BRILINTA® (ticagrelor) Tablets

WARNING: BLEEDING RISK
- BRILINTA, like other antiplatelet agents, can cause significant, sometimes fatal bleeding (5.1, 6.1).
- Do not use BRILINTA in patients with active pathological bleeding or a history of intracranial hemorrhage (4.1, 4.2).
- Do not start BRILINTA in patients planned to undergo urgent coronary artery bypass graft surgery (CABG). When possible, discontinue BRILINTA at least 5 days prior to any surgery (5.1).
- Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, percutaneous coronary intervention (PCI), CABG, or other surgical procedures in the setting of BRILINTA (5.1).
- If possible, manage bleeding without discontinuing BRILINTA. Stopping BRILINTA increases the risk of subsequent cardiovascular events (5.5).

WARNING: ASPIRIN DOSE AND BRILINTA EFFECTIVENESS
- Maintenance doses of aspirin above 100 mg reduce the effectiveness of BRILINTA and should be avoided. After any initial dose, use with aspirin 75-100 mg per day (5.2, 14).

DOSE AND ADMINISTRATION
- Initiate treatment with 180 mg (two 90 mg tablets) oral loading dose. (2)
- Continue treatment with 90 mg twice daily. (2)
- After the initial loading dose of aspirin (usually 325 mg), use BRILINTA with a daily maintenance dose of aspirin of 75-100 mg. (2)

DOSE FORMS AND STRENGTHS
- 90 mg tablets (3)

CONTRAINDICATIONS
- History of intracranial hemorrhage (4.1).
- Active pathological bleeding (4.2).
- Severe hepatic impairment (4.3).
- Hypersensitivity to ticagrelor or any component of the product (4.4).

WARNINGS AND PRECAUTIONS
- Like other antiplatelet agents, BRILINTA increases the risk of bleeding. (5.1)
- In PLATO, use of BRILINTA with maintenance doses of aspirin above 100 mg decreased the effectiveness of BRILINTA. (5.2, 14)
- Moderate Hepatic Impairment: Consider the risks and benefits of treatment, noting the probable increase in exposure to ticagrelor. (5.3)
- Dyspnea: Dyspnea was reported more frequently with BRILINTA than with clopidogrel. Dyspnea resulting from BRILINTA is self-limiting. Rule out other causes. (5.4)
- Discontinuation of BRILINTA: Premature discontinuation increases the risk of myocardial infarction, stent thrombosis, and death. (5.5)

ADVERSE REACTIONS
- Most common adverse reactions are bleeding 12% and dyspnea 14%. (5.1, 5.4, 6.1)
- To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS
- Avoid use with strong CYP3A inhibitors or CYP3A inducers. (7.1, 7.2)
- Patients receiving more than 40 mg per day of simvastatin or lovastatin may be at increased risk of statin-related adverse effects. (7.3)
- Monitor digoxin levels with initiation of or any change in BRILINTA. (7.4)

FULL PRESCRIBING INFORMATION: CONTENTS
- 6 ADVERSE REACTIONS
- 11 DESCRIPTION
- 12 CLINICAL PHARMACOLOGY
- 13 NONCLINICAL TOXICOLOGY
- 14 CLINICAL STUDIES
- 15 HOW SUPPLIED/STORAGE AND HANDLING
- 16 PATIENT COUNSELING INFORMATION and Medication Guide.

* Sections or subsections omitted from the Full Prescribing Information are not listed.
FULL PRESCRIBING INFORMATION

WARNING: BLEEDING RISK
• BRILINTA, like other antiplatelet agents, can cause significant, sometimes fatal bleeding (5.1, 6.1).
• Do not use BRILINTA in patients with active pathological bleeding or a history of intracranial hemorrhage (4.1, 4.2).
• Do not start BRILINTA in patients planned to undergo urgent coronary artery bypass graft surgery (CABG). When possible, discontinue BRILINTA at least 5 days prior to any surgery (5.1).
• Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, percutaneous coronary intervention (PCI), CABG, or other surgical procedures in the setting of BRILINTA (5.1).
• If possible, manage bleeding without discontinuing BRILINTA. Stopping BRILINTA increases the risk of subsequent cardiovascular events (5.5).

WARNING: ASPIRIN DOSE AND BRILINTA EFFECTIVENESS
• Maintenance doses of aspirin above 100 mg reduce the effectiveness of BRILINTA and should be avoided. After any initial dose, use with aspirin 75-100 mg per day (5.2, 14).

1 INDICATIONS AND USAGE
1.1 Acute Coronary Syndromes
BRILINTA is a P2Y12 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 [see Clinical Studies (14)].
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 [see Warnings and Precautions (5.2) and Clinical Studies (14)].

2 DOSAGE AND ADMINISTRATION
Initiate BRILINTA treatment with a 180 mg (two 90 mg tablets) loading dose and continue treatment with 90 mg twice daily. After the initial loading dose of aspirin (usually 325 mg), use BRILINTA with a daily maintenance dose of aspirin of 75-100 mg. ACS patients who have received a loading dose of clopidogrel may be started on BRILINTA. BRILINTA can be administered with or without food. A patient who misses a dose of BRILINTA should take one 90 mg tablet (their next dose) at its scheduled time.

3 DOSAGE FORMS AND STRENGTHS
BRILINTA (ticagrelor) 90 mg is supplied as a round, biconvex, yellow, film-coated tablet marked with a “90” above “T” on one side.

4 CONTRAINDICATIONS
4.1 History of Intracranial Hemorrhage
BRILINTA is contraindicated in patients with a history of intracranial hemorrhage (ICH) because of a high risk of recurrent ICH in this population [see Clinical Studies (14)].

4.2 Active Bleeding
BRILINTA is contraindicated in patients with active pathological bleeding such as peptic ulcer or intracranial hemorrhage [see Warnings and Precautions (5.1) and Adverse Reactions (6.1)].

4.3 Severe Hepatic Impairment
BRILINTA is contraindicated in patients with severe hepatic impairment because of a probable increase in exposure, and it has not been studied in these patients. Severe hepatic impairment increases the risk of bleeding because of reduced synthesis of coagulation proteins [see Clinical Pharmacology (12.3)].

4.4 Hypersensitivity
BRILINTA is contraindicated in patients with hypersensitivity (e.g., angioedema) to ticagrelor or any component of the product [see Adverse Reactions (6.2)].

5 WARNINGS AND PRECAUTIONS
5.1 General Risk of Bleeding
Drugs that inhibit platelet function including BRILINTA increase the risk of bleeding. BRILINTA increased the overall risk of bleeding (Major + Minor) to a somewhat greater extent than did clopidogrel. The increase was seen for non-CABG-related bleeding, but not for CABG-related bleeding. Fatal and life-threatening bleeding rates were not increased [see Adverse Reactions (6.1)].

In general, risk factors for bleeding include older age, a history of bleeding disorders, performance of percutaneous invasive procedures, and concomitant use of medications that increase the risk of bleeding (e.g., anticoagulant and fibrinolytic therapy, higher doses of aspirin, and chronic nonsteroidal anti-inflammatory drugs [NSAIDs]). When possible, discontinue BRILINTA five days prior to surgery. Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, PCI, CABG, or other surgical procedures, even if the patient does not have any signs of bleeding.

If possible, manage bleeding without discontinuing BRILINTA. Stopping BRILINTA increases the risk of subsequent cardiovascular events [see Warnings and Precautions (5.5) and Adverse Reactions (6.1)].

5.2 Concomitant Aspirin Maintenance Dose
In PLATO, use of BRILINTA with maintenance doses of aspirin above 100 mg decreased the effectiveness of BRILINTA. Therefore, after the initial loading dose of aspirin (usually 325 mg), use BRILINTA with a maintenance dose of aspirin of 75-100 mg [see Dosage and Administration (2) and Clinical Studies (14)].

5.3 Moderate Hepatic Impairment
BRILINTA has not been studied in patients with moderate hepatic impairment. Consider the risks and benefits of treatment, noting the probable increase in exposure to ticagrelor.

5.4 Dyspnea
In PLATO, dyspnea was reported in 14% of patients treated with BRILINTA and in 8% of patients taking clopidogrel. Dyspnea was usually mild to moderate in intensity and often resolved during continued treatment, but occasionally required discontinuation (0.9% of patients taking BRILINTA versus 0.1% of patients taking clopidogrel). If a patient develops new, prolonged, or worsened dyspnea during treatment with BRILINTA, exclude underlying diseases that may require treatment. If dyspnea is determined to be related to BRILINTA, no specific treatment is required; continue BRILINTA without interruption. In the case of intolerable dyspnea requiring discontinuation of BRILINTA, consider prescribing another antiplatelet agent.

In a substudy, 199 patients from PLATO underwent pulmonary function testing irrespective of whether they reported dyspnea. There was no significant difference between treatment groups for FEV1. There was no indication of an adverse effect on pulmonary function assessed after one month or after at least 6 months of chronic treatment.

Figure 1 Kaplan-Meier estimate of time to first PLATO-defined ‘Total Major’ bleeding event.
As shown in Table 1, BRILINTA was associated with a somewhat greater risk of non-CABG bleeding than was clopidogrel. No baseline demographic or clinical characteristic altered the relative risk of bleeding with BRILINTA compared to clopidogrel. In PLATO, 1584 patients underwent CABG surgery. The percentages of those patients who bled are shown in Table 2. Rates were very high but similar for BRILINTA and clopidogrel.

### Table 1: Non-CABG related bleeds (KM%)

<table>
<thead>
<tr>
<th></th>
<th>BRILINTA N=9235</th>
<th>Clopidogrel N=8168</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Major + Minor</td>
<td>8.7</td>
<td>7.0</td>
</tr>
<tr>
<td>Major</td>
<td>4.5</td>
<td>3.8</td>
</tr>
<tr>
<td>Fatal/Life-threatening</td>
<td>2.1</td>
<td>1.9</td>
</tr>
<tr>
<td>Fatal</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Intracranial (Fatal/Life-threatening)</td>
<td>0.3</td>
<td>0.2</td>
</tr>
</tbody>
</table>

### Table 2: CABG bleeds (KM%)

<table>
<thead>
<tr>
<th>Patients with CABG</th>
<th>BRILINTA N=770</th>
<th>Clopidogrel N=814</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Major</td>
<td>85.8</td>
<td>86.9</td>
</tr>
<tr>
<td>Fatal/Life-threatening</td>
<td>48.1</td>
<td>47.9</td>
</tr>
<tr>
<td>Fatal</td>
<td>0.9</td>
<td>1.1</td>
</tr>
</tbody>
</table>

Although the platelet inhibition effect of BRILINTA has a faster offset than clopidogrel in vitro tests and BRILINTA is a reversibly binding P2Y12 inhibitor, PLATO did not show an advantage of BRILINTA compared to clopidogrel for CABG-related bleeding. When antplatelet therapy was stopped 5 days before CABG, major bleeding occurred in 75% of BRILINTA treated patients and 79% on clopidogrel.

No data exist with BRILINTA regarding a hemostatic benefit of platelet transfusions.

### Drug Discontinuation

In PLATO, the rate of study drug discontinuation attributed to adverse reactions was 7.4% for BRILINTA and 5.4% for clopidogrel. Bleeding caused permanent discontinuation of study drug in 2.3% of BRILINTA patients and 1.0% of clopidogrel patients. Dyspnea led to study drug discontinuation in 0.9% of BRILINTA and 0.1% of clopidogrel patients.

### Common Adverse Events

A variety of non-hemorrhagic adverse events occurred in PLATO at rates of 3% or more. These are shown in Table 3. In the absence of a placebo control, whether these are drug related cannot be determined in most cases, except where they are more common on BRILINTA or clearly related to the drug's pharmacologic effect (dyspnea).

### Table 3: Percentage of patients reporting non-hemorrhagic adverse events at least 3% or more in either group

<table>
<thead>
<tr>
<th></th>
<th>BRILINTA N=9235</th>
<th>Clopidogrel N=918</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea1</td>
<td>13.8</td>
<td>7.8</td>
</tr>
<tr>
<td>Headache</td>
<td>6.5</td>
<td>5.8</td>
</tr>
<tr>
<td>Cough</td>
<td>4.9</td>
<td>4.6</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4.5</td>
<td>3.9</td>
</tr>
<tr>
<td>Nausea</td>
<td>4.3</td>
<td>3.8</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>4.2</td>
<td>4.4</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3.8</td>
<td>4.0</td>
</tr>
<tr>
<td>Non-cardiac chest pain</td>
<td>3.7</td>
<td>3.3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3.7</td>
<td>3.3</td>
</tr>
<tr>
<td>Back pain</td>
<td>3.6</td>
<td>3.3</td>
</tr>
<tr>
<td>Hypotension</td>
<td>3.2</td>
<td>3.3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3.2</td>
<td>3.2</td>
</tr>
<tr>
<td>Chest pain</td>
<td>3.1</td>
<td>3.5</td>
</tr>
</tbody>
</table>

### Concomitant Therapy

BRILINTA can be used with antihypertensive or lipid-lowering drugs, and antiplatelet agents, including aspirin, clopidogrel, dipyridamole, or warfarin. BRILINTA is associated with a lower incidence of bleeding compared to clopidogrel in patients with diabetes, peripheral arterial disease, or chronic renal failure.

### 8. USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy

Pregnancy Category C: There are no adequate and well-controlled studies of BRILINTA use in pregnant women. In animals, ticagrelor caused structural abnormalities at maternal doses above 120 mg/kg/day. The lowest dose of approximately 2 mg/kg/day was observed in rats at 100 mg/kg/day during late gestation and lactation. Pup death and effects on pup growth were observed at 180 mg/kg/day (approximately 10 times the MRHD on a mg/m² basis). Relative minor effects such as delays in pinna unfolding and eye opening occurred at doses of 10 and 60 mg/kg (approximately one-half and 3.2 times the MRHD on a mg/m² basis).

#### 8.3 Nursing Mothers

It is not known whether ticagrelor or its active metabolites are excreted in human milk. Ticagrelor is excreted in rat milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from BRILINTA, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

#### 8.4 Pediatric Use

The safety and effectiveness of BRILINTA in pediatric patients have not been established.

#### 8.5 Geriatric Use

In PLATO, 43% of patients were ≥85 years of age and 15% were ≥75 years of age. The relative risk of bleeding was similar in both treatment and age groups. No overall differences in safety or effectiveness were observed between these patients and younger patients. While this clinical experience has not identified differences in responses between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out.

#### 8.6 Hepatic Impairment

BRILINTA has not been studied in the patients with moderate or severe hepatic impairment. Ticagrelor is metabolized by the liver and impaired hepatic function can increase risks for bleeding and other adverse events. Hence, BRILINTA is contraindicated for use in patients with severe hepatic impairment and its use should be considered carefully in patients with moderate hepatic impairment. No dosage adjustment is needed in patients with mild hepatic impairment [see Contraindications (4), Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)].

#### 8.7 Renal Impairment

No dosage adjustment is needed in patients with renal impairment. Patients receiving dialysis have not been studied [see Clinical Pharmacology (12.3)].

#### 10 OVERDOSAGE

There is currently no known treatment to reverse the effects of BRILINTA, and ticagrelor is not expected to be dialyzable. Treatment of overdose should follow local standard medical practice. Bleeding is the expected pharmacologic effect of overdosage. If bleeding occurs, appropriate supportive measures should be taken.

Other effects of overdose may include gastrointestinal effects (nausea, vomiting, diarrhea) or ventricular pauses. Monitor the ECG.
BRILINTA contains ticagrelor, a cyclopytriazolopyrimidine, inhibitor of platelet activation and aggregation mediated by the P2Y_12 ADP-receptor. Chemically, it is \( (1S,2S,3R,5S)-3-[(1R,2S)-2-(3,4-difluorophenyl)cyclopropyl][amino]-5-(propyliothio)-3H[1,2,3]-triazolo[4,5-y]-5-(2-hydroxyethoxy)cyclopentane-1,2-diol \). The empirical formula of ticagrelor is \( C_{23}H_{28}F_2N_6O_4S \) and its molecular weight is 522.57. The chemical structure of ticagrelor is:

\[
\text{HO}
\]

\[
\text{HO}
\]

\[
\text{HO}
\]

\[
\text{HO}
\]

\[
\text{HO}
\]

Ticagrelor is a crystalline powder with an aqueous solubility of approximately 10 µg/mL at room temperature.

BRILINTA tablets for oral administration contain 90 mg of ticagrelor and the following ingredients: mannitol, dibasic calcium phosphate, sodium starch glycolate, hydroxypropyl cellulose, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, talc, polyethylene glycol 400, and ferric oxide yellow.

### 12. CLINICAL PHARMACOLOGY

#### 12.1 Mechanism of Action

Ticagrelor and its major metabolite reversibly interact with the platelet P2Y_12 ADP receptor to prevent signal transduction and platelet activation. Ticagrelor and its active metabolite are approximately equipotent.

#### 12.2 Pharmacodynamics

The inhibition of platelet aggregation (IPA) by ticagrelor and clopidogrel was compared in a 6 week study examining both acute and chronic platelet inhibition effects in response to 20 µM ADP as the platelet aggregation agonist.

The onset of IPA was evaluated on Day 1 of the study following loading doses of 180 mg ticagrelor or 600 mg clopidogrel. As shown in Figure 2, IPA was higher in the ticagrelor group at all time points. The maximum IPA effect of ticagrelor was reached at around 2 hours, and was maintained for at least 8 hours.

The offset of IPA was examined after 6 weeks on ticagrelor 90 mg twice daily or clopidogrel 75 mg daily, again in response to 20 µM ADP.

As shown in Figure 3, mean maximum IPA following the last dose of ticagrelor was 88% and 62% for clopidogrel. The insert in Figure 3 shows that after 24 hours, IPA in the ticagrelor group (58%) was similar to IPA in clopidogrel group (52%), indicating that patients who miss a dose of ticagrelor would still maintain IPA similar to the trough IPA of patients treated with clopidogrel. After 5 days, IPA in the ticagrelor group was similar to IPA in the placebo group. It is not known how either bleeding risk or thrombotic risk track with IPA, for either ticagrelor or clopidogrel.

Transitioning from clopidogrel to BRILINTA resulted in an absolute IPA increase of 26.4% and from BRILINTA to clopidogrel resulted in an absolute IPA decrease of 24.5%. Patients can be transitioned from clopidogrel to BRILINTA without interruption of antiplatelet effect [see Dosage and Administration (2)].

#### 12.3 Pharmacokinetics

Ticagrelor demonstrates dose proportional pharmacokinetics, which are similar in patients and healthy volunteers.

**Absorption**

Absorption of ticagrelor occurs with a median \( t_{\text{max}} \) of 1.5 h (range 1.0–4.0). The formation of the major circulating metabolite AR-124910XX (active) from ticagrelor occurs with a median \( t_{\text{max}} \) of 2.5 h (range 1.5–5.0).

The mean absolute bioavailability of ticagrelor is about 36%, (range 30%-42%). Ingestion of a high-fat meal had no effect on ticagrelor \( C_{\text{max}} \), but resulted in a 21% increase in AUC. The \( C_{\text{max}} \) of its major metabolite was decreased by 22% with no change in AUC. BRILINTA can be taken with or without food.

**Distribution**

The steady state volume of distribution of ticagrelor is 88 L. Ticagrelor and the active metabolite are extensively bound to human plasma proteins (>99%).

**Metabolism**

CYP3A4 is the major enzyme responsible for ticagrelor metabolism and the formation of its major active metabolite. Ticagrelor and its major active metabolite are weak P-glycoprotein substrates and inhibitors. The systemic exposure to the active metabolite is approximately 30–40% of the exposure of ticagrelor.

**Excretion**

The primary route of ticagrelor elimination is hepatic metabolism. When radiolabeled ticagrelor is administered, the mean recovery of radioactivity is approximately 84% (58% in feces, 26% in urine). Recoveries of ticagrelor and the active metabolite in urine were both less than 1% of the dose. The primary route of elimination for the major metabolite of ticagrelor is most likely to be biliary secretion. The mean \( t_{1/2} \) is approximately 7 hours for ticagrelor and 9 hours for the active metabolite.

**Special Populations**

The effects of age, gender, ethnicity, renal impairment and mild hepatic impairment on the pharmacokinetics of ticagrelor are presented in Figure 4. Effects are modest and do not require dose adjustment.

---

**Figure 2** Mean inhibition of platelet aggregation (±SE) following single oral doses of placebo, 180 mg ticagrelor, or 600 mg clopidogrel

**Figure 3** Mean inhibition of platelet aggregation (IPA) following 6 weeks on placebo, ticagrelor 90 mg twice daily, or clopidogrel 75 mg daily

---

BRILINTA® (ticagrelor) Tablets
Pediatric

Ticagrelor has not been evaluated in a pediatric population [see Use in Specific Populations (8.4)].

Body Weight

No dose adjustment is necessary for ticagrelor based on weight.

Smoking

Habitual smoking increased population mean clearance of ticagrelor by approximately 22% when compared to non-smokers. No dose adjustment is necessary for ticagrelor based on smoking status.

Effects of Other Drugs on BRILINTA

CYP3A4 is the major enzyme responsible for ticagrelor metabolism and the formation of its major active metabolite. The effects of other drugs on the pharmacokinetics of ticagrelor are presented in Figure 5 as change relative to ticagrelor given alone (test/reference). Strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, and clarithromycin) substantially increase ticagrelor exposure. Moderate CYP3A inhibitors have lesser effects (e.g., diltiazem). CYP3A inducers (e.g., rifampin) substantially reduce ticagrelor blood levels.

Effects of BRILINTA on Other Drugs

In vitro metabolism studies demonstrate that ticagrelor and its major active metabolite are weak inhibitors of CYP3A4, potential activators of CYP3A4 and inhibitors of the P-gp transporter. Ticagrelor and AR-C124910XX were shown to have no inhibitory effect on human CYP1A2, CYP2C19, and CYP2E1 activity. For specific in vivo effects on the pharmacokinetics of simvastatin, atorvastatin, ethinyl estradiol, levonorgesterol, tolbutamide, and digoxin, see Figure 6.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Ticagrelor was not carcinogenic in the mouse at doses up to 250 mg/kg/day or in the male rat at doses up to 120 mg/kg/day (19 and 15 times the MRHD of 90 mg twice daily on the basis of AUC, respectively). Uterine carcinomas, uterine adenocarcinomas and hepatocellular adenomas were seen in female rats at doses of 180 mg/kg/day (29-fold the maximally recommended dose of 90 mg twice daily on the basis of AUC), whereas 60 mg/kg/day (8-fold the MRHD based on AUC) was not carcinogenic in female rats.

Mutagenesis

Ticagrelor did not demonstrate genotoxicity when tested in the Ames bacterial mutagenicity test, mouse lymphoma assay and the rat micronucleus test. The active O-demethylated metabolite did not demonstrate genotoxicity in the Ames assay and mouse lymphoma assay.

Impairment of Fertility

Ticagrelor had no effect on male fertility at doses up to 180 mg/kg/day or on female fertility at doses up to 200 mg/kg/day (>15-fold the MRHD on the basis of AUC). Doses of ≥210 mg/kg/day given to female rats caused an increased incidence of irregular duration estrus cycles (1.5-fold the MRHD based on AUC).

14 CLINICAL STUDIES

The clinical evidence for the effectiveness of BRILINTA is derived from PLATO, a randomized double-blind study comparing BRILINTA (N=9333) to clopidogrel (N=9291), both given in combination with aspirin and other standard therapy, in patients with acute coronary syndromes (ACS). Patients were treated for at least 6 months and for up to 12 months. Study endpoints were obtained until the study was complete, even if drug was discontinued.

Patients who presented within 24 hours of onset of the most recent episode of chest pain or symptoms were randomized to receive BRILINTA or clopidogrel. Patients who had already been treated with clopidogrel could be enrolled and randomized to either study treatment. Patients could be included whether there was intent to manage the ACS medically or invasively, but patient randomization was not stratified by this intent. Subjects in the clopidogrel arm were treated with an initial loading dose of clopidogrel 300 mg, if previous clopidogrel therapy had not been given prior to...
randomization. Patients undergoing PCI could receive an additional 300 mg of clopidogrel at investigator discretion. All subjects randomized to BRILINTA received a loading dose of 180 mg followed by a maintenance dose of 90 mg twice daily. Concomitant aspirin was recommended at a loading dose of 160-500 mg. A daily maintenance dose of aspirin 75-100 mg was recommended, but higher maintenance doses of aspirin were allowed according to local judgment. Because of ticagrelor’s metabolism by CYP3A enzymes, the protocol recommended limiting the maximum dosage of simvastatin and lovastatin to 40 mg in both study arms. Because of an increased bleeding risk, the study excluded patients with previous intracranial hemorrhage, a gastrointestinal bleed within the past 6 months, or other factors that predispose to bleeding.

PLATO patients were predominantly male (72%) and Caucasian (92%). About 43% of patients were >65 years and 15% were >75 years.

The study’s primary endpoint was the composite of first occurrence of cardiovascular death, non-fatal MI (excluding silent MI), or non-fatal stroke. The components were assessed as secondary endpoints.

Median exposure to study drug was 277 days. About half of the patients received pre-study clopidogrel and about 99% of the patients received aspirin at some time during PLATO. About 35% of patients were receiving a statin at baseline and 93% received a statin sometime during PLATO.

Table 4 shows the study results for the primary composite endpoint and the contribution of each component to the primary endpoint. Separate secondary endpoint analyses are shown for the overall occurrence of CV death, MI, and stroke and overall mortality.

The difference between treatments on the composite resulted from effects on CV death and MI; each was statistically significant when considered as a secondary endpoint and there was no beneficial effect on strokes. For all-cause mortality the benefit was also statistically significant (p = 0.0003) with a hazard ratio of 0.78.

Among 11289 patients with PCI receiving any stent during PLATO, there was a lower risk of stent thrombosis (1.3% for adjudicated “definite”) than with clopidogrel (1.9%) (HR 0.67, 95% CI 0.50-0.91; p=0.0091). The results were similar for drug-eluting and bare metal stents.

The Kaplan-Meier curve (Figure 7) shows time to first occurrence of the primary composite endpoint of CV death, non-fatal MI or non-fatal stroke in the overall study. The curves separate by 30 days (RRR 12%) and continue to diverge throughout the 12 month treatment period (RRR 16%).

A wide range of demographic, concurrent baseline medications, and other treatment differences were examined for their influence on outcome. Many of these are shown in Figure 8. Such analyses must be interpreted cautiously, as differences can reflect the play of chance among a large number of analyses. Most of the analyses show effects consistent with the overall results, but there are two marked exceptions: a finding of heterogeneity by region and a strong influence of concomitant aspirin dose. These are considered further below.

Most of the characteristics shown are baseline characteristics, but some reflect post-randomization determinations (e.g., final diagnosis, aspirin maintenance dose, use of PCI). Patients were not stratified by initial diagnosis, but the effect in the unstable angina subset (determined after randomization) appeared smaller than the effect in the NSTE MI and STEMI subsets. The results in the subsets based on final diagnosis (STEMI, NSTEMI and unstable angina) are also presented in Figure 8.

Regional Differences

Results in the rest of the world compared to effects in North America (US and Canada) show a smaller effect in North America, numerically inferior to the control and driven by the US subset. The statistical test for the US/non-US comparison is statistically significant (p<0.009), and the same trend is present for both CV death and non-fatal MI. The individual results and nominal p-values, like all subset analyses, need cautious interpretation, and they could represent chance findings of heterogeneity by region and a strong influence of concomitant aspirin dose. These are considered further below.

### Table 4 Patients with Outcome Events, in PLATO (KM%)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>BRILINTA</th>
<th>Clopidogrel</th>
<th>Hazard Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death</td>
<td>9.8</td>
<td>11.7</td>
<td>0.84 (0.77, 0.92)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Ml death</td>
<td>2.9</td>
<td>4.0</td>
<td>0.74</td>
<td></td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>5.8</td>
<td>6.9</td>
<td>0.84</td>
<td></td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>1.4</td>
<td>1.1</td>
<td>1.24</td>
<td></td>
</tr>
</tbody>
</table>

**Secondary endpoints**

<table>
<thead>
<tr>
<th>Event</th>
<th>Hazard Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death</td>
<td>0.79 (0.69, 0.91)</td>
<td>0.0013</td>
</tr>
<tr>
<td>Ml</td>
<td>0.84 (0.75, 0.95)</td>
<td>0.0045</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.17 (0.91, 1.52)</td>
<td>0.22</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0.78 (0.69, 0.89)</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

1. First occurrence of specified event at any time 2. Including patients who could have had other non-fatal events or died

### Figure 7 Time to First Occurrence of CV Death, MI, or Stroke in PLATO

The Kaplan-Meier curve (Figure 7) shows time to first occurrence of the primary composite endpoint of CV death, non-fatal MI or non-fatal stroke in the overall study. The curves separate by 30 days (RRR 12%) and continue to diverge throughout the 12 month treatment period (RRR 16%).

A wide range of demographic, concurrent baseline medications, and other treatment differences were examined for their influence on outcome. Many of these are shown in Figure 8. Such analyses must be interpreted cautiously, as differences can reflect the play of chance among a large number of analyses. Most of the analyses show effects consistent with the overall results, but there are two marked exceptions: a finding of heterogeneity by region and a strong influence of concomitant aspirin dose. These are considered further below.

Most of the characteristics shown are baseline characteristics, but some reflect post-randomization determinations (e.g., final diagnosis, aspirin maintenance dose, use of PCI). Patients were not stratified by initial diagnosis, but the effect in the unstable angina subset (determined after randomization) appeared smaller than the effect in the NSTEMI and STEMI subsets. The results in the subsets based on final diagnosis (STEMI, NSTEMI and unstable angina) are also presented in Figure 8.

Regional Differences

Results in the rest of the world compared to effects in North America (US and Canada) show a smaller effect in North America, numerically inferior to the control and driven by the US subset. The statistical test for the US/non-US comparison is statistically significant (p<0.009), and the same trend is present for both CV death and non-fatal MI. The individual results and nominal p-values, like all subset analyses, need cautious interpretation, and they could represent chance findings of heterogeneity by region and a strong influence of concomitant aspirin dose. These are considered further below.
findings. The consistency of the differences in both the CV mortality and non-fatal MI components, however, supports the possibility that the finding is reliable.

A wide variety of baseline and procedural differences between the US and non-US (including intended invasive vs. planned medical management, use of GPIIb/IIIa inhibitors, use of drug eluting vs. bare-metal stents) were examined to see if they could account for regional differences, but with one exception, aspirin maintenance dose, these differences did not appear to lead to differences in outcome.

Aspirin Dose

The PLATO protocol left the choice of aspirin maintenance dose up to the investigator and use patterns were very different in the US and elsewhere, with about 8% of non-US investigators using aspirin doses above 100 mg, and about 2% using doses above 300 mg, in contrast with US practice, where 57% of patients received doses above 100 mg and 54% received doses above 300 mg. Overall results favored BRILINTA when used with low maintenance doses (≤100 mg) of aspirin, and results analyzed by aspirin dose were similar in the US and elsewhere. Figure 8 shows overall results by median aspirin dose. Table 5 shows results by dose.

Like any unplanned subset analysis, especially one where the characteristic is not a true baseline characteristic (but may be determined by usual investigator practice), the above analyses must be treated with caution. It is notable, however, that aspirin dose predicts outcome in both regions with a similar pattern, and that the pattern is similar for the two major components of the primary endpoint, CV death and non-fatal MI.

Despite the need to treat such results cautiously, there appears to be good reason to restrict aspirin maintenance dosage accompanying ticagrelor to 100 mg. Higher doses do not have an established benefit in the ACS setting, and there is a strong suggestion that use of such doses reduces the effectiveness of BRILINTA.

Pharmacogenetics

In a genetic substudy of PLATO (n=10,285), the effects of BRILINTA compared to clopidogrel on thrombotic events and bleeding were not significantly affected by CYP2C19 genotype.

16 HOW SUPPLIED/STORAGE AND HANDLING

BRILINTA (ticagrelor) 90 mg is supplied as a round, biconvex, yellow, film-coated tablet marked with a “90” above “T” on one side.

Bottles of 60 – NDC 0186-0777-60
Bottles of 180 – NDC 0186-0777-18
100 count Hospital Unit Dose – NDC 0186-0777-39

Storage and Handling

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP controlled room temperature].

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide)

17.1 Benefits and Risks

• Tell patients to take BRILINTA exactly as prescribed.
• Inform patients not to discontinue BRILINTA without discussing it with the prescribing physician.
• Tell patients daily doses of aspirin should not exceed 100 mg and to avoid taking any other medications that contain aspirin.
• Tell patients to read the Medication Guide.

17.2 Bleeding

Inform patients that they:
• Will bleed and bruise more easily
• Will take longer than usual to stop bleeding
• Should report any unanticipated, prolonged or excessive bleeding, or blood in their stool or urine.

17.3 Other Signs and Symptoms Requiring Medical Attention

Inform patients that BRILINTA can cause shortness of breath. Tell them to contact their doctor if they experience unexpected shortness of breath, especially if severe.

17.4 Invasive Procedures

Instruct patients to:
• 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.

17.5 Concomitant Medications

Tell patients to list all prescription medications, over-the-counter medications or dietary supplements they are taking or plan to take so the physician knows about other treatments that may affect bleeding risk (e.g. warfarin, heparin).
What is the most important information I should know about BRILINTA?

BRILINTA is used to lower your chance of having a heart attack or dying from a heart attack or stroke. But BRILINTA (and similar drugs) can cause bleeding that can be serious and sometimes lead to death. In cases of serious bleeding, such as internal bleeding, the bleeding may result in the need for blood transfusions or surgery. While you take BRILINTA:

- you may bruise and bleed more easily
- you are more likely to have nose bleeds
- it will take longer than usual for any bleeding to stop

Call your doctor right away, if you have any of these signs or symptoms of bleeding while taking BRILINTA:

- bleeding that is severe or that you cannot control
- pink, red or brown urine
- vomiting blood or your vomit looks like “coffee grounds”
- red or black stools (looks like tar)
- coughing up blood or blood clots

Do not stop taking BRILINTA without talking to the doctor who prescribes it for you. People who are treated with a stent, and stop taking BRILINTA too soon, have a higher risk of getting a blood clot in the stent, having a heart attack, or dying. If you stop BRILINTA because of bleeding, or for other reasons, your risk of a heart attack or stroke may increase.

When instructed by your doctor, you should stop taking BRILINTA 5 days before you have elective surgery. This will help to decrease your risk of bleeding with your surgery or procedure. Your doctor should tell you when to start taking BRILINTA again, as soon as possible after surgery.

Taking BRILINTA with aspirin

BRILINTA is taken with aspirin. Talk to your doctor about the dose of aspirin that you should take with BRILINTA. You should not take a dose of aspirin higher than 100 mg daily because it can affect how well BRILINTA works. Do not take doses of aspirin higher than what your doctor tells you to take. Tell your doctor if you take other medicines that contain aspirin, and do not take new over-the-counter medicines with aspirin in them.

What is BRILINTA?

BRILINTA is a prescription medicine used to treat people who:

- have had a recent heart attack or severe chest pain that happened because their heart was not getting enough oxygen.
- have had a heart attack or chest pain and are being treated with medicines or with a procedure to open blocked arteries in the heart.

BRILINTA is used with aspirin to lower your chance of having another serious problem with your heart or blood vessels, such as heart attack, stroke, or blood clots in your stent. These can be fatal. Platelets are blood cells that help with normal blood clotting. BRILINTA helps prevent platelets from sticking together and forming a clot that can block an artery.

It is not known if BRILINTA is safe and effective in children.

Who should not take BRILINTA?

Do not take BRILINTA if you:

- are bleeding now
- have a history of bleeding in the brain
- have bleeding from your stomach or intestine now (an ulcer)
- have severe liver problems
- are allergic to ticagrelor or any of the ingredients in BRILINTA. See the end of this Medication Guide for a complete list of ingredients in BRILINTA.

What should I tell my doctor before taking BRILINTA?

Before you take BRILINTA, tell your doctor if you:

- have had bleeding problems in the past
- have had any recent serious injury or surgery
- plan to have surgery or a dental procedure
- have a history of stomach ulcers or colon polyps
- have lung problems, such as COPD or asthma
- have liver problems
- have a history of stroke
- are pregnant or plan to become pregnant. It is not known if BRILINTA will harm your unborn baby. You and your doctor should decide if you will take BRILINTA.
• are breastfeeding or plan to breastfeeding. It is not known if BRILINTA passes into your breast milk. You and your doctor should decide if you will take BRILINTA or breastfeed. You should not do both without talking with your doctor.

Tell all of your doctors and dentists that you are taking BRILINTA. They should talk to the doctor who prescribed BRILINTA for you before you have any surgery or invasive procedure.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

BRILINTA may affect the way other medicines work, and other medicines may affect how BRILINTA works.

Especially tell your doctor if you take:

• an HIV-AIDS medicine
• medicine for heart conditions or high blood pressure
• medicine for high blood cholesterol levels
• an anti-fungal medicine by mouth
• an anti-seizure medicine
• a blood thinner medicine
• rifampin (Rifater, Rifamate, Rimactane, Rifadin)

Ask your doctor or pharmacist if you are not sure if your medicine is listed above.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I take BRILINTA?

• Take BRILINTA exactly as prescribed by your doctor.
• Your doctor will tell you how many BRILINTA tablets to take and when to take them.
• Take BRILINTA with a low dose (not more than 100 mg daily) of aspirin. You may take BRILINTA with or without food.
• Take your doses of BRILINTA around the same time every day.
• If you forget to take your scheduled dose of BRILINTA, take your next dose at its scheduled time. Do not take two doses at the same time unless your doctor tells you to.
• If you take too much BRILINTA or overdose, call your doctor or poison control center right away, or go to the nearest emergency room.

What are the possible side effects of BRILINTA?

BRILINTA can cause serious side effects, including:

• See “What is the most important information I should know about BRILINTA?”

• Shortness of breath. Call your doctor if you have new or unexpected shortness of breath when you are at rest, at night, or when you are doing any activity. Your doctor can decide what treatment is needed.

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all of the possible side effects of BRILINTA. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store BRILINTA?

• Store BRILINTA at room temperature between 68°F to 77°F (20°C to 25°C).

Keep BRILINTA and all medicines out of the reach of children.

General information about BRILINTA

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use BRILINTA for a condition for which it was not prescribed. Do not give BRILINTA to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about BRILINTA. If you would like more information about BRILINTA, talk with your doctor. You can ask your pharmacist or doctor for information about BRILINTA that is written for health professionals.

For more information call 1-800-236-9933 or go to www.Brilinta.com.

What are the ingredients in BRILINTA?

Active ingredient: ticagrelor

Inactive ingredients: mannitol, dibasic calcium phosphate, sodium starch glycolate, hydroxypropyl cellulose, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, talc, polyethylene glycol 400, and ferric oxide yellow.