DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022433

NDA APPROVAL

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) dated November 13, 2009, received November 16, 2009, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) 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, October 1 and December 21, 2010, and January 20, 24, February 18 (3), 23 (2), March 7, 8, 11, 16, 21, 23, 28, 31, April 1, 8, 15 (2), 19, May 2, 4, 5, 23, June 2, 3 and July 6, 13 (2) and 14 (2), 2011.

The January 20, 2011 submission constituted a complete response to our December 16, 2010, action letter.

This new drug application provides for the use of Brilinta (ticagrelor) 90 mg tablets to reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) (unstable angina, non-ST elevation myocardial infarction, or ST elevation myocardial infarction). Brilinta has been shown to reduce the rate of a combined endpoint of cardiovascular death, myocardial infarction, or stroke compared to clopidogrel. The difference between treatments was driven by CV death and MI with no difference in stroke. In patients treated with PCI, it also reduces the rate of stent thrombosis.

Brilinta has been studied in ACS in combination with aspirin. Maintenance doses of aspirin above 100 mg decreased the effectiveness of Brilinta. Avoid maintenance doses of aspirin above 100 mg daily.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 022433**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable. There are too few children with this disease/condition to study.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (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)].

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for Brilinta (ticagrelor) to ensure the benefits of the drug outweigh the risks of bleeding and loss of efficacy when co-administered with maintenance doses of aspirin ≥ 100 mg daily.

In accordance with section 505-1 of the FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR 208. Pursuant to 21 CFR 208, FDA has determined that Brilinta (ticagrelor) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Brilinta (ticagrelor). FDA has determined that Brilinta (ticagrelor) is a product for which patient labeling could help prevent serious adverse effects and that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use Brilinta (ticagrelor) and that the Medication Guide is important to health and patient adherence to directions for use is crucial to the drug's effectiveness. Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Brilinta (ticagrelor).

We have also determined that a communication plan is necessary to support implementation of the REMS.

Your proposed REMS, submitted on July 13, 2011, and appended to this letter, is approved. The REMS consists of a Medication Guide, a communication plan, and a timetable for submission of assessments of the REMS.

Your REMS must be fully operational before you introduce Brilinta (ticagrelor) into interstate commerce.

The REMS assessment plan should include, but is not limited to, the following:

1. An evaluation of patients' understanding of the serious risks of Brilinta (ticagrelor).

2. An evaluation of healthcare providers' understanding of the serious risks of Brilinta (ticagrelor).

3. Number of Dear Healthcare Professional letters electronically sent, received, undeliverable, and opened.

4. Number of Dear Healthcare Professional letters sent via mail and number distributed by sales representatives.

5. Information on the status of any post-approval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such post-approval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such post-approval clinical trial, you must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any material or significant updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA.

If you plan to distribute an authorized generic product under this NDA, you must submit a complete proposed REMS that relates only to the authorized generic product. Submit a proposed REMS, REMS supporting document, and any required appended documents as a prior approval supplement. Approval of the proposed REMS is required before you may market your authorized generic product.

Prominently identify the submission containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

NDA 022433 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 022433
PROPOSED REMS MODIFICATION

REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 022433
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, please call Michael Monteleone, Regulatory Project Manager, at (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(S):
Content of Labeling
Carton and Container Labeling
REMS

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
07/20/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022433/S-022

SUPPLEMENT APPROVAL

AstraZeneca Pharmaceuticals, LP
Attention: Robert Griffin
Global Regulatory Affairs Director
One MedImmune Way
Gaithersburg, MD 20878

Dear Mr. Griffin:

Please refer to your Supplemental New Drug Application (sNDA) dated and received February 9, 2018, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Brilinta (ticagrelor) 60 mg and 90 mg Tablets.

We also refer to our letter dated January 9, 2018, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for ticagrelor. This information pertains to the risk of decreased absorption of ticagrelor when used concomitantly with morphine.

This supplemental new drug application provides for revisions to the labeling for ticagrelor. The agreed upon changes to the language included in our January 9, 2018 letter, and our February 28, 2018 e-mail, containing revisions to our January 9, 2018 required language, are as follows (additions are noted by underline and deletion are noted by ~~strikethrough~~):

1. In **HIGHLIGHTS/DRUG INTERACTIONS**, a bullet was added:

    - Opioids: Decreased exposure to ticagrelor. Consider use of parenteral anti-platelet agent (7.4)

2. Under **DRUG INTERACTIONS**, the following section was added:

    7.4 Opioids
    As with other oral $P2Y_{12}$ inhibitors, co-administration of opioid agonists delay and reduce the absorption of ticagrelor and its active metabolite presumably because of slowed gastric emptying *[see Clinical Pharmacology* (12.3)*]*. Consider the use of a parenteral anti-platelet agent in acute coronary syndrome patients requiring co-administration of morphine or other opioid agonists.

3. Under **CLINICAL PHARMACOLOGY/Pharmacokinetics**, the following text was added/deleted from the second and third paragraphs in the "Effects of Other Drugs on BRILINTA" section:

    Co-administration of 5 mg intravenous morphine with 180 mg loading dose of ticagrelor in decreased observed mean ticagrelor exposure by up to 25% in healthy adults and up to 36% in ACS patients undergoing PCI. Tmax was delayed by 1-2 hours. Exposure of the

active metabolite decreased to a similar extent. Morphine co-administration did not delay or decrease platelet inhibition in healthy adults. Mean platelet aggregation was higher up to 3 hours post loading -dose in ACS patients co-administered with morphine.

Co-administration of intravenous fentanyl with 180 mg loading dose of ticagrelor in ACS patients undergoing PCI resulted in similar effects on ticagrelor exposure and platelet inhibition.

4. Under **CLINICAL PHAMACOLOGY**, Figure 6 was updated to include morphine and fentanyl.

5. The table of Contents and the revision date were updated.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. 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 provide appropriate annotations, including supplement number(s) and annual report date(s).

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call:

Lori Anne Wachter, RN, BSN, RAC
Safety Regulatory Project Manager
(301) 796-3975

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth PharmD.
Deputy Director for Safety
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

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

/s/

MARY R SOUTHWORTH
03/09/2018