

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**201811Orig1s000**

**OTHER ACTION LETTERS**



NDA 201811

**COMPLETE RESPONSE**

Fresenius Kabi USA, LLC.  
Attention: Aditi Dron  
Manager, Regulatory Affairs  
Three Corporate Drive  
Lake Zurich, IL 60047

Dear Ms. Dron:

Please refer to your New Drug Application (NDA) dated September 13, 2013, received on September 13, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Argatroban Injection, 100 mg/mL (250 mg/2.5 mL vial).

We acknowledge receipt of your amendment dated September 27, 2013. The September 13, 2013 submission constituted a complete response to our April 5, 2013 action letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

**LABELING**

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

**FACILITY INSPECTIONS**

During a recent inspection of the Fresenius Kabi USA, LLC, Grand Island, NY manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.)

**SAFETY UPDATE**

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

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
  - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
  - Present tabulations of the new safety data combined with the original NDA data.
  - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
  - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

### **OTHER**

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have

such a meeting, submit your meeting request as described in the FDA Guidance for Industry, “Formal Meetings Between the FDA and Sponsors or Applicants,” May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

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

If you have any questions, call Beatrice Kallungal, Regulatory Project Manager, at (301) 796-9304.

Sincerely,

*{See appended electronic signature page}*

Ann T. Farrell, M.D.  
Division Director  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

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

/s/  
-----

ANN T FARRELL  
02/28/2014



NDA 201811

**COMPLETE RESPONSE**

Fresenius Kabi USA, LLC.  
Attention: Aditi Dron  
Manager, Regulatory Affairs  
1501 East Woodfield Road  
Suite 300 East  
Schaumburg, IL 60173

Dear Ms. Dron:

Please refer to your New Drug Application (NDA) dated October 12, 2012, received October 12, 2012, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Argatroban Injection 250 mg/2.5 mL vial (100 mg/mL).

We acknowledge receipt of your amendment dated February 11, 2013. The October 12, 2012 submission constituted a complete response to our July 23, 2012 action letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

**PRODUCT QUALITY**

1. Provide the Analytical Procedure and Validation of Analytical Procedure for the method used in the Identification Test cited in "Table 3.2.S.5-1 Specification for Individual Isomers Argatroban 21-S and 21-R" and demonstrated adequacy of the method to distinguish the individual isomers.
2. Provide drug product stability data for all attributes, utilizing all test methods listed in the specifications.

**LABELING**

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

## **FACILITY INSPECTIONS**

During a recent inspection of the APP Pharmaceuticals, LLC, Grand Island, NY manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

## **SAFETY UPDATE**

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

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
  - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
  - Present tabulations of the new safety data combined with the original NDA data.
  - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
  - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

**OTHER**

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

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

If you have any questions, call Beatrice Kallungal, Regulatory Project Manager, at (301) 796-9304.

Sincerely,

*{See appended electronic signature page}*

Ann T. Farrell, M.D.  
Division Director  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

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

/s/  
-----

ANN T FARRELL  
04/05/2013



NDA 201811

**COMPLETE RESPONSE**

APP Pharmaceuticals, LLC  
Attention: Aditi Dron  
Regulatory Affairs Manager  
1501 East Woodfield Road  
Suite 300 East  
Schaumburg, IL 60173

Dear Ms. Dron:

Please refer to your New Drug Application (NDA) dated January 31, 2012, received January 31, 2012, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Argatroban Injection, 100 mg/mL.

We acknowledge receipt of your amendments dated May 11, May 14, June 07, and July 20, 2012.

The January 31, 2012, submission constituted a complete response to our February 24, 2011, action letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

**PRODUCT QUALITY**

1. The HPLC method for determination of argatroban and impurities and identification of argatroban (10-08-03-6457) and validation report PR-08-00037 contain acceptance criteria for impurities in the raw material and finished product with unjustifiably high values [for example, the percent relative standard deviation (RSD) for precision of NMT (b) (4) % at an impurity level of more than (b) (4) and the percent RSD for precision of NMT (b) (4) % at an impurity level of less than (b) (4)]. The same high values are observed in the proposed acceptance criteria for the percent RSD for intermediate precision as well as the percent change in solutions from the initial timepoint. Therefore, revise the acceptance criteria to more accurately match your analytical data ((b) (4) %) and conduct the proposed future validation utilizing the revised criteria prior to future testing.
2. Provide the certificates of analysis and control testing data for all argatroban, API lots used in the preparation of the drug product for any proposed manufacturing site(s), utilizing the proposed NDA test methods. Note that the Summary of Test Results (SOTR)

submitted for lots of drug substance (1002935, 1009636 and 1002937) used to manufacture the exhibit lots of drug product (R340-032, R340-033 and R340-034), reported test results using the defunct isomeric ratio test method (10-08-03-6457) instead of the current method (10-08-03-6689).

3. Include full quality control specifications for the individual 21-R and 21-S isomers of argatroban as part of the methodology proposed for isomeric ratio. The proposal to submit manufacture's Certificate of Analysis and to confirm the structure of using proton NMR is does not provide sufficient quality control for these reference standards. Provide specifications, including attribute, test method and acceptance criteria.
4. Provide comparative purity profile data for the RLD and the proposed product. The file of the referenced Report #PD11-NPA-018 in the Complete Response was not included in the submission.
5. Provide specifications at release and during stability for impurities (b) (4). Refer to ICH Q3B(R2) - Impurities in New Drug Products. The file of the referenced Report #PD11-NPA-018 in the Complete Response, submitted to support the proposal to omit impurities, was not included in the submission.
6. In the drug product stability protocol, revise the specifications to include other individual impurities. The proposal to omit the impurities was not supported due to the absence of Report #PD11-NPA-018 from the submission.
7. Report the test method (including version) and indicate the date testing was conducted on all submitted data – including Summary of Test Result (SOTR), certificates of analysis, batch analysis reports and stability reports.
8. Provide acceptance, release and stability test data conducted using the current submitted methods for all lots of drug substance and drug product. Identify any test data conducted using outdated test methods.
9. Provide drug product stability data for all attributes, utilizing all test methods listed in the specifications.

## **LABELING**

1. Submit draft labeling that incorporates revisions in the attached labeling. In addition, submit updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations that support any proposed changes.

2. Please submit draft carton and container labeling revised as attached.

### **FACILITY INSPECTIONS**

During a recent inspection of the APP Pharmaceuticals manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

### **SAFETY UPDATE**

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

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
  - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
  - Present tabulations of the new safety data combined with the original NDA data.
  - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
  - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

**OTHER**

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

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

If you have any questions, call Lara Akinsanya, Regulatory Project Manager, at (301) 796-9634.

Sincerely,

*{See appended electronic signature page}*

Ann T. Farrell, M.D.  
Division Director  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

ENCLOSURE(S):  
Labeling

34 Page(s) of Draft Labeling have been Withheld in Full  
as b4 (CCI/TS) immediately following this page

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

/s/  
-----

ANN T FARRELL  
07/23/2012



NDA 201-811

**COMPLETE RESPONSE**

APP Pharmaceuticals, LLC  
Attention: Aditi Dron  
Regulatory Scientist  
1501 East Woodfield Road  
Suite 300E  
Schaumburg, IL 60173

Dear Ms. Dron:

Please refer to your New Drug Application (NDA) dated April 5, 2010, received April 30, 2010, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Argatroban Injection.

We acknowledge receipt of your amendments dated November 22, 2010, October 15, 2010, September 3, 2010, August 5, 2010, July 1, 2010, and June 28, 2010.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

**NONCLINICAL**

1. The proposed specification of (b) (4) % for impurity (b) (4) is not acceptable. You should reduce the specification according to ICH Q3B(R2) or adequately justify the proposed level based on nonclinical or clinical data. Alternatively, you may justify this specification based on the level of impurity (b) (4) present in the reference listed drug using adequate analytical method(s). We note your statement regarding impurity (b) (4) being a metabolite of argatroban. You have not provided data to support this claim; therefore, your justification for the proposed level of (b) (4) % is not acceptable.

**PRODUCT QUALITY**

2. As you confirmed in the 19-Nov-2010 teleconference, all information in the submitted Module 3 applies to a manufacturing site that is no longer manufacturing the proposed drug product. Therefore, the submitted information does not support a commercially viable product.
3. Although the submitted information applies to a commercially non-viable product, the following deficiencies were identified during this review cycle and are provided for your

reference. While these deficiencies are not comprehensive, consider these deficiencies, as applicable, in your development of a complete and updated Module 3.

- a. For Related Compounds (b) (4) revise the acceptance limits to conform with ICH Q3A- Impurities in New Drug Substances, or provide appropriate qualification data.
- b. Report all individual impurities/related compounds present at levels at or above (b) (4) %.
- c. Include a test and propose criteria for (b) (4) content in the proposed specification.
- d. Establish a base line resolution for the isomeric ratio in the proposed quantitation method (10-08-03-6457). Confirm that the acceptance limit for resolution between the individual *R*- and *S*-isomers of argatroban is at least (b) (4).
- e. For the method of determination of the isomeric ratio of argatroban (10-08-03-6457), provide for the use of the individual *R*- and *S*- isomers reference standards of argatroban, and utilize them to adequately evaluate the accuracy, precision, linearity, intermediate precision and quantitation limit of this test.
- f. The HPLC method for determination of argatroban and impurities and identification of argatroban (10-08-03-6457) and validation report PR-08-00037 contain acceptance criteria for impurities in the raw material and finished product with unjustifiably high values [for example, the percent relative standard deviation (RSD) for precision of NMT (b) (4) % at an impurity level of more than (b) (4) (b) (4) and the percent RSD for precision of NMT (b) (4) % at an impurity level of less than (b) (4)]. The same high values are observed in the proposed acceptance criteria for the percent RSD for intermediate precision as well as the percent change in solutions from the initial timepoint. Therefore, revise the acceptance criteria to more accurately match your analytical data.
- g. Provide the certificates of analysis and control testing data for all argatroban, API lots used in the preparation of the drug product for any proposed manufacturing site(s).
- h. Include full quality control specifications for the individual 21-*R* and 21-*S* isomers of argatroban as part of the methodology proposed for testing identification, assay and isomeric ratio.
- i. Provide certificates of analysis for the individual 21-*R* and 21-*S* isomers of argatroban, as generated by the reference standard supplier.
- j. Revise the drug product specifications by adding testing and acceptance criteria for isomeric ratio at release and during stability studies.

- k. Provide comparative purity profile data for the RLD and the proposed product.
- l. Provide specifications at release and during stability for impurities (b) (4). Refer to ICH Q3B(R2) - Impurities in New Drug Products.
- m. In addition to the testing proposed, include the following in the stability protocol:
  - A test for individual 21-(*R*) and 21-(*S*) argatroban diastereomers at specified time intervals consistent with ICH Guidance Q1A(R2) –Stability Testing of New Drug Substance and Products.
  - Revise specifications for Impurity (b) (4) and other individual impurities as described above.
- n. Submit validation for the analytical method for isomeric ratio determination in argatroban injection using the individual 21-*R* and 21-*S* argatroban diastereomers as reference standards.
- o. Provide the specific location in DMF (b) (4), including volume, page numbers and date, in which the appropriate cross-referenced information on the stopper is located.
- p. Provide container closure integrity test methods and data sets using (b) (4) vial presentation if this vial will be used for marketed product.

### **LABELING**

- 4. We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

### **FACILITY INSPECTIONS**

Our field investigator could not complete inspection of the APP Pharmaceuticals, LLC manufacturing facility at Barceloneta, Puerto Rico (FEI 3005724920) because the facility was not ready for inspection. Satisfactory inspection is required before this application may be approved. Please notify us in writing when this facility is ready for inspection.

### **SAFETY UPDATE**

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

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
  - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
  - Present tabulations of the new safety data combined with the original NDA data.
  - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
  - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

### **OTHER**

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have

such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

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

If you have any questions, call Ebla Ali Ibrahim, Regulatory Health Project Manager, at (301) 796-3691.

Sincerely,

*{See appended electronic signature page}*

Ann Farrell, M.D.  
Acting Division Director  
Division of Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research

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

/s/  
-----

ANN T FARRELL  
02/24/2011