

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022433Orig1s000**

**OTHER REVIEW(S)**

022433 Brilinta (ticagrelor)

Project Manager Overview  
**NDA 022433**  
**Brilinta (ticagrelor) Tablets (90 mg)**

**Background:**

NDA 022433 was submitted pursuant to section 505(b)(1) of the FD&C act and was received on November 16, 2009. The applicant requested that the application be considered as a Priority Review, FDA determined that the review priority would be Standard with a September 16, 2010 PDUFA goal date. A major amendment received June 21, 2010 extended the PDUFA user fee goal date to December 16, 2010. The Agency issued a complete response letter on December 16, 2010. The applicant resubmitted the NDA on January 20, 2011, the Agency considered this submission a complete response and determined it to be a Class 2 resubmission with a July 20, 2011 PDUFA user fee goal date, this resubmission is the subject of the current review cycle.

This NDA was the subject of investigations under IND 065808. The following milestone meetings were held with the applicant under that IND:

- Pre-IND (December 5, 2002)
- End of Phase 2 (December 8, 2005)
- Pre-NDA (April 20, 2009)
- Phase 3 Results discussion (August 5, 2009)

The applicant proposed the following indication:



The final approved indication is:

*Brilinta is a P2Y<sub>12</sub> platelet inhibitor indicated 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.*

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This application was reviewed by the Pediatric Review Committee (PeRC) on August 11, 2010 and granted a full waiver.

This application was discussed at a July 28, 2010 Advisory Committee Meeting. The advisory committee voted 7-1 in favor of approval.

This application was discussed at a September 10, 2010 Regulatory Briefing.

### **NDA Reviews and Memos**

#### **Office Director's Memo**

**Dr. Robert Temple; December 16, 2010; July 20, 2011**

In his memo of July 20, 2011, Dr. Temple identifies the main issue in the review as **“whether PLATO, which overall showed clear superiority to clopidogrel, provided evidence that ticagrelor is effective in the population for which it is intended, people living in the United States, and the extent to which regional differences in the dose of aspirin used explained the observed regional difference in the outcome.”**

In his July 20, 2011 memo Dr. Temple summarizes his conclusion that, **“ticagrelor should be approved for treatment of patients with ACS to reduce the rate of thrombotic cardiovascular events, whether the US/OUS difference represents a play of chance or the consequence of differences in aspirin dose in the two regions. If the former, there is perhaps no need to urge lower aspirin dose strongly, but if the aspirin dose effect is reasonably persuasive, even if not considered definitive, a strong recommendation to use maintenance doses  $\leq 100$  mg is warranted. There is no known harm from selection of this dose and a strong possibility (very strong in my view) that use of higher doses will reduce the beneficial effect of ticagrelor.”**

In his memo of December 16, 2010, regarding the first cycle review, Dr. Temple describes the overall study results, subset analyses, and laid out the concerns about the aspirin conclusion. Dr. Temple described the concerns relating to the US/OUS differences and a reluctance to dismiss the finding, but concluded that the idea of the aspirin dose explanation, if stringently defined and tested and consistent, could be a basis for a favorable conclusion on resubmission.

#### **Division Director's Memo**

**Dr. Norman Stockbridge; October 7, 2010; July 8, 2011**

In his memo of July 8, 2011, Dr. Stockbridge conveys the Division's recommendation that the application be approved. Dr. Stockbridge describes his understanding of the Agency's decision to issue a Complete Response during the previous cycle as being critically dependent upon the persuasiveness of the aspirin hypothesis. Dr. Stockbridge summarizes the applicant's resubmission as containing non-clinical data and additional requested aspirin analyses.

Dr. Stockbridge concludes that the non-clinical data is consistent with their being no further benefit of aspirin when used with complete P2Y12 receptor blockade, but provides little support for the hypothesis that **high-dose aspirin leads to “harm”** of increased vascular resistance in the presence of P2Y12 blockade.

Dr. Stockbridge comments that the aspirin hypothesis (that aspirin dose accounts for regional differences in outcome) is **not highly persuasive – by mechanism or analyses as**

a factor in the study outcomes. He reasons, however, that if the regional difference is, in fact attributable to dose of aspirin, then the problem is resolved by advising use with low-dose aspirin, in most patients, and if this is wrong, then there does not appear to be any harm in advising use with low-dose aspirin. He reasons further that unless one can identify a factor intrinsic to US patients or their care that explains the regional disparity in outcomes and then cannot circumvent the effect of that factor, then, despite residual doubts, one is forced to conclude that the evidence favoring true regional differences is far less compelling than is the overall study result.

In his memo of October 7, 2010, regarding the first review cycle, Dr. Stockbridge recommended a Complete Response action until evidence is developed that ticagrelor provides benefit likely to be realized in US practice. Ideally, he proposes, that would be an outcome study in the US, but it could be independent support for the aspirin hypothesis as an outcome study anywhere and in ACS or some closely related condition. It might also be possible to support the hypothesis that higher degrees of P2Y12 inhibition adversely affect the response to high dose aspirin using measures short of outcomes. Dr. Stockbridge disagreed with Dr. Marciniak's approval recommendation, for the first cycle, commenting that the conclusion seems to have been reached after a highly selective analysis.

**CDTL Memo**

**Dr. Thomas Marciniak; September 17, 2010**

**Recommended Action: Approval**

Dr. Marciniak conducted the efficacy review of ticagrelor in the second cycle of review, for his comments regarding the second cycle; see the summary of his clinical efficacy reviews below.

In his memo of September 17, 2010 regarding the first cycle review, Dr. Marciniak recommended that ticagrelor be approved for the treatment of ACS except for STEMI patients undergoing early PCI, with a PMR for a US study addressing STEMI patients undergoing early PCI. Dr. Marciniak commented that his recommendation was a difficult one, and not the only regulatory action he would support, stating that he would not support unrestricted approval of ticagrelor for all ACS patients.

**Clinical Efficacy Review; May 14, 2011; June 8, 2011**

**Dr. Thomas Marciniak**

**Recommended Action: No Approval**

In his review of May 14, 2011, Dr. Marciniak recommends against approval. Dr. Marciniak summarizes his conclusion that, at best, the US results are representative of ticagrelor's efficacy, i.e., ticagrelor is inferior to clopidogrel in efficacy and safety. Dr. Marciniak concludes further that, ticagrelor appears to perform less well than clopidogrel in patients undergoing early PCI, and that the interaction between ticagrelor and early PCI is more consistent than the interaction between ticagrelor and aspirin on the mortality endpoint, as are the interactions between ticagrelor and statin use and diabetes and aspirin. Dr. Marciniak recommends confirmation of efficacy and safety in ACS by a second study in the US in invasively managed patients.

In a memo filed June 8, 2011, Dr. Marciniak documents his concerns regarding the applicant's handling of adverse events which he did not feel were correctly captured in the minutes of an April 20, 2011 meeting with the applicant. Dr. Marciniak believes that

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the applicant's management of adverse events in PLATO was inadequate and further describes his arguments in favor of a second clinical trial for ticagrelor prior to approval.

**Clinical Efficacy Review; June 25, 2010; August 25, 2010**

**Dr. Robert Fiorentino**

**Recommended Action: No Approval**

In the addendum to his review, Dr. Fiorentino comments that the outcome in the US is unlikely to be an entirely random occurrence, and that there is a real possibility that ticagrelor may behave differently in the US than in the non-US population.

Dr. Fiorentino suggests that a separate study in the US could be designed to address the uncertainties surrounding the US outcome, and lays out some key items such a study should address.

**Clinical Safety Review; June 28, 2010; July 20, 2010; August 25, 2010; June 5, 2011**

**Dr. Melanie Blank**

**Recommended Action: No Approval**

In her review of June 5, 2011, Dr. Blank provides her assessment of the aspirin hypothesis, assessment of thromboembolic events, assessment of the reasons for discontinuation of study drug and an updated version of her safety summary from the first review cycle. In her review, regarding the aspirin hypothesis Dr. Blank summarizes that with the absence of clinical benefit for ticagrelor in the US and the possibility that this absence is not caused by high dose aspirin but rather by other factors, it is difficult to justify an approval decision and another study should be required.

In the addendum to her June 28, 2010 review, Dr. Blank comments that despite the favorable safety profile and impressive overall efficacy of ticagrelor, it is very troublesome that ticagrelor trends toward doing harm in the US population. Dr. Blank commented that the trend was not sufficiently explained by aspirin dose or other known modifiable condition. Dr. Blank also commented that chance seemed a highly unlikely explanation of the disparity in efficacy between the US and the rest of the world.

Dr. Blank recommended during the first cycle review that if approved, another long term study should be required.

**Statistical Review; June 29, 2010; August 31, 2010; April 28, 2011**

**Dr. Jialu Zhang**

In her April 28, 2011 review regarding the second cycle review, Dr. Zhang concludes that various aspirin definitions appear to demonstrate some degree of consistency in the analysis, though these analyses are limited by the fact that there were only a small number of high aspirin dose subjects OUS. Dr. Zhang comments on her analysis of potential treatment-aspirin interaction in the TRITON study and concluded that she could not find such an interaction. Dr. Zhang concludes that she remains concerned whether aspirin is truly the only factor that might affect the ticagrelor effect.

Dr. Zhang recommended in the first cycle review that further data be gathered to either confirm or dismiss the US/OUS finding and that without this data, the drug should not be approved.

In the addendum to her review of June 29, 2010 review of the first cycle, Dr. Zhang commented that neither the play of chance, nor concurrent use of ASA provided a

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satisfactory explanation for the US versus non-US disparity observed in PLATO. Dr. Zhang comments that although multiple factors have been screened for potential causes, the question remains unsolved.

**Clinical Pharmacology; June 27, 2010; August 29, 2010**

**Dr. Islam Younis**

**Recommended Action: Approval**

In his review, Dr. Younis comments that the Office of Clinical Pharmacology has reviewed the submission and cannot resolve the differential effectiveness of ticagrelor in the US and Non-US sites. Dr. Younis comments that several factors, such as ASA usage, statin usage, compliance and differences in ticagrelor exposure were investigated, but that none of these satisfactorily explained the differential effectiveness. Given the overall results, the Office recommended approval of ticagrelor with a post-approval study aimed to reconcile the findings from the US region.

**Pharmacology Review; June 23, 2010; August 10, 2010; April 25, 2011**

**Dr. Elizabeth Hausner**

**Recommended action: Approvable**

During the second cycle Dr. Hausner filed a review of the non-clinical data submitted by the sponsor in support of the aspirin hypothesis. Dr. Hausner summarizes her conclusion that there is no clear explanation why aspirin's proposed inhibition of endothelial prostacyclin is able to outweigh ticagrelor's, but not clopidogrel's, beneficial effects of TXZ<sub>2</sub> inhibition, platelet inhibition, and interactions with phosphodiesterase isoforms.

In her review dated June 23, 2010 Dr. Hausner concluded that the application was approvable for the purpose of preventing platelet aggregation.

**Chemistry Review; July 23, 2010; August 12, 2010**

**Drs. Thomas Wong (DP) and Chhagan Tele (DS)**

**Recommended action: Approval**

The overall recommendation from the Office of Compliance was Acceptable, (August 9, 2010).

**REMs**

This application will be approved with a REMS consisting of a Medication Guide and Communication Plan, the goals of which are:

1. To inform healthcare professionals and patients of the serious risks associated with BRILINTA, particularly the increased risk of bleeding.
2. To inform healthcare professionals and patients that the daily maintenance dose of aspirin, co-administered with BRILINTA, should not exceed 100 mg.

The REMS and REMS materials were cleared by the Safety Requirements Team on July 15, 2011.

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**Consult/Other Reviews:**

**DMEPA**

August 2, 2010

May 11, 2011

July 13, 2011

**Trade Name**

February 17, 2010;

July 7, 2010

December 2, 2010

April 14, 2011

**MHT**

August 5, 2010

**SEALD**

August 17, 2010

**DRISK**

September 10, 2010

July 7, 2011

July 15, 2011

**DDMAC**

August 4, 2010;

August 20, 2010

July 8, 2011

July 11, 2011

**DSI**

May 20, 2010

**Environmental Assessment**

March 5, 2010;

March 7, 2010

**Biopharm**

July 23, 2010

**Action Items:**

An Approval letter will be drafted for Dr. Temple's signature.

*By Michael Monteleone*

*July 21, 2011*

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/s/  
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MICHAEL V MONTELEONE  
07/21/2011

## SEALD LABELING: PI SIGN-OFF REVIEW

APPLICATION NUMBER	NDA 022433 Class 2 Resubmission
APPLICANT	Astra Zeneca
PRODUCT NAME	BRILINTA (ticagrelor)
SUBMISSION DATE	20 Jan 2011
PDUFA DATE	20 July 2011
SEALD SIGN-OFF DATE	20 July 2011
OND ASSOCIATE DIRECTOR FOR STUDY ENDPOINTS AND LABELING	Laurie Burke

This memo confirms that all critical prescribing information (PI) deficiencies noted in the SEALD Labeling Review filed 20 July 2011 have been addressed in the final agreed-upon PI. SEALD has no objection to PI approval at this time.

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LAURIE B BURKE  
07/20/2011

## **MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications

### **\*\*PRE-DECISIONAL AGENCY MEMO\*\***

**Date:** July 11, 2011

**To:** Mike Monteleone – Regulatory Project Manager  
Division of Cardiovascular and Renal Products (DCRP)

**From:** Emily Baker – Regulatory Review Officer  
Division of Drug Marketing, Advertising, and Communications (DDMAC)

**CC:** Sheila Ryan – Group Leader  
Division of Drug Marketing, Advertising, and Communications (DDMAC)

**Subject:** **DDMAC draft labeling comments**  
**NDA 022433 BRILINTA™ (ticagrelor) Tablets**

DDMAC has reviewed the proposed product labeling (PI) for BRILINTA (ticagrelor) Tablets (Brilinta), submitted for consult on April 19, 2010. Please note DDMAC previously provided comments on the proposed PI on August 20, 2010, based on the proposed PI sent via email on August 12, 2010.

The following comments are provided in response to the updated proposed PI sent via email on July 8, 2011 by Mike Monteleone. If you have any questions about DDMAC's comments, please do not hesitate to contact me.

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EMILY K BAKER  
07/11/2011



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: July 13, 2011

Application Type/Number: NDA 022433

To: Norman Stockbridge, MD, Director  
Division of Cardiovascular and Renal Products

Thru: Zachary Oleszczuk, Pharm.D., Team Leader  
Carol Holquist, RPh, Director  
Division of Medication Error Prevention and Analysis (DMEPA)

From: Manizheh Siahpoushan, Pharm.D., Safety Evaluator  
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Label and Labeling Review

Drug Name and Strength: Brilinta (Ticagrelor) Tablets  
90 mg

Applicant: AstraZeneca LP

OSE RCM #: 2011-195-1

## **1 INTRODUCTION**

This review evaluates the revised container labels (8 count sample, 60 count, and 180 count) and carton labeling (100 count) for Brilinta (Ticagrelor) Tablets, 90 mg, in response to comments from the Division of Medication Error Prevention and Analysis in OSE Review #2011-195, dated May 10, 2011.

## **2 METHODS AND MATERIALS**

The Division of Medication Error Prevention and Analysis uses Failure Mode and Effects Analysis (FMEA)<sup>1</sup>, principals of human factors, and lessons learned from postmarketing experience in our evaluation of labels and labeling of drug products. Additionally, we reviewed the recommendations provided in OSE Review #2011-195, dated May 10, 2011, to ensure all of DMEPA's recommendations have been implemented. This review evaluates the labels and labeling submitted on May 23, 2011 (see Appendices A and B).

## **3 RESULTS**

The Applicant implemented DMEPA's recommendations from OSE Review #2011-195, dated May 10, 2011. We have no further comments for the Applicant regarding Brilinta container labels and carton labeling.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact, Nina Ton, OSE Project Manager, at 301-796-1648.

## **4 REFERENCES**

Toombs, L. OSE Review 2011-195, Brilinta Label and Labeling Review, May 10, 2011.

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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/  
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MANIZHEH SIAHPOUSHAN  
07/13/2011

ZACHARY A OLESZCZUK  
07/13/2011

CAROL A HOLQUIST  
07/13/2011

## **MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications

### **\*\*PRE-DECISIONAL AGENCY MEMO\*\***

**Date:** July 8, 2011

**To:** Michael Monteleone – Regulatory Project Manager  
Division of Cardiovascular and Renal Products  
(DCRP)

**From:** Zarna Patel, PharmD – Regulatory Review Officer  
Division of Drug Marketing, Advertising, and  
Communications (DDMAC)

**CC:** Amy Toscano, PharmD – Group Leader  
DDMAC

**Subject:** **DDMAC draft labeling comments  
NDA 22433 Brilinta® (ticagrelor) Tablets**

DDMAC has reviewed the proposed Medication Guide for Brilinta (ticagrelor) Tablets (Brilinta), submitted for consult on April 19, 2010. Please note DDMAC previously provided comments on the proposed Medication Guide on August 20, 2010, based on the proposed PI sent via email on August 12, 2010.

The following comments are provided in response to the updated proposed PI sent via email on July 8, 2011 by Michael Monteleone. If you have any questions about DDMAC's comments, please do not hesitate to contact me.

We also reviewed the comments on the Medication Guide from the Division of Risk Management (DRISK). We agree with DRISK's comments and have the following additional comments (provided directly on DRISK's version of the Med Guide sent to DCRP on July 5, 2011).

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/s/  
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ZARNA PATEL  
07/08/2011

## SEALD LABELING REVIEW

This SEALD Labeling Review identifies major aspects of the draft labeling that do not meet the requirements of 21 CFR 201.56 and 201.57 and related CDER labeling policies.

APPLICATION NUMBER	NDA-22433 Class 2 Resubmission
APPLICANT	Astra Zeneca
PRODUCT NAME	Ticagrelor (Brilinta)
SUBMISSION DATE	January 20, 2011
PDUFA DATE	June 20, 2011
SEALD REVIEW DATE	June 20, 2011
SEALD LABELING REVIEWER	Perry Mackrill/Ann Marie Trentacosti

The following checked Selected Requirements for Prescribing Information items are outstanding labeling issues that must be corrected before the final draft labeling is approved.

# 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:

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

Per division: This section includes a description of adverse reactions based on the regulatory definition. Adverse events are also included for events in which the causal relationship between the drug and occurrence of the event cannot be determined.

- 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)”

**SEALD LABELING REVIEW**

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ANN M TRENTACOSTI  
07/20/2011



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: May 10, 2011

Application Type/Number: NDA 022433

To: Norman Stockbridge, MD, Director  
Division of Cardiovascular and Renal Products

Thru: Irene Z. Chan, PharmD, BCPS, Team Leader  
Carol Holquist, RPh, Director  
Division of Medication Error Prevention and Analysis (DMEPA)

From: L. Shenee' Toombs, Pharm.D., Safety Evaluator  
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Label and Labeling Review

Drug Name(s): Brilinta (Ticagrelor) Tablets  
90 mg

Applicant: AstraZeneca LP

OSE RCM #: 2011-195

## 1 INTRODUCTION

This review evaluates the labels and labeling for Brilinta submitted on August 24, 2010 and January 20, 2011 from a medication error perspective. DMEPA previously reviewed labels and labeling for Brilinta in OSE Review #2009-2288 dated July 30, 2010.

## 2 METHODS AND MATERIALS

The Division of Medication Error Prevention and Analysis uses Failure Mode and Effects Analysis (FMEA)<sup>1</sup>, principals of human factors, and lessons learned from postmarketing experience in our evaluation of labels and labeling of drug products. This review evaluates the labels and labeling submitted on August 24, 2010 and January 20, 2011 (see Appendices A through C).

## 3 RECOMMENDATIONS

Our evaluation noted areas where the presentation of information on the container labels and carton labeling can be improved for increased understanding and readability. We provide comments to the Division for the insert labeling in Section 3.1 for discussion at the labeling meetings. We provide recommendations for the container labels and carton labeling in Section 3.2 that aim at reducing the risk of medication errors. We request the recommendations for the container labels and carton labeling in Section 3.2 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact, Nina Ton, OSE Project Manager, at 301-796-1648.

### 3.1 COMMENTS TO THE DIVISION

#### *A. Package Insert Labeling - Full Prescribing Information*

*DOSAGE AND ADMINISTRATION*- DMEPA questions the appropriateness of the statement, "A patient who misses a dose....scheduled time." in the Dosage and Administration section of the insert labeling. This information is for the patient and is better suited in the Patient Counseling Information section of the insert labeling (Section 17).

### 3.2 COMMENTS TO THE APPLICANT

#### *A. General Comments (All labels and Labeling)*

1. We note the proprietary name is presented in all-caps. Consider revising the proprietary name to appear in title case (i.e. Brilinta). Words set in upper and lower case form recognizable shapes, making them easier to read than the rectangular shape that is formed by words set in all-caps.
2. Ensure the presentation of the established name is at least half the size of the proprietary name in accordance to 21 CFR 201.10(g)(2), which requires that the established name shall be printed in letters that are at least half as large and a

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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

prominence commensurate to the proprietary name, taking into consideration all pertinent factors, including typography, layout, contrast and other printing features.

***B. Container Labels-180 count***

1. We note that although the 180 count bottle may be a unit-of-use container, it may also be used for more than one patient. Ensure a sufficient number of medication guides are provided.
2. Minimize the size of the company name and logo.

***C. Container Labels-60 count***

1. See comment B.1. and B.2. above.
2. The principal display panel is crowded. To minimize overcrowding condense the manufacturer's address statement.

***D. Professional Samples-8 count***

The principal display panel of the container label is crowded. To minimize overcrowding, "relocate the statement, "Each tablet contains 90 mg ticagrelor" to the top of the left side panel. In order to accommodate this, minimize or remove the statement "Brilinta is a trademark...AstraZeneca 2010".

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

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IRENE Z CHAN  
05/10/2011

CAROL A HOLQUIST  
05/11/2011

**SUMMARY For the EXECUTIVE CAC**

NDA 22433

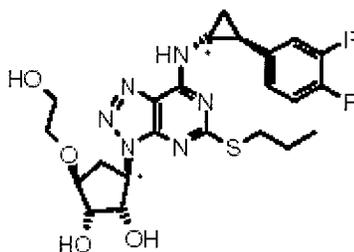
Sponsor's Sequence Number And DARRTS number	Date of submission	Type of submission
042	July 16, 2010	Summary for the Executive CAC

Sponsor: AstraZeneca, LP  
 Manufacturer for drug substance : AstraZeneca

Reviewer name: Elizabeth Hausner, D.V.M.  
 Division name: DCRP  
 Review completion date: July 26, 2010

**Drug:**

Trade name: Brilinta®  
 Generic name: ticagrelor  
 Code name: AZD6140 (formerly AR-C126532XX)  
 Chemical name: (1S,2S,3R,5S)-3-[7-{{(1R,2S)-2-(3,4-Difluorophenyl)cyclopropyl}amino}-5-(propylthio)-3H-1,2,3-triazol[4,5-d]pyrimidin-3-yl]-5-(2-hydroxyethoxy)cyclopentane-1,2-diol  
 CAS registry number: 274693-27-5  
 Mole file number:  
 Molecular formula/molecular weight: C<sub>23</sub>H<sub>28</sub>F<sub>2</sub>N<sub>6</sub>O<sub>4</sub>S 522.57  
 Structure:

**Figure 2.0-1 Structure of AZD6140:**

Related applications: IND65808. Clopidogrel (approved NDA 20839) and Prasugrel (NDA 22307) are other drugs of the same mechanistic class .  
 Drug class: ADP receptor antagonist, specifically P2Y<sub>12</sub>(P<sub>2T</sub>) antagonist

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## Executive Summary

The Executive Carcinogenicity Committee reviewed the results of the rodent carcinogenicity studies in September of 2009. It was the conclusion of the committee that the increased incidence of uterine tumors and hepatocellular adenomas in the HD females was drug-associated. (b) (4)

The sponsor proposes a decreased prolactin hypothesis as the mechanism of uterine tumorigenesis. No additional studies have been conducted to support this. Circulating prolactin levels have not been measured in either animals or humans. The sponsor further proposes that the hepatocellular adenomas are irrelevant to humans and proposes an adaptive mechanism of tumorigenesis. The Division has the following three questions for the Exec CAC:

1. Does the Executive CAC agree with the sponsor's proposed prolactin hypothesis?
2. Does the Executive CAC agree that ticagrelor has no carcinogenic potential for humans?
3. Does the Executive CAC agree that the hepatic tumors are irrelevant to humans?

## Regulatory History

Ticagrelor is an ADP receptor antagonist, specifically antagonizing the P2Y<sub>12</sub>(P2T) receptor. The sponsor is seeking an indication for (b) (4)

September 8, 2009, the 2 year rodent carcinogenicity reports were reviewed by the Executive Carcinogenicity Assessment Committee. The minutes of that meeting are provided as Appendix 3. In addition, the Executive CAC also reviewed the sponsor's studies examining the hypothesis of a testosterone-based mechanism. At that time, the Executive CAC came to the following conclusions about the rodent carcinogenicity studies:

### Rats

- The Committee concluded that the study was adequate, noting prior Exec CAC concurrence with the protocol.
- The Committee concluded that the study showed positive carcinogenicity findings, noting a statistically significant increase in hepatocellular adenoma, uterine adenocarcinoma and uterine squamous cell carcinoma in females.
- The Committee reviewed the sponsor's mechanistic findings but was not convinced that the studies had demonstrated lack of clinical relevance of the tumor findings.

### Mice

- The Committee concluded that the study was adequate, noting prior Exec CAC concurrence with the protocol.
- The Committee concluded that the study did not result in significant

carcinogenicity findings. It was noted that all tumor incidences were within historical control range.

The sponsor has since proposed a prolactin hypothesis for the tumors but has not conducted any further studies to support this proposed mechanism. Prolactin levels have not been measured in either rats or humans. The sponsor's summary statement of the evidence for its hypothesis is attached as Appendix 2.

### Reviewer's Assessment of Proposed Prolactin Hypothesis

The sponsor proposes that the uterine tumors reported for the rats were due to a sustained decrease in prolactin levels and metabolic adaptive changes in the liver. To support this, the sponsor re-assessed the existing non-clinical data and cites the following points:

1. Reduced incidence of pituitary hyperplasia and tumors. The sponsor proposes a decreased hypothalamic drive to produce prolactin, resulting in a decreased number of pituitary tumors. The incidence of pituitary tumors is provided in Appendix 1. The sponsor then proposes that the decreased number of pituitary tumors further augments the decrease in circulating prolactin.
2. Reduced incidence of mammary tumors. The postulated decrease in prolactin is believed to contribute to a decreased incidence of mammary tumors. The incidence of mammary tumors is shown in Appendix 1.

*Reviewer comment for points 1 & 2: I find it difficult to interpret the decreased incidence of pituitary and mammary tumors in the high dose females due to significantly decreased survival in this group. Results from the CDER statistician's dose-mortality trend tests, both the Cox and Kruskal-Wallis tests, were significant for the female rats (Cox:  $p=0.018$ , Kruskal-Wallis:  $p=0.0424$ ). Also, based on the <sup>(b) (4)</sup> Database listing of historical control incidences (provided in Appendix 1), it is possible that these decreased tumor incidences are within the realm of normal variability. Another possibility is that decreased survival and decreased tumors are independent of each other.*

#### Summary of Premature Decedents

	Dose of ticagrelor mg/kg				
	0	0	20	60	180
Found dead	1/50	5/50	3/50	2/50	9/50
Euthanized prematurely	18/50	15/50	19/50	13/50	22/50
Total premature decedents	19/50	20/50	22/50	15/50	31/50

3. Decreased bodyweight after 6 months. Decreased body weight due to dietary restriction in Wistar rats (Roe et al 1995; Keenan et al 1994; Keenan et al 1995a,

Keenan et al 1995b) was associated with a decreased incidence of pituitary tumors and mammary tumors and an increased incidence of uterine tumors. The sponsor feels that the decreased body weight gain shown by the high dose female rats treated with ticagrelor is consistent with a prolactin mechanism.

*Reviewer comment: The high dose females did show a lower rate of body weight gain than the controls. This is however, a non-specific sign. Keenan's publications support a decreased rate of certain neoplasias with decreased dietary intake.*

4. Inhibition of dopamine transporters. *In vitro*, ticagrelor binds to the dopamine receptors with a  $K_i$  of 135nM and an  $IC_{50}$  of 169nM.
5. Studies with dopamine agonists. The sponsor states that bromocriptine shows a similar pattern of decreased mammary and pituitary tumors with increased uterine tumors.

*Reviewer Comment: Other citations suggest the opposite. For example, Yoshida et al (2009. J Reprod Dev. Apr; 55(2):105-109 Long-term treatment with bromocriptine inhibits endometrial adenocarcinoma) used Donyru rats treated with N-ethyl-N'-nitro-N-nitrosoguanidine (ENNG) as a tumor initiator. Bromocriptine was injected subcutaneously 4 times per week until 14.5 months of age to block prolactin surges. The study was terminated when the rats reached 15 months of age. The incidence of uterine adenocarcinomas was decreased from 34.6% in the controls to 13.0% in the bromocriptine group ( $p < 0.05$ ). Cyclicity was reported as unaffected in the bromocriptine group.*

Overall, the sponsor's hypothesis is not without merit. However, a specific deficiency is that prolactin has not been measured either in animals or humans. Some endocrine related adverse events have been noted clinically. The lack of a placebo group complicates the correlation to animal findings.

#### Summary of Clinically Reported Hormonally-Related Adverse Events

Characteristic	Ticagrelor	Clopidogrel	RR
All patients	N= 9235	N= 9186	
Females only	N= 2634	N= 2603	
Males only	N= 6601	N= 6583	
	<u>n(percent)</u>	<u>n(percent)</u>	
Vaginal bleeding (females)	22 (0.84)	17 (0.65)	1.3
Gynecomastia/ swelling/ mass (males)	17 (0.26)	3 (0.05)	5.2
Prostate cancer (males)	13 (0.19)	12 (0.18)	1.1
BPH (males)	10 (0.15)	8 (0.12)	1.3
Breast Cancer (females)	4 (0.15)	10 (0.38)	1
Sexual Dysfunction (males)	3 (0.05)	11 (0.17)	0.3
Cervical/ uterine malignancy (females)	1 (0)	0 (0)	0

Slide courtesy of Melanie Blank, M.D., Medical Officer

6. The liver tumors reported in female rats are explained as due to an adaptive response, typified by hepatomegaly, centrilobular hepatocellular hypertrophy and induction of drug metabolizing enzymes.

*Reviewer's comment: Centrilobular hypertrophy was inconsistently reported (rats  $\geq$ 180 mg/kg/day). The potential of ticagrelor to induce hepatic CYP enzymatic activity was studied in vivo after 3 days oral dosing, after 1 week, 1-month and 3 months oral treatment. Female rats given 180 mg/kg ticagrelor (the high dose in females in the carcinogenicity study) for up to 1 month showed 5-6 fold induction of CYP1A2 compared to control animals. A 2-fold induction of CYP4A1 compared to control was seen regardless of duration of treatment. After 3 months of treatment with 180 mg/kg/day ticagrelor, CYP1A2 activity was slightly increased.*

*Liver effects in rats in general occurred as doses  $\geq$ 80 mg/kg and included indications of altered function or damage evidenced by decreased triglycerides (67%,  $p < 0.001$ ), increased AST (20%,  $p < 0.001$ ) or ALP (31%,  $p < 0.001$ ) when compared to the control groups.*

**Appendix I. Sponsor’s Summary of Pituitary and Mammary Tumors**

Summary of micropathology observations: females – Main study survivors and decedents split

HISTOLOGICAL FINDINGS	GROUP DOSE	GROUP TOTALS							
		Survivors				Decedents			
		Grp 1 0 µmol/ kg/day	Grp 3 38 µmol/ kg/day	Grp 4 115 µmol/ kg/day	Grp 5 344 µmol/ kg/day	Grp 1 0 µmol/ kg/day	Grp 3 38 µmol/ kg/day	Grp 4 115 µmol/ kg/day	Grp 5 344 µmol/ kg/day
<b>ENDOCRINE SYSTEM</b>									
<b>ADRENAL GLAND</b>									
		(61)	(28)	(35)	(19)	(39)	(22)	(15)	(31)
Focal cortical cell hyperplasia, unilateral		7	2	2	1	0	2	3*	0
<b>PITUITARY GLAND</b>									
		(60)	(28)	(35)	(19)	(38)	(22)	(15)	(31)
No abnormality detected		19	9	10	7	9	6	5	17*
CARCINOMA, ANTERIOR LOBE [M]		1	0	0	0	0	0	0	0
ADENOMA, ANTERIOR LOBE [B]		24	9	21	6	25	12	8	11*
ADENOMA, INTERMEDIATE LOBE [B]		1	0	1	0	0	2	0	0
Focal hyperplasia, anterior lobe		14	10	4	5	3	1	3	3
Infiltration by leukaemia cells		0	0	0	0	0	1	0	0
Tubular remnants, craniopharyngeal		0	0	0	0	0	0	1	0
Diffuse hyperplasia, intermediate lobe		1	0	0	0	0	0	0	0
<b>MAMMARY GLAND</b>									
		(60)	(28)	(35)	(18)	(37)	(22)	(14)	(29)
No abnormality detected		39	17	21	17*	20	12	10	25**
ADENOCARCINOMA [M]		1	0	2	0	1	1	1	0
CARCINOSARCOMA [M]		0	0	0	0	1	0	0	0
FIBROADENOMA [B]		8	6	7	0	6	5	1	1
ADENOMA [B]		1	0	0	0	1	0	1	0
Focal hyperplasia		3	1	2	1	4	1	1	1
Lobular hyperplasia		4	1	4	0	2	0	0	1
Infiltration by leukaemia cells		0	0	0	0	0	1	0	0
Galactocoele		11	4	7	0	3	4	0	2

Significantly different from the Control: \* P<0.05, \*\* P<0.01, \*\*\* P<0.001

[B] Benign tumour

[M] Malignant tumour

Figures in brackets represent the number of animals from which this tissue was examined microscopically

Group 1 = Groups 1 and 2 Controls combined

Historical control data from the <sup>(b) (4)</sup> Database

Location and tumor	#of studies	#organs #lesions	Minimum percent	Maximum percent
<b>MAMMARY GLAND</b>	10	565 organs		
Mammary adenoma		8 lesions	1.82	3.64
Mammary adenocarcinoma		31 lesions	1.82	13.33
Mammary fibroadenoma		125 lesions	10.91	33.85
<b>PITUITARY GLAND</b>	10	565organs		
Pituitary adenoma		265	1.67	61.82
Pituitary adenocarcinoma		23	1.82	10.91

**Appendix 2: Sponsor's Summary of Supportive Data**

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**NDA 22-433 Ticagrelor tablets.****Re-evaluation of the mechanism of the change in tumour pattern seen in the rat carcinogenicity study with Ticagrelor**

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## 1. EXECUTIVE SUMMARY

Ticagrelor has no carcinogenic potential relevant for humans. Ticagrelor was not carcinogenic in the mouse or in the male rat. Only at the high dose in females there was a change in tumour spectrum noted, consisting of an increased incidence of uterine tumours associated with a reduced incidence of pituitary hyperplasia and tumours and reduced incidence of mammary tumours, as well as a slight increase of hepatocellular tumours. A weight of evidence analysis for the increased uterine and hepatocellular tumours indicated that both are due to rat specific mechanisms, respectively sustained reduction of prolactin levels and metabolic adaptive changes in the liver.

## 2. MECHANISM OF INCREASED INCIDENCE OF UTERINE TUMOURS

The observed tumor spectrum of increased uterine tumours and reduced mammary and pituitary hyperplasia/tumours is pathognomonic for sustained reduced prolactin levels in the high dose group females, which provides exposures over 25-fold higher than therapeutic exposures observed in man. Several observations indicate that the prolactin mechanism is responsible for the increased incidence of uterine tumours in high dose rats.

**Reduced incidence of pituitary hyperplasia and tumours:** the incidence of pituitary tumours is reduced when the hypothalamic drive to produce prolactin is reduced. In addition, rat pituitary tumours commonly produce large amounts of prolactin, so a reduction in their incidence will greatly augment the reduction in circulating prolactin (Gopinath 1987; Kovacs et al 1977; Neumann 1991).

**Reduced incidence of mammary tumours:** prolactin has a direct trophic effect in the mammary; therefore a reduction in prolactin causes a reduction in mammary tumours. This is a well established phenomenon (Welsch et al 1970; Blankenstein et al 1984; O'Connor et al 2000; Greaves and Faccini 1984).

**Reduced bodyweight after 6 months:** Dietary restriction and resulting reduction in bodyweight gain has been shown to be associated with lower prolactin release. Studies in Wistar rats with diet restriction showed a reduced incidence of pituitary tumours and mammary tumours and an increased incidence of uterine tumours (Roe et al 1995; Keenan et al 1994; Keenan et al 1995a, Keenan et al 1995b). The high dose group rats in the carcinogenicity study with ticagrelor showed a reduction in body weight gain of >20%, consistent with these observations. (Roe et al 1995).

**Inhibition of dopamine transporters:** Ticagrelor binds to the dopamine receptors with a  $K_i$  of 135nM and an  $IC_{50}$  of 169nM (Demaria et al 2000). Free  $C_{max}$  concentration observed in man showed no effect in contrast to free  $C_{max}$  concentration at high dose females.

**Studies with dopamine agonists:** Studies with Bromocriptine showed a similar tumour pattern of reduced mammary and pituitary tumours and increased incidence of uterine tumours (Griffith 1977; Richardson et al 1984) but no associated increased risks with use in man. (A more extensive analysis is given in Appendix 1).

These patterns are consistent with the tumour pattern being the result of a sustained reduction in prolactin, as seen in studies with Bromocriptine and dietary restriction.

#### **Conclusion on the prolactin hypothesis**

Even though prolactin levels were not measured in any of the toxicology studies with ticagrelor, its role is well known, since other drugs or treatments leading to reduced body weight gain or directly affect dopamine have similar changes in tumourigenic pattern in the rat to that of ticagrelor. These findings along with detailed pathogenetic analysis are well documented (Griffith 1977; Richardson et al 1984; Roe et al 1995). AstraZeneca therefore believes that the tumour profile observed in the study, combined with known effects of reduced prolactin in rats, that exists in the literature precludes the need for further studies to determine prolactin levels following dosing with ticagrelor. Literature shows that prolactin is strongly luteotrophic in rats (Ben-Jonathan et al 2008; Smith et al 1976), essential for the progestin-dominated phase of the rodent oestrous cycle. Reduced prolactin therefore leads to a relative increase in the unopposed oestrogen phase of the oestrous cycle. Chronically, this likely contributes to the trophic promotion of uterine tumours (Neumann 1991). Prolactin is not luteotrophic in primates, so this mechanism is irrelevant in man. (Alison and Capen 1994; Ben-Jonathan et al 2008; Freeman et al 2000).

### **3. MECHANISM OF INCREASED INCIDENCE OF HEPATOCELLULAR TUMOURS**

A mild positive liver tumour response was observed only in the high dose female rat carcinogenicity study. The low and mid dose were a NOEL in this respect. The mechanisms identified are considered rat specific as described below. Furthermore, the effects occurred at exposure levels which provide an adequate safety margin (over 25-fold) to human therapeutic exposures.

Administration of xenobiotics to rodents, especially at high doses, can induce a pleiotropic response in the liver which is considered adaptive to the high levels of compound to which the liver is exposed. This adaptive response, also seen in the ticagrelor studies, is typified by hepatomegaly, centrilobular hepatocellular hypertrophy and induction of drug metabolizing enzymes (Graham and Lake 2008, Greaves 2007, Schulte-Hermann 1974). Chronic administration of compounds that cause such an adaptive response is often associated with formation of hepatic adenomas and carcinomas, as seen with chronic administration of ticagrelor. Absolute liver weights were increased after 3 and 6 months of dosing, in females only, at 180mg/kg/day (up to 27% compared to controls). Increases of this magnitude are considered to be a threshold for non-genotoxic tumourigenicity of the rodent liver (reviewed by Graso and Hinton 1991). It is accepted that such tumours, consequent upon chronic

maintenance of the rodent liver adaptive response. are rodent specific (reviewed by Graham and Lake 2008). The low incidence of hepatic tumours observed in the rat carcinogenicity study with ticagrelor, are considered to be a consequence of this adaptive response.

#### 4. CONCLUSION

Based on these observations, AstraZeneca proposes the following wording for product labeling:

##### *Carcinogenesis*



#### 5. REFERENCES (AVAILABLE UPON REQUEST)

##### **Alison and Capen 1994**

Alison RH, Capen CC, Prentice DE. Neoplastic lesions of questionable significance to humans Toxicologic Pathology 1994;22, 179-186.

##### **Ben-Jonathan et al 2008**

Ben-Jonathan N, LaPensee CR, LaPensee EW. What can we learn from rodents about prolactin in humans endocrine Rev 2008;29:1-41.

##### **Blankenstein et al 1984**

Blankenstein MA, Broerse JJ, van Zwieten MJ, van der Molen IJJ. Prolactin concentration in plasma and susceptibility to mammary tumors in female rats from different strains treated chronically with estradiol-17beta. Breast Cancer Res Treatment 1984;4:137-141.

##### **Demaria et al 2000**

Demaria JE, Nagy GM, Lerant AA, Fekete MLE, Levenson CW, Freeman ME. Dopamine transporters participate in the physiological regulation of prolactin. Endocrinol 2000;141:366-374.

##### **Freeman et al 2000**

Freeman MF, Kanyeska B, Lerant A, Nagy G. Prolactin: structure, function and regulation of secretion. Physiol Review 2000;80(4):1523-1631.

**Gopinath 1987**

Gopinath C, Prentice DE, Lewis DJ (1987) Atlas of experimental toxicological pathology MTP Press Lancaster.

**Graham and Lake 2008**

Graham MJ and Lake BG. Induction of drug metabolism: species differences and toxicological relevance. *Toxicology* 2008;254,184–191.

**Graso and Hinton 1991**

Grasso P and Hinton RH. Evidence for and possible mechanisms of non-genotoxic carcinogenesis in rodent liver. *Mutation Research* 1991;248:271-290.

**Greaves and Faccini 1984**

Greaves P, Faccini JM (1984) Rat histopathology Elsevier Amsterdam

**Greaves 2007**

Greaves, P. Histopathology of Preclinical Toxicity Studies (3rdEd) 2007 Pub. Elsevier.

**Griffith 1977**

Griffith RW. Bromocriptine and uterine neoplasia *Br Med J* 1977;1605.

**Keenan et al 1994**

Keenan KP, Smith PF, Hertzog P, Soper K, Ballam GC, and Clark RL. The Effects of Overfeeding and Dietary Restriction on Sprague-Dawley Rat Survival and Early Pathology Biomarkers of Aging. *Toxicologic Pathology* 1994;22(3):300-315.

**Keenan et al 1995a**

Keenan KP, Soper KA, Smith PF, Ballam GC and Clark RL. Diet, Overfeeding, and Moderate Dietary Restriction in Control Sprague-Dawley Rats: I. Effects on Spontaneous Neoplasms. *Toxicologic Pathology* 1995a;23:269-286.

**Keenan et al 1995b**

Keenan KP, Soper KA, Hertzog PR, Gumprecht LA, Smith PF, Mattson BA, Ballam GC, Clark RL. Diet, Overfeeding, and Moderate Dietary Restriction in Control Sprague-Dawley Rats: II. Effects on Age-Related Proliferative and Degenerative Lesions. *Toxicologic Pathology* 1995b;23:287-302.

**Kovacs et al 1977**

Kovacs K, Horwath E, Ilse RG, Ezrin C, Ilse D. Spontaneous pituitary adenomas in aging rats. A light microscopic, immunocytochemical and fine structural study. *Beitr Pathol* 1977;197;161:1-16.

**Neumann 1991**

Neumann F. Early factors for carcinogenesis in sex hormone sensitive organs *Mut Res* 1991;248:341-356.

**O'Connor et al 2000**

O'Connor JC, Plowchalk DR, Van Pelt CS, Davis LG, Cook J. Role of prolactin in chloro-s-triazine rat mammary tumorigenesis. *Drug and Cem Toxicol* 2000;23:575-601.

**Richardson et al 1984**

Richardson BP, Turkali I, Flueckiger E. Bromocriptine. In: Safety testing of new drugs. Laurence DR, McLean AEM, Wheatherall M (eds) Academic Press London 1984;pp 19-63.

**Roe et al 1995**

Roe FJC, Lee PN, Conybeare G, Kelly D, Matter B, Prentice D, Tobin G. The biosure study: Influence of composition of diet and food consumption on longevity, degenerative diseases and neoplasia in Wistar rats studied for up to 30 months post weaning. *Fd Cem Toxic* 1995;33, s1-100.

**Schulte-Hermann 1974**

Schulte-Hermann R. Induction of liver growth by xenobiotic compounds and other stimuli. *Crit Rev Toxicol* 1974;3:97-158.

**Smith et al 1976**

Smith MS, McLean BK, Neill JD. Prolactin: the initial luteotropic stimulus of pseudopregnancy in the rat. *Endocrinol* 1976;98;(6):1370-1377.

**Welsch et al 1970**

Welsch CW, Nagasawa H, Meites J. Increased incidence of spontaneous mammary tumors in female rats with induced hypothalamic lesions. *Cancer Res* 1970;30:2310-2313.

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/s/  
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ELIZABETH A HAUSNER  
01/06/2011

Project Manager Overview

**NDA 022433  
Brilinta (ticagrelor) Tablets (90 mg)**

**Background:**

This NDA was submitted pursuant to section 505(b)(1) of the FD&C act and received on November 16, 2009. The sponsor requested that their application be considered as a Priority Review, FDA determined that the review priority would be Standard.

The sponsor seeks the indication:

*Ticagrelor is indicated to reduce the rate of thrombotic events (including stent thrombosis) for patients with ACS (unstable angina, non ST elevation myocardial infarction or ST elevation myocardial infarction) who are to be managed medically or are to be managed invasively with percutaneous coronary intervention (with or without stent) and/or CABG.*

*Ticagrelor as compared to clopidogrel has been shown to decrease the rate of a combined endpoint of cardiovascular death, MI or stroke. The difference between treatments was driven predominantly by CV death and MI with no difference on strokes.*

*Ticagrelor as compared to clopidogrel has also been shown separately to reduce the rate of:*

- *CV Death*
- *MI*

This application was reviewed by the Pediatric Review Committee (PeRC) on August 11, 2010 and granted a full waiver.

This application was discussed at a July 28, 2010 Advisory Committee Meeting. The advisory committee voted 7-1 in favor of approval.

This application was discussed at a September 10, 2010 Regulatory Briefing.

The original PDUFA goal date was extended to December 16, 2010 due to a major amendment.

**NDA Reviews and Memos**

**Office Director's Memo**

**Dr. Robert Temple; December 16, 2010**

In his memo, Dr. Temple described the overall study results, subset analyses, and laid out the concerns about the aspirin conclusion. Dr. Temple described the concerns relating to the US/OUS difference and a reluctance to dismiss the finding, but concluded that the idea of the ASA dose explanation, if stringently defined and tested and consistent, could be a basis for a favorable conclusion on resubmission.

**Division Director's Memo  
Dr. Norman Stockbridge; October 7, 2010**

In his memo, Dr. Stockbridge recommended a Complete Response action until evidence is developed that ticagrelor provides benefit likely to be realized in US practice. Ideally, that would be an outcome study in the US, but it could be independent support for the aspirin hypothesis as an outcome study anywhere and in ACS or some closely related condition. It might also be possible to support the hypothesis that higher degrees of P2Y12 inhibition adversely affect the response to high dose aspirin using measures short of outcomes.

Dr. Stockbridge disagreed with Dr. Marciniak's approval recommendation, commenting that the conclusion seems to have been reached after a highly selective analysis.

**CDTL Memo  
Dr. Thomas Marciniak; September 17, 2010  
Recommended Action: Approval**

In his memo, Dr. Marciniak recommended that ticagrelor be approved for the treatment of ACS except for STEMI patients undergoing early PCI, with a PMR for a US study addressing STEMI patients undergoing early PCI. Dr. Marciniak commented that his recommendation was a difficult one, and not the only regulatory action he would support, stating that he would not support unrestricted approval of ticagrelor for all ACS patients.

**Clinical Efficacy Review; June 25, 2010; August 25, 2010  
Dr. Robert Fiorentino  
Recommended Action: No Approval**

In the addendum to his review, Dr. Fiorentino comments that the outcome in the US is unlikely to be an entirely random occurrence, and that there is a real possibility that ticagrelor may behave differently in the US than in the non-US population.

Dr. Fiorentino suggests that a separate study in the US could be designed to address the uncertainties surrounding the US outcome, and lays out some key items such a study should address.

**Clinical Safety Review; June 28, 2010; July 20, 2010; August 25, 2010  
Dr. Melanie Blank  
Recommended Action: No Approval**

In the addendum to her review, Dr. Blank comments that despite the favorable safety profile and impressive overall efficacy of ticagrelor, it is very troublesome that ticagrelor trends toward doing harm in the US population. Dr. Blank commented that the trend was not sufficiently explained by aspirin dose or other known modifiable condition. Dr. Blank also commented that chance seemed a highly unlikely explanation of the disparity in efficacy between the US and the rest of the world.

Dr. Blank recommends that if approved, another long term study should be required.

022433 Brilinta (ticagrelor)

**Statistical Review; June 29, 2010; August 31, 2010**

**Dr. Jialu Zhang**

**Recommended Action: No Approval**

In the addendum to her review, Dr. Zhang commented that neither the play of chance, nor concurrent use of ASA provided a satisfactory explanation for the US versus non-US disparity observed in PLATO. Dr. Zhang comments that although multiple factors have been screened for potential causes, the question remains unsolved.

Dr. Zhang recommends that further data be gathered to either confirm or dismiss the US/OUS finding and that without this data, the drug should not be approved.

**Clinical Pharmacology; June 27, 2010; August 29, 2010**

**Dr. Islam Younis**

**Recommended Action: Approval**

In his review, Dr. Younis comments that the Office of Clinical Pharmacology has reviewed the submission and cannot resolve the differential effectiveness of ticagrelor in the US and Non-US sites. Dr. Younis comments that several factors, such as ASA usage, statin usage, compliance and differences in ticagrelor exposure were investigated, but that none of these satisfactorily explained the differential effectiveness. Given the overall results, the Office recommended approval of ticagrelor with a post-approval study aimed to reconcile the findings from the US region.

**Pharmacology Review; June 23, 2010; August 10, 2010**

**Dr. Elizabeth Hausner**

**Recommended action: Approvable**

Please see review for details.

**Chemistry Review; July 23, 2010; August 12, 2010**

**Drs. Thomas Wong (DP) and Chhagan Tele (DS)**

**Recommended action: Approval**

The overall recommendation from the Office of Compliance was Acceptable, (August 9, 2010)

**REMs**

The review team recommended a Medguide REMS for bleeding. Discussion was given to whether or not additional REMS measures should be taken to avoid high dose aspirin. This concern will be revisited when the sponsor responds to our Complete Response letter if the validity of the aspirin hypothesis is accepted.

**Consult/Other Reviews:**

**DMEPA**

August 2, 2010

022433 Brilinta (ticagrelor)

**Trade Name**

December 2, 2010;  
February 17, 2010;  
July 7, 2010

**MHT**

August 5, 2010

**SEALD**

August 17, 2010

**DRISK**

September 10, 2010

**DDMAC**

August 4, 2010;  
August 20, 2010

**DSI**

May 20, 2010

**Environmental Assessment**

March 5, 2010;  
March 7, 2010

**Biopharm**

July 23, 2010

**Action Items:**

A Complete Response letter will be drafted for Dr. Temple's signature. In it we will have the following comments to the sponsor:

“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  $0\text{mg}$ ,  $1\text{mg}-100\text{mg}$ ,  $101\text{mg}-299\text{mg}$ , 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 ( $0\text{mg}$ ,  $\leq 100\text{mg}$ ,  $1\text{mg}-100\text{mg}$ ,  $101\text{mg}-299\text{mg}$ , 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.”

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/s/  
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MICHAEL V MONTELEONE  
12/20/2010

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: September 10, 2010

To: Normal Stockbridge, MD, Director  
**Division of Cardiovascular and Renal Products (DCRP)**

Through: Claudia Karwoski, PharmD, Director  
**Division of Risk Management (DRISK)**

Sharon R. Mills, BSN, RN, CCRP  
Senior Patient Labeling Reviewer, Acting Team Leader  
**Division of Risk Management**

From: Steve L. Morin, RN, BSN  
REMS Reviewer  
**Division of Risk Management**

Latonia Ford, MBA, BSN, RN  
Patient Labeling Reviewer  
**Division of Risk Management**

Jodi M. Duckhorn, MA  
Senior Social Science Reviewer  
**Division of Risk Management**

Subject: DRISK Review of Patient Labeling (Medication Guide), Proposed Risk Evaluation and Mitigation Strategy (REMS) Modification, and Proposed Methodology and Survey Instruments for REMS Assessments

Drug Name(s): BRILINTA (ticagrelor) tablets

Application Type/Number: NDA 22-433

Applicant/sponsor: AstraZeneca LP

OSE RCM #: 2010-27

## **1 INTRODUCTION**

This review is written in response to a request by the Division of Cardiovascular and Renal Products (DCRP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG), proposed Risk Evaluation and Mitigation Strategy (REMS) and REMS supporting documents for BRILINTA (ticagrelor) tablets.

Please send these comments to the Applicant and request a response within two weeks of receipt. Let us know if DCRP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant.

## **2 BACKGROUND**

On November 13, 2009 AstraZeneca LP submitted New Drug Application (NDA) 22-433 for BRILINTA (ticagrelor) tablets. The proposed indication for BRILINTA is to reduce the rate of thrombotic events (including stent thrombosis) for patients with ACS (unstable angina, non ST elevation myocardial infarction or ST elevation myocardial infarction) who are to be managed medically or are to be managed invasively with percutaneous coronary intervention (with or without stent) and/or CABG.

## **3 MATERIAL REVIEWED**

AstraZeneca voluntarily submitted a Risk Evaluation and Mitigation Strategy (REMS) and REMS supporting document.

- Draft BRILINTA (ticagrelor) tablets Prescribing Information (PI) submitted November 13, 2009 revised by the Review Division throughout the current review cycle and submitted to DRISK on August 13, 2010.
- Draft BRILINTA (ticagrelor) tablets Medication Guide (MG) submitted on November 13, 2009 and submitted to DRISK on August 13, 2010
- Proposed BRILINTA (ticagrelor) tablets Risk Evaluation and Mitigation Strategy (REMS) and REMS Supporting Document, submitted on November 13, 2009

## **4 RESULTS OF REVIEW**

### **4.1 In our review of the Medication Guide, we have:**

- Simplified wording and clarified concepts where possible
- Ensured that the MG is consistent with the PI
- Removed unnecessary or redundant information
- Ensured that the MG meets the Regulations as specified in 21CFR 208.24
- Ensured that the MG meets the criteria as specified in FDA's Guidance Useful Written Consumer Medication Information (published July 2006)

### **4.2 In our review of the proposed REMS and REMS Supporting Document, we have:**

- [cbk1]Ensured it meets the statutory requirements under the Food and Drug Administration Amendments Act (FDAAA) of 2007.
- Reviewed the survey methodology for acceptability in assessing the goal of the REMS

## 5 CONCLUSIONS AND RECOMMENDATIONS

DRISK concurs with the elements of the REMS as proposed by the Applicant.

We have the following comments and recommendations for the DCRP and Applicant with regard to the MG, the proposed REMS and the REMS Assessment methodology.

### **Comments to DCRP:**

Our annotated MG is appended to this memo (Appendix A Marked Copy, Appendix B Clean Copy). Any additional revisions to the PI should be reflected in the MG.

### **Comments to AstraZeneca LP:**

See the appended BRILINTA (ticagrelor) tablets REMS proposal (Appendix C of this memo) for track changes corresponding to comments in this review.

#### a. GOAL

Revise your goal as follows:

The goal of this REMS is to inform patients about the serious risks associated with the use of BRILINTA (ticagrelor) tablets.

#### b. Your Medication Guide distribution plan is acceptable. Your detailed plan for how you plan to distribute the Medication Guide in accordance with 21 CFR 208.24 is more appropriate for the REMS Supporting Document.

See our editorial comments on this section of the proposed REMS (see Appendix C).

#### c. Your proposed timetable for submission of assessments (18 months, 3 years, and 7 years) is acceptable.

We have some editorial comments in this section of the proposed REMS.

#### e. The submitted methodology lacks sufficient detail to complete a review.

Submit for review the detailed plan that will be used to evaluate patients' understanding about the risks associated with and safe use of Brilinta. This information **does not** need to be submitted for FDA review prior to approval of your REMS, however it should be submitted at least 90 days before the evaluation will be conducted. The submission should be coded "REMS Correspondence." If the plan is to conduct the required assessment using a survey, the submission should include all methodology and instruments that will be used to evaluate the patients' knowledge about the risks associated with and safe use of Brilinta.

#### 1. We encourage you to recruit respondents using a multi-modal approach. For example, patients could be recruited online, through physicians' offices, through pharmacies, managed care providers, or through consumer panels.

Explain how often non-respondent follow-up or reminders will be completed.

Explain how an incentive or honorarium will be offered, and the intended amount.

Explain how recruitment sites will be selected.

Submit for review any recruitment advertisements.

#### 2. Define the sample size and confidence intervals associated with that sample size.

3. Define the expected number of patients to be surveyed to obtain the final proposed sample size, and how the sample will be determined (selection criteria)

4.

(b) (4)

5. Explain the inclusion criteria; that is, who is an eligible respondent. For example, *patient* respondents might be:

- Age 18 or older
- Currently taking Brilinta or have taken in past 3 months
- Not currently participating in a clinical trial involving Brilinta
- Not a healthcare provider

Submit any screener instruments, and describe if any quotas of sub-populations will be used.

6. Explain how surveys will be administered, and the intended frequency.

Offer respondents multiple options for completing the survey. This is especially important for inclusion of the lower literacy population. For example, surveys could be completed online or through email, in writing or by mail, over the phone, or in person.

Explain how surveyors will be trained.

7. Explain controls used to compensate for the limitations or bias associated with the methodology.

8. The patient sample should be demographically representative of the patients who use Brilinta.

If possible and appropriate, sample should be diverse in terms of: age, race, ethnicity, sex, socio-economic status, education level, geography.

9. Submit for review the introductory text that will be used to inform respondents about the purpose of the survey.

Potential respondents should be told that their answers will not affect their ability to receive or take Brilinta, and that their answers and personal information will be kept confidential and anonymous.

10. Respondents should not be eligible for more than one wave of the survey.

11. The assessment is to evaluate the effectiveness of the REMS in achieving the REMS goal by evaluating patients' knowledge of the serious risks associated with use of Brilinta. The assessment is not to evaluate consumer comprehension of the Medication Guide.

Other than when the patient received the Medication Guide at the time the prescription was filled/dispensed, respondents should not be offered an opportunity to read or see the Medication Guide again prior to taking the survey.

12. Submit for review the survey instruments (questionnaires and/or moderator's guide), including any background information on testing survey questions and correlation to the messages in the Medication Guide.

13. The patient knowledge survey should include a section with questions asking about the specific risks or safety information conveyed in the Medication Guide to see if the patient not only understands the information, but knows what to do if they experience the event.

Most of the risk-specific questions should be derived from information located in the “What is the Most Important Information I should know about Brilinta?” section of the Medication Guide. The questions should be about understanding the risk, the symptoms, and what to do if the event occurs.

The risk-specific questions should be non-biased, non-leading, multiple choice questions with the instruction to “select all that apply.” Each question should have an “I don’t know” answer option.

The order of the multiple choice responses should be randomized on each survey.

14. The order of the questions should be such that the risk-specific questions are asked first, followed by questions about receipt of the Medication Guide. Demographic questions should be collected last or as part of any screener questions.

Respondents should not have the opportunity or ability to go back to previous questions in the survey.

Explain if and when any education will be offered for incorrect responses.

15. Include questions about receipt of the Medication Guide in the patient survey as a way to fulfill the obligation to report on the distribution of the Medication Guide.

16. Just prior to the questions about receipt of the Medication Guide, include text that describes a Medication Guide. For example,

Now we are going to ask you some questions about the Medication Guide you may have received with Brilinta. The Medication Guide is a paper handout that contains important information about the risks associated with use of Brilinta and how to use Brilinta safely. Medication Guides always include the title “Medication Guide”.

17. Use the following (or similar) questions to assess receipt and use of the Medication Guide.

- Who gave you the Medication Guide for Brilinta? (Select all that apply)
  - My doctor or someone in my doctor’s office
  - My pharmacist or someone at the pharmacy
  - Someone else - please explain: \_\_\_\_\_
  - I did not get a Medication Guide for Brilinta
- Did you read the Medication Guide?
  - All,
  - Most,
  - Some,
  - None
- Did you understand what you read in the Medication Guide?
  - All,
  - Most,
  - Some,
  - None
- Did someone offer to explain to you the information in the Medication Guide?

- Yes, my doctor or someone in my doctor's office
  - Yes, my pharmacist or someone at the pharmacy
  - Yes, someone else – please explain: \_\_\_\_\_
  - No
- Did you accept the offer? Yes or No
  - Did you understand the explanation that was given to you?
    - All,
    - Most,
    - Some,
    - None
  - Did or do you have any questions about the Medication Guide? Yes or No (If Yes, list your question(s) below) Note: This is an open text field that should be grouped/coded by the sponsor prior to submitting to FDA

18. Results should be analyzed on an item-by-item or variable-by-variable basis. The data may be presented using descriptive statistics, such as sample size, mean, standard deviation, median, minimum and maximum (for continuous variables), and frequency distributions (for categorical variables).

19. Data may be stratified by any relevant demographic variable, and also presented in aggregate. We encourage you to submit with your assessments all methodology and instruments that were used to evaluate the effectiveness of the REMS.

Please let us know if you have any questions.

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22433	ORIG-1	ASTRAZENECA LP	AZD6140

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LATONIA M FORD  
09/10/2010  
BRILINTA (ticagrelor) tablets DRISK MG-REMS Final Review

CLAUDIA B KARWOSKI  
09/10/2010  
concur

## **MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications

### **\*\*PRE-DECISIONAL AGENCY MEMO\*\***

**Date:** August 20, 2010

**To:** Mike Monteleone – Regulatory Project Manager  
Division of Cardiovascular and Renal Products (DCRP)

**From:** Emily Baker – Regulatory Review Officer  
Zarna Patel – Regulatory Review Officer  
Division of Drug Marketing, Advertising, and Communications (DDMAC)

**Through:** Sheila Ryan – Group Leader  
Division of Drug Marketing, Advertising, and Communications (DDMAC)

**Subject:** **DDMAC draft labeling comments**  
**NDA 022433 BRILINTA™ (ticagrelor) Tablets**

DDMAC has reviewed the proposed product labeling (PI) for BRILINTA (ticagrelor) tablets (Brilinta), submitted for consult on April 19, 2010.

The following comments are provided in response to the updated proposed PI sent via email on August 12, 2010 by Mike Monteleone. If you have any questions about DDMAC's comments, please do not hesitate to contact us.

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22433	ORIG-1	ASTRAZENECA LP	AZD6140

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/s/

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EMILY K BAKER  
08/20/2010

ZARNA PATEL  
08/20/2010

## SEALD LABELING REVIEW

This review identifies aspects of the draft labeling that do not meet the requirements of 21 CFR 201.56 and 201.57 and related CDER labeling policies.

APPLICATION NUMBER	NDA 022433
APPLICANT	AstraZeneca LP
DRUG NAME	Brilinta (ticagrelor)
SUBMISSION DATE	November 16, 2009
PDUFA DATE	September 16, 2010
SEALD REVIEW DATE	August 17, 2010
SEALD LABELING REVIEWER	Jun Yan, Pharm.D.

Outlined below are outstanding labeling issues to be corrected before the final draft labeling is approved.

If there are no issues for a particular heading in highlights (HL) or for sections in the full prescribing information (FPI), “none” is stated. If clearly inapplicable sections are omitted from the FPI, “not applicable” is stated. In addition, “not applicable” is stated if optional headings (i.e., Drug Interactions or Use in Specific Populations) are omitted from HL.

### Highlights (HL):

The applicant should re-format the labeling to comply with all regulations in 21 CFR 201.57(d) and guidelines in “Draft Guidance for Industry: Labeling for Human Prescription Drug and Biological Products --- Implementing the New Content and Format Requirements” (referred to as “Implementation Guidance” below). Fictitious examples of prescribing information can be found at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>.

The length of HL must be no more than a half page when printed in two columns with ½-inch margins on all sides, as required by 21 CFR 201.57(d)(8). A two-column format is recommended for HL by the Implementation Guidance. All section headings must be presented in the center of a horizontal line in upper-case letters and bold type as required by 21 CFR 201.57(d)(3); the headings in HL should not be flushed left.

The applicant should use the same font type throughout the label for consistency and readability.

- **Highlights Limitation Statement:** None.
- **Product Title Line:** To conserve space in HL, keep the proprietary name and established names on the same line as “BRILINTA (ticagrelor) tablets”. The dosage form should be all in lower case.

## SEALD LABELING REVIEW

- **Initial U.S. Approval:** None.
- **Boxed Warning:** N/A.
- **Recent Major Changes:** N/A.
- **Indications and Usage:**
  - The established pharmacologic class (“P2Y<sub>12</sub> platelet inhibitors”) will be applied to this drug per pharm/tox reviewer (Liz Hausner) and should be use in this section in HL. See 21 CFR 201.57(a)(6).
  - Spell out abbreviations (e.g., ACS, CABG, CV, MI) upon first mention.
  - Why is the first sentence italicized?
  - The meaning of the last sentence is unclear: (b) (4)
- **Dosage and Administration:** Bullet 1: The instruction is unclear as currently written. Suggest changing it to “Initial treatment: take two tablets of 90 mg Brilinta as a loading dose.”
- **Dosage Forms and Strengths:** None.
- **Contraindications:** None.
- **Warnings and Precautions:**
  - The subsection numbers referenced in HL do not match the subsection numbers in FPI. After FPI is finalized, HL should be carefully checked to ensure consistency.
  - The last bullet (CYP3A inhibitors or inducers) duplicates Drug Interactions section. Delete this bullet or the Drug Interaction section to avoid repetition and conserve space in HL. See Implementation Guidance.
  - Should “CYP3A” be “CYP3A4”?
- **Adverse Reactions:** None.
- **Drug Interactions:** The bolded sentence “To report SUSPECTED ADVERSE REACTIONS, contact ...” must be moved to the section “Adverse Reactions.” See 21 CFR 201.57(a)(11).
- **Use in Specific Populations:** None.
- **Patient Counseling Information Statement:** This statement is not a section heading. Delete the horizontal line around it.

## SEALD LABELING REVIEW

- **Revision Date:** The recommended format is “Revised: MM/YYYY.” For a new NDA, the revision date will be the month and year of the application approval. Do not leave blank.

### Table of Contents (TOC):

- A horizontal line must be added between the TOC and FPI. See 21 CFR 201.57(d)(2).
- Section 17.6 should be deleted from TOC, as SPL R4 specification no longer allows the inclusion of the Medication Guide (or Patient Labeling) as a subsection of Section 17. The Medication Guide should be appended at the end of the FPI.

### Full Prescribing Information (FPI):

Why is the first page of FPI left blank?

**Boxed Warning:** N/A.

#### **1 Indications and Usage:**

- If there is only one subsection under Section 1, delete the subheading (b) (4).” If the final labeling contains multiple subsections under Section 1, these subsections should be listed in bullets in HL.
- Spell out abbreviations (e.g., ACS, CABG, CV, MI) upon first mention.

#### **2 Dosage and Administration:**

- See comment on the same section in HL.
- The two sentences in paragraph 2 appear to be redundant or overlapping, as well as unclear. (b) (4)

#### **3 Dosage Forms and Strengths:** None.

**4 Contraindications:** As there is only one contraindication, the bolded, un-numbered subheading is not needed.

#### **5 Warnings and Precautions:**

- Section 5.1: Suggest deleting the word “General” as it does not convey any useful information and appears to downplay the risk of the drug.

(b) (4)

## SEALD LABELING REVIEW

### 6 Adverse Reactions:

- See 21 CFR 201.57(c)(7) and “Guidance for Industry: Adverse Reactions Section of Labeling for Human Prescription drug and Biological Products -- Content and Format” for specific requirements for reporting adverse reactions in the prescribing information. This section must report adverse reactions, not adverse events (see definition given in the regulation).
- One or more lists of the adverse reactions and their frequencies must be provided in this section, along with information necessary to interpret these adverse reactions. See 21 CFR 201.57(c)(7)(i) and (ii)(A).
- Throughout Section 6, it is unclear whether the safety data were based solely on the PLATO study or integrated from multiple studies.
- The subheadings and numbers appear to be incorrectly organized and must be fixed: 6.1 Clinical Trials Experience, 6.2 Dyspnea, 6.3 Bradycardia, 6.4 Other Adverse Events, and 6.3 Lab Abnormalities (out of order). The current presentation is confusing and unclear.

### 7 Drug Interactions: None.

### 8 Use in Specific Populations:

- Section 8.1: If additional details from animal toxicology studies are deemed necessary in the labeling, a subsection 13.3 Reproductive and Developmental Toxicology may be added and cross-referenced.
- Section 8.5: (b) (4)

### 9 Drug Abuse and Dependence: N/A.

### 10 Overdosage: None.

### 11 Description: None.

### 12 Clinical Pharmacology:

- Section 12.2: Is the name of the metabolite “AR-C124910XX” a company internal code? If yes, it should not be used in the labeling.
- Section 12.3: The un-numbered headings within this subsection have various and inconsistent fonts and format, making it confusing and difficult to follow. The sponsor should re-format these headings for consistency and readability. Bold type, which is reserved for numbered headings and subheadings, should be used sparingly in the text. Italics or underline, or a combination of both, may be used instead.

### 13 Nonclinical Toxicology: None.

### 14 Clinical Studies:

- For readability and consistency, abbreviations should be used judiciously and defined upon first use throughout the prescribing information.

## SEALD LABELING REVIEW

- Should the primary composite endpoint be [REDACTED] (b) (4)  
[REDACTED] The endpoint appears to refer to the occurrence of any one of the three outcomes, not all three outcomes. Need to correct throughout.
- [REDACTED] (b) (4)

**15 References:** N/A.

**16 How Supplied/Storage and Handling:** None.

**17 Patient Counseling Information:** First sentence: Delete “(17.6).” Per SPL R4 specifications, the Medication Guide or patient labeling is no longer a subsection of Section 17. Also delete the 17.6 subheading and simply append the Medication Guide at the end of the FPI.

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

-----  
NDA-22433

-----  
ORIG-1

-----  
ASTRAZENECA LP

-----  
AZD6140

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/s/  
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JUN YAN  
08/17/2010

LAURIE B BURKE  
08/17/2010

## **MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications

### **\*\*PRE-DECISIONAL AGENCY MEMO\*\***

**Date:** August 4, 2010

**To:** Mike Monteleone – Regulatory Project Manager  
Division of Cardiovascular and Renal Products (DCRP)

**From:** Emily Baker – Regulatory Review Officer  
Division of Drug Marketing, Advertising, and Communications (DDMAC)

**Subject:** **DDMAC draft labeling comments**  
**NDA 022433 Brilinta (ticagrelor) tablets**

DDMAC has reviewed the proposed carton and container labeling for Brilinta (ticagrelor) tablets (Brilinta), submitted for consult on April 19, 2010.

The following comments are provided in response to the proposed carton and container labeling sent via email on August 3, 2010 by Mike Monteleone.

DDMAC has no comments on the proposed carton and container labels at this time.

If you have any questions about DDMAC's comments, please do not hesitate to contact me.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22433	ORIG-1	ASTRAZENECA LP	AZD6140

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/s/

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EMILY K BAKER  
08/04/2010



## **INTRODUCTION**

On November 13, 2009, AstraZeneca submitted a new drug application (NDA 22-433) for Brilinta (ticagrelor) to the Division of Cardio-Renal Products (DCRP). The sponsor's proposed indication for Brilinta is to reduce the rate of thrombotic events (including stent thrombosis) for patients with Acute Coronary Syndromes (unstable angina, non ST elevation myocardial infarction or ST elevation myocardial infarction) who are to be managed medically or are to be managed invasively with percutaneous coronary intervention (with or without stent) and/or Coronary Artery Bypass Graft (CABG). The sponsor's proposed indication also states that:

- Brilinta, as compared to clopidogrel, decreases the rate of a combined endpoint of cardiovascular death, myocardial infarction (MI), or stroke. The difference between treatments was driven predominantly by cardiovascular death and MI with no difference on strokes.
- Brilinta, as compared to clopidogrel, separately reduces the rates of cardiovascular death and MI.

DCRP requested the Maternal Health Team's (MHT) review of the Pregnancy and Nursing Mothers subsections of the division's proposed Brilinta labeling.

## **BACKGROUND**

Brilinta contains the active ingredient ticagrelor, which is a selective and reversible adenosine diphosphate (ADP) receptor antagonist that does not interact with the ADP binding site itself. Ticagrelor acts on the P2Y<sub>12</sub> ADP-receptor and can prevent ADP-mediated platelet activation and aggregation.

The Maternal Health Team (MHT) has been working to develop a more consistent and clinically useful approach to the Pregnancy and Nursing Mothers subsections of labeling. This approach complies with current regulations but incorporates "the spirit" of the Proposed Pregnancy and Lactation Labeling Rule (published on May 29, 2008).

As part of the labeling review, the MHT reviewer conducts a literature search to determine if relevant published pregnancy and lactation data are available that would add clinically useful information to the Pregnancy and Nursing Mothers label subsections. In addition, the MHT presents available animal data, in the Pregnancy subsection, in an organized, logical format that makes it as clinically relevant as possible for prescribers. This includes expressing animal data in terms of species exposed, timing and route of drug administration, dose expressed in terms of human dose equivalents (with the basis for calculation), and outcomes for dams and offspring. For the Nursing Mothers subsection, when animal data are available, only the presence or absence of drug in milk is presented in the label.

This review provides suggested revisions to the Pregnancy and Nursing Mothers subsections of the division's proposed Brilinta labeling.

## **SUMMITTED MATERIAL**

### **Division's Proposed Labeling Related to Pregnancy and Lactation**

#### **8.1 Pregnancy**

Teratogenic Effects: Pregnancy Category C

The safety of BRILINTA during pregnancy has not been established. Women of child bearing potential should use appropriate contraceptive measure to avoid pregnancy.

Doses of  $\geq 100$  mg/kg/day (5.5fold the maximum recommended human dose (MHRD) of 90 mg b.i.d for a 60 kg human on a  $\text{mg}/\text{m}^2$  basis) in rats were associated with supernumerary liver lobe, incomplete ossification of parietal bone and sternebrae, displaced articulation of pelvis, supernumerary ribs and misshapen or misaligned sternebrae. Doses of  $\geq 63$  mg/kg/day (6.8 fold the MRHD on a  $\text{mg}/\text{m}^2$  basis) given to rabbits were associated with delayed gall bladder development and incomplete ossification of the hyoid, pubis and sternebrae.

Doses of  $\geq 10$  mg/kg (approximately half the MRHD on a body surface area basis) given to rats in late gestation and lactation caused developmental delays in pinna unfolding and eye opening.

#### **8.3 Nursing Mothers**

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, BRILINTA should be used during nursing only if the potential benefit to the mother justifies the potential risk to the nursing infant.

Studies in rats have shown that ticagrelor and/or its active metabolites are excreted in the milk.

## **DISCUSSION AND CONCLUSIONS**

Brilinta is a selective and reversible adenosine diphosphate receptor antagonist indicated to reduce the rate of thrombotic events in patients with Acute Coronary Syndromes. For this review, the MHT made revisions to sections of the division's revised draft of the sponsor's proposed Brilinta labeling related to pregnancy and lactation.

The MHT's recommended revisions to the Pregnancy and Nursing Mothers subsections of Brilinta labeling are provided below.

## **RECOMMENDATIONS**

1. The MHT recommends the following language for the Highlights, Pregnancy, and Nursing Mothers sections of Brilinta labeling. A track changes, word version of labeling will be forwarded to the division.

1 Page of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page.

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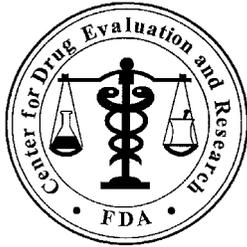
/s/  
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RICHARDAE T ARAOJO  
08/04/2010

Karen B FEIBUS  
08/04/2010

I agree with the content and recommendations contained in this review.

LISA L MATHIS  
08/05/2010



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: July 30, 2010

To: Norman Stockbridge, MD, Director  
Division of Cardiovascular and Renal Products

Thru: Carlos M. Mena-Grillasca, R.Ph., Team Leader  
Denise Toyer, Pharm D., Deputy Director  
Division of Medication Error Prevention and Analysis (DMEPA)

From: L. Shenee' Toombs, Pharm.D., Safety Evaluator  
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Label and Labeling Review

Drug Name(s): Brilinta (Ticagrelor) Tablets  
90 mg

Application Type/Number: NDA 022433

Applicant: AstraZeneca LP

OSE RCM #: 2009-2288

## 1 INTRODUCTION

This review summarizes the Division of Medication Error Prevention and Analysis evaluation of the proposed labels and labeling for Brilinta (NDA 22433) submitted on November 13, 2009.

## 2 METHODS AND MATERIALS

The Division of Medication Error Prevention and Analysis (DMEPA) used Failure Mode and Effects Analysis (FMEA) in our evaluation of the container labels, carton and insert labeling submitted on November 13, 2010. (see Appendices A through C for images).

## 3 RECOMMENDATIONS

Our evaluation noted areas where information on the container labels and carton labeling can be improved upon to provide more optimal presentation for increased understanding and readability. We provide comments to the Division, including recommendations for the insert labeling, in Section 3.1 for discussion at the labeling meetings. We provide recommendations for the container labels and carton labeling in Section 3.2 that aim at reducing the risk of medication errors. We request the recommendations for the container labels and carton labeling in Section 3.2 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact, Nina Ton, OSE Project Manager, at 301-796-1648.

### 3.1 COMMENTS TO THE DIVISION

#### A. PACKAGE INSERT LABELING

##### HIGHLIGHTS OF PRESCRIBING INFORMATION

*DOSAGE AND ADMINISTRATION*- To prevent confusion and maintain consistency with the Dosage and Administration Section in the Full Prescribing Information, revise the statement,   <sup>(b) (4)</sup>

### 3.2 COMMENTS TO THE APPLICANT

#### A. General Comments (All labels and Labeling)

1. We note the proprietary name is presented in all-caps. Consider revising the proprietary name to appear in title case (i.e. Brilinta). Words set in upper and lower case form recognizable shapes, making them easier to read than the rectangular shape that is formed by words set in all-caps.
2. Ensure the presentation of the established name is at least half the size of the proprietary name in accordance to 21 CFR 201.10(g)(2), which requires that the establish name shall be printed in letters that are at least half as large and with a prominence commensurate to the proprietary name, taking into consideration all pertinent factors, including typography, layout, contrast and other printing features.
3. Increase the prominence of the strength. The current presentation is difficult to read.

***B. Container Labels-180 count***

1. Relocate the statement “Dispense with Medication Guide” to the Principal Display Panel (PDP) to ensure the statement is not overlooked by health care practitioners. To accommodate this modification and prevent over-crowding of the PDP, relocate the statement, “Each tablet contains 90 mg ticagrelor” to the side panel of the container label.
2. We note that although the 180 count bottle may be a unit-of-use container, it may also be used for more than one patient. Ensure a sufficient number of medication guides are provided.

***C. Container Labels-60 count***

See comment B.1. above

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22433	ORIG-1	ASTRAZENECA LP	AZD6140

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/s/

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Latoya S TOOMBS  
07/30/2010

CARLOS M MENA-GRILLASCA  
07/30/2010

DENISE P TOYER  
08/02/2010

**SUMMARY For the EXECUTIVE CAC**

NDA 22433

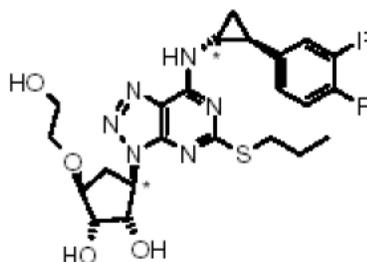
Sponsor's Sequence Number And DARRTS number	Date of submission	Type of submission
042	July 16, 2010	Summary for the Executive CAC

Sponsor: AstraZeneca, LP  
 Manufacturer for drug substance : AstraZeneca

Reviewer name: Elizabeth Hausner, D.V.M.  
 Division name: DCRP  
 Review completion date: July 26, 2010

**Drug:**

Trade name: Brilinta®  
 Generic name: ticagrelor  
 Code name: AZD6140 (formerly AR-C126532XX)  
 Chemical name: (1S,2S,3R,5S)-3-[7-{{[(1R,2S)-2-(3,4-Difluorophenyl)cyclopropyl]amino}-5-(propylthio)-3H-1,2,3-triazol[4,5-d]pyrimidin-3-yl]-5-(2-hydroxyethoxy)cyclopentane-1,2-diol  
 CAS registry number: 274693-27-5  
 Mole file number:  
 Molecular formula/molecular weight: C<sub>23</sub>H<sub>28</sub>F<sub>2</sub>N<sub>6</sub>O<sub>4</sub>S 522.57  
 Structure:

**Figure 2.0-1 Structure of AZD6140:**

Related applications: IND65808. Clopidogrel (approved NDA 20839) and Prasugrel (NDA 22307) are other drugs of the same mechanistic class .

Drug class: ADP receptor antagonist, specifically P<sub>2</sub>Y<sub>12</sub>(P<sub>2</sub>T) antagonist

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## Executive Summary

The Executive Carcinogenicity Committee reviewed the results of the rodent carcinogenicity studies in September of 2009. It was the conclusion of the committee that the increased incidence of uterine tumors and hepatocellular adenomas in the HD females was drug-associated. (b) (4)

(b) (4)  
No additional studies have been conducted to support this. Circulating prolactin levels have not been measured in either animals or humans. (b) (4)

The Division has the following three questions for the Exec CAC:

1. Does the Executive CAC agree with the sponsor's proposed prolactin hypothesis?
2. Does the Executive CAC agree that ticagrelor has no carcinogenic potential for humans?
3. Does the Executive CAC agree that the hepatic tumors are irrelevant to humans?

## Regulatory History

Ticagrelor is an ADP receptor antagonist, specifically antagonizing the P2Y<sub>12</sub>(P2T) receptor. (b) (4)

September 8, 2009, the 2 year rodent carcinogenicity reports were reviewed by the Executive Carcinogenicity Assessment Committee. The minutes of that meeting are provided as Appendix 3. In addition, the Executive CAC also reviewed the sponsor's studies examining the hypothesis of a testosterone-based mechanism. At that time, the Executive CAC came to the following conclusions about the rodent carcinogenicity studies:

### Rats

- The Committee concluded that the study was adequate, noting prior Exec CAC concurrence with the protocol.
- The Committee concluded that the study showed positive carcinogenicity findings, noting a statistically significant increase in hepatocellular adenoma, uterine adenocarcinoma and uterine squamous cell carcinoma in females.
- The Committee reviewed the sponsor's mechanistic findings but was not convinced that the studies had demonstrated lack of clinical relevance of the tumor findings.

### Mice

- The Committee concluded that the study was adequate, noting prior Exec CAC concurrence with the protocol.
- The Committee concluded that the study did not result in significant

carcinogenicity findings. It was noted that all tumor incidences were within historical control range.

The sponsor has since proposed a prolactin hypothesis for the tumors but has not conducted any further studies to support this proposed mechanism. Prolactin levels have not been measured in either rats or humans. The sponsor's summary statement of the evidence for its hypothesis is attached as Appendix 2.

### Reviewer's Assessment of Proposed Prolactin Hypothesis

The sponsor proposes that the uterine tumors reported for the rats were due to a sustained decrease in prolactin levels and metabolic adaptive changes in the liver. To support this, the sponsor re-assessed the existing non-clinical data and cites the following points:

1. Reduced incidence of pituitary hyperplasia and tumors. The sponsor proposes a decreased hypothalamic drive to produce prolactin, resulting in a decreased number of pituitary tumors. The incidence of pituitary tumors is provided in Appendix 1. The sponsor then proposes that the decreased number of pituitary tumors further augments the decrease in circulating prolactin.
2. Reduced incidence of mammary tumors. The postulated decrease in prolactin is believed to contribute to a decreased incidence of mammary tumors. The incidence of mammary tumors is shown in Appendix 1.

*Reviewer comment for points 1 & 2: I find it difficult to interpret the decreased incidence of pituitary and mammary tumors in the high dose females due to significantly decreased survival in this group. Results from the CDER statistician's dose-mortality trend tests, both the Cox and Kruskal-Wallis tests, were significant for the female rats (Cox:  $p=0.018$ , Kruskal-Wallis:  $p=0.0424$ ). Also, based on the <sup>(b) (4)</sup> Database listing of historical control incidences (provided in Appendix 1), it is possible that these decreased tumor incidences are within the realm of normal variability. Another possibility is that decreased survival and decreased tumors are independent of each other.*

#### Summary of Premature Decedents

	Dose of ticagrelor mg/kg				
	0	0	20	60	180
Found dead	1/50	5/50	3/50	2/50	9/50
Euthanized prematurely	18/50	15/50	19/50	13/50	22/50
Total premature decedents	19/50	20/50	22/50	15/50	31/50

3. Decreased bodyweight after 6 months. Decreased body weight due to dietary restriction in Wistar rats (Roe et al 1995; Keenan et al 1994; Keenan et al 1995a,

Keenan et al 1995b) was associated with a decreased incidence of pituitary tumors and mammary tumors and an increased incidence of uterine tumors. The sponsor feels that the decreased body weight gain shown by the high dose female rats treated with ticagrelor is consistent with a prolactin mechanism.

*Reviewer comment: The high dose females did show a lower rate of body weight gain than the controls. This is however, a non-specific sign. Keenan's publications support a decreased rate of certain neoplasias with decreased dietary intake.*

4. Inhibition of dopamine transporters. *In vitro*, ticagrelor binds to the dopamine receptors with a  $K_i$  of 135nM and an  $IC_{50}$  of 169nM.
5. Studies with dopamine agonists. The sponsor states that bromocriptine shows a similar pattern of decreased mammary and pituitary tumors with increased uterine tumors.

*Reviewer Comment: Other citations suggest the opposite. For example, Yoshida et al (2009. J Reprod Dev. Apr; 55(2):105-109 Long-term treatment with bromocriptine inhibits endometrial adenocarcinoma) used Donyru rats treated with N-ethyl-N'-nitro-N-nitrosoguanidine (ENNG) as a tumor initiator. Bromocriptine was injected subcutaneously 4 times per week until 14.5 months of age to block prolactin surges. The study was terminated when the rats reached 15 months of age. The incidence of uterine adenocarcinomas was decreased from 34.6% in the controls to 13.0% in the bromocriptine group ( $p < 0.05$ ). Cyclicity was reported as unaffected in the bromocriptine group.*

Overall, the sponsor's hypothesis is not without merit. However, a specific deficiency is that prolactin has not been measured either in animals or humans. Some endocrine related adverse events have been noted clinically. The lack of a placebo group complicates the correlation to animal findings.

#### Summary of Clinically Reported Hormonally-Related Adverse Events

Characteristic	Ticagrelor	Clopidogrel	RR
All patients	N= 9235	N= 9186	
Females only	N= 2634	N= 2603	
Males only	N= 6601	N= 6583	
	<u>n(percent)</u>	<u>n(percent)</u>	
Vaginal bleeding (females)	22 (0.84)	17 (0.65)	1.3
Gynecomastia/ swelling/ mass (males)	17 (0.26)	3 (0.05)	5.2
Prostate cancer (males)	13 (0.19)	12 (0.18)	1.1
BPH (males)	10 (0.15)	8 (0.12)	1.3
Breast Cancer (females)	4 (0.15)	10 (0.38)	1
Sexual Dysfunction (males)	3 (0.05)	11 (0.17)	0.3
Cervical/ uterine malignancy (females)	1 (0)	0 (0)	0

Slide courtesy of Melanie Blank, M.D., Medical Officer

6. The liver tumors reported in female rats are explained as due to an adaptive response, typified by hepatomegaly, centrilobular hepatocellular hypertrophy and induction of drug metabolizing enzymes.

*Reviewer's comment: Centrilobular hypertrophy was inconsistently reported (rats  $\geq 180$  mg/kg/day). The potential of ticagrelor to induce hepatic CYP enzymatic activity was studied in vivo after 3 days oral dosing, after 1 week, 1-month and 3 months oral treatment. Female rats given 180 mg/kg ticagrelor (the high dose in females in the carcinogenicity study) for up to 1 month showed 5-6 fold induction of CYP1A1/2 compared to control animals. A 2-fold induction of CYP4A1 compared to control was seen regardless of duration of treatment. After 3 months of treatment with 180 mg/kg/day ticagrelor, CYP1A1/2 activity was slightly increased.*

*Liver effects in rats in general occurred as doses  $\geq 80$  mg/kg and included indications of altered function or damage evidenced by decreased triglycerides (67%,  $p < 0.001$ ), increased AST (20%,  $p < 0.001$ ) or ALP (31%,  $p < 0.001$ ) when compared to the control groups.*

**Appendix 1. Sponsor’s Summary of Pituitary and Mammary Tumors**

Summary of micropathology observations: females – Main study survivors and decedents split

HISTOLOGICAL FINDINGS	GROUP DOSE	GROUP TOTALS							
		Survivors				Decedents			
		Grp 1 0 µmol/ kg/day	Grp 3 38 µmol/ kg/day	Grp 4 115 µmol/ kg/day	Grp 5 344 µmol/ kg/day	Grp 1 0 µmol/ kg/day	Grp 3 38 µmol/ kg/day	Grp 4 115 µmol/ kg/day	Grp 5 344 µmol/ kg/day
<b>ENDOCRINE SYSTEM</b>									
<b>ADRENAL GLAND</b>									
		(61)	(28)	(35)	(19)	(39)	(22)	(15)	(31)
Focal cortical cell hyperplasia, unilateral		7	2	2	1	0	2	3*	0
<b>PITUITARY GLAND</b>									
		(60)	(28)	(35)	(19)	(38)	(22)	(15)	(31)
No abnormality detected		19	9	10	7	9	6	5	17*
CARCINOMA, ANTERIOR LOBE [M]		1	0	0	0	0	0	0	0
ADENOMA, ANTERIOR LOBE [B]		24	9	21	6	25	12	8	11*
ADENOMA, INTERMEDIATE LOBE [B]		1	0	1	0	0	2	0	0
Focal hyperplasia, anterior lobe		14	10	4	5	3	1	3	3
Infiltration by leukaemia cells		0	0	0	0	0	1	0	0
Tubular remnants, craniopharyngeal		0	0	0	0	0	0	1	0
Diffuse hyperplasia, intermediate lobe		1	0	0	0	0	0	0	0
<b>MAMMARY GLAND</b>									
		(60)	(28)	(35)	(18)	(37)	(22)	(14)	(29)
No abnormality detected		39	17	21	17*	20	12	10	25**
ADENOCARCINOMA [M]		1	0	2	0	1	1	1	0
CARCINOSARCOMA [M]		0	0	0	0	1	0	0	0
FIBROADENOMA [B]		8	6	7	0	6	5	1	1
ADENOMA [B]		1	0	0	0	1	0	1	0
Focal hyperplasia		3	1	2	1	4	1	1	1
Lobular hyperplasia		4	1	4	0	2	0	0	1
Infiltration by leukaemia cells		0	0	0	0	0	1	0	0
Galactocoele		11	4	7	0	3	4	0	2

Significantly different from the Control: \* P<0.05, \*\* P<0.01, \*\*\* P<0.001

[B] Benign tumour

[M] Malignant tumour

Figures in brackets represent the number of animals from which this tissue was examined microscopically

Group 1 = Groups 1 and 2 Controls combined

Historical control data from the (b) (4) Database

Location and tumor	#of studies	#organs #lesions	Minimum percent	Maximum percent
<b>MAMMARY GLAND</b>	10	565 organs		
Mammary adenoma		8 lesions	1.82	3.64
Mammary adenocarcinoma		31 lesions	1.82	13.33
Mammary fibroadenoma		125 lesions	10.91	33.85
<b>PITUITARY GLAND</b>	10	565organs		
Pituitary adenoma		265	1.67	61.82
Pituitary adenocarcinoma		23	1.82	10.91

**Appendix 2: Sponsor's Summary of Supportive Data**

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**NDA 22-433 Ticagrelor tablets.****Re-evaluation of the mechanism of the change in tumour pattern seen in the rat carcinogenicity study with Ticagrelor**

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5.	REFERENCES (AVAILABLE UPON REQUEST).....	5

## 1. EXECUTIVE SUMMARY

Ticagrelor has no carcinogenic potential relevant for humans. Ticagrelor was not carcinogenic in the mouse or in the male rat. Only at the high dose in females there was a change in tumour spectrum noted, consisting of an increased incidence of uterine tumours associated with a reduced incidence of pituitary hyperplasia and tumours and reduced incidence of mammary tumours, as well as a slight increase of hepatocellular tumours. A weight of evidence analysis for the increased uterine and hepatocellular tumours indicated that both are due to rat specific mechanisms, respectively sustained reduction of prolactin levels and metabolic adaptive changes in the liver.

## 2. MECHANISM OF INCREASED INCIDENCE OF UTERINE TUMOURS

The observed tumor spectrum of increased uterine tumours and reduced mammary and pituitary hyperplasia/tumours is pathognomonic for sustained reduced prolactin levels in the high dose group females, which provides exposures over 25-fold higher than therapeutic exposures observed in man. Several observations indicate that the prolactin mechanism is responsible for the increased incidence of uterine tumours in high dose rats.

**Reduced incidence of pituitary hyperplasia and tumours:** the incidence of pituitary tumours is reduced when the hypothalamic drive to produce prolactin is reduced. In addition, rat pituitary tumours commonly produce large amounts of prolactin, so a reduction in their incidence will greatly augment the reduction in circulating prolactin ([Gopinath 1987](#); [Kovacs et al 1977](#); [Neumann 1991](#)).

**Reduced incidence of mammary tumours:** prolactin has a direct trophic effect in the mammary; therefore a reduction in prolactin causes a reduction in mammary tumours. This is a well established phenomenon ([Welsch et al 1970](#); [Blankenstein et al 1984](#); [O'Connor et al 2000](#); [Greaves and Faccini 1984](#)).

**Reduced bodyweight after 6 months:** Dietary restriction and resulting reduction in bodyweight gain has been shown to be associated with lower prolactin release. Studies in Wistar rats with diet restriction showed a reduced incidence of pituitary tumours and mammary tumours and an increased incidence of uterine tumours ([Roe et al 1995](#); [Keenan et al 1994](#); [Keenan et al 1995a](#), [Keenan et al 1995b](#)). The high dose group rats in the carcinogenicity study with ticagrelor showed a reduction in body weight gain of >20%, consistent with these observations. ([Roe et al 1995](#)).

**Inhibition of dopamine transporters:** Ticagrelor binds to the dopamine receptors with a  $K_i$  of 135nM and an  $IC_{50}$  of 169nM ([Demaria et al 2000](#)). Free  $C_{max}$  concentration observed in man showed no effect in contrast to free  $C_{max}$  concentration at high dose females.

**Studies with dopamine agonists:** Studies with Bromocriptine showed a similar tumour pattern of reduced mammary and pituitary tumours and increased incidence of uterine tumours (Griffith 1977; Richardson et al 1984) but no associated increased risks with use in man. (A more extensive analysis is given in Appendix 1).

These patterns are consistent with the tumour pattern being the result of a sustained reduction in prolactin, as seen in studies with Bromocriptine and dietary restriction.

#### **Conclusion on the prolactin hypothesis**

Even though prolactin levels were not measured in any of the toxicology studies with ticagrelor, its role is well known, since other drugs or treatments leading to reduced body weight gain or directly affect dopamine have similar changes in tumourigenic pattern in the rat to that of ticagrelor. These findings along with detailed pathogenetic analysis are well documented (Griffith 1977; Richardson et al 1984; Roe et al 1995). AstraZeneca therefore believes that the tumour profile observed in the study, combined with known effects of reduced prolactin in rats, that exists in the literature precludes the need for further studies to determine prolactin levels following dosing with ticagrelor. Literature shows that prolactin is strongly luteotropic in rats (Ben-Jonathan et al 2008; Smith et al 1976), essential for the progestin-dominated phase of the rodent oestrous cycle. Reduced prolactin therefore leads to a relative increase in the unopposed oestrogen phase of the oestrous cycle. Chronically, this likely contributes to the trophic promotion of uterine tumours (Neumann 1991). Prolactin is not luteotropic in primates, so this mechanism is irrelevant in man. (Alison and Capen 1994; Ben-Jonathan et al 2008; Freeman et al 2000).

### **3. MECHANISM OF INCREASED INCIDENCE OF HEPATOCELLULAR TUMOURS**

A mild positive liver tumour response was observed only in the high dose female rat carcinogenicity study. The low and mid dose were a NOEL in this respect. The mechanisms identified are considered rat specific as described below. Furthermore, the effects occurred at exposure levels which provide an adequate safety margin (over 25-fold) to human therapeutic exposures.

Administration of xenobiotics to rodents, especially at high doses, can induce a pleiotropic response in the liver which is considered adaptive to the high levels of compound to which the liver is exposed. This adaptive response, also seen in the ticagrelor studies, is typified by hepatomegaly, centrilobular hepatocellular hypertrophy and induction of drug metabolizing enzymes (Graham and Lake 2008, Greaves 2007, Schulte-Hermann 1974). Chronic administration of compounds that cause such an adaptive response is often associated with formation of hepatic adenomas and carcinomas, as seen with chronic administration of ticagrelor. Absolute liver weights were increased after 3 and 6 months of dosing, in females only, at 180mg/kg/day (up to 27% compared to controls). Increases of this magnitude are considered to be a threshold for non-genotoxic tumourigenicity of the rodent liver (reviewed by Graso and Hinton 1991). It is accepted that such tumours, consequent upon chronic

maintenance of the rodent liver adaptive response, are rodent specific (reviewed by [Graham and Lake 2008](#)). The low incidence of hepatic tumours observed in the rat carcinogenicity study with ticagrelor, are considered to be a consequence of this adaptive response.

#### 4. CONCLUSION

Based on these observations, AstraZeneca proposes the following wording for product labeling:

##### *Carcinogenesis*

No compound-related tumors were observed in a 2-year mouse study at oral doses up to 250 mg/kg/day (>18-fold the human therapeutic exposure). There was an increase in tumors (uterine adenocarcinomas and hepatocellular tumors) in female rats only, exposed to high doses (>25-fold the human therapeutic exposures). The uterine tumors seen only in rats were found to be the result of a non-genotoxic endocrine effect of hormonal imbalance present in rats given high doses of ticagrelor. The endocrine mechanism involved in the rat uterine tumors is not present in humans. The benign liver tumors are considered secondary to the adaptive response by the liver to the metabolic load placed on the liver from the high doses of ticagrelor. There is no known correlation between uterine and hepatocellular tumors occurring in ticagrelor-treated rats and human risk.

#### 5. REFERENCES (AVAILABLE UPON REQUEST)

##### **Alison and Capen 1994**

Alison RH, Capen CC, Prentice DE. Neoplastic lesions of questionable significance to humans Toxicologic Pathology 1994;22, 179-186.

##### **Ben-Jonathan et al 2008**

Ben-Jonathan N, LaPensee CR, LaPensee EW. What can we learn from rodents about prolactin in humans endocrine Rev 2008;29:1-41.

##### **Blankenstein et al 1984**

Blankenstein MA, Broerse JJ, van Zwieten MJ, van der Molen HJ. Prolactin concentration in plasma and susceptibility to mammary tumors in female rats from different strains treated chronically with estradiol-17beta. Breast Cancer Res Treatment 1984;4:137-141.

##### **Demaria et al 2000**

Demaria JE, Nagy GM, Lerant AA, Fekete MLE, Levenson CW, Freeman ME. Dopamine transporters participate in the physiological regulation of prolactin. Endocrinol 2000;141,366-374.

##### **Freeman et al 2000**

Freeman ME, Kanyeska B, Lerant A, Nagy G. Prolactin: structure, function and regulation of secretion. Physiol Review 2000;80(4):1523-1631.

**Gopinath 1987**

Gopinath C, Prentice DE, Lewis DJ (1987) Atlas of experimental toxicological pathology  
MTP Press Lancaster.

**Graham and Lake 2008**

Graham MJ and Lake BG. Induction of drug metabolism: species differences and toxicological  
relevance. Toxicology 2008;254,184-191.

**Graso and Hinton 1991**

Grasso P and Hinton RH. Evidence for and possible mechanisms of non-genotoxic  
carcinogenesis in rodent liver. Mutation Research 1991;248:271-290.

**Greaves and Faccini 1984**

Greaves P, Faccini JM (1984) Rat histopathology Elsevier Amsterdam

**Greaves 2007**

Greaves, P. Histopathology of Preclinical Toxicity Studies (3rdEd) 2007 Pub. Elsevier.

**Griffith 1977**

Griffith RW. Bromocriptine and uterine neoplasia Br Med J 1977:1605.

**Keenan et al 1994**

Keenan KP, Smith PF, Hertzog P, Soper K, Ballam GC, and Clark RL. The Effects of  
Overfeeding and Dietary Restriction on Sprague-Dawley Rat Survival and Early Pathology  
Biomarkers of Aging, Toxicologic Pathology 1994;22(3):300-315.

**Keenan et al 1995a**

Keenan KP, Soper KA, Smith PF, Ballam GC and Clark RL. Diet, Overfeeding, and Moderate  
Dietary Restriction in Control Sprague-Dawley Rats: I. Effects on Spontaneous Neoplasms,  
Toxicologic Pathology 1995a;23:269-286.

**Keenan et al 1995b**

Keenan KP, Soper KA, Hertzog PR, Gumprecht LA, Smith PF, Mattson BA, Ballam GC,  
Clark RL. Diet, Overfeeding, and Moderate Dietary Restriction in Control Sprague-Dawley  
Rats: II. Effects on Age-Related Proliferative and Degenerative Lesions, Toxicologic  
Pathology 1995b;23:287-302.

**Kovacs et al 1977**

Kovacs K, Horwath E, Ilse RG, Ezrin C, Ilse D. Spontaneous pituitary adenomas in aging rats.  
A light microscopic, immunocytological and fine structural study. Beitr Pathol  
1977;197;161:1-16.

**Neumann 1991**

Neumann F. Early factors for carcinogenesis in sex hormone sensitive organs Mut Res  
1991;248:341-356.

**O'Connor et al 2000**

O'Connor JC, Plowchalk DR, Van Pelt CS, Davis LG, Cook J. Role of prolactin in chloro-s-triazine rat mammary tumorigenesis. *Drug and Chem Toxicol* 2000;23:575-601.

**Richardson et al 1984**

Richardson BP, Turkali I, Flueckiger E. Bromocriptine. In: Safety testing of new drugs. Laurence DR, McLean AEM, Wheatherall M (eds) Academic Press London 1984;pp 19-63.

**Roe et al 1995**

Roe FJC, Lee PN, Conybeare G, Kelly D, Matter B, Prentice D, Tobin G. The biosure study: Influence of composition of diet and food consumption on longevity, degenerative diseases and neoplasia in Wistar rats studied for up to 30 months post weaning. *Fd Chem Toxicol* 1995;33, s1-100.

**Schulte-Hermann 1974**

Schulte-Hermann R. Induction of liver growth by xenobiotic compounds and other stimuli. *Crit Rev Toxicol* 1974;3:97-158.

**Smith et al 1976**

Smith MS, McLean BK, Neill JD. Prolactin: the initial luteotropic stimulus of pseudopregnancy in the rat. *Endocrinol* 1976;98;(6):1370-1377.

**Welsch et al 1970**

Welsch CW, Nagasawa H, Meites J. Increased incidence of spontaneous mammary tumors in female rats with induced hypothalamic lesions. *Cancer Res* 1970;30:2310-2313.

**Appendix 3. Minutes of the Executive CAC Meeting for Ticagrelor**BEST AVAILABLE  
COPY**Executive CAC****Date of Meeting: September 8, 2009**

Committee: David Jacobson Kram, Ph.D., OND-IO, Chair  
 Abby Jacobs, Ph.D., OND-IO, Member  
 Paul Brown, Ph.D., OND-IO, Member  
 John Leighton Ph.D., OODP, Alternate Member  
 Charles Resnick, Ph.D., DCRP, Pharm Tox Supervisor  
 Elizabeth Hausner D.V.M., DCRP, Presenting Reviewer

Coordinator: Adele Seifried, M.S. OND IO

Author of Minutes: E. Hausner, D.V.M.

IND#: 65808

Drug Name: ticagrelor(Brilinta™)

Sponsor: Astra Zeneca

**Background**

Ticagrelor (AZD6140) is a reversible P2Y<sub>12</sub>(P2T) antagonist, indicated for (b) (4)  
 (b) (4)  
 (b) (4) Mechanistically related drugs  
 include clopidogrel (NDA20839), prasugrel (NDA22307) and cangrelor (b) (4)

There is an active metabolite, ARC124910XX, present in human males at approximately 35% the plasma AUC<sub>0-24</sub> of the parent drug. Metabolite data for human females are unavailable or not provided. In rats, the AUC<sub>0-24</sub> value for the active metabolite is approximately 24-33% of the AUC<sub>0-24</sub> value for the parent drug for females and up to 83% for males. In mice, the AUC<sub>0-24</sub> values for the active metabolite typically exceed the plasma values determined for the parent drug. In male mice, the AUC<sub>0-24</sub> values for the active metabolite ranged from approximately 151-171% of the AUC<sub>0-24</sub> for the parent drug. In female mice, the AUC<sub>0-24</sub> values for the active metabolite ranged from approximately 109-135% of the AUC<sub>0-24</sub> for the parent drug. AZD6140 is highly protein bound (>98%) in all species examined.

**Two Year Carcinogenicity Study in Rats**

Wistar Han IGS (CrI: WI(Glx/BRL/Han)GSBR were administered 20, 60 and 120 mg/kg/day ticagrelor in 1% w/v sodium carboxymethylcellulose in 0.1% w/v polysorbate 80 for 2-years by oral gavage.

The Sponsor's basis of dose selection included gastrointestinal erosions, increased stomach weight and decreased body weight gain as dose-limiting factors. The sponsor used the doses proposed by the Exec CAC at the April 20, 2004 meeting.

Plasma levels of AZD6140 were determined from satellite animals Day 1, Day 3, Week 26, and Week 52. The multiples of human exposure achieved based on comparison of the AUC values from week 52 are summarized in the table below.

Multiples of human exposure\* achieved in 52 week oral gavage exposure study in rats

	Mid-Dose		High-dose	
	males	females	males	females
Rats: ticagrelor multiple of human AUC <sub>0-7</sub>	5X	6X	11X	22X

\*Human AUC<sub>0-7</sub> of 14203 µg.h/l achieved after 300 mg AZD6140 given bid for 5 days.

A maximally tolerated dose was achieved in males in that the HD males gained on average 12% less than the control group. A MTD was exceeded in the females as the HD females gained on average 32% less than the control group. A significant decrease in female survival was apparent (Cox: p=0.018, Kruskal-Wallis: p= 0.0424), possibly due to metastatic uterine neoplasia.

Summary of tumor findings for female rats with results of trend tests<sup>^</sup>

Dose mg/kg/day	0	20	60	180	P-value (exact method)	P-value (Asymptotic method)	Historical control* #lesions/#organs
# of livers examined	100	50	50	50			
# with hepatocellular adenoma	1	1	2	4	0.0104	0.0052	2/565
# of uteri examined	99	50	50	50			
# with uterine adenocarcinoma	10	5	6	21	0.000	0.000	13/565
# with uterine squamous cell carcinoma	0	0	1	3	0.0060	0.0010	1/565

<sup>^</sup>Results of pairwise comparisons of HD vs control: p<0.05 for hepatocellular adenoma and uterine squamous cell carcinoma; p<0.01 for uterine adenocarcinoma

(b) (4) database for Han Wistar rats, 2003, Giknis and Clifford

The sponsor provided in vitro and in vivo studies to support a rat-specific mechanism of altered liver function causing an endocrine imbalance leading to an excess of circulating testosterone causing the uterine tumors. The mechanistic studies included assessment of parent drug binding to steroid hormone receptors, inhibition of aromatase, CYP450 induction and circulating hormone levels in a 3-month repeat dose study in rats. Existing toxicology and fertility studies were re-examined for the possibility of data consistent with the sponsor’s hypothesis..

**Two Year Carcinogenicity Study in Mice**

CD-1(CrI:CD-1(ICR)BR) mice were administered 50, 100 and 250 mg/kg/day ticagrelor in 1% w/v sodium carboxymethylcellulose in 0.1% w/v polysorbate 80 by oral gavage. The Sponsor’s basis of dose selection was an MTD (one-third of the dose that caused mortality)

Plasma levels of AZD6140 were determined from satellite animals Day 1, Week 26, and Week 52. The multiples of human exposure achieved based on comparison of the AUC values from week 52 are summarized in the table below.

Multiples of human exposure\* achieved in 52 week oral gavage exposure study in mice

	Mid-Dose		High-dose	
	males	females	males	females
Mice: ticagrelor multiple of human AUC <sub>0-7</sub>	3X	5X	12X	16X

\*Human AUC<sub>0-7</sub> of 14203 µg.h/l achieved after 300 mg AZD6140 given bid for 5 days.

The study was acceptable in that the doses recommended by the Exec CAC were used. If the doses had been increased to a higher multiple of human exposure, it is unclear if survival would have decreased to a point that would have rendered the study uninterpretable.

The sponsor identified several statistically significant findings. However, when CDER statistical methods were used, the findings did not achieve significance. All values fell within historical incidence ranges reported for control animals of the same strain.

#### **Executive CAC Recommendations and Conclusions:**

##### Rats

- The Committee concluded that the study was acceptable, noting prior Exec CAC concurrence with the protocol.
- The Committee concluded that the study showed positive carcinogenicity findings, noting a statistically significant increase in hepatocellular adenoma, uterine adenocarcinoma and uterine squamous cell carcinoma in females.
- The Committee reviewed the sponsor's mechanistic findings but was not convinced that the studies had demonstrated lack of clinical relevance of the tumor findings.

##### Mice

- The Committee concluded that the study was adequate, noting prior Exec CAC concurrence with the protocol.
- The Committee concluded that the study did not result in significant carcinogenicity findings. It was noted that all tumor incidences were within historical control range.

David Jacobson Kram, Ph.D.  
Chair, Executive CAC

cc:\

Division File, DCRP  
C. Resnick, Ph.D., DCRP  
E. Hausner, D.V.M., DCRP  
A. Blaus, PM, DCRP  
A. Seifried, OND IO

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ELIZABETH A HAUSNER  
01/06/2011

**MEMORANDUM**

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

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**CLINICAL INSPECTION SUMMARY**

**DATE:** May 20, 2010

**TO:** Michael Monteleone, Regulatory Project Manager  
Robert Fiorentino, Medical Officer  
Division of Cardiovascular and Renal Products

**FROM:** Lauren Iacono-Connors, Ph.D.  
Good Clinical Practice Branch 2  
Division of Scientific Investigations

**THROUGH:** Tejashri Purohit-Sheth, M.D.  
Branch Chief  
Good Clinical Practice Branch 2  
Division of Scientific Investigations

**SUBJECT:** Evaluation of Clinical Inspections.

**NDA** 22-433

**APPLICANT:** AstraZeneca LP

**DRUG:** Brilinta (ticagrelor); AZD6140

**NME:** Yes

**THERAPEUTIC CLASSIFICATION:** Standard Review

**INDICATION:** BRILINTA is indicated to reduce the rate of thrombotic events (including stent thrombosis) for patients with ACS (unstable angina, non ST elevation myocardial infarction or ST elevation myocardial infarction) who are to be managed medically or are to be managed invasively with percutaneous coronary intervention (with or without stent) and/or CABG.

**CONSULTATION REQUEST DATE:** 12/3/2009

**DIVISION ACTION GOAL DATE:** 09/16/2010

**PDUFA DATE:** 09/16/2010

## I. BACKGROUND:

Astra Zeneca seeks approval of Brilinta™ (ticagrelor, also known as AZD6140) for the following indication:

To reduce the rate of thrombotic events (including stent thrombosis) for patients with ACS (unstable angina, non ST elevation myocardial infarction or ST elevation myocardial infarction) who are to be:

- managed medically
- managed invasively with percutaneous coronary intervention (with or without stent) and/or CABG.

The application is supported primarily by data from the pivotal study, Study D5130C05262 entitled, “A Randomised, Double-blind, Parallel Group, Phase 3, Efficacy and Safety Study of AZD6140 Compared with Clopidogrel for Prevention of Vascular Events in Patients with Non-ST or ST Elevation Acute Coronary Syndromes (ACS) [PLATO – A Study of PLATelet inhibition and Patient Outcomes.]” This pivotal study was targeted for inspection. Preliminary assessment of the data indicated that the efficacy results between sites in North America, specifically the United States, and sites in Eastern Europe, specifically in Poland and Hungary, were inconsistent in reporting response rates. The majority of clinical data were collected outside the United States.

The applicant claims that ticagrelor is superior to clopidogrel and, in fact, is superior at reducing CV mortality. While the applicant alleges clear superiority of ticagrelor to clopidogrel, results by region from the pivotal study, PLATO, are conflicting as mentioned above. The largest benefit was shown in Eastern Europe, predominantly in Poland and Hungary, while in the United States, treatment with ticagrelor actually appeared to be detrimental.

Six clinical sites were inspected in accordance with the CDER Clinical Investigator Data Validation Inspection using the Bioresearch Monitoring Compliance Program (CP 7348.811); that of Dr. Mátyás Sereg (site number 2611), Dr. Béla Merkely (site number 2615), Dr. András Vértes (site number 2619), Dr. Pawel Buszman (site number 3603), Dr. Wieslawa Tracz (site number 3642), and Dr. Wlodzimierz Musial (site number 3652). These sites were selected by the product review division because there was insufficient domestic data, and the domestic and foreign data showed conflicting results pertinent to decision-making by the agency. In addition, the NDA applicant, AstraZeneca LP, was inspected in accordance with the CDER Sponsor/Monitor/CRO Inspection using the Bioresearch Monitoring Compliance Program (CP 7348.810).

**II. RESULTS (by Site):**

<b>Name of CI, IRB, or Sponsor/CRO Location</b>	<b>Protocol #: and # of Subjects:</b>	<b>Inspection Date</b>	<b>Final Classification</b>
<b>CI#1: Mátyás Sereg</b> <b>Site #2611</b> (Hungary) Saint George Hospital, II Department of Medial Science H-8000 Szekesfehervar, Seregelyesi u. 3 Hungary	<u>Study:</u> PLATO  <u>Site:</u> #2611  <u>Number of subjects:</u> 152	February 22-26, 2010	NAI
<b>CI#2: Béla Merkely</b> <b>Site #2615</b> (Hungary) Semmelweis University, Department of Cardiovascular Surgery, Cardiovascular Centre, H-1122 Budapest, Varosmajor utca 68 Hungary	<u>Study:</u> PLATO  <u>Site:</u> #2615  <u>Number of subjects:</u> 226	March 16-19, 2010	VAI
<b>CI#3: András Vértes</b> <b>Site #2619</b> (Hungary) Saint Istvan Hospital, I Department of Medical Science H-1096 Budapest, Nagyvarad ter 1.1096 Hungary	<u>Study:</u> PLATO  <u>Site:</u> #2619  <u>Number of subjects:</u> 150	March 8-12, 2010	NAI
<b>CI#4: Pawel Buszman</b> <b>Site #3603</b> (Poland) Silesian Medical University Coronary Care Unit, Upper Silesian Centre of Cardiology ul. Ziolowa 47, 40-635 Katowice Poland	<u>Study:</u> PLATO  <u>Site:</u> #3603  <u>Number of subjects:</u> 133	March 1-5, 2010	Pending  Interim classification: NAI
<b>CI#5: Wieslawa Tracz</b> <b>Site #3642</b> (Poland) Head of the Jagiellonian Dept of Cardiac and Vascular Disease University Institute of Cardiology Pardnicka 80, 31-202 Karkow Poland	<u>Study:</u> PLATO  <u>Site:</u> #3642  <u>Number of subjects:</u> 92	February 22-26, 2010	Pending  Interim classification: NAI
<b>CI#6: Włodzimierz Musiał</b> <b>Site #3652</b> (Poland) Head of Department of Cardiology Medical University of Bialystok M. Sklodowska Curie Street 24A musialwj@poczta.onet.pl 15-276 Bialystok Poland	<u>Study:</u> PLATO  <u>Site:</u> #3652  <u>Number of subjects:</u> 108	March 1-5, 2010	Pending  Interim classification: VAI

Name of CI, IRB, or Sponsor/CRO Location	Protocol #: and # of Subjects:	Inspection Date	Final Classification
<b>Sponsor: AstraZeneca LP</b> 1800 Concord Pike P.O. Box 8355 Wilmington, DE 19803-8355	Study: PLATO/18624 Total patient population	March 18-31, 2010	VAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field;

EIR has not been received from the field and complete review of EIR is pending.

**1. CI#1: Dr. Matyas Sereg**

(Site Number 2611)

Saint George Hospital, II

Department of Medial Science

H-8000 Szekesfehervar, Seregelyesi u. 3

Hungary

- a. What was inspected:** The site screened 177 subjects, 152 of those were enrolled and treated. One hundred forty three subjects completed the study. The study records of 31 subjects were audited in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent forms.
- b. General observations/commentary:** Generally, the investigator's execution of the PLATO protocol was found to be adequate. The study was found to be well controlled and well documented. No significant regulatory deviations were observed. The primary efficacy endpoint data were verifiable through audit of the sponsor, AstraZeneca, see findings below. There was one minor observation, one instance of an unreported AE in which the subject had a sudden increase in blood pressure and was seen at the emergency room. In addition, the ECGs were not dated correctly or signed by the clinical investigator. Otherwise, there was no evidence of under reporting adverse events. The FDA field investigator reviewed subject's records, CRFs and source documents, for the primary efficacy values and verified their treatment regimens.

The field investigator confirmed that they were unable to verify the primary efficacy endpoint as this was not conducted by the site. The determination of all efficacy endpoints was made by a CRO, Duke Clinical Research Institute (DCRI), under a protocol-specific Independent Central Adjudication Committee.

Consistent with the routine clinical investigator compliance program assessments, the inspection verified data found in source documents and compared those measurements with that reported by the sponsor to the agency in NDA 22-433. No Form FDA 483 was issued.

- c. **Assessment of data integrity:** The data for Dr. Matyas Sereg's site, associated with Study PLATO submitted to the Agency in support of NDA 22-433, appear reliable based on available information. The general observations and actions on inspection are based upon review of the EIR.

## 2. CI#2: Dr. Bela Merkely

(Site Number 2615)

Semmelweis University, Department of Cardiovascular Surgery,  
Cardiovascular Centre,  
H-1122 Budapest, Varosmajor utca 68  
Hungary

- a. **What was inspected:** The site screened 274 subjects, 226 of those were enrolled and treated. The study records of 26 subjects were audited in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent forms.
- b. **General observations/commentary:** Generally, the investigator's execution of the PLATO protocol was found to be adequate. The study was found to be well controlled and well documented. No significant regulatory deviations were observed. The primary efficacy endpoint data were verifiable through audit of the sponsor, AstraZeneca, see findings below. The FDA field investigator reviewed subject's records, CRFs and source documents, for the primary efficacy values and verified their treatment regimens.

The field investigator confirmed that they were unable to verify the primary efficacy endpoint as this was not conducted by the site. The determination of all efficacy endpoints was made by a CRO, DCRI, under a protocol-specific Independent Central Adjudication Committee. However, the FDA field investigator compared suspected endpoint eCRF pages (listed in Investigator Endpoint and Bleeding Manual Table 1 and 2) with corresponding source documentation found at the site for selected subjects. No discrepancies were noted.

Consistent with the routine clinical investigator compliance program assessments, the inspection verified data found in source documents and compared those measurements with that reported by the sponsor to the agency in NDA 22-433. A Form FDA 483 was issued to the clinical investigator citing 1 inspectional observation.

**Observation 1:** Informed consent was not properly documented in that the written informed consent used in the study was not approved by the IRB. Specifically, 49

subjects were consented with an obsolete version of the IRB/Ethics Committee approved informed consent form. The site received the revised version of the IRB approved ICF, Hungarian Version Number 4, on April 8, 2008. However, from April 13, 2008 – July 11, 2008, the site continued to use the previous ICF, Hungarian Version Number 3, dated May 8, 2007, for 49 subjects consented during that time period. The FDA field investigator also noted that all subjects were re-consented with Version 4.

- c. **Assessment of data integrity:** The data for Dr. Merkely's site, associated with Study PLATO submitted to the Agency in support of NDA 22-433, appear reliable based on available information. The general observations and actions on inspection are based upon review of the EIR.

### 3. CI#3: Dr. Andras Vertes

(Site Number 2619)

Saint Istvan Hospital, I

Department of Medical Science

H-1096 Budapest, Nagyvarad ter 1.1096

Hungary

- a. **What was inspected:** The site screened 182 subjects, 150 of those were enrolled and treated. The study records of 23 subjects were audited in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent forms.
- b. **General observations/commentary:** Generally, the investigator's execution of the PLATO protocol was found to be adequate. The study was found to be well controlled and well documented. No significant regulatory deviations were observed. The primary efficacy endpoint data were verifiable through audit of the sponsor, AstraZeneca, see findings below. The FDA field investigator reviewed subject's records, CRFs and source documents, for the primary efficacy values and verified their treatment regimens.

The field investigator confirmed that they were unable to verify the primary efficacy endpoint as this was not conducted by the site. The determination of all efficacy endpoints was made by a CRO, DCRI, under a protocol-specific Independent Central Adjudication Committee. However, the FDA field investigator compared suspected endpoint eCRF pages (listed in Investigator Endpoint and Bleeding Manual Table 1 and 2) with corresponding source documentation found at the site for selected subjects. No discrepancies were noted.

Consistent with the routine clinical investigator compliance program assessments, the inspection verified efficacy data found in source documents and compared those measurements with that reported by the sponsor to the agency in NDA 22-433. No Form FDA 483 was issued.

- c. **Assessment of data integrity:** The data for Dr. Vertes' site, associated with Study PLATO submitted to the Agency in support of NDA 22-433, appear reliable based on available information. The general observations and actions on inspection are based upon review of the EIR.

4. **CI#4: Dr. Pawel Buszman**

(Site Number 3603)  
Silesian Medical University  
Coronary Care Unit, Upper Silesian  
Centre of Cardiology  
ul. Ziolowa 47, 40-635 Katowice  
Poland

- a. **What was inspected:** The site screened 133 subjects, 133 of those were enrolled and treated. The study records of 31 subjects were audited in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent forms.

**Note:** The EIR was not available at the time this CIS was written. 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:** Generally, the investigator's execution of the PLATO protocol was found to be adequate. The study was found to be well controlled and well documented. No significant regulatory deviations were observed. The primary efficacy endpoint data were verifiable through audit of the sponsor, AstraZeneca, see findings below.

The FDA field investigator reviewed subject's records, CRFs and source documents, for the primary efficacy values and verified their treatment regimens. The field investigator confirmed that they were unable to verify the primary efficacy endpoint as this was not conducted by the site. The determination of all efficacy endpoints was made by a CRO, DCRI, under a protocol-specific Independent Central Adjudication Committee.

Consistent with the routine clinical investigator compliance program assessments, the inspection verified efficacy data found in source documents and compared those measurements with that reported by the sponsor to the agency in NDA 22-433. No Form FDA 483 was issued.

- c. **Assessment of data integrity:** The data for Dr. Buszman's site, associated with Study PLATO submitted to the Agency in support of NDA 22-433, appear reliable based on available information. The general observations and actions on inspection are based on

preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon final review of the EIR.

**5. CI#5: Dr. Wiesława Tracz**

(Site Number 3642)

Department of Cardiac and Vascular Diseases

University Institute of Cardiology

Pardnicka 80, 31-202 Karkow

Poland

- a. What was inspected:** The site screened 92 subjects, 92 of those were enrolled and treated. The study records of 29 subjects were audited in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent forms.

**Note:** The EIR was not available at the time this CIS was written. 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:** Generally, the investigator's execution of the PLATO protocol was found to be adequate. The study was found to be well controlled and well documented. No significant regulatory deviations were observed. The primary efficacy endpoint data were verifiable through audit of the sponsor, AstraZeneca, see findings below. The FDA field investigator reviewed subject's records, CRFs and source documents, for the primary efficacy values and verified their treatment regimens.

The field investigator confirmed that they were unable to verify the primary efficacy endpoint as this was not conducted by the site. The determination of all efficacy endpoints was made by a CRO, DCRI, under a protocol-specific Independent Central Adjudication Committee.

Consistent with the routine clinical investigator compliance program assessments, the inspection verified efficacy data found in source documents and compared those measurements with that reported by the sponsor to the agency in NDA 22-433. No Form FDA 483 was issued.

- c. Assessment of data integrity:** The data for Dr. Tracz's site, associated with Study PLATO submitted to the Agency in support of NDA 22-433, appear reliable based on available information. The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon final review of the EIR.

**6. CI#6: Dr. Włodzimierz Musiał**

(Site Number 3652)

Department of Cardiology

Medical University of Białystok

M. Skłodowska Curie Street 24A

15-276 Białystok

Poland

- a. What was inspected:** The site screened 133 subjects, 108 of those were enrolled and treated. The study records of 28 subjects were audited in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent forms.

**Note:** The EIR was not available at the time this CIS was written. 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:** Generally, the investigator's execution of the PLATO protocol was found to be adequate. However, there were some observations related to protocol compliance and record keeping. Notably, the site randomized Subject E3652106 prior to receipt and review of all safety laboratory test results, hematology panel, albeit Subject E3652106 never received study medication. Site records for subject disposition indicated that Subject E3652106 withdrew consent however, according to the field investigator; the subject did not complete the study because they were inappropriately enrolled. No protocol violation was reported to the sponsor. In addition, the site failed to report an AE, syncope, for Subject E3652004 that occurred on [REDACTED] (b) (6)

The primary efficacy endpoint data were verifiable through audit of the sponsor, AstraZeneca, see findings below. The FDA field investigator reviewed subject's records, CRFs and source documents, for the primary efficacy values and verified their treatment regimens.

The field investigator confirmed that they were unable to verify the primary efficacy endpoint as this was not conducted by the site. The determination of all efficacy endpoints was made by a CRO, DCRI, under a protocol-specific Independent Central Adjudication Committee.

Consistent with the routine clinical investigator compliance program assessments, the inspection verified data found in source documents and compared those measurements with that reported by the sponsor to the agency in NDA 22-433. A Form FDA 483 was issued to the clinical investigator citing 6 inspectional observations.

**Observation 1:** The site failed to follow the protocol for enrollment and randomization in that Subject E3652106 was randomized into the PLATO study prior to receipt and review of subject safety laboratory test results (e.g. hematology panel) by the clinical investigator. This event resulted in the randomization of an ineligible subject.

According to the FDA field investigator, this subject did not receive study medication. The clinical investigator's response, dated March 24, 2010, stated the same, and that the subject's safety was not compromised by the error. However, the observation is valid. The CI response also proposed a corrective action plan for future studies to minimize the risk of the site randomizing a clinical research subject prior to completion of all enrollment/screening procedures.

**Observation 2:** The site-reported final disposition for Subject E3652106 was inaccurate. The CRF states Subject E3652106 withdrew consent from participation; however, this subject did not complete the study because the subject was inappropriately randomized. Additionally, this was not reported as a protocol violation.

**Observation 3:** Study records did not adequately document the appropriate review and evaluation of local safety laboratory test results (e.g. hematology and chemistry) prior to randomization of all subjects. Specifically, the local hematology and chemistry labs do not include a clinical investigator signature with date/time and/or a source note showing safety labs were evaluated prior to randomization.

The clinical investigator's response, dated March 24, 2010, stated that this observation is true; however, all haematology results were checked for signs of anemia and/or thrombocytopenia for all patients prior to randomization with the exception cited under item 1 of the Form FDA 483. The response also stated that the haematology results were confirmed and documented as such by the clinical staff as evidenced by their electronic signature in the eCRF for all patients indicating that they met inclusion/exclusion criteria. However, the CI proposed corrective actions to ensure that source records are signed and dated when initially reviewed by clinical investigators of future studies at the site.

**Observation 4:** An adverse event was not reported to the sponsor via CRF for a Syncope that was experienced by Subject E3652004 on [REDACTED] (b) (6).

The clinical investigator's response, dated March 24, 2010, stated that this event of syncope was considered to be a symptom of "weakness" by the investigator, and was recorded as such in the eCRF. In the future the CI will ensure that the wording of an adverse event in the medical records is consistent with the description of the adverse event that is captured in the eCRF.

**Observation 5:** An unscheduled visit was not reported in the CRF for Subject E3652004. This visit was on October 1, 2007.

The clinical investigator's response, dated March 24, 2010, stated that this unscheduled visit was due to weakness, which was reported as an adverse event. The CI considered this a routine out-patient visit and thus was not reported in the eCRF.

**Observation 6:** Source document for the ECG performed on Subject E3652003 at Visit 2 was not available in the study files.

- c. **Assessment of data integrity:** While a number of regulatory violations were noted during the inspection of Dr. Musial's site, in general the data associated with Study PLATO submitted to the Agency in support of NDA 22-433, appear reliable based on available information. The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon final review of the EIR.

## 7. Sponsor: AstraZeneca LP

**Richard F. Fante**

**CEO North America**

1800 Concord Pike

P.O. Box 8355

Wilmington, DE 19803-8355

- a. **What was inspected:** The sponsor was inspected completing the Sponsor/Monitor/CRO data validation compliance program, CP 7348.810. Specifically, the inspection covered adherence to Protocol PLATO, and review of the firm's SOPs, including monitoring SOPs, Ethics Committee/IRB approvals, completed Form FDA 1572s, monitoring reports, communications with the sites, subjects' randomization, drug accountability and review of data management from the clinical study sites to the submission of the NDA to the Agency. The firm used numerous CROs for conducting the study, in particular was DCRI, which was contracted to establish and manage the ICAC for clinical endpoint adjudication.

This inspection reviewed records for the following clinical investigator sites, 3 sites in Poland (3603, 3634, 3652) and 3 sites in Hungary (2611, 2615, 2619), and 1 additional site in the United States (site number 5238, Dr. Steven Guidera). The inspection reviewed and compared a sample of subject's electronic case report forms with their endpoint packets (EPP) generated by the study sites, and their adjudication tracker results (generated by the CRO, DCRI/Independent Central Adjudication Committee [ICAC] resulting from the ICAC's review of the EPPs), and subject's data listings for primary efficacy endpoints submitted to NDA 22-433, from each of the 7 sites listed above, with the exception of data listings for site 5238. Specifically, 10 subjects from Site #2611 (Subject # 001, 003, 015, 038, 044, 108, 117, 128, 131 and 153), 16 subjects from Site #2615 (Subject # 001, 006, 016, 025, 054, 064, 087, 099, 108, 142, 150, 163, 183, 199, 206 and 226), 10 subjects from Site #2619 (Subject # 003, 011, 036, 050, 060, 083, 096, 116, 122 and 134), 14 subjects from Site #3603 (Subject # 002, 006, 010, 027, 042, 054, 069, 074, 098, 101, 107, 122, 126 and 134), 10 subjects from Site #3642 (Subject # 003, 012, 027, 033, 035, 070, 072, 083, 086 and 087), 10 subjects from Site

#3652 (Subject # 004, 033, 035, 047, 050, 059, 071, 072, 095 and 102), and 10 subjects from Site #5238 (Subjects # 001, 003, 015, 019, 024, 026, 032, 041, 044 and 055) had their records audited for verification of efficacy endpoint data listings provided in NDA 22-433.

- b. General observations/commentary:** Records and procedures were clear, complete and well organized. There was nothing to indicate under-reporting of AEs/SAEs. Overall, site monitoring appeared adequate. The primary efficacy endpoint data were verifiable at the sponsor site. All efficacy endpoints were determined and adjudicated by a CRO, DCRI/ICAC during the study. At the conclusion of the PLATO Study, all records were returned by the CRO to AstraZeneca and the CRO's access to electronic records via password was rescinded. A sample of the efficacy endpoints reported to the Agency in NDA 22-433 for the 6 clinical sites listed above and one additional site selected randomly, Site number 5238, Dr. Steven Guidera, were verified against records retained at the sponsor's site, but initially generated by the CRO, DCRI/ICAC. No discrepancies were observed and there was no evidence of under-reporting adverse events. The FDA field investigator reported that the oversight of the CRO, DCRI/ICAC, by the sponsor AstraZeneca was not always consistent with what was described in the sponsor's internal procedures and agreed upon in the Agreement between AstraZeneca and DCRI.

A Form FDA 483 was issued to the Sponsor citing 1 inspectional observation.

**Observation 1:** Failure to ensure the study is conducted in accordance with the protocol and/or investigational plan.

Specifically, for the PLATO Study,

- a. The Clinical Events Committee (CEC), a division of the DCRI, Agreement, dated January 25, 2006, states that, "The DCRI CEC Director and AstraZeneca representatives will select the ICAC committee members." However, this selection was only conducted the DCRI CEC Director.
- b. The PLATO ICAC Charter, dated September 1, 2006, states that, "Ongoing quality adjudication events will be QC reviewed by the Faculty Committee." However, there was no ongoing quality assurance performed by the ICAC.
- c. There was no documentation to show that the ICAC committee members were segregated during their clinical endpoint event adjudications.
- d. The firm's Global Integrated Process SOP Number 210-G, dated January 27, 2006 states that, "The Monitor's line manager or a delegate reviews and signs a sample of the monitor's reports and corresponding follow-up letters at least every 3 months. *It is recommended that, for a full-time Monitor, all initiation visit reports and 10 other reports per quarter are reviewed.* Review of the 46 monitoring visit reports for Site number 5238, Dr. Steven Guidera, revealed that only 4 of these reports were reviewed, signed and dated by the reviewer.
- e. Nineteen out of 545 expedited serious adverse events were not reported to the FDA in a timely manner. This included twelve 7 day IND reports and seven 15 day IND reports.

The sponsor, AstraZeneca LP made a written response to the Form FDA 483 inspectional observations, dated April 19, 2010.

DSI reviewer Notes:

An inspection of the ICAC was not possible according AstraZeneca since all records associated with the Agreement between AstraZeneca and the CRO DCRI supporting the PLATO Study had been returned to the sponsor sometime after the study was closed and all ICAC functions were ceased. It should be noted that the DCRI was recently inspected by FDA previously as part of a data audit in support of [REDACTED]<sup>(b) (4)</sup> in 2008. The final classification of that inspection was NAI.

Regarding Item 1.a: The CEC Agreement between the DCRI and sponsor did state that representatives from the sponsor and the DCRI CEC Director, Dr. Kenneth W. Mahaffey, “will select ICAC committee members,” however, it did not state in detail how this should occur. The ICAC Charter was also silent on the matter. The FDA field investigator was not able to find any records that documented how the sponsor actively participated with Dr. Mahaffey in the selection of ICAC members. However, the sponsor stated in their response letter, dated April 19, 2010, that they did have ongoing communications with Dr. Mahaffey, to include this subject, but wanted to ensure “independence” of the ICAC. Evidence of sponsor awareness (passive participation) of ICAC member proposed selections was demonstrated in an email from Dr. Mahaffey dated January 28, 2008, providing an invitation list for the PLATO ICAC membership (as part of the CEC) where AstraZeneca LP personnel were copied, Nardev Khurmi and LuAnn Vanaman. In addition, a letter from Dr. Mahaffey to AstraZeneca dated March 19, 2010 was generated during the current inspection to provide additional insight of practices used by the CEC Director when selecting ICAC members and that the “selection process” used by DCRI was approved by the sponsor AstraZeneca. There is no evidence upon inspection to suggest that the sponsor’s passive participation in ICAC member selection compromised ICAC objectives or integrity of adjudicated efficacy endpoints.

Regarding Item 1.b: While ongoing QA of EPP adjudications was not done by the ICAC as described in the ICAC Charter QA/QC reviews were performed by DCRI for the PLATO Study for a 5% sample (a random sample of 586 events selected by AstraZeneca for the QC review). This QA/QC review was conducted on February 14<sup>th</sup>, 27<sup>th</sup>, and March 14<sup>th</sup>, 2009. A report of findings was included in the EIR. No significant issues were identified.

Regarding Item and 1.c: There was no proof that ICAC members were segregated at DCRI when they were working on EPPs to generate endpoint event adjudications, however, the sponsor pointed out in their response letter dated, April 19, 2010, that adjudicators were blinded to study treatments. The sponsor further explained that the electronic system used by adjudicators to record their event adjudication results could be audited to reveal trends or signals that may imply that two DCRI adjudicators worked

collaboratively and not separately as required. A review by the sponsor of the audit trail revealed no trends or signals suggesting adjudicator bias. In addition, the sponsor informed in their April 19, 2010 response letter that using the clinical investigator-designated events in an efficacy analysis yielded results consistent with those obtained using the ICAC-adjudicated events.

Regarding Item 1.d: The sponsor demonstrated limited compliance enforcement with their own SOP, *Global Integrated Process SOP Number 210-G*, dated January 27, 2006, which stated that for a “full-time monitor” all initiation visit reports and 10 other reports per quarter are to be reviewed and signed by the monitor’s line manager or delegate. Site 5238, Dr. Steven Guidera, had 46 monitoring visit reports audited by the FDA field investigator, but only 4 were found to have been signed and dated by the monitor’s reviewer. The sponsor concurred with the observation in their response letter dated, April 19, 2010, but described 2 other ongoing procedures that were in place during the conduct of the PLATO Study that contributed to oversight and review of monitoring conducted at the clinical sites. The sponsor stated that the PLATO Study team reviewed actions identified by the monitors in their monitoring visit reports as these reports were entered electronically in the AstraZeneca clinical trial management system (IMPACT). The study team reviewed a “percentage” of these reports, however, it was not clear what percentage of monitoring reports were reviewed by the PLATO Study team. Second, the sponsor indicated that the monitoring plan also stated that the study team and monitors were to work together to provide timely issue resolution reported in final monitoring reports. The sponsor also provided a report of all monitoring issues raised at Site 5238. The report showed that these issues were closed prior to or during the close out visit for that site which occurred on May 26, 2009. The sponsor stated that they believe this report is exemplar of adequate study oversight for all clinical investigators. With that said the sponsor promised a complete review of their operating procedures for monitoring and will make necessary revisions to ensure proper reviews of monitoring reports are documented.

Regarding Item 1.e: Nineteen of 545 SAE reports were not reported to the FDA in a timely manner. The sponsor concurred with this observation and provided findings of root cause for each of the 19 late reports in their Form FDA 483 response letter dated April 19, 2010. They promised corrective actions to strengthen SAE reporting processes. The late reports represent ~3.5% of all SAE reports sent to the Agency and should have no impact on data integrity; all SAE reports were ultimately submitted to FDA.

- c. **Assessment of data integrity:** Based on a complete review of the EIR, the Form FDA inspectional observations and the sponsor’s response to the Form FDA 483 Inspectional Observations dated April 19, 2010, and notwithstanding the deviations from established procedures and the failure of timely reporting of all SAEs listed in the Form FDA 483 Inspectional Observations, the study appears to have been conducted adequately, and the data submitted by the sponsor may be used in support of the respective indication. The findings are unlikely to significantly impact data integrity for the PLATO Study submitted to the Agency in support of NDA 22-433.

### III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Based on the review of preliminary inspectional findings for Dr. Buszman, Dr. Tracz, and Dr. Musial, and on the review of complete inspectional findings for Dr. Sereg, Dr. Merkely, Dr. Vértés, and AstraZeneca LP, the study data collected by appear reliable. The inspection of the sponsor, AstraZeneca LP, found that records and procedures were clear, complete and well organized, that reporting of AEs/SAEs appeared adequate, and a review of monitoring reports found no major issues. Samples of primary efficacy endpoints for these 6 CI sites were able to be verified against source records maintained at the sponsor's site.

The determination of all efficacy endpoints was made by a CRO, Duke Clinical Research Institute (DCRI), under a protocol-specific Independent Central Adjudication Committee (ICAC). The ICAC performed adjudication and evaluation of all efficacy endpoints. An inspection of the ICAC was not possible according AstraZeneca since all records associated with the Agreement between AstraZeneca and the CRO DCRI supporting the PLATO Study had been returned to the sponsor sometime after the study was closed and all ICAC functions were ceased. It should be noted that the DCRI was inspected by FDA previously as part of a data audit in support of [REDACTED] (b)(4) in 2008. The final classification of that inspection was NAI.

Regarding the establishment of the primary efficacy endpoints, the clinical investigators were responsible for compiling relevant source documentation for each suspected endpoint according to procedures described in the "Investigator Endpoint and Bleeding Manual" and sending the data as an "Endpoint Package" (EPP) to the AstraZeneca Hungary Office. These EPPs were then forwarded to AstraZeneca in the U.S. who then in turn forwarded them to the ICAC for adjudication in accordance with the protocol.

Form FDA 483, Inspectional Observations, were issued to Dr. Merkely and Dr. Musial, as well as the sponsor, AstraZeneca. Briefly, Dr. Merkely's site consented 49 subjects with an obsolete version of the informed consent form but ultimately all 49 subjects were reconsented with the proper version of the informed consent form. Dr. Musial's site randomized Subject E3652106 prior to receipt and review of all safety laboratory test results, hematology panel, albeit Subject E3652106 never received study medication. Site records for subject disposition indicated that the Subject E3652106 withdrew consent however, according to the FDA field investigator, the subject did not complete the study because they were inappropriately enrolled. No protocol violation was reported to the sponsor. In addition, Dr. Musial's site failed to report an AE, syncope, for Subject E3652004 that occurred on [REDACTED] (b)(6).

The inspection of the sponsor, AstraZeneca LP, included review and comparison of a sample of subject's electronic case report forms with their endpoint packets (EPP) generated by the study sites, and their adjudication tracker results (generated by the CRO, Duke Clinical Research Inc. (DCRI), Independent Central Adjudication Committee [ICAC] resulting from the ICAC's review of the EPPs), and the subject's data listings for primary efficacy endpoints submitted to NDA 22-433, from each of the 6 sites listed

above. Specifically, 10 subjects from Site #2611, 16 subjects from Site #2615, 10 subjects from Site #2619, 14 subjects from Site #3603, 10 subjects from Site #3642, and 10 subjects from Site #3652, had their records audited for verification of efficacy endpoint data listings provided in NDA 22433. No discrepancies were observed and there was no evidence of under-reporting adverse events.

The FDA field investigator reported that the oversight of the CRO, DCRI/ICAC, by the sponsor AstraZeneca was not always consistent with what was described in the sponsor's internal procedures and agreed upon in the Agreement between AstraZeneca and DCRI. Briefly, selection of ICAC members, ongoing QA of ICAC performance and proof of segregation of ICAC members when performing adjudication functions were not consistent with the terms of their Agreement. However, the sponsor did provide records and explanations during the inspection and in their response to the Form FDA 483, dated April 19, 2010, that showed AstraZeneca was aware of selection procedures used by DCRI for ICAC member selections although not actively influential. Further, QA/QC reviews of ICAC adjudicated results were performed by DCRI for the PLATO Study for a 5% sample (a random sample of 586 events were selected by AstraZeneca for the QC review). Finally, the sponsor explained that adjudicators were blinded to study treatments, and that the electronic system used by adjudicators to record their event adjudication results did not reveal trends or signals that suggested that two DCRI adjudicators worked collaboratively and not separately as required.

AstraZeneca demonstrated limited compliance with their own SOP for clinical site monitoring oversight. Briefly, the SOP states that for a "full-time monitor" all initiation visit reports and 10 other reports per quarter are to be reviewed and signed by the monitor's line manager or delegate. However, for Site #5238, Dr. Guidera, only 4 of 46 monitoring visit reports were found to have been signed and dated by the monitor's reviewer. The sponsor provided a report of all monitoring issues raised at Site #5238 in the EIR. The report showed that these issues were closed prior to or during the close out visit for that site which occurred on May 26, 2009. The sponsor stated that they believe this report is exemplar of adequate study oversight for all clinical investigators, albeit they recognize the violation of their own SOP and promised corrective actions to remedy monitoring oversight procedures.

Lastly, the sponsor failed to provide 19 of 545 SAE reports to the FDA in a timely manner. The sponsor concurred with this observation and provided root cause for each occurrence in their Form FDA 483 response, dated April 19, 2010. They promised corrective actions to strengthen SAE reporting processes. The late reports represent ~3.5% of all SAE reports sent to the Agency and should have no impact on data integrity; all SAE reports were ultimately submitted to FDA.

Based on a complete review of the inspectional observations, in particular those reported for sponsor inspection, the EIR and sponsor response the data submitted to NDA 22-433 appear reliable. The data can be used in support of the application.

**Note:** Observations noted above for Sites #3603, #3642 and #3652 are based on the preliminary communications provided by the FDA field investigators and preliminary review of available Form FDA 483, inspectional observations. An inspection summary addendum will be generated if conclusions change significantly upon receipt and complete review of the EIRs.

**Follow-Up Actions:** DSI will generate an inspection summary addendum if the conclusions change significantly upon final review of the outstanding EIRs and 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}*

Tejashri Purohit-Sheth, M.D.  
Branch Chief  
Good Clinical Practice Branch II  
Division of Scientific Investigations

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22433	ORIG-1	ASTRAZENECA LP	AZD6140

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

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/s/

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LAUREN C IACONO-CONNORS  
05/20/2010

TEJASHRI S PUROHIT-SHETH  
05/20/2010

## RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

Application Information		
NDA # 022433 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Brilinta Established/Proper Name: ticagrelor Dosage Form: tablets Strengths: 90mg		
Applicant: Astra Zeneca Agent for Applicant (if applicable):		
Date of Application: 11-13-2009 Date of Receipt: 11-16-2009 Date clock started after UN:		
PDUFA Goal Date: 9-16-2010		Action Goal Date (if different):
Filing Date: 01-15-2010		Date of Filing Meeting: 12-17-2009
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication(s)/Proposed change(s):  Brilinta is a selective and reversible P2Y <sub>12</sub> ADP-receptor antagonist indicated to:  Reduce the rate of thrombotic events (including stent thrombosis) for patients with ACS (unstable angina, non ST elevation myocardial infarction or ST elevation myocardial infarction) who are to be: -managed medically -managed invasively with percutaneous coronary intervention (with or without stent) and/or CABG  Brilinta as compared to clopidogrel has been shown to decrease the rate of combined endpoint of cardiovascular death, MI or stroke. The difference between treatments was driven predominantly by CV death and MI with no difference on strokes.  Brilinta as compared to clopidogrel has also been shown separately to reduce the rate of: -CV death -MI		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:</i> <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html</a> <i>and refer to Appendix A for further information.</i>		<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
Review Classification:  <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>  <i>If a tropical disease priority review voucher was submitted, review</i>		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority  <input type="checkbox"/> Tropical Disease Priority

<i>classification is Priority.</i>		Review Voucher submitted			
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>			
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device			
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:		<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division ( <i>if OTC product</i> ):					
List referenced IND Number(s): IND (b) (4); IND (b) (4)					
<b>Goal Dates/Names/Classification Properties</b>		<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
PDUFA and Action Goal dates correct in tracking system?  <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>		X			
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>		X			
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system?  <i>If not, ask the document room staff to make the appropriate entries.</i>		X			
<b>Application Integrity Policy</b>		<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>			X		
If yes, explain in comment column.				X	
If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:				X	
<b>User Fees</b>		<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?		X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid  <input type="checkbox"/> Exempt (orphan, government)  <input type="checkbox"/> Waived (e.g., small business, public health)  <input type="checkbox"/> Not required</p>
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears  <input type="checkbox"/> In arrears</p>
<p><i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).</i></p>	

505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment																
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?			X																	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).			X																	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))?  <i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i>			X																	
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? <b>Check the Electronic Orange Book at:</b> <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a>  <b>If yes, please list below:</b>			X																	
<table border="1"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i>																				
Exclusivity	YES	NO	NA	Comment																
Does another product have orphan exclusivity for the same indication? <b>Check the Electronic Orange Book at:</b> <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a>		X																		
<b>If another product has orphan exclusivity</b> , is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?  <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i>			X																	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (NDAs/NDA efficacy supplements only)  <b>If yes, # years requested: 5</b>  <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	X																			

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use ( <i>NDAs only</i> )?		X		
<b>If yes</b> , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?  <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>			X	

<b>Format and Content</b>				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)  <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<b>If mixed (paper/electronic) submission</b> , which parts of the application are submitted in electronic format?				
<b>Overall Format/Content</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>If electronic submission</b> , does it follow the eCTD guidance <sup>1</sup> ? <b>If not</b> , explain (e.g., waiver granted).	X			
<b>Index</b> : Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 ( <i>NDAs/NDA efficacy supplements</i> ) or under 21 CFR 601.2 ( <i>BLAs/BLA efficacy supplements</i> ) including:  <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)  <b>If no</b> , explain.	X			
<b>Controlled substance/Product with abuse potential</b> : Is an Abuse Liability Assessment, including a proposal for scheduling, submitted?  <i>If yes, date consult sent to the Controlled Substance Staff:</i>			X	
<b>BLAs only</b> : Companion application received if a shared or divided manufacturing arrangement?  <b>If yes</b> , BLA #			X	

<b>Forms and Certifications</b>				
<p><i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, <b>paper</b> forms and certifications with hand-written signatures must be included. <b>Forms</b> include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); <b>Certifications</b> include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature?	X			
<i>If foreign applicant, <b>both</b> the applicant and the U.S. agent must sign the form.</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a?	X			
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature?	X			
<i>Forms must be signed by the <b>APPLICANT</b>, not an Agent.</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 3674 included with authorized signature?	X			
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a correctly worded Debarment Certification included with authorized signature? ( <i>Certification is not required for supplements if submitted in the original application</i> )	X			
<i>If foreign applicant, <b>both</b> the applicant and the U.S. Agent must sign the certification.</i>				
<i>Note: Debarment Certification should use wording in FD&amp;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...”</i>				

<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>				

<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b><u>PREA</u></b></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	X			
<p><b>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</b></p>	X			
<p><b>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</b></p> <p><i>If no, request in 74-day letter</i></p>	X			
<p><b>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)</b></p> <p><i>If no, request in 74-day letter</i></p>	X			314.55(c)(2)
<p><b><u>BPCA</u> (NDAs/NDA efficacy supplements only):</b></p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)</i></p>		X		

<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted?  <i>If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.</i>	X			
<b>Prescription Labeling</b>	<input type="checkbox"/> <b>Not applicable</b>			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?  <i>If no, request in 74-day letter.</i>	X			
Is the PI submitted in PLR format?	X			
<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request PLR format in 74-day letter.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			
REMS consulted to OSE/DRISK?	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?	X			
<b>OTC Labeling</b>	<input checked="" type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?  <i>If no, request in 74-day letter.</i>				

Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
<b>Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>				

<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s)? <b>Date(s):</b> 12-08-2005  <i>If yes, distribute minutes before filing meeting</i>	X			
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> 04-20-2009  <i>If yes, distribute minutes before filing meeting</i>	X			
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b> 12-14-2007; 10-1-2009  <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	X			

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** 12-17-2009

**BLA/NDA/Supp #:** 022433

**PROPRIETARY NAME:** BRILINTA

**ESTABLISHED/PROPER NAME:** ticagrelor

**DOSAGE FORM/STRENGTH:** 90mg

**APPLICANT:** AstraZeneca

**PROPOSED INDICATION(S)/PROPOSED CHANGE(S):**

Brilinta is a selective and reversible P2Y<sub>12</sub> ADP-receptor antagonist indicated to:

Reduce the rate of thrombotic events (including stent thrombosis) for patients with ACS (unstable angina, non ST elevation myocardial infarction or ST elevation myocardial infarction) who are to be:

- managed medically
- managed invasively with percutaneous coronary intervention (with or without stent) and/or CABG

Brilinta as compared to clopidogrel has been shown to decrease the rate of combined endpoint of cardiovascular death, MI or stroke. The difference between treatments was driven predominantly by CV death and MI with no difference on strokes.

Brilinta as compared to clopidogrel has also been shown separately to reduce the rate of:

- CV death
- MI

**BACKGROUND:** Sponsor submitted new NDA 022433 on 11-16-09 for ticagrelor tablets. Clinical investigations were conducted under IND 065808.

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Michael Monteleone	Y
	CPMS/TL:	Ed Fromm	Y
Cross-Discipline Team Leader (CDTL)	Thomas Marciniak		Y
Clinical	Reviewer:	Rob Fiorentino – Efficacy	Y

		Melanie Blank - Safety	Y
	TL:	Thomas Marciniak	Y
Social Scientist Review ( <i>for OTC products</i> )	Reviewer:	NA	
	TL:	NA	
OTC Labeling Review ( <i>for OTC products</i> )	Reviewer:	NA	
	TL:	NA	
Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:	NA	
	TL:	NA	

Clinical Pharmacology	Reviewer:	Islam Younis Jiang Liu-Pharmacometrics	Y Y
	TL:	Raj Madabushi	Y
Biostatistics	Reviewer:	Jialu Zhang	Y
	TL:	Jim Hung	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Elizabeth Hausner	Y
	TL:	Patricia Harlow	Y
Statistics (carcinogenicity)	Reviewer:	NA	
	TL:	NA	
Immunogenicity (assay/assay validation) ( <i>for BLAs/BLA efficacy supplements</i> )	Reviewer:	NA	
	TL:	NA	
Product Quality (CMC)	Reviewer:	Chhagan Tele – DS Thomas Wong - DP	Y Y
	TL:	Kasturi Srinivasachar	N
Quality Microbiology ( <i>for sterile products</i> )	Reviewer:	NA	
	TL:	NA	
CMC Labeling Review ( <i>for BLAs/BLA supplements</i> )	Reviewer:	NA	
	TL:	NA	
Facility Review/Inspection	Reviewer:		

	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		

Other reviewers		
Other attendees		

**FILING MEETING DISCUSSION:**

<b>GENERAL</b>	
<ul style="list-style-type: none"> <li>505(b)(2) filing issues?</li> </ul> <p><b>If yes, list issues:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>	<input type="checkbox"/> Not Applicable
<b>CLINICAL</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>Comments:</b></p> <ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li><i>this drug/biologic is not the first in its class</i></li> <li><i>the clinical study design was acceptable</i></li> <li><i>the application did not raise significant safety or efficacy issues</i></li> <li><i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	<input checked="" type="checkbox"/> YES Date if known: 7-28-10 <input type="checkbox"/> NO <input type="checkbox"/> To be determined  Reason:

<ul style="list-style-type: none"> <li>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?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>PRODUCT QUALITY (CMC)</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<b>Comments:</b>	
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<p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no</b>, was a complete EA submitted?</p> <p><b>If EA submitted</b>, consulted to EA officer (OPS)?</p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><b><u>Quality Microbiology (for sterile products)</u></b></p> <ul style="list-style-type: none"> <li>• Was the Microbiology Team consulted for validation of sterilization? (<b>NDAs/NDA supplements only</b>)</li> </ul> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ?</li> </ul> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b><u>CMC Labeling Review (BLAs/BLA supplements only)</u></b></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>

<b>REGULATORY PROJECT MANAGEMENT</b>	
<b>Signatory Authority:</b> Robert Temple	
<b>21<sup>st</sup> Century Review Milestones (see attached)</b> (optional):	
<b>Comments:</b>	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing.  <u>Review Issues:</u>  <input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter.  <input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):  <u>Review Classification:</u>  <input checked="" type="checkbox"/> Standard Review  <input type="checkbox"/> Priority Review
<b>ACTIONS ITEMS</b>	
<input checked="" type="checkbox"/>	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> <li>• notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)</li> <li>• notify DMPQ (so facility inspections can be scheduled earlier)</li> </ul>
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Other

## Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy 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).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22433	ORIG-1	ASTRAZENECA LP	AZD6140

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

/s/

MICHAEL V MONTELEONE  
01/25/2010

## DSI CONSULT: Request for Clinical Inspections

**Date:** December 3, 2009 (Amended January 6, 2010)

**To:** Constance Lewin, M.D., M.P.H, Branch Chief, GCP1  
Tejashri Purohit-Sheth, M.D., Branch Chief, GCP2  
Lauren Iacono-Connor, M.D.  
Division of Scientific Investigations, HFD-45  
Office of Compliance/CDER

**Through:** Robert Fiorentino, MD, MPH , Medical Reviewer for Efficacy  
Melanie Blank, MD, Medical Reviewer for Safety  
Thomas Marciniak, MD, Cross Disciplinary Team Leader  
Norman Stockbridge, MD, PhD, Division Director  
Division of Cardiovascular and Renal Products

**From:** Michael Monteleone, MS, Regulatory Project Manager

**Subject:** **Request for Clinical Site Inspections**

### **I. General Information**

Application#: NDA-022433  
Applicant/ Applicant contact information (to include phone/email):

Astra Zeneca  
1800 Concord Pike  
P.O. Box 8355  
Wilmington, DE 19803-8355

Contact  
Emery Gigger  
302-885-4048  
Emery.Gigger@astrazeneca.com

Drug Proprietary Name: Brilinta (proposed)  
NME or Original BLA (Yes/No): Yes  
Review Priority (Standard or Priority): Standard

Study Population includes < 17 years of age (Yes / No): NO  
Is this for Pediatric Exclusivity (Yes/No): NO

DSI Consult  
version: 5/08/2008

Proposed New Indication(s):

**“Acute Coronary Syndromes**

**(unstable angina, non ST elevation myocardial infarction or ST elevation myocardial infarction)**

BRILINTA is indicated to reduce the rate of thrombotic events (including stent thrombosis) for patients with ACS (unstable angina, non ST elevation myocardial infarction or ST elevation myocardial infarction) who are to be managed medically or are to be managed invasively with percutaneous coronary intervention (with or without stent) and/or CABG.

BRILINTA as compared to clopidogrel has been shown to decrease the rate of a combined endpoint of cardiovascular death, MI or stroke. The difference between treatments was driven predominantly by CV death and MI with no difference on strokes.

BRILINTA as compared to clopidogrel has also been shown separately to reduce the rate of:

- CV Death
- MI”

PDUFA:

Action Goal Date: September 16, 2010

Inspection Summary Goal Date: June 27, 2010

**II. Protocol/Site Identification**

*Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table.*

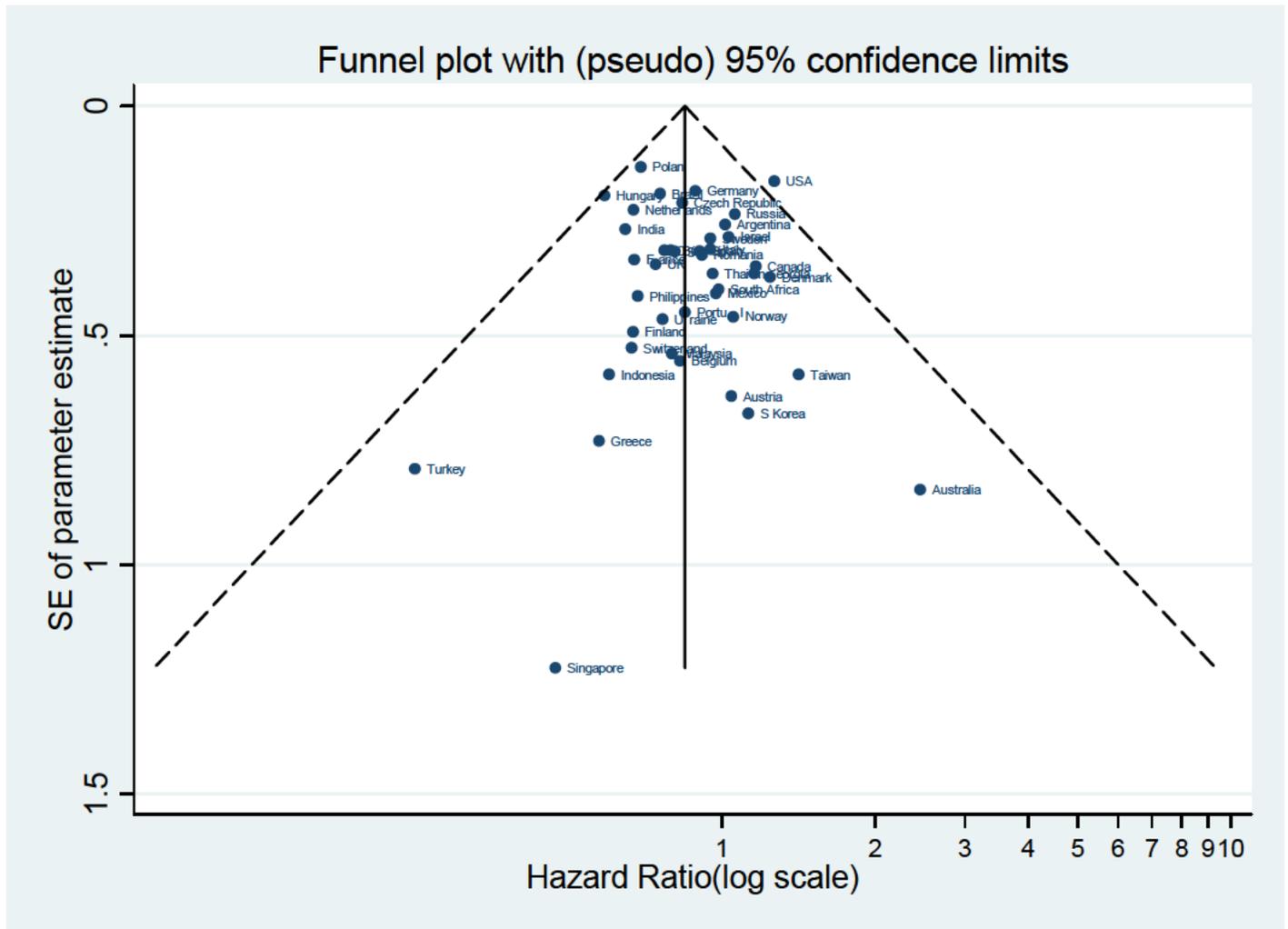
<b>Site # (Name,Address, Phone number, email, fax#)</b>	<b>Protocol ID</b>	<b>Number of Subjects</b>	<b>Indication</b>
<b>2611</b> (Hungary) Mátyás Sereg Szfvár, Kh. II.Bel II. Belgyógyászat Seregélyesi út 3 8000 Székesfehérvár	D5130C05262 [PLATO – A Study of PLATelet inhibition and Patient Outcomes.	152	Acute Coronary Syndrome

<b>Site # (Name,Address, Phone number, email, fax#)</b>	<b>Protocol ID</b>	<b>Number of Subjects</b>	<b>Indication</b>
<b>2615 (Hungary)</b> Béla Merkely Semmelweis Egyetem; Ér- és Szívsebészeti Klinika Városmajor u. 68. 1112 Budapest	same	226	same
<b>2619 (Hungary)</b> András Vértes Szent István Kórház, II. Belgyógyászat Nagyváradi tér 1.1096 Budapest	same	152	same
<b>3603 (Poland)</b> Paweł Buszman Buszman Oddział Ostrego Zespołów Wieńcowych SP Szpital Kliniczny nr 7 ŚAM Ul. Ziołowa 45/47 40-635 Katowice	same	133	same
<b>3642 (Poland)</b> Kraków (31-202) – Tracz Oddział Kliniczny Chorób Serca i Naczyń Instytut Kardiologii Collegium Medicum UJ Ul. Prądnicka 80 31-202 Kraków	same	92	same
<b>3652 (Poland)</b> Włodzimierz Musiał Białystok (15-276) – Musiał Klinika Kardiologii SP Szpital Kliniczny Akademii Medycznej ul. Skłodowskiej 24a Z15-276 Białystok	same	108	same

### **III. Site Selection/Rationale**

In the overall combined analysis ticagrelor as shown to be superior to clopidogrel, HR=0.84, p=0.0003. However there was a significant interaction by region, explained predominantly by discordant results in North America and *specifically* the United States, which trended toward a worse outcome on ticagrelor compared to clopidogrel, HR=1.27, 95%CI(0.92, 1.75), n=1,413. Further analysis by country suggested Hungary, HR=0.59, 95%CI(0.40, 0.86) as being a potentially

significant outlier, followed by Poland, HR=0.69, 95%CI(0.53, 0.90) (See below). Both Poland (n=2,666) and Hungary (n=1,267) were also the two largest enrollers, by country.



We further identified sites in Poland and Hungary based on 1) the number of subjects enrolled and 2) the generally favorable outcomes observed in those sites. Also noted were low number of events and low number of subjects with protocol deviations or violations in some of these sites:

<u>CENTER#</u>	<u>Location</u>	<u>N</u>	<u>HR</u>	<u>p-value</u>	<u>Min</u> <u>95%CI</u>	<u>Max</u> <u>95%CI</u>	<u>N subjects with</u> <u>maj deviations or</u> <u>violations (%)</u>	<u>Dropouts or</u> <u>discontinuations</u> <u>(non-death)</u>
<u>2611</u>	<u>40 mi SW of</u> <u>Budapest</u>	<u>151</u>	<u>0.49</u>	<u>0.245</u>	<u>0.148</u>	<u>1.630</u>	<u>3 (2%)</u>	<u>2 (1.3%)</u>
<u>2615</u>	<u>Budapest</u>	<u>226</u>	<u>0.34</u>	<u>0.023</u>	<u>0.134</u>	<u>0.863</u>	<u>0 (0%)</u>	<u>0 (0%)</u>
<u>2619</u>	<u>Budapest</u>	<u>152</u>	<u>0.00</u>	<u>1.000</u>	<u>0</u>	<u>:</u>	<u>1 (0.7%)</u>	<u>3 (2.0%)</u>
<u>3603</u>	<u>40 mi NE of</u> <u>Krakow</u>	<u>133</u>	<u>0.33</u>	<u>0.057</u>	<u>0.107</u>	<u>1.032</u>	<u>1 (0.8%)</u>	<u>2 (1.5%)</u>
<u>3642</u>	<u>Krakow</u>	<u>92</u>	<u>0.00</u>	<u>0.5</u>				
<u>3652</u>	<u>NE Poland</u>	<u>108</u>	<u>0.43</u>	<u>0.220</u>	<u>0.111</u>	<u>1.659</u>	<u>0 (0%)</u>	<u>5 (4.6%)</u>

**Domestic Inspections:**

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify):

**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) The majority of clinical data was collected outside the US. Poland and Hungary each had the most favorable outcomes for the study drug combined with the enrollment of a large proportion of the total subjects in PLATO.

**Five or More Inspection Sites (delete this if it does not apply):**

We have requested these sites for inspection (international and/or domestic) because of the following reasons: *state reason(s) and prioritize sites.*

**Ticagrelor is a potential replacement for clodidogrel, the second highest selling drug in the US and worldwide with worldwide sales of (b) (4) annually. Hence this submission is a critical submission for CDER. It is also critical to complete inspections within a standard review timeframe because the last submission of potential replacement for clopidogrel (prasugrel) was not approved within the PDUFA deadline, generating bad publicity about CDER review processes.**

**While the sponsor alleges clear superiority to clopidogrel, results by region are conflicting as discussed under site selection above: The largest benefit was shown in Eastern Europe, predominantly Poland and Hungary, while the effects in the US were actually detrimental. We have seen this pattern of greater benefit in Eastern Europe in other submissions. A good example is ximelagatran, a warfarin replacement for anticoagulation in atrial fibrillation. A blinded US study showed ximelagatran inferior to warfarin while an open-label European study showed ximelagatran superior to warfarin. Eastern Europe accounted for 60% of the benefit but only 20% of the patients in the European study. Hungarian and Polish sites reported no primary endpoints in 212 ximelagatran subjects. While the ximelagatran study was open-label and the ticagrelor PLATO study was “blinded”, PLATO sites could easily unblind: PLATO was a double dummy study with the clopidogrel control consisting of a standard clopidogrel tablet cut in half and stuffed into a**

**capsule. We note that at least four of the ximelagatran sites also participated in PLATO and we are recommending one of these sites (2611 for PLATO) for audit.**

**Determining whether there is a problem with site conduct at Eastern European sites is an important issue for CDER for the following reasons: (1) To determine the validity of the data for this critical submission; (2) To address the general issue of whether Eastern European submission deserve close scrutiny for the increasing numbers of submissions dependent upon Eastern European data. As an example, we note that the next large study for prasugrel is enrolling predominantly in Eastern Europe.**

**While we favor auditing all six sites identified above, the site that we would drop first is 3652. The other five sites are located in two major metropolitan areas, Krakow in Poland and Budapest in Hungary.**

**Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DSI.**

#### **IV. 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.*

Should you require any additional information, please contact *Michael Monteleone* at 301-796-1952 or *Robert Fiorentino* at 301-796-4106.

Concurrence: (as needed)

*Thomas A. Marciniak* \_ Medical Team Leader

*Norman Stockbridge* \_\_\_ Division Director (for foreign inspection requests or requests for 5 or more sites only)

**\*\*\*Things to consider in decision to submit request for DSI Audit**

- *Evaluate site specific efficacy. Note the sites with the greatest efficacy compared to active or placebo comparator. Are these sites driving the results?*
- *Determine the sites with the largest number of subjects. Is the efficacy being driven by these sites?*
- *Evaluate the financial disclosures. Do sites with investigators holding financial interest in the sponsor's company show superior efficacy compared to other sites?*
- *Are there concerns that the data may be fraudulent or inconsistent?*
  - *Efficacy looks too good to be true, based on knowledge of drug based on previous clinical studies and/or mechanism of action*
  - *Expected commonly reported AEs are not reported in the NDA*
- *Evaluate the protocol violations. Are there a significant number of protocol violations reported at one or more particular sites? Are the types of protocol violations suspicious for clinical trial misconduct?*
- *Is this a new molecular entity or original biological product?*
- *Is the data gathered solely from foreign sites?*
- *Were the NDA studies conducted under an IND?*

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- NDA-22433	----- ORIG-1	----- ASTRAZENECA LP	----- AZD6140

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

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/s/

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MICHAEL V MONTELEONE  
01/06/2010

NORMAN L STOCKBRIDGE  
01/06/2010

## DSI CONSULT: Request for Clinical Inspections

**Date:** December 3, 2009

**To:** Constance Lewin, M.D., M.P.H, Branch Chief, GCP1  
Tejashri Purohit-Sheth, M.D., Branch Chief, GCP2  
Lauren Iacono-Connor, M.D.  
Division of Scientific Investigations, HFD-45  
Office of Compliance/CDER

**Through:** Robert Fiorentino, MD, MPH , Medical Reviewer for Efficacy  
Melanie Blank, MD, Medical Reviewer for Safety  
Thomas Marciniak, MD, Cross Disciplinary Team Leader  
Norman Stockbridge, MD, PhD, Division Director  
Division of Cardiovascular and Renal Products

**From:** Michael Monteleone, MS, Regulatory Project Manager

**Subject:** **Request for Clinical Site Inspections**

### **I. General Information**

Application#: NDA-022433  
Applicant/ Applicant contact information (to include phone/email):

Astra Zeneca  
1800 Concord Pike  
P.O. Box 8355  
Wilmington, DE 19803-8355

Contact  
Emery Gigger  
302-885-4048  
Emery.Gigger@astrazeneca.com

Drug Proprietary Name: Brilinta (proposed)  
NME or Original BLA (Yes/No): Yes  
Review Priority (Standard or Priority): Priority

Study Population includes < 17 years of age (Yes / No): NO  
Is this for Pediatric Exclusivity (Yes/No): NO

DSI Consult  
version: 5/08/2008

Proposed New Indication(s):

**“Acute Coronary Syndromes**

**(unstable angina, non ST elevation myocardial infarction or ST elevation myocardial infarction)**

BRILINTA is indicated to reduce the rate of thrombotic events (including stent thrombosis) for patients with ACS (unstable angina, non ST elevation myocardial infarction or ST elevation myocardial infarction) who are to be managed medically or are to be managed invasively with percutaneous coronary intervention (with or without stent) and/or CABG.

BRILINTA as compared to clopidogrel has been shown to decrease the rate of a combined endpoint of cardiovascular death, MI or stroke. The difference between treatments was driven predominantly by CV death and MI with no difference on strokes.

BRILINTA as compared to clopidogrel has also been shown separately to reduce the rate of:

- CV Death
- MI”

PDUFA:

Action Goal Date: May 16, 2010 (Sunday)

Inspection Summary Goal Date: MARCH 13, 2010

**II. Protocol/Site Identification**

*Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table.*

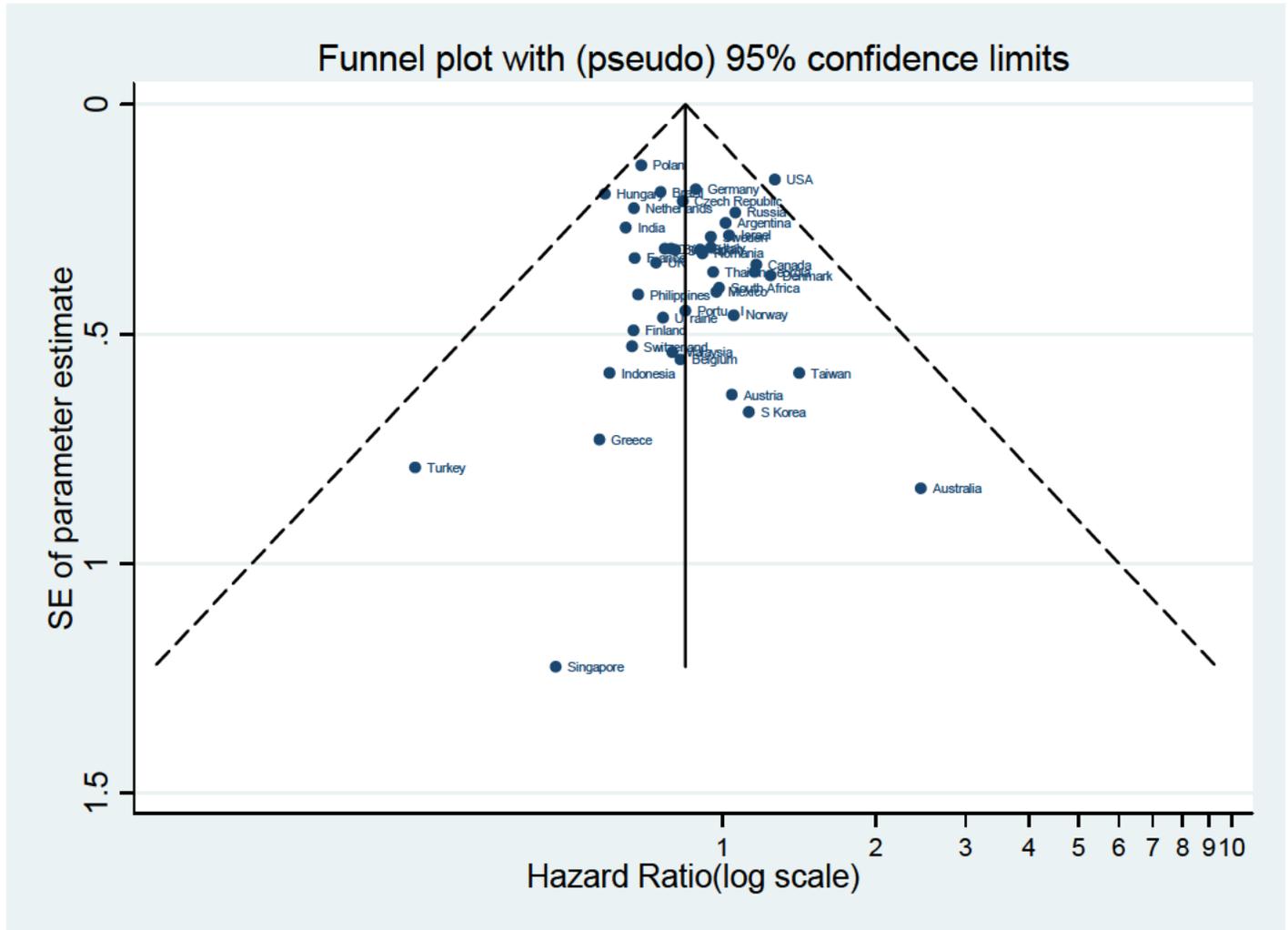
<b>Site # (Name,Address, Phone number, email, fax#)</b>	<b>Protocol ID</b>	<b>Number of Subjects</b>	<b>Indication</b>
<b>2611</b> (Hungary) Mátyás Sereg Szfvár, Kh. II.Bel II. Belgyógyászat Seregélyesi út 3 8000 Székesfehérvár	D5130C05262 [PLATO – A Study of PLATelet inhibition and Patient Outcomes.	152	Acute Coronary Syndrome

<b>Site # (Name,Address, Phone number, email, fax#)</b>	<b>Protocol ID</b>	<b>Number of Subjects</b>	<b>Indication</b>
<b>2615 (Hungary)</b> Béla Merkely Semmelweis Egyetem; Ér- és Szívsebészeti Klinika Városmajor u. 68. 1112 Budapest	same	226	same
<b>2619 (Hungary)</b> András Vértes Szent István Kórház, II. Belgyógyászat Nagyváradi tér 1.1096 Budapest	same	152	same
<b>3603 (Poland)</b> Paweł Buszman Buszman Oddział Ostroch Zespołów Wieńcowych SP Szpital Kliniczny nr 7 ŚAM Ul. Ziołowa 45/47 40-635 Katowice	same	133	same
<b>3642 (Poland)</b> Kraków (31-202) – Tracz Oddział Kliniczny Chorób Serca i Naczyń Instytut Kardiologii Collegium Medicum UJ Ul. Prądnicka 80 31-202 Kraków	same	92	same
<b>3652 (Poland)</b> Włodzimierz Musiał Białystok (15-276) – Musiał Klinika Kardiologii SP Szpital Kliniczny Akademii Medycznej ul. Skłodowskiej 24a Z15-276 Białystok	same	108	same

### **III. Site Selection/Rationale**

In the overall combined analysis ticagrelor as shown to be superior to clopidogrel, HR=0.84, p=0.0003. However there was a significant interaction by region, explained predominantly by discordant results in North America and *specifically* the United States, which trended toward a worse outcome on ticagrelor compared to clopidogrel, HR=1.27, 95%CI(0.92, 1.75), n=1,413. Further analysis by country suggested Hungary, HR=0.59, 95%CI(0.40, 0.86) as being a potentially

significant outlier, followed by Poland, HR=0.69, 95%CI(0.53, 0.90) (See below). Both Poland (n=2,666) and Hungary (n=1,267) were also the two largest enrollers, by country.



We further identified sites in Poland and Hungary based on 1) the number of subjects enrolled and 2) the generally favorable outcomes observed in those sites. Also noted were low number of events and low number of subjects with protocol deviations or violations in some of these sites:

<u>CENTER#</u>	<u>Location</u>	<u>N</u>	<u>HR</u>	<u>p-value</u>	<u>Min</u> <u>95%CI</u>	<u>Max</u> <u>95%CI</u>	<u>N subjects with</u> <u>maj deviations or</u> <u>violations (%)</u>	<u>Dropouts or</u> <u>discontinuations</u> <u>(non-death)</u>
<u>2611</u>	<u>40 mi SW of</u> <u>Budapest</u>	<u>151</u>	<u>0.49</u>	<u>0.245</u>	<u>0.148</u>	<u>1.630</u>	<u>3 (2%)</u>	<u>2 (1.3%)</u>
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<u>3603</u>	<u>40 mi NE of</u> <u>Krakow</u>	<u>133</u>	<u>0.33</u>	<u>0.057</u>	<u>0.107</u>	<u>1.032</u>	<u>1 (0.8%)</u>	<u>2 (1.5%)</u>
<u>3642</u>	<u>Krakow</u>	<u>92</u>	<u>0.00</u>	<u>0.5</u>				
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**Domestic Inspections:**

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify):

**International Inspections:**

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
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- 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.
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We have requested these sites for inspection (international and/or domestic) because of the following reasons: *state reason(s) and prioritize sites.*

**Ticagrelor is a potential replacement for clodidogrel, the second highest selling drug in the US and worldwide with worldwide sales of (b) (4) annually. The sponsor claims that this drug is superior to clopidogrel and in fact is superior at reducing CV mortality, hence justifying a priority review. Hence this submission is a critical submission for CDER. It is also critical to complete inspections within a priority review timeframe because the last submission of potential replacement for clopidogrel (prasugrel) was not approved within the PDUFA deadline, generating bad publicity about CDER review processes.**

**While the sponsor alleges clear superiority to clopidogrel, results by region are conflicting as discussed under site selection above: The largest benefit was shown in Eastern Europe, predominantly Poland and Hungary, while the effects in the US were actually detrimental. We have seen this pattern of greater benefit in Eastern Europe in other submissions. A good example is ximelagatran, a warfarin replacement for anticoagulation in atrial fibrillation. A blinded US study showed ximelagatran inferior to warfarin while an open-label European study showed ximelagatran superior to warfarin. Eastern Europe accounted for 60% of the benefit but only 20% of the patients in the European study. Hungarian and Polish sites reported no primary endpoints in 212 ximelagatran subjects. While the ximelagatran study was open-label and the ticagrelor PLATO study was “blinded”, PLATO sites could easily unblind: PLATO was a double dummy study with the**

**clopidogrel control consisting of a standard clopidogrel tablet cut in half and stuffed into a capsule. We note that at least four of the ximelagatran sites also participated in PLATO and we are recommending one of these sites (2611 for PLATO) for audit.**

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**Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DSI.**

#### **IV. 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.*

Should you require any additional information, please contact *Michael Monteleone* at 301-796-1952 or *Robert Fiorentino* at 301-796-4106.

Concurrence: (as needed)

*Thomas A. Marciniak* \_ Medical Team Leader  
*Robert Fiorentino* \_\_\_\_\_ Medical Reviewer

*Norman Stockbridge* \_\_\_ Division Director (for foreign inspection requests or requests for 5 or more sites only)

**\*\*\*Things to consider in decision to submit request for DSI Audit**

- *Evaluate site specific efficacy. Note the sites with the greatest efficacy compared to active or placebo comparator. Are these sites driving the results?*
- *Determine the sites with the largest number of subjects. Is the efficacy being driven by these sites?*
- *Evaluate the financial disclosures. Do sites with investigators holding financial interest in the sponsor's company show superior efficacy compared to other sites?*
- *Are there concerns that the data may be fraudulent or inconsistent?*
  - *Efficacy looks too good to be true, based on knowledge of drug based on previous clinical studies and/or mechanism of action*
  - *Expected commonly reported AEs are not reported in the NDA*
- *Evaluate the protocol violations. Are there a significant number of protocol violations reported at one or more particular sites? Are the types of protocol violations suspicious for clinical trial misconduct?*
- *Is this a new molecular entity or original biological product?*
- *Is the data gathered solely from foreign sites?*
- *Were the NDA studies conducted under an IND?*

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22433	ORIG-1	ASTRAZENECA LP	AZD6140

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/s/

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12/03/2009

NORMAN L STOCKBRIDGE  
12/03/2009