

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022433Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**



**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 15, 2011

To: Norman Stockbridge, M.D., Ph.D.
Director, Division of Cardiovascular and Renal Products (DCRP)

Thru: Claudia Karwoski, Pharm.D.
Director, Division of Risk Management (DRISK)

From: **DRISK Scientific Lead**
Cynthia LaCivita, Pharm.D., Risk Management Analyst (RMA)

DRISK Review Team
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Division of Drug Marketing, Advertising and Communications (DDMAC)
Emily Baker, Regulatory Review Officer, DDMAC

Office of Compliance
LCDR Danielle Pearson-Jackson, B.S.N., Consumer Safety Officer

Subject: Final review of the proposed Risk Evaluation and Mitigation Strategy for Brilinta (ticagrelor)

Drug Name(s): Brilinta (ticagrelor)

Therapeutic Class: Antithrombotic, P2Y₁₂ ADP-receptor antagonist

Submission Number: Resubmission /Class 2, dated January 20, 2011, sequence number 0094

Application Type/Number: NDA 22-433

Applicant/sponsor: AstraZeneca

OSE RCM #: 2010-27

1 INTRODUCTION

This is DRISK's final review of AstraZeneca's proposed Risk Evaluation and Mitigation Strategy (REMS) for Brilinta (ticagrelor) NDA 22-433. DRISK provided interim comments to DCRP on July 7, 2011; these comments were conveyed to the sponsor. Additional comments were communicated to AstraZeneca regarding the proposed REMS via e-mail on July 11, 2011 and during telephone conferences on July 11, 12, and 13, 2011. This amendment is in response to these communications and provides the necessary changes to the proposed REMS, REMS materials and REMS Supporting Documents.

2 BACKGROUND

Brilinta is a selective and reversibly binding adenosine diphosphate (ADP) receptor antagonist of the P2Y₁₂ ADP-receptor, which mediates ADP-dependent platelet inhibition. The sponsor is seeking approval for the indication of reducing 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).

3 MATERIALS

- Proposed REMS and REMS Supporting Document for Brilinta (ticagrelor), sequence 0094, dated July 13, 2011.
- Substantially complete labeling, dated July 11, 2011.

4 RESULTS OF REVIEW

4.1 Overview of the Clinical Program

PLATO was the pivotal trial used to determine safety and efficacy, and support the proposed indication for Brilinta. PLATO was a large, phase 3 study (N=18,624) which randomized patients with ACS to receive a loading dose of ticagrelor 180 mg, followed by 90 mg BID or clopidogril, with a loading dose of 300 mg (treatment-naive patients only) and a 75 mg daily dose. All patients in the study were managed medically or invasively with percutaneous coronary intervention (with or without stent), and/or coronary artery bypass graft (CABG). Both study arms were given in combination with aspirin and other standard therapies. The selection of the aspirin dose was left to the discretion of the investigator and ranged from 75 mg to 325 mg. Dr Zhang's analysis of the treatment effect of Brilinta when compared to clopidogrel for the primary composite endpoints of cardiovascular death, myocardial infarction and stroke, produced a hazard ratio estimate for the overall population of 0.84 [95% CI (0.77, 0.92)] favoring Brilinta, although there was no benefit for preventing strokes.¹

¹ Jiaul Zhang, Ph.D., Statistical Review and Evaluation dated June 29, 2010.

4.2 Safety Concerns

4.2.1 Bleeding

Patients assigned to ticagrelor had more bleeds (major, life-threatening, fatal and minor) than patients on clopidogrel, and this difference was statistically significant. The criteria for major bleeding were transfusion of 2 or more units of packed red blood cells or whole blood. Patients treated with ticagrelor vs. patients treated with clopidogrel experienced an increase in both major and minor bleeding; which was attributed to spontaneous non-procedural/non-CABG bleeds.

Patients treated with ticagrelor had an increased frequency and presented earlier for overall stroke and intracranial hemorrhagic bleeding events. The number of hemorrhagic strokes reported in patients who received ticagrelor vs. clopidogrel were 27 and 14, respectively. There were 11 deaths that were attributed to intracranial hemorrhage in the ticagrelor arm and 1 in the clopidogrel arm.

4.2.2 Decreased Efficacy Associated with Higher Aspirin Doses

The treatment effect of Brilinta over clopidogrel appeared to be consistent across multiple patient subgroups by demographic characteristics except North America (U.S. and Canada). Further analysis of the U.S. patients reported unfavorable outcomes for the composite endpoints for Brilinta when compared to clopidogrel; the estimate hazard ratio for the U.S. was 1.27 [0.95% CI (0.92, 1.75)]. Post analysis of differences in the aspirin dose appears to be the most plausible cause for the difference in outcomes with the U.S. patients. A subset analysis of US patient receiving Brilinta and high dose aspirin (> 300 mg per day) was associated with an increased risk of clinical events.² Labeling, which also includes a boxed warning, states that maintenance doses of aspirin above 100 mg appear to decrease the efficacy of Brilinta and maintenance doses of aspirin should not exceed 100 mg daily.

4.2.3 Dyspnea

In PLATO the incidence of dyspnea in patients treated with ticagrelor was 14.6% vs. 8.7% in patients treated with clopidogrel. Patients that experienced dyspnea were more likely to discontinue therapy if they were receiving ticagrelor vs. clopidogrel, 0.9% and 0.1%, respectively. Dyspnea appeared to be self limiting and resolved in the majority of the patients during the study. Included in PLATO was a pulmonary function substudy; unfortunately issues with the study design and limitations prevented it from generating helpful information about ticagrelor's effect on pulmonary function tests.

4.2.4 Arrhythmias

Phase 1 and 2 trials identified sinus pauses, ventricular pauses and adverse events associated with bradycardia in patients who received ticagrelor. PLATO patients in the ticagrelor arm experienced an increased frequency of atrial arrhythmias and pauses, but a lower frequency of ventricular arrhythmias and sudden death. It should be noted that PLATO excluded patients with sick sinus syndrome and no pacemaker, second or third degree AV block or history of documented syncope secondary to bradycardia without a

² Jiaul Zhang, Ph.D. Statical Review and Evaluation dated April 28, 2011.

pacemaker. Symptoms of syncope, vertigo, dizziness and giddiness were reported slightly more frequently in patients who received ticagrelor when compared to clopidogrel.

5 ASTRAZENCA'S PROPOSED REMS FOR BRILINTA

5.1 Goals

The sponsor's proposed goals for the REMS are:

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

5.2 REMS Elements

Below is a summary of the sponsor's proposed REMS.

5.2.1 Medication Guide

A Medication Guide (MG) will be dispensed with each Brilinta prescription in accordance with 21 CFR 208.24.

5.2.2 Communication Plan



5.2.3 Elements to Assure Safe Use

AstraZeneca did not believe that elements to assure safe use were necessary.

5.2.4 Implementation Plan

AstraZeneca did not believe that an implementation plan was necessary.

6 DISCUSSION

Arrhythmias and dyspnea, which were reported in PLATO, are believed to be attributed to Brilinta's effect on endogenous adenosine in other organs. Dr. Blank reported that although dyspnea occur in 14.6 % of patients who received Brilinta, it was a symptom that resolved in 2/3 of the patients without the serious sequelae.³ Although it was the

³ Clinical Safety Reviews by Melanie Blank, M.D., dated June 28, 2010 and May 6, 2011

most common reason for drug discontinuation (0.9% Brilinta vs. 0.1% clopidogrel), most patients that experienced dyspnea continued on therapy and had favorable clinical outcomes. Patients with structural heart disease were excluded from PLATO; post marketing data may be helpful to access and adverse events in these patients.

In PLATO, Brilinta was associated with an increased risk of bleeding across all degrees of severity with an increase in major and minor bleeding being attributed to spontaneous non-procedural/non-CABG bleeds. Effient (presugrel), Plavix (clopidogrel), and Ticlid (ticlopidine) are irreversible P2Y₁₂ ADP-receptor inhibitors which are currently approved in the U.S. Hemorrhagic events and increased risk of bleeding are associated with all of the antiplatelet agents. Effient was associated with significant increased risk of bleeding, including fatal bleeding compared to clopidogrel; the Agency determined that a REMS was necessary for the approval of Effient. The Effient REMS includes a MG and CP to inform prescribers and patients about the serious risks of bleeding and the need for appropriate patient selection with emphasis on which patients Effient should not be used. There was no direct comparison of Effient and Brilinta, however there is similarity with regard to the need to inform healthcare professionals and patients about increased risk of bleeding when compared to clopidogrel.

The post analysis of differences in the aspirin dose suggest that to achieve the best possible therapeutic outcomes with Brilinta, high dose aspirin (> 300 mg per day) should be avoided. The recommendation to limit the daily maintenance dose of aspirin to 100 mg is clearly identified in the labeling and included as a boxed warning. Aspirin is an over-the-counter drug found in multiple products. Because patients can self medicate with aspirin, and higher doses of aspirin decrease the efficacy of Brilinta, additional actions such as MG and CP should be employed to ensure this information is disseminated to patients and prescribers.

DCRP and DRISK concur that a REMS is necessary to ensure that the benefits of Brilinta outweigh the serious risk of bleeding, and to ensure that patients have the best possible therapeutic outcomes, inform patients and prescribers that the daily maintenance dose of aspirin should not exceed 100 mg.

7 COMMENTS

7.1 Comments for the Review Division

The REMS elements include: Medication Guide and communication plan and a timetable for submission of assessments. The DRISK Review Team finds the proposed REMS for Brilinta to be acceptable provided the sponsor address all comments in the OCC-cleared REMS document as well as comments listed below.

The REMS, including the REMS materials are appended.

7.2 Comments for the sponsor

7.2.1 Supporting Document

- a. Make the necessary corrections on page 2, paragraph 6.



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/s/

CYNTHIA L LACIVITA
07/15/2011

MARY E WILLY
07/15/2011
Mary Willy, Deputy Director signing for Claudia Karwoski
I concur

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

**U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
ODE1/Division of Cardiovascular and Renal Products**

NDA/BLA #s: 022433
Products: Brilinta (ticagrelor) Tablets, 90 mg
APPLICANT: AstraZeneca
FROM: Robert Temple
Director, Office of Drug Evaluation I
DATE: July 7, 2011

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. Section 505-1(a)(1) provides the following factors:

- (A) The estimated size of the population likely to use the drug involved;
- (B) The seriousness of the disease or condition that is to be treated with the drug;
- (C) The expected benefit of the drug with respect to such disease or condition;
- (D) The expected or actual duration of treatment with the drug;
- (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
- (F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary for Brilinta (ticagrelor) to ensure that the benefits of the drug outweigh the risks of bleeding and loss of efficacy when co-administered with maintenance doses of aspirin >100 mg daily. In reaching this determination, we considered the following:

- A. Over 1.4 million hospitalizations for Acute Coronary Syndrome (ACS) occur in the United States each year¹. Patients with unstable angina (UA) or non-ST-segment elevation myocardial infarction (NSTEMI) comprise approximately 70% of the population presenting with ACS².
- B. Acute coronary syndrome (ACS) is associated with cardiac ischemia and infarction which can lead to death or serious morbidity including heart failure.

¹ Rosamond W, et al. American Heart Association Statistics Committee—2008 update. *Circulation* 117 (4):e25-146.

² Goldberg RJ et al. Six-month outcomes in a multinational registry of patients hospitalized with an acute coronary syndrome (GRACE). *Am J Cardiol* 93 (3):288-293.

- C. Brilinta (ticagrelor) has been shown to reduce the rate of thrombotic cardiovascular events (unstable angina, myocardial infarction, and cardiovascular death, stent thrombosis) in patients with ACS.
- D. ACS is an acute condition. However, there is no limitation on duration of use in the labeling because Brilinta (ticagrelor) may be used chronically for the prevention of future events in patients who have had an ACS.
- E. A major risk associated with Brilinta (ticagrelor) is bleeding. This includes intracranial and other life-threatening or fatal bleeding.

The effectiveness of Brilinta (ticagrelor) is decreased when it is co-administered with maintenance doses of aspirin >100 mg daily.

In addition to these risks, Brilinta (ticagrelor) has been associated with dyspnea and an increased rate of cardiovascular ischemic events upon discontinuation.

- F. Brilinta is a new molecular entity.

In accordance with section 505-1 of FDCA and under 21 CFR 208, FDA has determined that a Medication Guide is required for Brilinta (ticagrelor) FDA has determined that Brilinta (ticagrelor) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Brilinta (ticagrelor). FDA has determined that Brilinta (ticagrelor) is a product:

- For which patient labeling could help prevent serious adverse effects
- That has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decisions to use, or continue to use ticagrelor (Brilinta)
- That the drug product is important to health and patient adherence to directions for use is crucial to the drug's effectiveness.

The elements of the REMS will be a Medication Guide, a communication plan and a timetable for submission of assessments of the REMS.

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/s/

ROBERT TEMPLE
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: July 7, 2011

To: Norman Stockbridge, M.D., Ph.D.
Director, Division of Cardiovascular and Renal Products (DCRP)

Thru: Claudia Karwoski, Pharm.D.
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Division of Drug Marketing, Advertising and Communications (DDMAC)
Emily Baker, Regulatory Review Officer, DDMAC

Office of Compliance
LCDR Danielle Pearson-Jackson, B.S.N., Consumer Safety Officer

Subject: Interim Review of the proposed Risk Evaluation and Mitigation Strategy for Brilinta (ticagrelor)

Drug Name(s): Brilinta (ticagrelor)

Therapeutic Class: Antithrombotic, P2Y₁₂ ADP-receptor Antagonist

Submission Number: Resubmission /Class 2, dated January 20, 2011, sequence numbers 0065 and 0083 Proposed REMS and REMS amendment

Application Type/Number: NDA 22-433

Applicant/sponsor: AstraZeneca

OSE RCM #: 2010-27

I INTRODUCTION

The purpose of this review is to provide interim comments on AstraZeneca's proposed Risk Evaluation and Mitigation Strategy (REMS) for Brilinta (ticagrelor) NDA 22-433 submitted on January 20, 2011, as part of a Resubmission/Class 2.

2 MATERIALS REVIEWED

- Proposed REMS and REMS Supporting Document for Brilinta (ticagrelor), sequence 0065, dated 1/20/2011
- REMS Amendment, sequence 0083 REMS amendment, REMS materials, dated 4/15/2011
- Substantially completed labeling dated June 29, 2011.

3 SUMMARY OF ASTRAZENCA'S PROPOSED REMS FOR BRILINTA

The sponsor's proposed goals for the REMS are:

█  (b) (4)

Reviewer Comments: DRISK revisions to the goals, REMS document and REMS materials included in Attachments A-D.

The proposed REMS is comprised of a Medication Guide (MG) and communication plan. The communication plan includes:

-  (b) (4)
- █ 
- █ 

The proposed timetable for submission of assessments is 18 months, 3 years and 7 years from the date of the initial approval of the REMS.

4 RECOMMENDATIONS FOR THE REVIEW DIVISION

The following recommendations on the proposed Brilinta REMS should be sent to the AstraZeneca as soon as possible. In addition to the recommendations in Section 5 below, the REMS materials in attachments A-D, that include our track changes, should also be sent to the applicant:

Attachment A: REMS Document

Attachment B: Medication Guide with track changes

Attachment C: Dear Healthcare Professional Letter, revised.

Attachment D: Landing page of the Brilinta REMS Website with track changes

Please copy DRISK on the communication sent to the applicant. If there are questions, concerns, or disagreement with our recommendations, please contact DRISK to discuss.

Please notify the applicant that these are interim comments and there may be additional comments on the documents as they progress through the final clearance process. Please indicate to the sponsor to respond to these comments as soon as possible to facilitate further review in order to meet the action date.

5 RECOMMENDATIONS FOR THE APPLICANT

Please note that these are interim comments, there may be additional comments on the REMS and REMS materials as they are routed through the Agency's final clearance process.

5.1 REMS Document

Attachment A contains the necessary revisions to the REMS document. The following materials are part of the REMS and must be appended to the REMS:

- Medication Guide
- Dear Healthcare Professional Letter
- Landing page of the Brilinta REMS Website
- Professional Organization Letter

5.2 Medication Guide

Attachment B contains all the necessary revisions to the Medication Guide.

5.3 Dear Healthcare Professional Letter and Professional Organization Letter

The Dear Healthcare Professional Letter (DHCPL) has been revised for clarity and to reflect the most recent version of the Prescribing Information. Use the DHCPL as the template for a Professional Organization Letter.

The REMS proposes that the initial delivery of the DHCPL will be electronic, that letter should be formatted so links to the Prescribing Information and Medication Guide appear in the letter. The format of the e-mail should be such that the DHCPL appears in the body of the email, and not as a separate link embedded in the email.

Attachment C contains all the necessary revisions to the DHCPL.

5.4 Brilinta REMS Website

5.4.1 The REMS website landing page has been edited for clarity and to reflect the most recent version of the Prescribing Information.

Attachment D contains the necessary revisions to the text located on the landing page of the Brilinta REMS website.

5.4.2 [REDACTED] (b) (4)

5.4.3 Provide an obvious link on the Brilinta home page that directs the viewer to the Brilinta REMS website.

5.4.4 Include only the REMS landing page, as part of the communication materials in the REMS document.

5.5 REMS Supporting Document

5.5.1 All changes in the REMS and Prescribing Information (PI) should also be reflected in the REMS Supporting Document.

5.5.2 Describe the exact mechanism(s) you will use to identify the providers to be targeted in communication plan. If using a third party database, provide more detail to justify that this database provides a comprehensive listing of the target audience in communication plan. Include this information in the Supporting Document.

5.6 Information Needed for Assessments

The assessment plan should include the number of Dear Healthcare Professional letter electronically, number received, number undeliverable, and number opened. Also include the number of letters sent via mail and number distributed by the sales representatives.

5.7 Surveys

We acknowledge that you provided a brief description of the survey methodology and instrument to assess the REMS and that you plan to submit the full methodology 90 days before conducting the survey. We will defer our comment until the full methodology is submitted, but offer the following guidance as you develop your proposal.

Submit for review the detailed plan you propose to use to evaluate patients' and prescribers' understanding about the safe use of Brilinta. You may submit the proposed plan after approval of the REMS, however submit it at least 90 days before you conduct the evaluation. Code the submission "REMS Correspondence." Make sure the submission includes all methodology and instruments used to evaluate the knowledge about the risks associated with and safe use of Brilinta.

1. Recruit respondents using a multi-modal approach. For example, you might recruit respondents through physicians' offices, pharmacies, managed care providers, consumer panels, or on-line.

Explain how often you perform non-respondent follow-up or reminders.

If you use an incentive or honorarium, provide details on what is offered and the estimated dollar value.

Explain how you select recruitment sites.

Submit for review any recruitment advertisements.

2. Describe the rationale for your sample size. Report the 95% confidence interval around the expected level(s) of knowledge for each key risk(s).
3. Define the expected number of people to be contacted to obtain the proposed sample size, and how the sample is determined (selection criteria).
4. Ensure the sample is demographically representative of the population who use the drug (patients), or prescribe the drug (doctors), regardless of the condition for which they use or prescribe it.
5. When possible and appropriate, ensure the sample is diverse in terms of age, race, ethnicity, sex, socio-economic status, education level, and geographically.
6. List the inclusion criteria for patients, and prescribers. For example, eligible *patient* respondents must be:
 - Age 18 or older
 - Currently taking Brilinta or have taken the drug in the past 3 months
 - Not currently participating in a clinical trial involving Brilinta
 - Not a healthcare provider

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

7. Explain how you administer surveys and the intended frequency.

Offer respondents multiple options for completing the survey. Be sure to include an option for the lower literacy population. For example, respondents might complete surveys online or through email, in writing or by mail, over the phone, and in person.

Explain how you train surveyors.

8. Explain how you control for limitations or bias associated with the methodology and survey instruments.
9. Submit for review the introductory text used to inform respondents about the purpose of the survey.

Tell potential respondents that their answers will not affect their ability to receive or take (patients), or prescribe (doctors) and that their answers and personal information will be kept confidential and anonymous.

Tell respondents not to guess the answers, and to choose “I don’t know” rather than guess.

10. Clarify in your methodology that respondents are eligible for one wave of the survey only.

11. Analyze results on an item-by-item or variable-by-variable basis. You may present the data using descriptive statistics, such as sample size, mean, standard deviation, median, minimum and maximum (for continuous variables), and frequency distributions (for categorical variables).

You may stratify the data by any relevant demographic variable, and presented in aggregate. Submit with your assessments all methodology and instruments utilized.

Regarding an assessment of patients' knowledge:

12. The assessment evaluates the effectiveness of the REMS in achieving the goal by evaluating patients' knowledge of the serious risks associated with use of the drug. The assessment does not evaluate consumer comprehension of the Medication Guide.

According to regulation (21 CFR 208.24), patients receive the Medication Guide at the time the prescription is filled/dispensed. Do not offer respondents an opportunity to read or see the Medication Guide, Package Insert, or any other related educational materials again prior to taking the survey.

13. 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.
14. Ensure the patient knowledge survey includes questions that ask about the specific risks or safety information conveyed in the Medication Guide to determine if the patient understands the information and knows what to do if they experience an adverse event.

Derive the risk-specific questions from information located in the "What is the Most Important Information I should know about Brilinta?" section of the Medication Guide.

Ensure the risk-specific questions are not biased or leading, and that multiple choice questions include an instruction to "select all that apply." Ensure that each question has an "I don't know" answer option.

Randomize the order of the multiple choice responses on each survey.

15. Order questions so the risk-specific questions are asked first, followed by questions about receipt of the Medication Guide. Collect demographic questions last or as part of any screener questions.

Do not allow respondents 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.

16. 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.
17. 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” followed by the word Brilinta and its pronunciation. The Medication Guide usually has sections titled “What is the most important information I should know about Brilinta,” “What is Brilinta,” and “Who should not take Brilinta.”

18. 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)
 - a) My doctor or someone in my doctor’s office
 - b) My pharmacist or someone at the pharmacy
 - c) Someone else - please explain: _____
 - d) I did not get a Medication Guide for Brilinta
 - Did you read the Medication Guide?
 - a) All,
 - b) Most,
 - c) Some,
 - d) None
 - Did you understand what you read in the Medication Guide?
 - a) All,
 - b) Most,
 - c) Some,
 - d) None
 - Did someone offer to explain to you the information in the Medication Guide?
 - a) Yes, my doctor or someone in my doctor’s office
 - b) Yes, my pharmacist or someone at the pharmacy
 - c) Yes, someone else – please explain: _____
 - d) No
 - Did you accept the offer? Yes or No
 - Did you understand the explanation that was given to you?
 - a) All,
 - b) Most,
 - c) Some,
 - d) None
 - Did or do you have any questions about the Medication Guide? Yes or No (If Yes, list your question(s) below) Note: Group/code this open text field prior to submitting to FDA

Regarding an assessment of healthcare providers’ (prescribers) knowledge:

19. The assessment evaluates how effective the REMS is in achieving the goal(s) by evaluating healthcare providers’ knowledge of the risks:

- the serious risks associated with use of Brilinta,
- how to properly prescribe or dispense Brilinta,
- how to properly monitor for the serious risks associated with the use of Brilinta;

The assessment does not assess healthcare providers' comprehension of the educational materials.

Do not offer respondents an opportunity to read or see any educational materials (prescribing information, communications, promotional materials, websites, videos, etc.) again prior to taking the survey.

20. 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 any educational materials.
21. Ensure the healthcare provider knowledge survey includes a section with questions asking about the specific risks and safety information conveyed in the educational materials.

Ensure questions are not biased or leading, and that multiple choice questions include an instruction to "select all that apply." Ensure each question has an "I don't know" answer option.

Randomize the order of the multiple choice responses on each survey.

22. Order the survey questions so the risk-specific questions are asked first, followed by questions about receipt of the educational materials. Collect demographic questions last or as part of any screener questions.

Do not allow respondents 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.

23. Use the following (or similar) questions to assess receipt and use of the educational materials.
 - Prior to today, which of the following were you aware of or received with regard to Brilinta? (Select all that apply)

Educational Material	Aware	Received
Full Prescribing Information	<input type="checkbox"/>	<input type="checkbox"/>
Medication Guide	<input type="checkbox"/>	<input type="checkbox"/>
Dear Healthcare Professional Letter	<input type="checkbox"/>	<input type="checkbox"/>
Something else - please explain:	<input type="checkbox"/>	<input type="checkbox"/>

None of the above



- Did you read the Full Prescribing Information?
 - a) All,
 - b) Most,
 - c) Some,
 - d) None
 - e) I did not receive the Brilinta Full Prescribing Information
- Did you read the Medication Guide?
 - a) All,
 - b) Most,
 - c) Some,
 - d) None
 - e) I did not receive the Brilinta Medication Guide
- Did you read the Dear Healthcare Professional Letter?
 - a) All,
 - b) Most,
 - c) Some,
 - d) None
 - e) I did not receive the Brilinta Dear Healthcare Professional Letter
- Do you have any questions about any of the educational materials related to Brilinta? Yes or No (If Yes, list your question(s) below) Note: Group/code this open text field prior to submitting to FDA

5.8 Submission Instructions

Provide a WORD document with track changes and a clean WORD version of all revised materials and documents. WORD is necessary because it makes review of these materials more efficient and it facilitates web postings to of the documents to be 508 compliant.

Submit the REMS and the REMS Supporting Document as two separate WORD documents. It is preferable that the entire REMS document and attached materials should a single WORD document.

All REMS materials should be updated to reflect the final approved label as agreed upon with FDA. Please remember that REMS materials are not appropriate for use in a promotional manner.

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/s/

CYNTHIA L LACIVITA
07/07/2011

CLAUDIA B KARWOSKI
07/07/2011
concur

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of Drug Evaluation I
Division of Cardiovascular and Renal Products

NDA #: 22433
Products: Brilinta (ticagrelor) AZD 6140
SPONSOR: AstraZeneca
FROM: Robert Temple
Director, Office of Drug Evaluation I
DATE: 12/16/2010

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorize FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). Section 505-1(a)(1) provides the following factors:

- (A) The estimated size of the population likely to use the drug involved;
- (B) The seriousness of the disease or condition that is to be treated with the drug;
- (C) The expected benefit of the drug with respect to such disease or condition;
- (D) The expected or actual duration of treatment with the drug;
- (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
- (F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary for Brilinta (ticagrelor) to ensure that the benefits of the drug outweigh the risk of bleeding. In reaching this determination, we considered the following:

- A. Over 1.4 million hospitalizations for Acute Coronary Syndrome (ACS) occur in the United States each year.¹ Patients with unstable angina (UA) or non-ST-segment elevation myocardial infarction (NSTEMI) comprise approximately 70% of the population presenting with ACS.²

¹ Rosamond W, Flegal K, Furie K, Go A, Greenlund K, Haase N, Hailpern SM, Ho M, Howard V, Kissela B, Kittner S, Lloyd-Jones D, McDermott M, Meigs J, Moy C, Nichol G, O'Donnell C, Roger V, Sorlie P, Steinberger J, Thom T, Wilson M, Hong Y; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. 2008. Heart disease and stroke statistics--2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 117(4):e25-146.

² Goldberg RJ, Currie K, White K, Brieger D, Steg PG, Goodman SG, Dabbous O, Fox KA, Gore JM. 2004. Six-month outcomes in a multinational registry of patients hospitalized with an acute coronary syndrome (the Global Registry of Acute Coronary Events [GRACE]). *Am J Cardiol* 93(3):288-293.

- B. Acute coronary syndrome (ACS) is associated with cardiac ischemia and infarction which can lead to death or serious morbidity including heart failure.
- C. Ticagrelor (Brilinta) would be expected to reduce the rate of thrombotic events (stroke, MI) and cardiovascular death in patients with ACS.
- D. ACS is an acute condition. However, there is no limitation on duration of use in the labeling because ticagrelor (Brilinta) may be used chronically for the prevention of future events in patients who have had an ACS.
- E. The primary risk associated with ticagrelor (Brilinta) is bleeding. This includes intracranial, pericardial and other life-threatening or fatal bleeding. The incidences of life-threatening and fatal bleeding in the placebo arm of a trial in a similar population³ were 1.8% and 0.2%, respectively. In addition to bleeding, ticagrelor (Brilinta) has also been associated with dyspnea. Discontinuation of ticagrelor (Brilinta) increases the risk of cardiovascular ischemic events.
- F. Brilinta is a new molecular entity.

In accordance with section 505-1 of FDCA and under 21 CFR 208, FDA has determined that a Medication Guide is required for Brilinta (ticagrelor). FDA has determined that Brilinta (ticagrelor) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Brilinta (ticagrelor). FDA has determined that Brilinta (ticagrelor) is a product:

- For which patient labeling could help prevent serious adverse effects.
- That has a serious risk (relative to benefits) of which patients should be made aware because information concerning the risk could affect patients' decisions to use or continue to use ticagrelor (Brilinta).
- That the Medication Guide is important to health and patient adherence to directions for use is crucial to the drug's effectiveness.

The elements of the REMS will be a Medication Guide and a timetable for submission of assessments of the REMS.

³ Bleeding incidence from placebo arm of the CURE trial (clopidogrel+aspirin vs placebo+aspirin in certain acute coronary syndrome patients) source: Plavix label, August 2010. The bleeding incidences in CURE and the ticagrelor program may not be directly comparable because of differences in rates of invasive management.

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