

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022433Orig1s000

OTHER ACTION LETTERS



NDA 022433

COMPLETE RESPONSE

AstraZeneca LP
Attention: Emery Gigger
Regulatory Affairs Director
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803

Dear Mr. Gigger:

Please refer to your New Drug Application (NDA) submitted November 13, 2009 under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Brilinta (ticagrelor) 90 mg tablets.

We acknowledge receipt of your submissions received November 20, 24, 25 and December 8, 16, 18 (2), 22 and 24, 2009, and February 12, 16 (2), 26, March 5, 10, 15, 16, 18, April 8, 9, 26, 27, 30, May 3, 7, 12, 24, 28, June 3, 4 (2), 10 (2), 11 (2), 17, 18, 21, 22, 25, 30, July 16 (2), 20 (2), 23, 27 (2), 29, 30, August 4, 10, 11, 13, 18, 19 (2), 20 (2), 24, September 1, 8, and October 1, 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.

CLINICAL

We recognize and generally share a skeptical view of subset differences in large trials, and the overall result of PLATO is strongly positive. The difference between overall results of PLATO and results in North America or US may well be a random effect in a small subset (about 10%), as the Cardiovascular and Renal Drugs Advisory Committee concluded. We remain concerned, however, that the North American results are not a chance finding, given the overall statistical significance of the regional heterogeneity, and the similar trend of results on cardiovascular mortality, non-fatal myocardial infarction, and stroke. There is, however, an alternative explanation for the US/outside of US (OUS) difference that deserves close examination: the effect of aspirin dose.

The analysis you presented of the marked impact of aspirin dose on the US/OUS differences is striking; the difference in results between the US and OUS population essentially disappears. Moreover, the similarity in the effect on the primary endpoint seen in both populations when they are divided by aspirin dose, the absence of any apparent effect on outcome of many potentially important baseline covariates or treatment-determined variables (e.g., choice of

procedure) all appear to provide a plausible and statistically strong basis for the US/OUS difference. As you recognize, however, such a post-facto explanation would be an unusual basis for drug approval and demands very close scrutiny, particularly as aspirin dose is not a baseline characteristic, and there are multiple ways to impute and characterize aspirin doses for individual patients. We therefore need further detailed analyses of the following issues:

1. A key issue bearing on interpretation of the various aspirin analyses is an understanding of the methods used to determine the aspirin dose for each subject for each study day, up to the time of an endpoint event or censoring, and irrespective of whether a subject continued (or discontinued) the randomized study drug. To enable us to understand the basis for the aspirin categorizations used in these analyses, please provide the specific raw dataset(s), detailed algorithm, and corresponding program used to derive the daily aspirin dose for each subject.
2. In analyzing the importance of aspirin dose on US/OUS findings, you utilized a number of methods to categorize aspirin dose for each subject, including:
 - a. the median of the daily aspirin doses of patients who took at least 5 days of aspirin during the study drug period (MEDIAN10)
 - b. the median of the daily aspirin doses of patients who took at least 5 days of aspirin up to the time of the primary event during the study drug period (MEDIAN20)
 - c. the median of the daily aspirin doses of patients who took at least 2 days of aspirin up to the time of the primary event during the study drug period (MEDIAN24)
 - d. the median of the daily aspirin doses of patients who took at least 1 day of aspirin up to the time of the primary event during the study drug period (MEDIAN25)
 - e. the median of the daily aspirin doses of patients who took at least 1 day of aspirin up to the time of the primary event during the study drug period and excluding the first day loading dose (MEDIAN55)
 - f. the mean of the daily aspirin doses of patients who took at least 1 day of aspirin up to the time of the primary event during the study drug period and excluding the first day loading dose (MEAN55)

We have considered a number of other possible ways of defining aspirin dose. All the definitions of aspirin dose we suggest here are irrespective of whether a subject continued the randomized study drug.

- g. The median/mean of the daily aspirin doses taken in the last 5 days prior to the primary event or censoring date, as appropriate
- h. The median/mean of the daily aspirin doses taken in the last 10 days prior to the primary event or censoring date, as appropriate
- i. The last aspirin dose taken within 30 days prior to the primary event or censoring date, as appropriate

- j. The median/mean of the daily aspirin doses taken in the last month prior to the primary event or censoring date, as appropriate
- k. Time-dependent analysis with aspirin dose as a time-varying covariate
- l. For analyses of events that occurred within 30 days of randomization, the aspirin dose can be defined as:
 - The mean of the daily aspirin doses in the first 30 days
 - The median of the daily aspirin doses in the first 30 days
 - The maximum of the daily aspirin doses in the first 30 days
- m. For analyses of events that occurred after 30 days from randomization, the aspirin dose can be defined as:
 - The median of the daily aspirin doses throughout the trial excluding the first 30 days
 - The median of the daily aspirin doses throughout the trial excluding the first day loading dose
 - The last daily aspirin dose prior to the primary event or censoring date

You should provide the critical analyses listed below using all of the definitions described above. Analyses should be performed using aspirin dose as both a continuous variable and a categorized variable in two different ways ($\leq 100\text{mg}$, $101\text{mg}-299\text{mg}$, and $\geq 300\text{mg}$; or 0mg , $1\text{mg}-100\text{mg}$, $101\text{mg}-299\text{mg}$, and $\geq 300\text{mg}$) and on the primary endpoint (major adverse cardiovascular events [MACE]) and its components (cardiovascular death, non-fatal myocardial infarction and non-fatal stroke):

- i. Comparison of ticagrelor and clopidogrel adjusted for aspirin dose using a proportional hazards model with terms for treatment group, aspirin dose and no interaction.
- ii. Test of treatment-aspirin interaction for overall population using a proportional hazards model with terms for treatment group, aspirin dose and the treatment-aspirin interaction
- iii. Comparison of ticagrelor and clopidogrel in US and in OUS adjusted for aspirin dose using similar model as in i, and assessment of regional differences, as appropriate
- iv. Test of interaction of treatment-aspirin by region (US/OUS) using similar model as in ii
- v. Comparison of ticagrelor and clopidogrel using a proportional hazards model with terms for treatment group, aspirin dose, region (US/OUS), treatment-aspirin interaction and treatment-region interaction.
- vi. Comparison of ticagrelor and clopidogrel using a proportional hazards model with terms for treatment group, aspirin dose, region (US/OUS) and all two-way and three-way interactions
- vii. Comparison of ticagrelor and clopidogrel in each aspirin stratum (0mg , $\leq 100\text{mg}$, $1\text{mg}-100\text{mg}$, $101\text{mg}-299\text{mg}$, and $\geq 300\text{mg}$) by region (US/OUS) using a forest plot

For the preferred aspirin dose analyses, you should also analyze effects by aspirin dose in major subgroups, including ST-elevation myocardial infarction (STEMI) versus non-ST-elevation myocardial infarction (NSTEMI) by initial ECG; initial “invasive” versus “non-invasive” strategy by intent; and early (< 12 hours) versus no early invasive intervention. You should analyze effects for the primary endpoint, site-reported MACE, mortality, and adjudicated and site-reported bleeding for both early (30-day) and late (entire study period) timepoints.

You or your consultants may suggest on treatment analyses or other analyses, as well.

3. As noted, aspirin dose is not a baseline characteristic, and it could be determined in part by outcome development, a potential problem. It could also be affected by patient status (going to angioplasty, presence of stent, type of stent), but this would appear to be a problem only if choice of dose were different for the clopidogrel and ticagrelor groups; whether this is the case should be examined.

We would like to meet with you at your earliest convenience to discuss the above analyses (1, 2, and 3 above).

4. In addition, please consider modifying the ongoing PEGASUS study in people one year post-MI to have a second randomization to low-dose or high-dose aspirin.

LABELING

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.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a REMS if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)].

We acknowledge receipt of your proposed REMS, included in your submission dated November 13, 2009, which contains a Medication Guide and a timetable for submission of assessments of the REMS. In accordance with section 505-1 of the FDCA, we agree that a REMS will be necessary for Brilinta (ticagrelor), if it is approved, to ensure that the benefits of the drug outweigh the risk of bleeding. The REMS, should it be approved, will create enforceable obligations. We will continue discussion of your proposed REMS after your complete response to this action letter has been submitted.

Under 21 CFR 208.24(d), you are responsible for ensuring that the label of each container or package includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and states how the Medication Guide is provided. You should submit marked up carton and container labels of all strengths and formulations with the required statement alerting the dispenser to provide the Medication Guide. We recommend one of the following statements, depending upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):

- “Dispense the enclosed Medication Guide to each patient.” or
- “Dispense the accompanying Medication Guide to each patient.”

For administrative purposes, designate all submissions related to the proposed REMS “**PROPOSED REMS-AMENDMENT for NDA 022433.**” If you do not submit electronically, please send 5 copies of your REMS-related submissions

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, please call Michael Monteleone, Regulatory Project Manager, at (301) 301-796-1952.

Sincerely,

{See appended electronic signature page}

Robert Temple, MD
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE: Draft Labeling

16 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/

ROBERT TEMPLE
12/16/2010