	The recommended dose of icatibant is one subcutaneous (SC) injection of 30 mg. In the majority of cases, a single injection of icatibant is sufficient to treat an attack of hereditary angioedema (HAE). In case of insufficient relief or recurrence of symptoms, a second SC injection of icatibant 30 mg can be administered after 6 hours. If the second injection produces insufficient relief or a recurrence of symptoms is observed, a third injection of icatibant 30 mg can be administered after a further 6 hours. No more than 3 injections of icatibant should be administered in a 24 hour period.	
Maximum tolerated dose	1.6 mg/kg intravenous (IV) infusion over 1 hour (Study JE049 #1001) 45 mg SC (Study JE049 #2101)r	
Principal adverse events	Almost all subjects who were treated with SC icatibant in clinical trials developed reactions at the site of injection including erythema, swelling, warm sensation, burning, itching, and/or cutaneous pain. These reactions were generally mild in severity, transient, and resolved without further intervention.	
Maximum dose tested	Single Dose	IV: 3.2 mg/kg infused over 1 hour (Study JE049 #1001) SC: 45 mg (Study JE049 #2101)
	Multiple Dose	NA
Exposures Achieved at Maximum Tested Dose	Single Dose	<u>IV 3.2 mg/kg infused over 1 hours (Study JE049 #1001)</u> <ul style="list-style-type: none"> C_{max} = 7493 ng/mL AUC = 10384 ng•h/mL <u>SC: 45 mg (Study JE049 #2101)</u> <ul style="list-style-type: none"> C_{max} = 2230 ng/mL (CV=18%) AUC = 5687 ng•h/mL (CV=20%)
	Multiple Dose	Icatibant t _{1/2} is 1 to 2 hours, and icatibant is not expected to accumulate with multiple dosing.
Range of linear PK	IV: 0.1 to 3.2 mg/kg, 1 to 4 hour infusion (Study JE043 #1001) SC: nonlinear dose proportionality from 30 to 45 mg SC (mean C _{max} increased 1.7-fold, mean AUC increased 2.1-fold) (Study JE049 #2101)	
Accumulation at steady state	Icatibant t _{1/2} is approximately 1 to 2 hours, and icatibant is not expected to accumulate with multiple dosing at 6-hour intervals.	
Metabolites	Icatibant is primarily metabolized to two inactive metabolites, namely M1 and M2, by unidentified proteolytic enzymes (see Figure 1 below). Icatibant is not metabolized by hepatic CYP450 enzymes.	
Absorption	Absolute/Relative Bioavailability	mean absolute bioavailability for icatibant 0.4 mg/kg SC administration is 97% (10 mg/mL solution, Study JE049 #1102)
	T _{max}	<u>SC 30 mg (Study JE049 #2101)</u> <ul style="list-style-type: none"> T_{max} = 0.75 h (CV=39%)

Distribution	Vd/F or Vd	<u>SC 30 mg (Study JE049 #1103, young men)</u> • Vd/F = 18 L (CV=6%)
	% bound	44% bound (CV=7%) (Study JE049-0310)
Elimination	Route	• Icatibant is primarily metabolized to M1 and M2 by unidentified proteolytic enzymes (see Figure 1 below). • 1.5% to 5% of the icatibant dose is recovered un urine as unchanged parent drug. (Study JE049 #9101)
	Terminal t _{1/2}	<u>30 mg SC (Study JE049 #2101)</u> • T _{1/2} = 1.1 h (CV=23%)
	CL/F or CL	<u>30 mg SC (Study JE049 #1103, young men)</u> • CL/F = 25 L/h (CV=5%)
Intrinsic Factors	Age	<u>30 mg SC (Study JE049 #1103)</u> • C _{max} ↑ 20% in elderly • AUC ↑ 60% to 126% in elderly Population PK analysis shows a smaller age difference of 50% to 60% higher AUC in elderly (pooled studies JE049 #1001, #1101, #1102, #1103, #2001, #2002, and #2101 – Report JE049-5120).
	Sex	<u>30 mg SC (Study JE049 #1103)</u> • C _{max} ↑ 23% to 126% in women • AUC ↑ 44% to 76% in women Population PK analysis shows a smaller sex difference (pooled studies JE049 #1001, #1101, #1102, #1103, #2001, #2002, and #2101 – Report JE049-5120).
	Race	Not evaluated
	Hepatic & Renal Impairment	No effect of hepatic impairment on icatibant, M1, and M2 (Studies JE049 #2001 and #2002) No effect of renal impairment on icatibant, M1, and M2 (Studies JE049 #2001)
Extrinsic Factors	Drug interactions	Drug interaction studies were not performed
	Food Effects	Not applicable for SC administration
Expected High Clinical Exposure Scenario	Hepatic impairment and renal impairment do not alter icatibant clearance, and there are no known metabolic drug interactions that are expected to increase icatibant C _{max} or AUC. Elderly subjects have higher icatibant exposure than adults and women have slightly higher icatibant exposure than men, partially explained by smaller body weight (study JE049 #1103). However, the interpretation of this study is confounded by a few PK outlier elderly men and women. A population	

PK analysis of pooled data from several studies indicates that the difference between men and women may be smaller than the difference seen in study JE049 #1103. Therefore, a suprathreshold dose of 90 mg SC (3-fold higher than the standard dose of 30 mg SC) is considered sufficient to cover the worst case scenario.

Additionally, nonlinear dose proportionality was seen between 30 mg SC and 45 mg SC doses (mean C_{max} increased 1.7-fold, mean AUC increased 2.1-fold, Study JE049 #2101), implying that the suprathreshold dose of 90 mg SC may provide more than 3-fold higher C_{max} and AUC than the standard therapeutic dose of 30 mg SC

Figure 1 Structure of icatibant showing the positions of radiolabeling and also the structures of the principal metabolites M1 and M2



6.2 TABLE OF STUDY ASSESSMENTS

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/s/

MOH JEE NG
05/26/2011

JOANNE ZHANG
05/26/2011

HAO ZHU
05/26/2011
Dr. Fang Li is the primary Clinical Pharmacology reviewer.

SUCHITRA M BALAKRISHNAN
05/26/2011

NORMAN L STOCKBRIDGE
05/26/2011

**ADRA Rev #1 of Action Package for NDA 22-150, Firazyr
30 mg/3 mL**

(b) (4)

Reviewer: Lee Ripper, HFD-102
Date received: 3-28-08
Date of review: 4-1 and 23-08
Date original NDA received: 10-26-07
UF goal date: 4-25-08

Proposed Indication: Tx of hereditary angioedema in patients 18 yo and older
Action type: NA
RPM: Carol Hill
Drug Classification: 1P
505(b)(1) application

Debarment Certification: AC
Financial Disclosure: AC, no disclosable financial arrangements
Safety Update: No amendment was identified by the applicant as a SU. However, the MOR notes that "In the revised ISS submitted December 28, 2007, the Applicant included updated safety data up to September 30, 2007." Acceptable for this NA action.
Risk Management Plan: N/A
Clinical Inspection Summary: Data appear reliable 3/31/08
DMEDP Review of Proprietary Name: AC 5/9/07 and 3/10/08
DRISK Review of PPI: No PPI
DDMAC Review: Proprietary name AC per DMETS review of 5/9/07; PI and labeling review 11/20/07
SEALD Review of PLR: None
EA: Categorical exclusion granted per DD review 3/17/08
EER: 5 facilities pending as of 4/1/08
PSC/WU Mtg: N/A
CDTL Review: Sally Seymour, 3/20/08

CMC DD review completed by Blair Fraser 3/17/08
P/T section to Paul Brown 4/1/08, CM 4/3/08

At the time of action on 4/23/08, inspections for four foreign facilities were outstanding. We were later notified that the inspection results for (b) (4) were unacceptable. A warning letter to (b) (4) is possible. Scheduling for the other two foreign inspections has not been confirmed but is in process.

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/s/

Leah Ripper
4/23/2008 04:06:34 PM
CSO

REGULATORY PROJECT MANAGER PLR FORMAT LABELING REVIEW

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: NDA 22150

Name of Drug: Firazyr (icatibant)

Applicant: Shire Human Genetic Therapies, Inc.

Labeling Reviewed

Submission Date: February 25, 2011

Receipt Date: February 25, 2011

Background and Summary Description

This is a resubmission to the “Not Approvable” action, dated April 23, 2008, for this original NDA submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Firazyr (icatibant) injection for the treatment of hereditary angioedema. The sponsor has submitted their proposed labeling in PLR format.

Review

The submitted labeling was reviewed in accordance with 21 CFR 201.56 and 201.57 and relevant labeling guidance. The PLR label review tool was used to review the labeling. The following should be addressed by the sponsor:

Highlights

1. Extend the dashed line, which separates the headings in this section, to the end of each side of the column.
2. For the 4th bullet in Dosage and Administration, command language should be used as follows:
Change From: (b) (4)
Change To: Do not administer more than 3 injections in 24 hours.
3. With regard to the Patient Counseling Information, use the following statement:
 - a. See 17 for Patient Counseling information and FDA-approved patient labeling (Instructions for Use)

4. The revision date at the end of the highlights replaces the “revision” or “issued” date at the end of the Full Prescribing Information and should not appear in both places.

Full Prescribing Information: Contents

5. The headings under the Table of Contents must be identical to the headings in the Full Prescribing information.

For Example:

- a. Change From: [REDACTED] (b) (4)
Change To: 8.6 Hepatic and Renal Insufficiency

5. [REDACTED] (b) (4) The Instructions for Use [REDACTED] (b) (4) section should be included at the end of the package insert [REDACTED] (b) (4).

Recommendations

All labeling issues identified in the review will be conveyed to the applicant in an information request. The applicant will be asked to resubmit labeling that addresses all the identified labeling issues by April 29, 2011. The resubmitted labeling will be used for further labeling discussions.

Eunice Chung-Davies	April 20, 2011
Regulatory Project Manager	Date
Sandy Barnes	April 22, 2011
Chief, Project Management Staff	Date

Selected Requirements for Prescribing Information (SRPI)

This document is meant to be used as a checklist in order to identify critical issues during labeling development and review. For additional information concerning the content and format of the prescribing information, see regulatory requirements (21 CFR 201.56 and 201.57) and labeling guidances. When used in reviewing the PI, only identified deficiencies should be checked.

Highlights (HL)

- **General comments**

- HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
- HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.
- There is no redundancy of information.
- If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
- A horizontal line must separate the HL and Table of Contents (TOC).
- All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
- Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- Section headings are presented in the following order:

• Highlights Limitation Statement (required statement)
• Drug names, dosage form, route of administration, and controlled substance symbol, if applicable (required information)
• Initial U.S. Approval (required information)
• Boxed Warning (if applicable)
• Recent Major Changes (for a supplement)
• Indications and Usage (required information)
• Dosage and Administration (required information)
• Dosage Forms and Strengths (required information)
• Contraindications (required heading – if no contraindications are known, it must state “None”)
• Warnings and Precautions (required information)
• Adverse Reactions (required AR contact reporting statement)
• Drug Interactions (optional heading)
• Use in Specific Populations (optional heading)
• Patient Counseling Information Statement (required statement)
• Revision Date (required information)

- **Highlights Limitation Statement**
 - Must be placed at the beginning of HL, **bolded**, and read as follows: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

- **Product Title**
 - Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.

- **Initial U.S. Approval**
 - The verbatim statement “Initial U.S. Approval” followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.

- **Boxed Warning**
 - All text in the boxed warning is **bolded**.
 - Summary of the warning must not exceed a length of 20 lines.
 - Requires a heading in UPPER-CASE, **bolded** letters containing the word “**WARNING**” and other words to identify the subject of the warning (e.g., “**WARNING: LIFE-THREATENING ADVERSE REACTIONS**”).
 - Must have the verbatim statement “*See full prescribing information for complete boxed warning.*” If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.

- **Recent Major Changes (RMC)**
 - Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
 - The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, “Dosage and Administration, Coronary Stenting (2.2) --- 2/2010.”
 - For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line (“margin mark”) on the left edge.
 - A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.
 - Removal of a section or subsection should be noted. For example, “Dosage and Administration, Coronary Stenting (2.2) --- removal 2/2010.”

- **Indications and Usage**

- If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)).” Identify the established pharmacologic class for the drug at:

<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>.

- **Contraindications**

- This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”
- All contraindications listed in the FPI must also be listed in HL.
- List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.
- For drugs with a pregnancy Category X, state “Pregnancy” and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).
- For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**” must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**

- Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”)**”.

- **Revision Date**

- A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval.

Contents: Table of Contents (TOC)

- The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:
 - 8.1 Pregnancy
 - 8.3 Nursing Mothers (not 8.2)
 - 8.4 Pediatric Use (not 8.3)
 - 8.5 Geriatric Use (not 8.4)
- If a section or subsection is omitted from the FPI and TOC, the heading “**Full Prescribing Information: Contents**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Full Prescribing Information (FPI)

• General Format

- A horizontal line must separate the TOC and FPI.
- The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
- The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

• Boxed Warning

- Must have a heading, in UPPER CASE, **bold** type, containing the word “**WARNING**” and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.
- Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

• Contraindications

- For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided.

- For the “Clinical Trials Experience” subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

- For the “Postmarketing Experience” subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

- **Use in Specific Populations**

- Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

- **Patient Counseling Information**

- This section is required and cannot be omitted.

- Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling (insert type of patient labeling).” should appear at the beginning of Section 17 for prominence. For example:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

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/s/

EUNICE H CHUNG-DAVIES
04/22/2011

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: March 26, 2008

TO: Carol Hill, Regulatory Project Manager
Susan Limb, M.D., Medical Officer

FROM: Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

THROUGH: Joseph Salewski
Acting Branch Chief, Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 22150

APPLICANT: Jerini US, Inc.

DRUG: Firazyr (icatibant)

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATION: For the treatment of hereditary angioedema (HAE).

CONSULTATION REQUEST DATE: December 28, 2007

DIVISION ACTION GOAL DATE: April 11, 2008

PDUFA DATE: April 26, 2008

I. BACKGROUND:

Jerini US Inc., seeks approval of Firazyr (icatibant), a bradykinin antagonist administered by subcutaneous injection, for the treatment of hereditary angioedema (HAE) in this NDA 22150. HAE is a rare, inherited condition characterized by potentially life-threatening, sporadic and unpredictable attacks of angioedema. The swelling can affect various regions of the body including the gastrointestinal tract, cutaneous sites, and the larynx/airway. An attack usually lasts between 2 to 5 days. There are no therapies approved in the US for the treatment of acute HAE attacks, however several agents are available for prophylaxis. Two clinical sites were inspected; that of Alejandro Malbrán, M.D. regarding his conduct of phase III study JE049 #2103 and that of Werner Aberer, Prof. Dr med, regarding his conduct of phase III study JE049 #2102. Since this is a new molecular entity inspection of the sponsor, Jerini US, Inc. was also conducted.

These sites were selected because they enrolled a large number of subjects relative to total enrollment. In particular, for study JE049 #2103 the results are largely driven by data from a single, international site, that of Dr. Malbrán, site 040. This site enrolled 14 of 56 total subjects randomized; 25% of the entire study population. The comparability of the standard of care at this location to that of the US standard of care is uncertain and therefore a site visit and inspection is warranted.

For study JE049 #2102 the site selected for inspection, that of Dr. Aberer, site 070, appears to have had a very poor placebo response compared to the other sites in that study. Therefore, in addition to assessing the site's study conduct the inspection assessed if the unusually low placebo response rate is valid and supported by study documentation and study compliance.

JE049 #2102 (active-controlled), “Randomized, double blind, controlled, parallel group multicenter study of a subcutaneous formulation of Icatibant versus oral Tranexamic acid for the treatment of hereditary angioedema (HAE).”

JE049 #2103 (placebo-controlled), “Randomized, double blind, controlled, multicenter study of a subcutaneous formulation of Icatibant for the treatment of hereditary angioedema (HAE).”

II. RESULTS (by Site):

Name of CI, IRB, or Sponsor City, State or Country	Indication: Protocol #: and # of Subjects:	Insp. Date	Final Classification
CI #1: Alejandro Malbrán, M.D. Hospital Británica de Buenos Aires Consultorio 11 Servicio de Alergia e Inmunología Perdriel 74 (C1280AEB) Buenos Aires Argentina Site Number 040	HAE: JE049 #2103: 14	3/3/08-3/7/08	Pending

CI#2: Werner Aberer, Prof, Dr med University of Graz Department of Dermatology and Venerology Auenbruggerplatz 8 8036 Graz Austria Site Number 070	HAE: JE049 #2102: 7	2/25/08-2/29/08	Pending
Sponsor: Jerini US, Inc. Dr. Jochen Knolle Chief Scientific Officer 55 Madison Ave., Suite 400 Morristown, NJ 07960	HAE: JE049 #2102: 74 HAE: JE049 #2103: 56	1/30/08-2/7/08	Pending

Key to Classifications

NAI = No deviation from regulations.

VAI-No Response Requested= Deviations(s) from regulations.

VAI-R = Response Requested = Deviation(s) from regulations.

OAI = Significant deviations from regulations.

Pending = Preliminary classification based on information in 483; EIR has not been received from the field and/or complete review of EIR is pending.

1. **CI#1: Werner Aberer, Prof, Dr med**
 University of Graz
 Department of Dermatology and Venerology
 Auenbruggerplatz 8
 8036 Graz
 Austria
 Site Number 070

- a. **What was inspected:**

Seventeen subjects were screened and of those 7 were randomized into study JE049 #2102. The study records of all 7 subjects randomized into the double-blind portion of study JE049 #2102, and under the care of Dr. Aberer, were audited in accordance with the clinical investigator compliance program, CP 7348.811. The subjects audited were study subject numbers 003, 004, 006, 007, 013, 015 and 017. Documents reviewed include CRF pages for the double blind visit and some portions of the open label visits, concomitant meds, AEs, SAEs, rescue medication, patient diaries for the double blind visit and some portions of the open label visits, local lab results, lab results from the central lab in Italy, subject medical histories, and source documents related to AEs and SAEs if they existed, sample shipping records and drug storage and accountability records. A tour of the hospital and laboratory were provided including areas where subjects were treated during their attacks and where the investigational drug was, and is currently being stored. IRB approvals and correspondence was also reviewed.

Informed consent documentation was reviewed for all subjects screened. Problems were not observed. Some attacks in the modified open label phase were also audited from the above subjects.

Three subjects withdrew from the study prematurely; subject 003 for an SAE (coronary heart disease and bypass surgery), subject 013 for as SAE (pregnancy), and subject 017 for unknown reason. There were no deaths.

The EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the FDA field investigator. The EIR is currently being finalized and will be submitted to DSI upon completion. The general observations described below are based on preliminary communication from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

- b. **General observations/commentary:** The investigator was found to be adequate in the execution of study JE049 #2102. However, several regulatory deviations were observed. Consistent with the routine clinical investigator compliance program assessments the inspection focused on compliance with the protocol and consistency of efficacy data found in source documents with that reported by the sponsor to the agency. CRFs were assessed for data consistency with the source documents.

Edema location, primary symptom, date/time the attack became moderate, date/time the drug was administered and the patient diaries documenting the time of symptom relief were compared with that provided to FDA in the NDA. Discrepancies were not found.

Two subjects received rescue medication, subjects 15 and 17. Subject 17 (Tranexamic acid) received Berinert at 21:40 on 4/5/06 (double blind visit) and subject 15 received Berinert at 10:00am on 12/18/05. Subject 15's double blind visit began on 12/17/05.

Dr. Aberer had poor placebo response relative to other sites in this study. However, this inspection found no evidence that Dr. Aberer or any sub-investigator under dosed subjects receiving the active placebo. In addition, there was no evidence to suggest that they were not blinded as to which subjects received the study drug vs. the placebo. Dr. Aberer's sub-investigators, (b) (4) treated a majority of the subjects. Dr. Aberer stated that he saw the subjects often but was not the one treating them.

The placebo and investigational drug came prepackaged in small ampoules. The drug was then injected into the subjects. Of the data reviewed, which included the CRFs and the individual subject charts containing patient source data, no information was found which would support the idea that subjects were underdosed. Dosing was specifically discussed during a meeting with (b) (4) was not present during the inspection. Subject diaries were reviewed and were found to be complete for each subject.

A Form FDA 483 was issued citing 4 observations.

OBSERVATION 1

Informed consent was not properly documented in that the written informed consent used in the study was not approved by the IRB and was not dated by the subject or the subject's legally authorized representative at the time of consent.

Specifically,

- Subject 009 signed and dated the informed consent document for the study on 6/30/05. The signature of the responsible person on the informed consent document is dated 4/22/05. According to site documentation Subject 009 was verbally consented and screened on 4/22/05, although they did not sign the informed consent document until 6/30/05.
- Subject No. 005 did not date the informed consent document upon signing.
- Subject No. 007 did not date the informed consent document upon signing.

OBSERVATION 2

Investigational drug disposition records are not adequate with respect to dates.

Specifically, the temperature of the refrigerator used to hold the investigational product during the course of the study was not recorded during the times listed below. During this time at least 61 patient kits were stored in the refrigerator.

- February 21, 2005 - February 22, 2005,
- May 5, 2005 - December 5, 2005, and
- June 20, 2006 - July 1, 2006

OBSERVATION 3

An investigation was not conducted in accordance with the investigational plan.

Specifically, the protocol dated June 2, 2006 requires that vital signs be taken at Visit A1 and that a total of three blood samples be taken within five hours after injection for the first four angioedema episodes. No blood samples are documented as being collected within the first five hours of Subject 007 receiving his/her second treatment (1st treatment in the MOLE phase) on November 8, 2006. Vital signs were also not documented as being performed at the A1 visit during the attack on November 8, 2006.

OBSERVATION 4

The informed consent document did not contain an explanation of the purposes of the research, and the expected duration of the subject's participation.

Specifically, for the trial entitled, "Randomized, Double-Blind, Controlled, Parallel Group, Multicenter Study of a Subcutaneous Formulation of Icatibant Versus Tranexamic Acid for the Treatment of Hereditary Angioedema" Study Plan no. JE 049 #2102 the versions of the informed consent document dated February 9, 2005 and October 25, 2005 do not state the duration of the trial. The consents state "During the Study's open-label extension, all moderately severe to very severe episodes of angioedema will be treated with Icatibant...the total dose may not exceed 8 injections in four weeks" and "Independently of the occurrence of an episode of angioedema, regular visits to the study center are planned at six-month intervals, and your physician will contact you by telephone three months after each of these visits". The third version of the informed consent document dated June 2, 2006 states that the trial will last about two years.

- c. **Assessment of data integrity:** The data for Dr. Aberer's site, associated with study JE049 #2102 submitted to the Agency in support of NDA 22150, appear reliable based on available information. The general observations described above are based on preliminary communication from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

2. **CI#2: Alejandro Malbrán, M.D.**
Hospital Británica de Buenos Aires
Consultorio 11
Servicio de Alergia e Inmunología
Perdriel 74
(C1280AEB) Buenos Aires
Argentina
Site Number 040

- a. **What was inspected:**

Thirty six subjects were screened and of those 14 were randomized into study JE049 #2103 double-blind portion and 1 to the open label laryngeal study option. The study records of 13 subjects randomized into the double-blind portion of study JE049 #2103, and under the care of Dr. Malbrán, were audited in accordance with the clinical investigator compliance program, CP 7348.811. The subjects audited were study subject numbers 001, 003, 004, 005, 008, 009, 010, 014, 018, 019, 023, 033 and 035.

Documents reviewed include CRF pages for the double blind visit and some portions of the open label visits, concomitant meds, AEs, SAEs, rescue medication, patient diaries for the double blind visit and some portions of the open label visits, local lab results, lab results from the central lab in Italy, subject medical histories, and source documents related to AEs and SAEs if they existed, sample shipping records and drug storage and accountability records. A tour of the hospital and the doctor's office were provided including areas where subjects were treated during their attacks and where the investigational drug was, and is currently being stored. IRB, independent Ethics committee and MoH approvals and correspondence was also reviewed. Informed consent documentation was reviewed for all subjects screened. One subject withdrew for an SAE (pregnancy). There were no deaths.

The EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the FDA field investigator. The EIR is currently being finalized and will be submitted to DSI upon completion. The general observations described below are based on preliminary communication from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

- b. **General observations/commentary:** The investigator was found to be adequate in the execution of study JE049 #2103. However, there was one regulatory deviation observed. Consistent with the routine clinical investigator compliance program assessments the inspection focused on compliance with the protocol and consistency of efficacy data found in source documents with that reported by the sponsor to the agency. CRFs were assessed for data consistency with the source documents.

Edema location, primary symptom, date/time the attack became moderate, date/time the drug was administered and the patient diaries documenting the time of symptom relief were compared with the provided FDA data. Discrepancies were not found.

Subject 004 received rescue medication on his/her double blind visit (11/12/05). Subject 010 received rescue medication on his/her second open label visit. Subject 035 received rescue medication during his/her 4/19/06 visit (double blind).

Regarding this site being an unusually high enroller, according to the inspected entity, Argentina has a database of subjects with some form of HAE. Dr. Malbrán stated that he was able to screen a large number of subjects because patients were referred to him by the main doctor who treats patients with the disease. Dr. Malbrán also stated that these patients are well educated relative to the disease and most of them know one another. Since this is the case, most patients who have this disease and lived somewhat close to the area were aware that this trial was ongoing.

A Form FDA 483 was issued citing 1 observation.

OBSERVATION 1

An investigation was not conducted in accordance with the investigational plan.

Specifically, temperature records were not found for the hospital freezer from November of 2005 to September 30, 2007. The freezer is used to store complement blood samples and antibody samples prior to shipment for the study entitled, "Randomized, Double Blind, Placebo-Controlled, Multicenter Study of a Subcutaneous Formulation of Icatibant for the Treatment of Hereditary Angioedema". The protocol, version A2, April 10, 2006 requires plasma samples to be stored at -20°C and that serum samples be stored frozen.

During the inspection Dr. Malbrán informed the FDA investigator that he had spoken with the head of the hospital laboratory who informed him that the temperature of the freezer had been recorded, but the records had been thrown out. Dr. Malbrán agreed that the site should have had the freezer temperature records available and stated that he would respond in writing within 30 days.

- c. **Assessment of data integrity:** The data for Dr. Malbrán's site, associated with study JE049 #2103 submitted to the Agency in support of NDA 22150, appear reliable based on available information. The general observations described above are based on preliminary communication from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

3. Jerini US, Inc.

Dr. Jochen Knolle
Chief Scientific Officer
55 Madison Ave., Suite 400
Morristown, NJ 07960

- a. **What was inspected:** The FDA field investigator reviewed the conduct of studies JE049 #2102 and JE049 #2103. The inspection focused on validating data submitted to the agency in support of NDA 22150. Sponsor organizational structure and CRO roles and responsibilities were assessed. The sponsor operates largely out of their headquarters located in Berlin, Germany. Persons interviewed during the inspection informed the FDA investigator that the company majority of internal expertise is in research and development and that as such, the "clinical side" of the operations are "outsourced." There were at least 11 CROs with formal responsibilities related to the conduct of the 2 studies targeted for inspection; 2 of the 11 CROs are located within the US.

The inspection covered selection of clinical investigators/IRB, clinical monitoring, selection of monitors (CROs), monitoring procedures/record keeping and data handling, AEs for both studies, test article accountability, and

data listing verification. There were no limitations of inspection. There have been no previous inspections conducted at this facility.

- b. **General observations/commentary:** The FDA Investigator did issue a Form FDA 483 citing 4 observations. With respect to data listing verification the data submitted for the study “2103” appeared adequate, and for study “2102” except for minor discrepancies the data appeared adequate. Briefly, for study “2102” subjects 003 and 004 from site #70 (Aberer site) had missing information regarding primary symptoms associated with attack number 7 for each of them.

OBSERVATION 1

Failure to obtain a complete investigator statement, Form FDA-1572, before permitting an investigator to participate in an investigation.

Specifically, the name and address of pertinent clinical laboratory facilities to be used in study JE049 #2103 were not documented for 26 out of 30 sites.

The designated clinical laboratory facilities were not properly documented on the Form FDA-1572.

OBSERVATION 2

Failure to obtain a curriculum vitae or other statement of the qualifications of the investigator, before permitting an investigator to participate in an investigation.

Specifically, no information was gathered from any of the participating investigators involved in the JE049 #2102 and JE049 #2103 studies of whether they had been involved in any studies which had been terminated or concluded prematurely for any reason.

Pre-study monitoring visits were noted for all sites, however, only to determine that the investigator had adequate facilities and did not have financial conflicts of interest.

OBSERVATION 3

Failure to ensure proper monitoring of the study.

Specifically, the sponsor’s CRO failed to ensure proper monitoring was conducted by monitors in that monitors failed to send follow-up letters after monitoring visits, there were untimely submissions of site monitoring visit reports as per CRO monitoring guidelines, inadequate review and approval of site monitoring visit reports, and lack of source data verification form documentation.

OBSERVATION 4

Failure to ensure that an investigation was conducted in accordance with the general investigational plan and protocols as specified in the IND.

- a. The sponsor failed to ensure that monitors were provided with all the necessary study specific training to ensure proper monitoring of a study as per CRO monitoring guidelines and that records of verification of training were documented completely and maintained adequately.

For example, in the JE049 #2103 study, 8 out of 16 monitors reviewed did not appear to have study specific training or internal training related to the conduct of monitoring a clinical study. In the JE049 #2102 study, 5 out of 9 monitors reviewed did not appear to have study specific training.

- b. The sponsor failed to ensure that documents of IRB/EC continuation of study approval was obtained.
- c. **Assessment of data integrity:** The data collected and maintained at the sponsor's site, as it pertains to the 2 studies audited in accordance with the sponsor-monitor oriented BIMO compliance program, CP 7348.810, are consistent with that submitted to the agency as part and in support of NDA 22150.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The study data collected by Dr. Aberer, and Dr. Malbrán appear reliable. The inspection of Jerini US Inc., did identify issues of concern regarding study oversight and monitoring. However, these oversight and monitoring issues did not appear to significantly impact study execution and data quality. Only the sponsor inspection has completed the EIR which was provided to DSI for support of the CIS. The 2 CIs final reports (EIRs) have not been completed to date. While the 2 clinical investigators inspected were issued Form FDA 483 inspection observations, it does not appear that the compliance deviations would significantly alter overall study outcome.

The sponsor inspection revealed compliance violations related to proper pre-study CI documentation (inadequate Form FDA 1572s), assessment and collection of CI qualifications prior to study participation, inadequate clinical monitoring of study sites (specifically, failure to send certain follow up site visit letters, untimely monitoring reports, inadequate review of monitoring reports, and lack of source data verification form documentation), and inadequate training and preparation of clinical monitors (protocols and documentation maintenance).

Notwithstanding these sponsor and CRO deficiencies, the data submitted to the agency in support of NDA 22150 appear reliable. The sponsor acknowledges their deficiencies and promised the FDA investigator a written response to the Form FDA 483 as well as corrective actions.

Observations noted above are based in part on the preliminary communications provided by the field investigators. Only the findings at the sponsor, Jerini US Inc., are based on a final EIR. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final remaining EIRs.

Follow-Up Actions: DSI will generate an inspection summary addendum if the conclusions change significantly upon receipt and review of the pending EIRs and the supporting inspection evidence and exhibits.

{See appended electronic signature page}

Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Joseph Salewski
Acting Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations
Office of Compliance

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

/s/

Lauren Iacono-Connors
3/31/2008 12:57:50 PM
UNKNOWN

Joseph Salewski
3/31/2008 04:51:59 PM
CSO

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-150 Supplement # Efficacy Supplement Type SE-

Proprietary Name: Firazyr
Established Name: icatibant
Strengths: 30 mg solution for subcutaneous injection

Applicant: Jerini US Inc.
Agent for Applicant (if applicable): Glen Park, Pharm D, Target Health Inc., 261 Madison Avenue, 24th floor,
New York, NY 10016

Date of Application: 10/22/07
Date of Receipt: 10/26/07
Date clock started after UN:
Date of Filing Meeting: December 18, 2007
Filing Date: December 25, 2007
Action Goal Date (optional): User Fee Goal Date: 04/26/08

Indication(s) requested: Treatment of attacks of hereditary angioedema

Type of Original NDA: (b)(1) (b)(2)
AND (if applicable)
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 or efficacy supplement is a (b)(2), complete Appendix B.*

Review Classification: S P
Resubmission after withdrawal? Resubmission after refuse to file?
Chemical Classification: (1,2,3 etc.) **1**
Other (orphan, OTC, etc.) **Orphan**
11/25/03

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 by contacting the User Fee staff in the Office of Regulatory Policy. 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 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 any approved (b)(1) or (b)(2) application? YES NO
If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- 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
If no, explain:
- 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:
- Answer 1, 2, or 3 below (do not include electronic content of labeling as a partial electronic submission).

1. This application is a paper NDA YES
2. This application is an eNDA or combined paper + eNDA YES
This application is: All electronic Combined paper + eNDA
This application is in: NDA format CTD format
Combined NDA and CTD formats

Does the eNDA, follow the guidance?
(<http://www.fda.gov/cder/guidance/2353fml.pdf>) YES NO

If an eNDA, all forms and certifications must be in paper and require a signature.

If combined paper + eNDA, which parts of the application were submitted in electronic format?

Additional comments:

3. This application is an eCTD NDA. YES
If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES NO
- Exclusivity requested? YES, _____ 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 . . .”

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES NO **Orphan Drug, none required.**
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? **Orphan Drug, none required.**
YES NO

- Is this submission a partial or complete response to a pediatric Written Request? YES NO

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES NO
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)

NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.

- Field Copy Certification (that it is a true copy of the CMC technical section) YES NO

- PDUFA and Action Goal dates correct in tracking system? YES NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. YES

- List referenced IND numbers: (b) (4)

- Are the trade, established/proper, and applicant names correct in COMIS? YES NO
If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) July 1, 2004, January 24, 2007 NO
If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) March 1, 2005 NO
If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) July 29, 2004 NO
If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES NO
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
Was the PI submitted in PLR format? YES NO

If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:
- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES NO
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES NO
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS? N/A YES NO
- Risk Management Plan consulted to OSE/IO? N/A YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA YES NO

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES NO
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? 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 EA officer, OPS? YES NO
To be assessed by the reviewer.
- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO
- If a parenteral product, consulted to Microbiology Team? YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: December 18, 2007

NDA #: 22-150

DRUG NAMES: Firazyr (b) (4)

APPLICANT: Jerini US

BACKGROUND:

Jerini US has submitted a new application for icatibant (Firazyr), a bradykinin type-2 receptor antagonist for the treatment of acute attacks of hereditary angioedema (HAE). The product is classified as a new molecular entity. It was previously developed by Aventis AG under IND (b) (4) for treatment of allergic rhinitis, asthma and post-operative pain. After its withdrawal (not for safety reasons) on August 9, 1996, Jerini acquired the drug product and the right of reference to IND (b) (4) and opened IND 68,214 (April 8, 2004) as a treatment for HAE. Icatibant has not yet been approved for marketing for any indication

ATTENDEES: Badrul Chowdhury, Sally Seymour, Susan Limb, Anthony Durmowicz, Prasad Peri, Eugenia Nashed, Timothy McGovern, Molly Shea, Wei Qiu, Partha Roy, Qian Li, Carol Hill

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline/Organization

Reviewer

Medical:	Susan Limb, MD; Anthony Durmowicz, MD
Secondary Medical:	Sally Seymour, MD
Statistical:	Qian H. Li, PhD
Pharmacology:	Molly Shea, PhD
Chemistry:	Eugenia Nashed, PhD
Biopharmaceutical:	Partha Roy, PhD
Regulatory Project Management:	Carol Hill, MS
Statistical Pharmacology:	
Environmental Assessment (if needed):	
Microbiology, sterility:	Anastasia Lolas
Microbiology, clinical (for antimicrobial products only):	
DSI:	
OPS:	
Other Consults:	

Per reviewers, are all parts in English or English translation? YES NO

If no, explain:

CLINICAL FILE REFUSE TO FILE

• Clinical site audit(s) needed? YES NO

If no, explain:

• Advisory Committee Meeting needed? YES, date if known **February** NO

20, 2008

Meeting scheduled for February 20, 2008 was cancelled

- 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 N/A FILE REFUSE TO FILE

BIOPHARMACEUTICS FILE REFUSE TO FILE

- Biopharm. study site audits(s) needed? YES NO

PHARMACOLOGY/TOX N/A FILE REFUSE TO FILE

- GLP audit needed? YES NO

CHEMISTRY FILE REFUSE TO FILE

- Establishment(s) ready for inspection? YES NO

- Sterile product? YES NO

- If yes, was microbiology consulted for validation of sterilization? YES NO

ELECTRONIC SUBMISSION:

Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

(Refer to 21 CFR 314.101(d) for filing requirements.)

The application is unsuitable for filing. Explain why:

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:

- Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS. **Checked**
- If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER. **NA**
- 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. **NA**
- If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.), **January 8, 2008.**
- Convey document filing issues/no filing issues to applicant by Day 74, **January 8, 2008.**

Carol Hill, MS
Regulatory Project Manager

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/s/

Carol F. Hill
1/8/2008 08:04:29 AM
CSO

Sandra Barnes
1/16/2008 11:09:21 AM
CSO

DSI CONSULT: Request for Clinical Inspections

Date: December 27, 2007

To: Leslie Ball, M.D., Branch Chief, GCP2
Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: Susan Limb, MD/ Medical Officer/ Division of Pulmonary and Allergy
Products (DPAP)/ HFD-570
Sally Seymour, MD/ Medical Team Leader (DPAP)
Badrul Chowdhury, MD, PhD/ Division Director (DPAP)

From: Carol Hill/RPM/DPAP/HFD-570

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA-22-150

Sponsor/Sponsor contact information (to include phone/email):

Jerini US Inc.
Morristown, NJ
973-285-3274
973-285-3267 (fax)

US representative for Jerini
Glen D. Park, PharmD
Target Health Inc.
New York, NY
212-681-2100
212-681-2105 (fax)

Drug: Firazyr (icatibant)

NME: Yes

Standard or Priority: Priority

Study Population < 18 years of age: No

Pediatric exclusivity: N/A since orphan drug product

PDUFA: April 26, 2008

Action Goal Date: April 11, 2008

Inspection Summary Goal Date: March 28, 2008

II. Background Information

Jerini AG has submitted a new application for icatibant (Firazyr), a bradykinin antagonist administered by subcutaneous injection for the treatment of hereditary angioedema (HAE). HAE is a rare, inherited condition characterized by potentially life-threatening, sporadic, and unpredictable attacks of angioedema. The swelling can affect various regions of the body, including the gastrointestinal tract, cutaneous sites, and the larynx/airway. Currently, there are no therapies approved in the United States for treatment of acute HAE attacks. Several agents are available for prophylaxis, but their efficacy is moderate at best.

The Application relies on two small pivotal safety and efficacy studies, one active controlled study (2102) and one placebo-controlled study (2103). Additional supportive efficacy and safety information is based on results of the extension phases of each these studies, as well as a Phase 2, open-label dose-ranging study in HAE patients (2101).

Of the two pivotal studies, only the active-controlled study (2102) demonstrated efficacy for icatibant in the treatment of acute GI or cutaneous attacks of HAE. The active control was tranexamic acid, which is not approved for this indication in the US. The primary efficacy endpoint was time to onset of symptom relief as measured by a Visual Analogue Scale (VAS). Although numerically supportive, Study 2103 failed to demonstrate statistically significant efficacy over placebo for the primary endpoint.

III. Protocol/Site Identification

Include the Protocol Title/# for all protocols to be audited. Complete the following table.

Site # (Name,Address, Phone number, email, fax#)	Protocol #	Number of Subjects	Indication
Site #040 Alejandro Malbrán, MD Hospital Británico de Buenos Aires Consultorio 11 Servicio de Alergia e Inmunología Perdriel 74 (C1280AEB) Buenos Aires Argentina Tel: 54 11 4309-6400 ext.6805 amalbran1@gmail.com	2103	14	HAE
Site #070 Prof. Dr. Werner Abere University of Graz Department of Dermatology Auenbruggerplatz 8, 8036 Graz, Austria	2102	7	HAE

IV. Site Selection/Rationale

The efficacy review will take into consideration the limitations of sample size given the rarity of the disease and difficulty of performing prospective studies in this patient population. However, concerns regarding the validity of the data remain. The placebo-controlled study (2103) results are largely driven by data from a single, international site (Site 040) due to a higher patient enrollment. The comparability of the standard of care at this location to the US standard of care is uncertain. For the active-controlled study (2102), another international site with high patient enrollment (Site 040) appears to have had a markedly poor placebo response compared to the other sites.

International Inspections:

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.

Other (specify) This is an application for an NME for a disease in which there are currently no approved therapies for treatment of acute attacks. Most of the limited experience with this drug has been at foreign sites. It would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study.

V. Tables of Specific Data to be Verified (if applicable)

If you have specific data that needs to be verified, please provide a table for data verification, if applicable.

The results of these studies are in the EDR and the patient data listings are in PDF format. Please verify the primary endpoint and the conduct of the study.

Should you require any additional information, please contact *Carol Hill* at Ph: 301-796-1226 or *Susan Limb* at Ph: 301-796-1951.

Concurrence: (as needed)

Susan Limb, MD, Medical Reviewer
Sally Seymour, MD, Medical Team Leader
Badrul Chowdhury, MD, PhD Director, Division Director (for foreign inspection requests only)

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/s/

Susan L Limb
12/26/2007 04:45:39 PM

Sally Seymour
12/28/2007 12:08:38 PM

Badrul Chowdhury
12/28/2007 01:18:23 PM

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Pulmonary and Allergy Products

Application Number: NDA 22-150

Name of Drug: Firazyr (b) (4) 30 mg (b) (4)

Applicant: Jerini US Inc.

Material Reviewed:

Submission Date(s): October 22, 2007

Receipt Date(s): October 26, 2007

Submission Date of Structure Product Labeling (SPL): October 22, 2007

Type of Labeling Reviewed: WORD/SPL

Background and Summary

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

Review

The following issues/deficiencies have been identified in your proposed labeling.

General Comments

1. For specific requirements on the content and format of labeling for human prescription drug and biologic products refer to 21 CFR 201.57. Also see Draft Guidance for Industry: Labeling for human Prescription Drug and Biological Products – Implementing the New Content and Format Requirements (Implementation Guidance).
2. Refer to <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for fictitious

examples of labeling format.

Highlights

3. In the DOSAGE AND ADMINISTRATION section include critical differences among population subsets; monitoring recommendations, and other clinically significant clinical pharmacologic information that affects dosing recommendations if applicable.
4. Also in the DOSAGE AND ADMINISTRATION section, major limitations for use (e.g., lack of effect in particular subsets of the population, or second line therapy status) must be briefly noted. [See 21 CFR 201.57(a)(6)]
5. In the CONTRAINDICATIONS section the summarized labeling information does not match the cited references. [Redacted] (b) (4)
6. The drug name should be followed by the drug's dosage form and route of administration. [See 21 CFR 201.57(a)(2)] [Redacted] (b) (4)
7. In the ADVERSE REACTIONS section provide the manufacturer's phone number for reporting of suspected adverse reaction or provide the web address of the direct link to the site for voluntary reporting of adverse reactions. An email address or general link to a company's website cannot be used to meet the requirement to have adverse reactions reporting contact information. [See 21 CFR 201.57(a)(110)]
8. A horizontal line must separate the Highlights and FPI:C. [See 21 CFR 201.57(d)(2)]

Full Prescribing Information: Contents

9. The table of contents should be limited in length to one-half page.
10. The format and wording of the section and subsection headings used in the table of contents must match the section and subsection headings used in the FPI. [See 21 CFR 201.57(b)] Subsections of section 2, 4, 5, 8, and 12 in the table of contents do not match those listed in the FPI.
11. When a section or subsection is omitted from the FPI, the section or subsection must also be omitted from the Contents. The heading "Full Prescribing Information: Contents" must be followed by an asterisk and the following statement must appear at the end of the Contents: "*Sections or subsections omitted from the Full Prescribing Information are not listed." [Redacted] (b) (4)

Full Prescribing Information:

12. See comments 10 and 11.
13. The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. Fore example, [*see Warnings and Precautions (5.3)*] not (*see section 5.3*). the cross-reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print. [See Implementation Guidance] Also ensure that the section referenced is listed in the FPI.
14. In the section CONTRAINDICATIONS, (b) (4)
[REDACTED] Also the subsection title does not match the same subsection number in the FPI:C. See comment 10 and arrange the subsections so that they match those in the FPI:C.
15. Include the manufacturer information at the end of the labeling

Recommendations

Please address the identified deficiencies/issues and re-submit labeling on or before January 18, 2008. This updated version of labeling will be used for further labeling discussions.

Carol Hill
Regulatory Project Manager

Supervisory Comment/Concurrence:

Sandy Barnes
Chief, Project Management Staff

Drafted: chill/November 30, 2007

Revised/Initialed: Barnes/December 11, 2007; Limb/December 12, 2007; Seymour/December 12, 2007

Finalized: chill/December 20, 2007

Filename: CSO Labeling Review Template (updated 1-16-07).doc

CSO LABELING REVIEW OF PLR FORMAT

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/s/

Carol F. Hill
12/20/2007 04:43:53 PM
CSO

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12/21/2007 03:15:58 PM
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Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

MEMORANDUM

Pre-Decisional Agency Information

Date: November 20, 2007

To: Carol Hill – Regulatory Project Manager
Division of Pulmonary and Allergy Products

From: Michelle Safarik, PA-C – Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: DDMAC labeling comments for Firazyr [REDACTED] (b) (4)
NDA 22-150

DDMAC has reviewed the proposed product labeling (PI) and proposed carton and container labeling for Firazyr [REDACTED] (b) (4) (Firazyr) submitted for consult on November 16, 2007.

We acknowledge that this may be the first prescription product to have icatibant (bradykinin B2 receptor antagonist) as the active ingredient and may be the first drug product approved for the treatment of hereditary angioedema attacks, a rare disease for which no specific treatment is thus far approved in the United States. Therefore, we acknowledge that icatibant was granted Orphan Drug Designation on October 25, 2003, and was granted Fast Track Designation on June 15, 2004 (Priority Review).

We offer the following comments.

HIGHLIGHTS

General

1. We are unable to locate the proposed patient labeling in the EDR for Firazyr and therefore cannot provide comments on its acceptability.
2. We recommend revising the sections listed under “**FULL PRESCRIBING INFORMATION: CONTENTS**” (emphasis original) for consistency with the sections of the proposed PI.

Contraindications

1. [REDACTED] (b) (4)

According to the “Guidance for Industry Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format” (page 6), “Only known hazards, and not theoretical possibilities, must be listed.” [REDACTED] (b) (4)

Warnings and Precautions

[REDACTED] (b) (4)

Adverse Reactions

[REDACTED] (b) (4)

PI

Contraindications

1. (Please see comment under “Highlights – Contraindications”).

Warnings and Precautions

1. (Please see comment under “Highlights – Warnings and Precautions”).

(b) (4)

Adverse Reactions

1. We recommend revising (b) (4) to “hereditary angioedema (HAE).”

(b) (4)

Is this information essential for the prescriber to know? If not, it is promotional in tone and minimizes the risks of Firazyr therapy, and we recommend deletion.

5. (b) (4)

This statement does not add any substantive information to the proposed PI. Therefore, we recommend deletion.

Use in Specific Populations

Pregnancy

1. We recommend revising (b) (4) to “subcutaneous” and replacing the British English (b) (4) with the American English “fetal.”

(b) (4)

Hepatic Impairment

1. [Redacted] (b) (4)

We recommend revising the above statement for clarity [Redacted] (b) (4)

Description

[Redacted] (b) (4)

As this information is more appropriate in the How Supplied section of the proposed PI, we recommend deleting it from this section.

Nonclinical Toxicology

[Redacted] (b) (4)

Clinical Studies

[Redacted] (b) (4)

Patient Counseling Information

1. We are unable to locate the proposed patient labeling in the EDR for Firazyr and therefore cannot provide comments on its acceptability.

Carton and Container Labeling

1. For consistency with the proposed and established name, we recommend revising [Redacted] (b) (4)

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/s/

Michelle Safarik
11/20/2007 04:07:16 PM
DDMAC REVIEWER