Initial REMS Approval: 07/2011

BRILINTA REMS DOCUMENT

NDA 22-433

BRILINTA™ (ticagrelor) tablets

Class of Product: cyclopentyltriazolopyrimidines (CPTPs)

AstraZeneca LP
1800 Concord Pike
P.O.Box 8355
Wilmington, DE 19850

Contact: The Information Center at AstraZeneca

1-800-236-9933

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOALS:

The goals of the BRILINTA REMS 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.

II. REMS ELEMENTS:

A. Medication Guide

A Medication Guide will be dispensed with each BRILINTA prescription in accordance with 21 CFR 208.24.

The Medication Guide is part of the REMS and is appended.

B. Communication Plan

AstraZeneca will implement a communication plan targeted to healthcare professionals who are likely to prescribe and dispense BRILINTA to inform them of the serious risks associated with BRILINTA, particularly the increased risk of bleeding and that the daily maintenance dose of aspirin, co-administered with BRILINTA, should not exceed 100 mg. This element of the REMS is not intended to continue over the lifetime of the product; it will function for a period of 2 years after the approval of the REMS. The communication plan will include the following:

1. Dear Healthcare Professional Letter

A Dear Healthcare Professional Letter (DHCPL) will be distributed to: interventional cardiologists; clinical cardiologists; emergency medicine physicians; internal medicine physicians; primary care physicians; nurse practitioners; physician assistants; pharmacists; critical care nurses, and cardiac nurse specialists. The letter will be distributed within 60 days of the REMS approval date, again at 6 months, 12 months and 24 months after the approval of the REMS, via electronic distribution or by mail.

In addition, for 2 years after the approval of the REMS new prescribers will be sent the DHCPL and the sales force will provide a copy of the letter upon initial contact with all potential BRILINTA prescribers.

The DHCPL will be distributed to the target audience using the PDR Network as well as other 3rd party lists. The DHCPL will be delivered electronically via email or fax. If DHCPL cannot be delivered electronically to the target professional for any reason or, in the case of email, remains unopened for 72 hours, a hardcopy will be sent via mail.

Product labeling and the Medication Guide will be provided in conjunction with the letter.

The Dear Healthcare Professional Letter is part of the REMS and is appended.

2. BRILINTA REMS Website

Within 30 days of REMS approval, AstraZeneca will post information for healthcare professionals and patients on the BRILINTA REMS website (www.Brilintarems.com). This information will remain on the website for a period of 2 years.

The content of the web-based material will include the following:

- Goals of the REMS
- Information about the risk
- Prescribing information for BRILINTA
- Medication Guide for BRILINTA
- DHCP letter (for a period of 2 years)

The web-based material is part of the REMS and is appended.

3. Letters to Professional Organizations

A Professional Organization Letter will be distributed within 60 days of the REMS approval date. This communication to professional organizations will include the same information as that contained in the Dear Healthcare Professional Letter. AstraZeneca will request that these organizations disseminate this information to their members. AstraZeneca will communicate via letter to the leadership of the following professional organizations:

- The American Heart Association (AHA)
- The American College of Cardiologists (ACC)
- The Society for Cardiovascular Angiography and Interventions (SCIA)
- Association of Emergency Physicians (AEP)
- The American College of Chest Physicians (ACCP)
- Association of Black Cardiologists (ABC)
- The American Academy of Family Physicians (AAFP)
- The American College of Physicians (ACP)
- The National Medical Association (NMA)
- The American Academy of Nurse Practitioners (AANP)
- The American Academy of Physician Assistants (AAPA)
- American College of Clinical Pharmacy (ACCP)
- American Society of Health-System Pharmacists (ASHP)
- American Pharmacists Association (APhA)
- American Association of Critical-Care Nurses (AACCN)
- National Association of Clinical Nurse Specialists (NACNS)

Product labeling and the Medication Guide will be provided in conjunction with the letter.

The Professional Organization Letter is part of the REMS and is appended.

C. Timetable for Submission of Assessments

AstraZeneca will submit REMS Assessments to FDA at 18 months, 3 years and 7 years from the date of the approval of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. AstraZeneca will submit each assessment so that it will be received by the FDA on or before the due date.

IMPORTANT DRUG WARNING

SUBJECT:
- **Risk of Increased Bleeding**
- **Decreased Efficacy with BRILINTA (ticagrelor) in Combination with Aspirin Doses Exceeding 100 mg**

Dear Healthcare Professional:

The purpose of this letter is to inform you of important safety information for BRILINTA (ticagrelor), a $P2Y_{12}$ platelet inhibitor recently approved by the FDA. BRILINTA is 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 appear to decrease the efficacy of BRILINTA. Maintenance doses of aspirin should not exceed 100 mg daily.

The FDA has determined that a Risk Evaluation and Mitigation Strategy (REMS) is necessary to ensure that the benefits of BRILINTA outweigh the following potential risks:

- Increased risk of bleeding
- Decreased efficacy of BRILINTA with higher aspirin doses (above 100 mg)

Increased Risk of Bleeding

- BRILINTA, like other antiplatelet agents, can cause significant, sometimes fatal, bleeding.
- Do not use BRILINTA in patients with active bleeding or history of intracranial hemorrhage.

If possible, manage bleeding without discontinuing BRILINTA. Stopping BRILINTA increases the risk of subsequent cardiovascular events.

Importance of Appropriate Aspirin Dose

- BRILINTA has been studied in combination with aspirin. Use with aspirin maintenance dose of 75-100 mg once daily.
- Higher aspirin doses (above 100 mg) appear to decrease the efficacy of BRILINTA.

Talk to Your Patients:

Tell patients that they:

- Will bleed and bruise more easily
- Will take longer than usual to stop bleeding

Instruct patients to:

- Report any unanticipated, prolonged or excessive bleeding, or blood in their stool or urine
- Not take aspirin maintenance doses greater than 100 mg daily
- Not take any products containing aspirin for other conditions.
- List all prescription medications, over the counter medications or dietary supplements they are taking or plan to take so the physician knows about other treatment that may affect bleeding risk (e.g. warfarin, heparin).
- Inform physicians and dentists that they are taking BRILINTA before any surgery or dental procedure
- Tell the doctor performing any surgery or dental procedure to talk to the prescribing physician before stopping BRILINTA.

Medication Guide

The Medication Guide contains information to support patient counseling regarding the risks and benefits of treatment with BRILINTA. [The BRILINTA Medication Guide may be obtained from the website www.brilintarems.com or by calling Sponsor at 1-800-236-9933.]

Reporting Adverse Events

To report any adverse events with the use of BRILINTA contact:

- Sponsor at 1-800-236-9933 and/or
- FDA MedWatch program by phone at 1-800-FDA-1088 or online at www.fda.gov/medwatch/report.htm

This letter is not intended as a complete description of the benefits and risks associated with the use of BRILINTA. Please refer to the full Prescribing Information and Medication Guide (www.brilintarems.com).

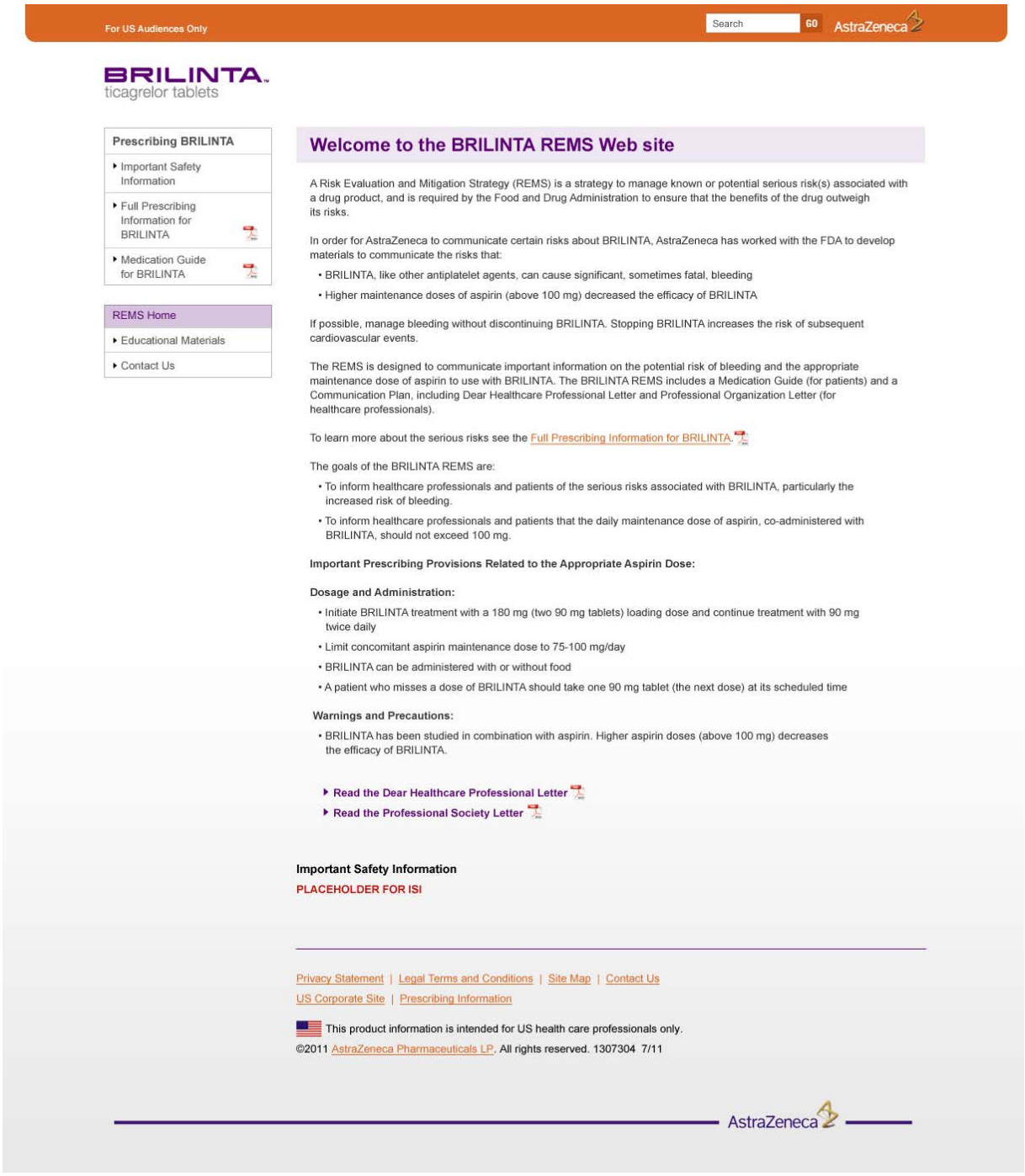
For additional information, please call Sponsor at 1-800-236-9933 or visit www.brilintarems.com.

Sincerely,

James W. Blasetto, M.D., MPH
Vice President
US Strategic Development
AstraZeneca LP
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Enclosure: BRILINTA Full Prescribing Information and Medication Guide

Landing page of the BRILINTA REMS website



IMPORTANT DRUG WARNING

Disseminate this information to your members

SUBJECT:
- **Risk of Increased Bleeding**
- **Decreased Efficacy with BRILINTA (ticagrelor) in Combination with Aspirin Doses Exceeding 100 mg**

Dear Professional Organization:

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- List all prescription medications, over the counter medications or dietary supplements they are taking or plan to take so the physician knows about other treatment that may affect bleeding risk (e.g. warfarin, heparin).
- Inform physicians and dentists that they are taking BRILINTA before any surgery or dental procedure

Tell the doctor performing any surgery or dental procedure to talk to the prescribing physician before stopping BRILINTA.

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For additional information, please call Sponsor at 1-800-236-9933 or visit www.brilintarems.com.

Sincerely,

James W. Blasetto, M.D., MPH
Vice President
US Strategic Development
AstraZeneca LP
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Enclosure: BRILINTA Full Prescribing Information and Medication Guide

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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.

/s/

ROBERT TEMPLE
07/20/2011