CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202155Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202155

COMPLETE RESPONSE

Bristol-Myers Squibb
ATTENTION: Linda Gambone, Ph.D.
Associate Director, Global Regulatory Sciences
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Dr. Gambone:

Please refer to your New Drug Application (NDA) dated September 28, 2011, received September 28, 2011, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Eliquis (apixaban) tablets.

We also refer to your submissions dated October 4, 7, 13, 14, 19, and 28; November 4, 10, 17, 18, and 22; December 2, 7, 9, 15, 19, 21, 22, 23, 28, and 30, 2011; and January 4, 5, 10, 11, 17, 20, 25 26, 30, and 31; February 2, 7, 8, 9, 10, 13, 14, 17, 21, 23, 24, 27, 28, and 29; March 21, 22, 23, 26, 27, and 28; April 2, 3, 5, 10 (two), 13, 20, and 27; and May 9, 2012.

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

1. As you are aware, some subjects in ARISTOTLE were given the wrong study drug (e.g. active instead of placebo and vice-versa). Knowledge of the study drugs actually dispensed to subjects is crucial to understanding the outcomes of the study. While we recognize your efforts to better define the rate and nature of dosing errors, which suggest a lower rate than initially reported, we believe the information you have submitted for us to review has not adequately characterized the frequency of errors in dispensing study drugs. Before we can approve your NDA you will need to submit reliable information regarding the following:

    - The frequency of a subject in ARISTOTLE receiving the wrong study medication, specifically:
        a. dispensing active warfarin instead of placebo warfarin to a subject randomized to apixaban;
        b. dispensing active apixaban instead of placebo apixaban to a subject randomized to warfarin;
        c. dispensing placebo apixaban instead of apixaban to a subject randomized to apixaban;
        d. dispensing placebo warfarin instead of warfarin to a subject randomized to warfarin, and
        e. dispensing the wrong dose of apixaban to a subject randomized to apixaban

    - The frequency of dispensing to a subject a bottle with a serial number other than the one assigned by the interactive voice response system (IVRS).

- The frequency with which the serial number on the tear-off label from a study drug bottle did not match the IVRS assigned serial number.

- The frequency with which the IVRS assigned serial number did not match each of the following and any one of the following: the eCRF entry of the serial number of dispensed study drug bottles, the eCRF entry of the serial number of returned study drug bottles, and the eCRF entry of the serial number of study drug bottles brought in to a visit but not returned.

You should use whatever sources of information you have available to respond to our requests. We believe that that the best source of information for responding to the first two bulleted items requested above is the tear off labels on which are printed the serial numbers of the study drug bottles. You may choose to collect all of these labels from investigative sites. However you recently submitted to us a summary report (but not the full report) you prepared for the European Medicines Agency (EMA), detailing your assessment of the errors in dispensing study drugs in a random 12% sample of subjects. The full report of this assessment might constitute an adequate response to our requests above, or may serve as a template for designing a response to our requests. A brief review of the summary report raises some questions that will need to be addressed if the full report is used to respond to our requests. For example, your analysis included only legible labels whereas it seems to us that a bottle with a difficult to read label is more likely to be dispensed in error.

You assert in the report you prepared for EMA that the frequency of a wrong study drug being dispensed to a subject was less than 0.1%. If the frequency is much greater than that, we may have additional requests for information. One of those will be identification of all primary endpoint events, deaths, and ISTH major bleeds that occur at times a subject may have been on two active study drugs or no active study drug. Another will be determining the frequency with which site monitoring identified and did not identify a subject whose eCRF indicates they may have been dispensed a bottle with an incorrect serial number.

2. Investigators in the ARISTOTLE study were supposed to report all instances in which they scratched off a coating on the tear-off labels to unblind a subject. We do not believe you have checked tear-off labels to verify that all instances of unblinding by investigators were reported in the 12% sample. If you have not done so, submit a plan to us to determine the frequency of unblinding by the investigator not reported to you. If the frequency is more than minimal, we may have additional requests.

3. In submissions to your NDA, you describe the intensity with which certain eCRF fields were monitored and checked during the conduct of ARISTOTLE. For example, you have told us that the entry on the eCRF listing the serial number of the bottle dispensed was subjected to more intense monitoring and edit checks than the entry listing the serial number of the bottle returned. To help us understand these different procedures, you need to provide us with all plans used to monitor and verify the accuracy of the entries on the eCRF. We note that the final monitoring plan you submitted in your NDA was dated after data-lock, and so may not have been a working plan actually used during the conduct of ARISTOTLE. You should provide the initial monitoring plan with all subsequent changes to that plan, both formal and informal. Indicate when and how changes in monitoring were implemented. Include all communications to sites, and identify the organizations responsible for all monitoring in the original monitoring plan, and any changes made.

4. You recently informed us that manual changes were made to a dataset containing the serial numbers of bottles assigned by the IVRS to subjects in ARISTOTLE. You stated that these changes were made in response to information provided by investigators directly to the IVRS vendor, (b) (4) to ensure that a bottle dispensed in error would be removed from inventory so it could not be assigned.

Manual changes to the IVRS concern us because of the possibility of alterations to the randomization dataset. You therefore should provide the following:

- All agreements between BMS and (b) (4) concerning the role of (b) (4) in the conduct of ARISTOTLE.
- All SOPs from (b) (4) related to the conditions under which manual changes to data from the IVRS could be made and the documentation required to do so.
- An IVRS dataset that flags all subjects whose original IVRS-assigned bottle serial number was later changed, the serial number originally assigned and the altered serial number, and the reason for the change. Original IVRS datasets with codes to create the dataset (kitassgn) that was provided to the Agency may be helpful.
- Most importantly, an audit trail of the changes indicating who, when and why manual changes were made to the data set containing IVRS assigned bottle serial numbers. If the changes were made in response to information provided by an investigative site, please include the communication from the site documenting the information provided.
- A statement signed by responsible individuals that no changes were made to the randomization dataset.

5. We are concerned that the trial datasets submitted in your NDA do not accurately reflect the information in the eCRFs. In our brief review of your medication error dataset (smed.xpt) (used for most of your medication error analyses), we identified an observation with a valid date in the eCRF that was misrepresented by a period in the dataset, indicating that a valid date was missing. We also found medication data (indicating that drug was dispensed and taken until the end of treatment) for which there were no corresponding eCRFs in one subject. We can provide more details concerning these mismatches on request.

   We are concerned about these errors because they were found after a cursory examination of these datasets, leading us to believe that there may be important errors in the datasets used for critical analyses. You should explain how these and similar errors, if any, occurred. If you believe that the datasets for important analyses are accurate, please provide the basis for your belief.

6. Some subjects have a unique adverse event listed multiple times as both non-serious and serious. This appears to be because the site personnel completed a non-serious AE CRF and a serious adverse event (SAE) CRF for the same event. You should prepare an adverse event analysis dataset (adae.xpt) in which all adverse events are listed a single time with the correct designation as serious or non-serious.

We expect that you will anticipate and answer any reasonable questions we are likely to have after reviewing the information you submit in your complete response.

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.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

As described in our letter dated February 3, 2012, in accordance with section 505-1 of the FDCA, we have determined that a risk evaluation and mitigation strategy (REMS) is necessary for Eliquis to ensure that the benefits of the drug outweigh the increased risk of thrombotic events, including stroke, if Eliquis is discontinued.

We note that your February 13, 2012, amendment contained a response to our February 3, 2012, letter; this amendment was not reviewed for this action. We will continue discussion of your proposed REMS after your complete response to this action letter has been submitted.

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

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. We strongly encourage you to schedule this meeting with us to discuss your plans for providing us with the additional information we have requested.
Please 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.
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.

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, please call:

Alison Blaus
Regulatory Project Manager
(301) 796-1138

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Deputy Director
Office of Drug Evaluation I
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/

ROBERT TEMPLE
06/22/2012