IMPORTANT SAFETY INFORMATION FOR BRILINTA® (ticagrelor) 60-MG AND 90-MG TABLETS (CONT'D)

WARNINGS AND PRECAUTIONS

- Dyspnea was reported more frequently with BRILINTA than in patients treated with control agents. Dyspnea from BRILINTA is often self-limiting
- Discontinuation of BRILINTA will increase the risk of MI, stroke, and death. When possible, interrupt therapy with BRILINTA for 5 days prior to surgery that has a major risk of bleeding. If BRILINTA must be temporarily discontinued, restart as soon as possible
- Ticagrelor can cause ventricular pauses. Bradyarrhythmias including AV block have been reported in the post-marketing setting. Clinical trials excluded patients at increased risk of bradyarrhythmias not protected by a pacemaker, and they may be at increased risk of developing bradyarrhythmias
- Avoid use of BRILINTA in patients with severe hepatic impairment. Severe hepatic impairment is likely to increase serum concentration of ticagrelor and there are no studies of BRILINTA in these patients
- In patients with Heparin Induced Thrombocytopenia (HIT): False negative results for HIT-related platelet functional tests, including the heparin-induced platelet aggregation (HIPA) assay, have been reported with BRILINTA. BRILINTA is not expected to impact PF4 antibody testing for HIT

ADVERSE REACTIONS

- The most common adverse reactions (>5%) associated with the use of BRILINTA included bleeding and dyspnea

DRUG INTERACTIONS

- Avoid use with strong CYP3A inhibitors and strong CYP3A inducers. BRILINTA is metabolized by CYP3A4/5. Strong inhibitors substantially increase ticagrelor exposure and so increase the risk of adverse events. Strong inducers substantially reduce ticagrelor exposure and so decrease the efficacy of ticagrelor
- As with other oral $P2Y_{12}$ inhibitors, co-administration of opioid agonists delay and reduce the absorption of ticagrelor. Consider use of a parenteral anti-platelet in ACS patients requiring co-administration
- Patients receiving more than 40 mg per day of simvastatin or lovastatin may be at increased risk of statin-related adverse events
- Monitor digoxin levels with initiation of, or change in, BRILINTA therapy

SPECIAL POPULATIONS

- Lactation: Breastfeeding not recommended

DOSING

In the management of ACS, initiate BRILINTA treatment with a 180-mg loading dose. Administer 90 mg twice daily during the first year after an ACS event. After one year administer 60 mg twice daily.
In patients with CAD but no prior stroke or MI, administer 60 mg twice daily.
Use BRILINTA with a daily maintenance dose of aspirin of 75-100 mg.

ACC=American College of Cardiology; ACS=acute coronary syndrome; AHA=American Heart Association; CAD=coronary artery disease; CV=cardiovascular; DAPT=dual antiplatelet therapy; DRG=Decisions Resource Group; FDA=Food and Drug Administration; LOE=level of evidence; MI=myocardial infarction; NSTE-ACS=non–ST-elevation ACS; OAP=oral antiplatelet; PCI=percutaneous coronary intervention; PEGASUS=Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin; PLATO=PLATelet inhibition and patient Outcomes; RCT=randomized controlled trial; STEMI=ST-elevation myocardial infarction; THEMIS=Effect of Ticagrelor on Health Outcomes in DiabEtes Mellitus Patients Intervention Study; T2D=type 2 diabetes.

References: 1. Data on file, REF-71954, AstraZeneca Pharmaceuticals LP. **2.** BRILINTA® (ticagrelor) [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2020. **3.** Wallentin L, Becker RC, Budaj A, et al; for the PLATO Investigators. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med.* 2009;361(11):1045-1057 and Supplementary Appendix. **4.** Sahlén A, Varenhorst C, Lagerqvist B, et al. Outcomes in patients treated with ticagrelor or clopidogrel after acute myocardial infarction: experiences from SWEDEHEART registry. *Eur Heart J.* 2016;37(44):3335-3342. **5.** Bonaca MP, Bhatt DL, Cohen M, et al, for the PEGASUS-TIMI 54 Steering Committee and Investigators. Long-term use of ticagrelor in patients with prior myocardial infarction. *N Engl J Med.* 2015;372:1791-1800. **6.** Steg PG, Bhatt DL, Simon T, et al; for the THEMIS Steering Committee and Investigators. Ticagrelor in patients with stable coronary disease and diabetes. *N Engl J Med.* 2019;381(14):1309-1320. **7.** Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease. *Circulation.* 2016;134(10):e123-e155. **8.** Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. *Circulation.* 2014;130(25):e344-e426. **9.** Department of Health and Human Services. US Food and Drug Administration. Revised Plavix labeling. Published September 16, 2016. Accessed June 12, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2016/020839Orig1s062,s064ltr.pdf

Please read additional Important Safety Information throughout and accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

AstraZeneca

BRILINTA® ticagrelor tablets

CONFIDENCE IN BRILINTA

#1 INITIATED OAP* IN...[1]
- ▶ STEMI
- ▶ PCI IN ACS

*Based on monthly market share performance in patients with STEMI and in patients with ACS who underwent PCI for OAP initiation data, among $P2Y_{12}$ inhibitors, for all hospitals within DRG dataset, as of October 2019.

BACKED BY EXPERIENCE EVALUATED IN MORE THAN 100,000 PATIENTS

- ▶ **18,000 PATIENTS WITH ACS** STUDIED IN PLATO[2]
- ▶ **45,000 PATIENTS WITH ACS** STUDIED IN REAL-WORLD REGISTRY THAT CONFIRMED PLATO OUTCOMES[3,4]
- ▶ **21,000 PATIENTS WITH PRIOR MI** STUDIED IN PEGASUS[5]
- ▶ **>19,000 HIGH-RISK PATIENTS WITH CAD+T2D WITH NO HISTORY OF MI OR STROKE** STUDIED IN THEMIS[6]

INDICATIONS

BRILINTA is indicated to reduce the risk of cardiovascular death, myocardial infarction (MI), and stroke in patients with acute coronary syndrome (ACS) or a history of myocardial infarction. For at least the first 12 months following ACS, it is superior to clopidogrel. BRILINTA also reduces the risk of stent thrombosis in patients who have been stented for treatment of ACS.
BRILINTA is indicated to reduce the risk of a first MI or stroke in patients with coronary artery disease (CAD) at high risk for such events. While use is not limited to this setting, the efficacy of ticagrelor was established in a population with type 2 diabetes.

DOSING

In the management of ACS, initiate BRILINTA treatment with a 180-mg loading dose. Administer 90 mg twice daily during the first year after an ACS event. After one year administer 60 mg twice daily.
In patients with CAD but no prior stroke or MI, administer 60 mg twice daily.
Use BRILINTA with a daily maintenance dose of aspirin of 75-100 mg.

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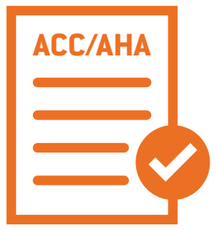
BRILINTA® ticagrelor tablets

PREFERRED IN GUIDELINES FOR PATIENTS WITH ACS



BRILINTA PREFERRED OVER CLOPIDOGREL IN ACS IN 2016 ACC/AHA DAPT GUIDELINE[7]

- According to the 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy (DAPT), **BRILINTA is preferred over clopidogrel in ACS (Class IIa; LOE B-R)**
  - First time preferred in patients with STEMI who have received a coronary stent
  - Preferred in patients with NSTE-ACS who have received a coronary stent or are managed with medical therapy alone

CLASS I RECOMMENDATION (LOE B-R)

- Use of dual antiplatelet therapy for **at least 12 months** in patients with ACS
- BRILINTA as a treatment option in patients with ACS who undergo stent implantation or who are managed with medical therapy alone

PREFERRED OVER CLOPIDOGREL FOR THE MANAGEMENT OF NSTE-ACS IN THE 2014 AHA/ACC NSTE-ACS GUIDELINE[8]

- Class IIa recommendation for use of BRILINTA over clopidogrel in patients with NSTE-ACS with early invasive or ischemia-guided strategy or receiving a coronary stent (LOE-B)
- Class I recommendation for BRILINTA as a treatment option in the management of patients with NSTE-ACS (LOE-B)

CLASS OF RECOMMENDATION AND LEVEL OF EVIDENCE: Class I recommends that the procedure/treatment should be performed/administered; Class IIa states that it is reasonable to perform procedure/administer treatment; Level B-R is moderate-quality evidence from 1 or more RCTs or meta-analyses of moderate-quality RCTs; Level B is based on data derived from a single randomized clinical trial or nonrandomized studies.

FDA NARROWED ACS INDICATION FOR CLOPIDOGREL[9]

- **FDA has removed the reduction of CV death and death from the ACS indication for Plavix® (clopidogrel bisulfate) tablets**
- **Plavix is not indicated in patients with STEMI undergoing PCI**

2016 REVISIONS TO PLAVIX ACS INDICATIONS*

Plavix is indicated to reduce the rate of myocardial infarction and stroke ~~For~~ in patients with non-ST-segment elevation ACS [unstable angina (UA)/non-ST-elevation myocardial infarction (NSTEMI)], including patients who are to be managed medically and those who are to be managed with coronary revascularization. Plavix should be administered in conjunction with aspirin. ~~Plavix has been shown to decrease the rate of a combined endpoint of cardiovascular death, myocardial infarction (MI), or stroke as well as the rate of a combined endpoint of cardiovascular death, MI, stroke, or refractory ischemia.~~

Plavix is indicated to reduce the rate of myocardial infarction and stroke ~~For~~ in patients with acute ST-elevation myocardial infarction (STEMI) who are to be managed medically. Plavix should be administered in conjunction with aspirin. ~~Plavix has been shown to reduce the rate of death from any cause and the rate of a combined endpoint of death, re-infarction, or stroke. The benefit for patients who undergo primary percutaneous coronary intervention is unknown. The optimal duration of Plavix therapy in ACS is unknown.~~

*Additions are shown as underlined text; deletions are shown as ~~strikethrough~~ text.
Plavix is a registered trademark of sanofi-aventis.
For complete information on changes to the Plavix Prescribing Information, go to www.MedicationUpdate.com Approval Letter.

IMPORTANT SAFETY INFORMATION FOR BRILINTA® (ticagrelor) 60-MG AND 90-MG TABLETS

WARNINGS:

A. BLEEDING RISK

- **BRILINTA, like other antiplatelet agents, can cause significant, sometimes fatal bleeding**
- **Do not use BRILINTA in patients with active pathological bleeding or a history of intracranial hemorrhage**
- **Do not start BRILINTA in patients undergoing urgent coronary artery bypass graft surgery**
- **If possible, manage bleeding without discontinuing BRILINTA. Stopping BRILINTA increases the risk of subsequent cardiovascular events**

B. ASPIRIN DOSE AND BRILINTA EFFECTIVENESS

- **Maintenance doses of aspirin above 100 mg reduce the effectiveness of BRILINTA and should be avoided**

IMPORTANT SAFETY INFORMATION FOR BRILINTA® (ticagrelor) 60-MG AND 90-MG TABLETS (CONT'D)

CONTRAINDICATIONS

- BRILINTA is contraindicated in patients with a history of intracranial hemorrhage or active pathological bleeding such as peptic ulcer or intracranial hemorrhage. BRILINTA is also contraindicated in patients with hypersensitivity (eg, angioedema) to ticagrelor or any component of the product

Please read additional Important Safety Information throughout and accompanying full Prescribing Information, including Boxed WARNINGS, and Medication Guide.

BRILINTA®
ticagrelor tablets