

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**022433Orig1s000**

**LABELING**

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use BRILINTA safely and effectively. See full prescribing information for BRILINTA.

BRILINTA™ (ticagrelor) tablets, for oral use  
Initial U.S. Approval: 2011

**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).

**-----INDICATIONS AND USAGE-----**

BRILINTA is a P2Y<sub>12</sub> platelet inhibitor indicated to reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) (unstable angina, non-ST elevation myocardial infarction, or ST elevation myocardial infarction). BRILINTA has been shown to reduce the rate of a combined endpoint of cardiovascular death, myocardial infarction, or stroke compared to clopidogrel. The difference between treatments was driven by CV death and MI with no difference in stroke. In patients treated with PCI, it also reduces the rate of stent thrombosis. (1)

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. (1, 5.2, 14).

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**-----DOSAGE 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)

**-----DOSAGE FORMS AND STRENGTHS-----**

- 90 mg tablets (3)

**-----CONTRAINDICATIONS-----**

- History of intracranial hemorrhage (4.1)
- Active pathological bleeding (4.2)
- Severe hepatic impairment (4.3)

**-----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)

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Revised: 07/2011

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## 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

### Acute Coronary Syndromes

BRILINTA is a P2Y<sub>12</sub> platelet inhibitor indicated to reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) (unstable angina, non-ST elevation myocardial infarction, or ST elevation myocardial infarction). BRILINTA has been shown to reduce the rate of a combined endpoint of cardiovascular death, myocardial infarction or stroke compared to clopidogrel. The difference between treatments was driven by CV death and MI with no difference in stroke. In patients treated with PCI, it also reduces the rate of stent thrombosis [*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)*].

### **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**

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. 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 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 FEV<sub>1</sub>. There was no indication of an adverse effect on pulmonary function assessed after one month or after at least 6 months of chronic treatment.

## **5.5 Discontinuation of BRILINTA**

Avoid interruption of BRILINTA treatment. If BRILINTA must be temporarily discontinued (e.g., to treat bleeding or for elective surgery), restart it as soon as possible. Discontinuation of BRILINTA will increase the risk of myocardial infarction, stent thrombosis, and death.

## **5.6 Strong Inhibitors of Cytochrome CYP3A**

Ticagrelor is metabolized by CYP3A4/5. Avoid use with strong CYP3A inhibitors, such as atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole [*see Drug Interactions (7.1) and Clinical Pharmacology (12.3)*].

## **5.7 Cytochrome CYP3A Potent Inducers**

Avoid use with potent CYP3A inducers, such as rifampin, dexamethasone, phenytoin, carbamazepine, and phenobarbital [*see Drug Interactions (7.2), and Clinical Pharmacology (12.3)*].

# **6 ADVERSE REACTIONS**

## **6.1 Clinical Trials Experience**

The following adverse reactions are also discussed elsewhere in the labeling:

- Dyspnea [see Warnings and Precautions (5.4)]

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

BRILINTA has been evaluated for safety in more than 10000 patients, including more than 3000 patients treated for more than 1 year.

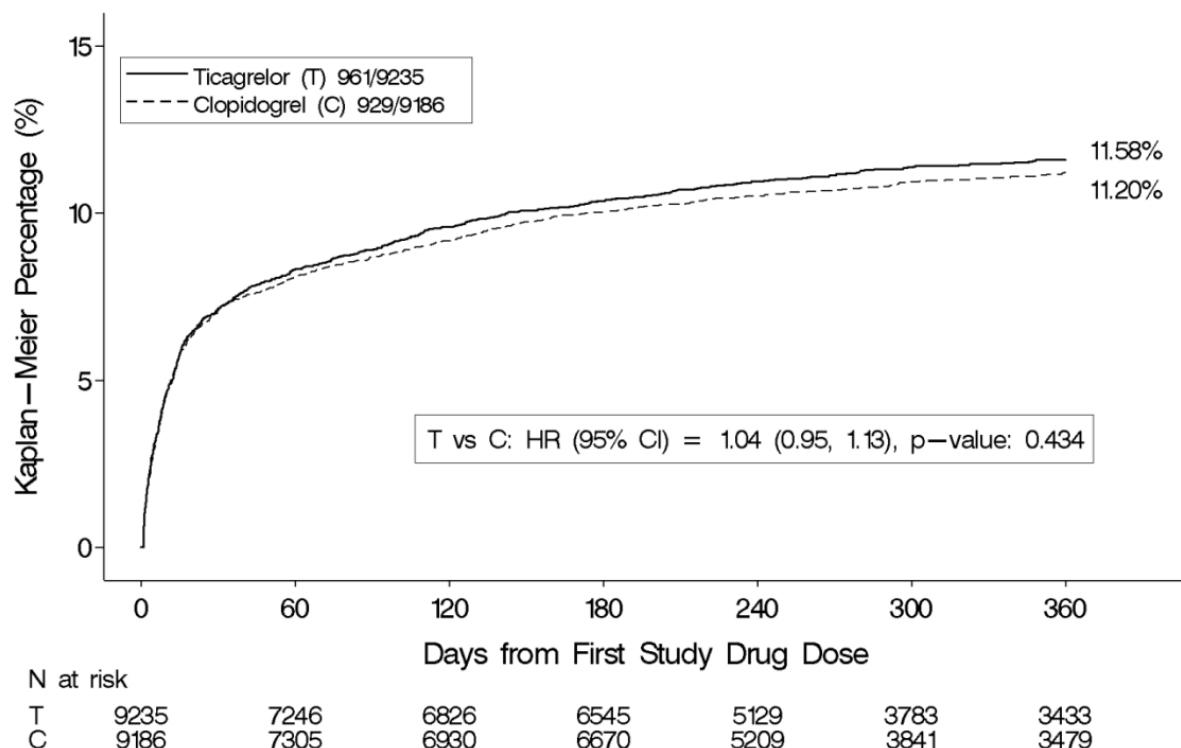
### Bleeding

PLATO used the following bleeding severity categorization:

- Major bleed – fatal/life-threatening. Any one of the following: fatal; intracranial; intrapericardial bleed with cardiac tamponade; hypovolemic shock or severe hypotension due to bleeding and requiring pressors or surgery; clinically overt or apparent bleeding associated with a decrease in hemoglobin (Hb) of more than 5 g/dL; transfusion of 4 or more units (whole blood or packed red blood cells (PRBCs)) for bleeding.
- Major bleed – other. Any one of the following: significantly disabling (e.g., intraocular with permanent vision loss); clinically overt or apparent bleeding associated with a decrease in Hb of 3 g/dL; transfusion of 2-3 units (whole blood or PRBCs) for bleeding.
- Minor bleed. Requires medical intervention to stop or treat bleeding (e.g., epistaxis requiring visit to medical facility for packing).
- Minimal bleed. All others (e.g., bruising, bleeding gums, oozing from injection sites, etc.) not requiring intervention or treatment.

Figure 1 shows major bleeding events over time. Many events are early, at a time of coronary angiography, PCI, CABG, and other procedures, but the risk persists during later use of antiplatelet therapy.

**Figure 1 - Kaplan-Meier estimate of time to first PLATO-defined ‘Total Major’ bleeding event**



Annualized rates of bleeding are summarized in Table 1 below. About half of the bleeding events were in the first 30 days.

**Table 1 - Non-CABG related bleeds (KM%)**

	<b>BRILINTA</b> N=9235	<b>Clopidogrel</b> N=9186
Total (Major + Minor)	8.7	7.0
Major	4.5	3.8
Fatal/Life-threatening	2.1	1.9
Fatal	0.2	0.2
Intracranial (Fatal/Life-threatening)	0.3	0.2

As shown in Table 1, BRILINTA was associated with a somewhat greater risk of non-CABG bleeding than was clopidogrel. No baseline demographic factor 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 2 –CABG bleeds (KM%)**

	Patients with CABG	
	BRILINTA N=770	Clopidogrel N=814
Total Major	85.8	86.9
Fatal/Life-threatening	48.1	47.9
Fatal	0.9	1.1

Although the platelet inhibition effect of BRILINTA has a faster offset than clopidogrel in *in vitro* tests and BRILINTA is a reversibly binding P2Y<sub>12</sub> inhibitor, PLATO did not show an advantage of BRILINTA compared to clopidogrel for CABG-related bleeding. When antiplatelet 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**

	<b>BRILINTA N=9235</b>	<b>Clopidogrel N=9186</b>
Dyspnea <sup>a</sup>	13.8	7.8
Headache	6.5	5.8
Cough	4.9	4.6
Dizziness	4.5	3.9
Nausea	4.3	3.8
Atrial fibrillation	4.2	4.6
Hypertension	3.8	4.0
Non-cardiac chest pain	3.7	3.3
Diarrhea	3.7	3.3
Back pain	3.6	3.3
Hypotension	3.2	3.3
Fatigue	3.2	3.2
Chest pain	3.1	3.5

<sup>a</sup>Includes: dyspnea, dyspnea exertional, dyspnea at rest, nocturnal dyspnea, dyspnea paroxysmal nocturnal

#### Bradycardia

In clinical studies BRILINTA has been shown to increase the occurrence of Holter-detected bradyarrhythmias (including ventricular pauses). PLATO excluded patients at increased risk of bradycardic events (e.g., patients who have sick sinus syndrome, 2nd or 3rd degree AV block, or bradycardic-related syncope and not protected with a pacemaker). In PLATO, syncope, pre-syncope and loss of consciousness were reported by 1.7% and 1.5% of BRILINTA and clopidogrel patients, respectively.

In a Holter substudy of about 3000 patients in PLATO, more patients had ventricular pauses with BRILINTA (6.0%) than with clopidogrel (3.5%) in the acute phase; rates were 2.2% and 1.6% respectively after 1 month.

#### Gynecomastia

In PLATO, gynecomastia was reported by 0.23% of men on BRILINTA and 0.05% on clopidogrel.

Other sex-hormonal adverse reactions, including sex organ malignancies, did not differ between the two treatment groups in PLATO.

#### Lab abnormalities

##### Serum Uric Acid:

Serum uric acid levels increased approximately 0.6 mg/dL from baseline on BRILINTA and approximately 0.2 mg/dL on clopidogrel in PLATO. The difference disappeared within 30 days of discontinuing treatment. Reports of gout did not differ between treatment groups in PLATO (0.6% in each group).

##### Serum Creatinine:

In PLATO, a >50% increase in serum creatinine levels was observed in 7.4% of patients receiving BRILINTA compared to 5.9% of patients receiving clopidogrel. The increases typically did not progress with ongoing treatment and often decreased with continued therapy. Evidence of reversibility upon discontinuation was observed even in those with the greatest on treatment increases. Treatment groups in PLATO did not differ for renal-related serious adverse events such as acute renal failure, chronic renal failure, toxic nephropathy, or oliguria.

## **7 DRUG INTERACTIONS**

### Effects of other drugs

Ticagrelor is predominantly metabolized by CYP3A4 and to a lesser extent by CYP3A5.

### **7.1 CYP3A inhibitors**

Avoid use of strong inhibitors of CYP3A (e.g., ketoconazole, itraconazole, voriconazole, clarithromycin, nefazodone, ritonavir, saquinavir, nelfinavir, indinavir, atazanavir and telithromycin) [*see Warnings and Precautions (5.6) and Clinical Pharmacology (12.3)*].

### **7.2 CYP3A inducers**

Avoid use with potent inducers of CYP3A (e.g., rifampin, dexamethasone, phenytoin, carbamazepine and phenobarbital) [*see Warnings and Precautions (5.7) and Clinical Pharmacology (12.3)*].

### **7.3 Aspirin**

Use of BRILINTA with aspirin maintenance doses above 100 mg reduced the effectiveness of BRILINTA [*see Warnings and Precautions (5.2) and Clinical Studies (14)*].

### Effect of BRILINTA on other drugs

Ticagrelor is an inhibitor of CYP3A4/5 and the P-glycoprotein transporter.

### **7.4 Simvastatin, lovastatin**

BRILINTA will result in higher serum concentrations of simvastatin and lovastatin because these drugs are metabolized by CYP3A4. Avoid simvastatin and lovastatin doses greater than 40 mg [*see Clinical Pharmacology (12.3)*].

### **7.5 Digoxin**

*Digoxin:* Because of inhibition of the P-glycoprotein transporter, monitor digoxin levels with initiation of or any change in BRILINTA therapy [*see Clinical Pharmacology (12.3)*].

### **7.6 Other Concomitant Therapy**

BRILINTA can be administered with unfractionated or low-molecular-weight heparin, GPIIb/IIIa inhibitors, proton pump inhibitors, beta-blockers, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers.

## **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 animal studies, ticagrelor caused structural abnormalities at maternal doses about 5 to 7 times the maximum recommended human dose (MRHD) based on body surface area. BRILINTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In reproductive toxicology studies, pregnant rats received ticagrelor during organogenesis at doses from 20 to 300 mg/kg/day. The lowest dose was approximately the same as the MRHD of 90 mg twice daily for a 60 kg human on a mg/m<sup>2</sup> basis. Adverse outcomes in offspring occurred at doses of 300 mg/kg/day (16.5 times the MRHD on a mg/m<sup>2</sup> basis) and included supernumerary liver lobe and ribs, incomplete ossification of sternbrae, displaced articulation of pelvis, and misshapen/misaligned sternbrae. When pregnant rabbits received ticagrelor during organogenesis at doses from 21 to 63 mg/kg/day, fetuses exposed to the highest maternal dose of 63 mg/kg/day (6.8 times the MRHD on a mg/m<sup>2</sup> basis) had delayed gall bladder development and incomplete ossification of the hyoid, pubis and sternbrae occurred.

In a prenatal/postnatal study, pregnant rats received ticagrelor at doses of 10 to 180 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/m<sup>2</sup> basis). Relatively 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/m<sup>2</sup> 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 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 ≥65 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)*].

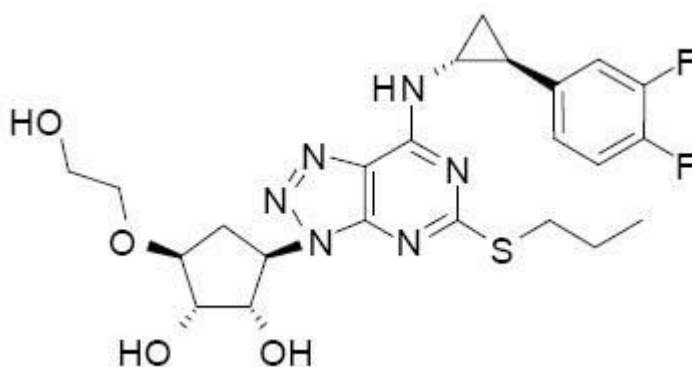
## 10 OVERDOSAGE

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 overdosing. 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.

## 11 DESCRIPTION

BRILINTA contains ticagrelor, a cyclopentyltriazolopyrimidine, inhibitor of platelet activation and aggregation mediated by the P2Y<sub>12</sub> ADP-receptor. Chemically it is (1*S*,2*S*,3*R*,5*S*)-3-[7-[(1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl]amino]-5-(propylthio)-3*H*-[1,2,3]-triazolo[4,5-*d*]pyrimidin-3-yl]-5-(2-hydroxyethoxy)cyclopentane-1,2-diol. The empirical formula of ticagrelor is C<sub>23</sub>H<sub>28</sub>F<sub>2</sub>N<sub>6</sub>O<sub>4</sub>S and its molecular weight is 522.57. The chemical structure of ticagrelor is:



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<sub>12</sub> ADP-receptor to prevent signal transduction and platelet activation. Ticagrelor and its active metabolite are approximately equipotent.

### **12.2 Pharmacodynamics**

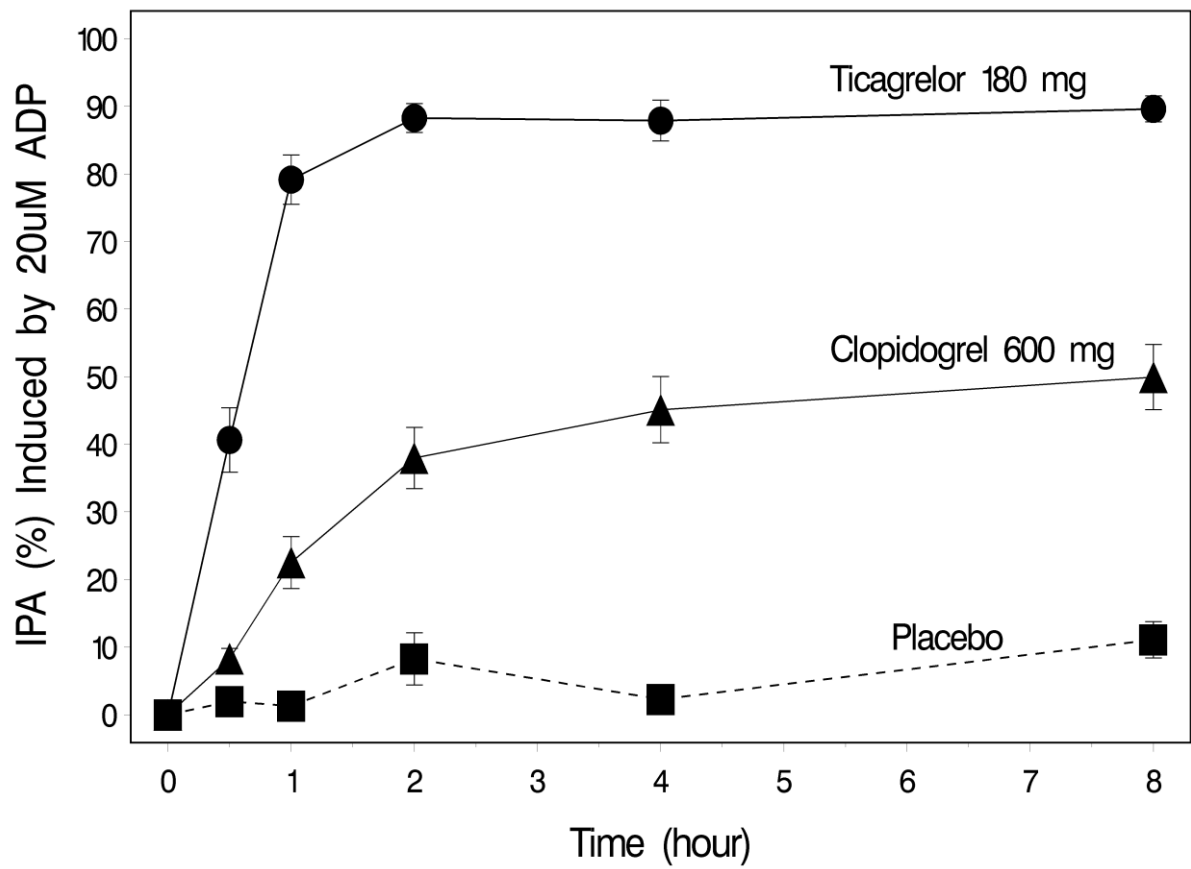
The inhibition of platelet aggregation (IPA) by ticagrelor and clopidogrel was compared in a 6 week study examining both acute and chronic platelet inhibition effects in response to 20 µM ADP as the platelet aggregation agonist.

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.

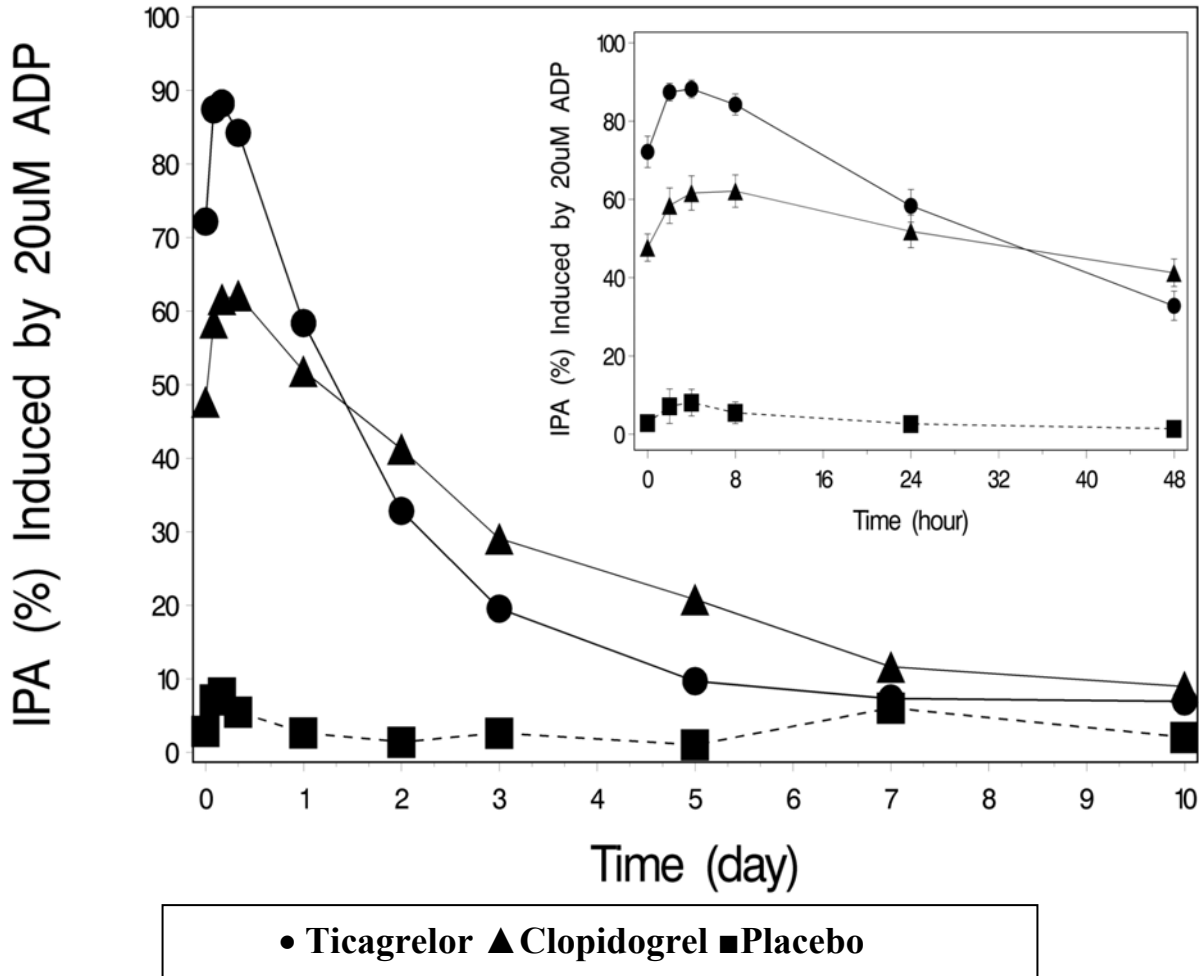
The offset of IPA was examined after 6 weeks on ticagrelor 90 mg twice daily or clopidogrel 75 mg daily, again in response to 20 µM ADP.

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.

**Figure 2 - Mean inhibition of platelet aggregation ( $\pm$ 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**



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  $t_{max}$  of 1.5 h (range 1.0–4.0). The formation of the major circulating metabolite AR-C124910XX (active) from ticagrelor occurs with a median  $t_{max}$  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  $C_{max}$ , but resulted in a 21% increase in AUC. The  $C_{max}$  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.

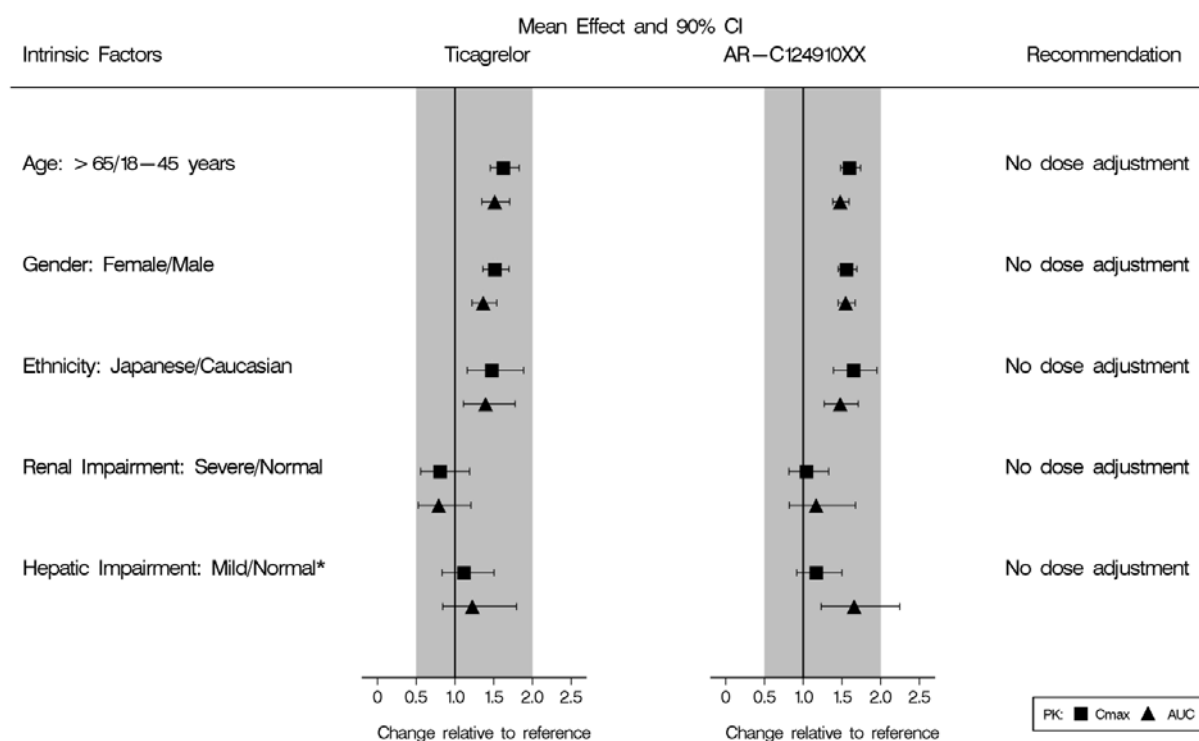
### Excretion

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 4 – Impact of intrinsic factors on the pharmacokinetics of ticagrelor**



\*BRILINTA has not been studied in patients with moderate or severe hepatic impairment.



## 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.

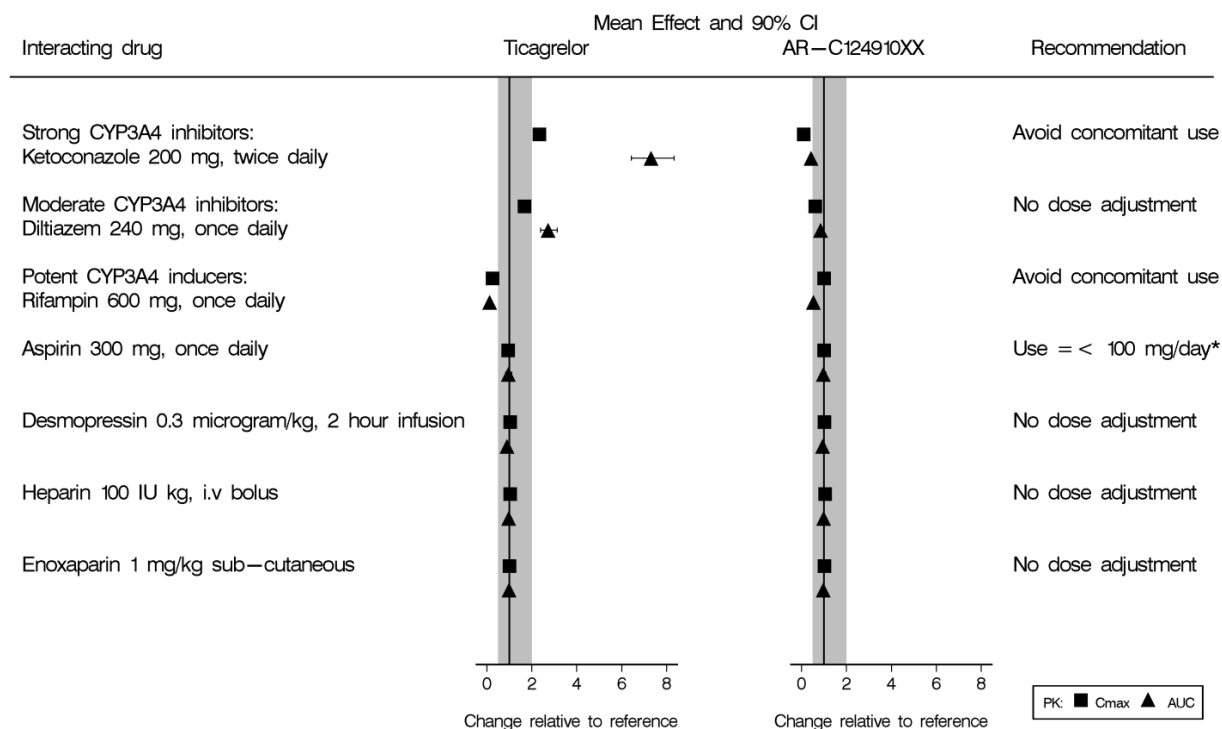
## Smoking

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.

**Figure 5 – Effect of co-administered drugs on the pharmacokinetics of ticagrelor**



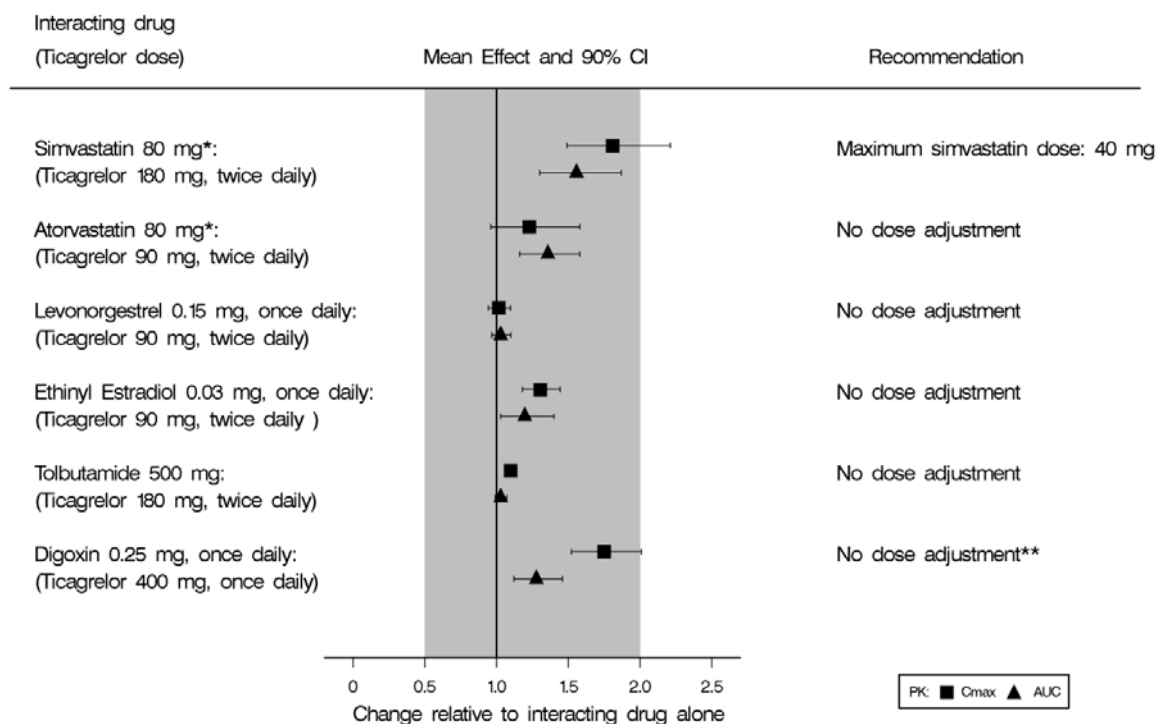
\*See *Dosage and Administration (2)*.

## 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 CYP3A5 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, levonorgestrel, tolbutamide, and digoxin, see Figure 6.

**Figure 6 – Impact of BRILINTA on the pharmacokinetics of co-administered drugs**



\*Similar increases in AUC and C<sub>max</sub> were observed for all metabolites  
 \*\*Monitor digoxin levels with initiation of or change in BRILINTA therapy

### 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  $\geq 10$  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.

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

	<b>BRILINTA N=9333</b>	<b>Clopidogrel N=9291</b>	<b>Hazard Ratio (95% CI)</b>	<b>p-value</b>
Composite of CV death, MI, or stroke	9.8	11.7	0.84 (0.77, 0.92)	0.0003
CV death	2.9	4.0	0.74	
Non-fatal MI	5.8	6.9	0.84	
Non-fatal stroke	1.4	1.1	1.24	
Secondary endpoints <sup>a</sup>				
CV death	4.0	5.1	0.79 (0.69, 0.91)	0.0013
MI <sup>b</sup>	5.8	6.9	0.84 (0.75, 0.95)	0.0045
Stroke <sup>b</sup>	1.5	1.3	1.17 (0.91, 1.52)	0.22
All-cause mortality	4.5	5.9	0.78 (0.69, 0.89)	0.0003

<sup>a</sup> First occurrence of specified event at any time

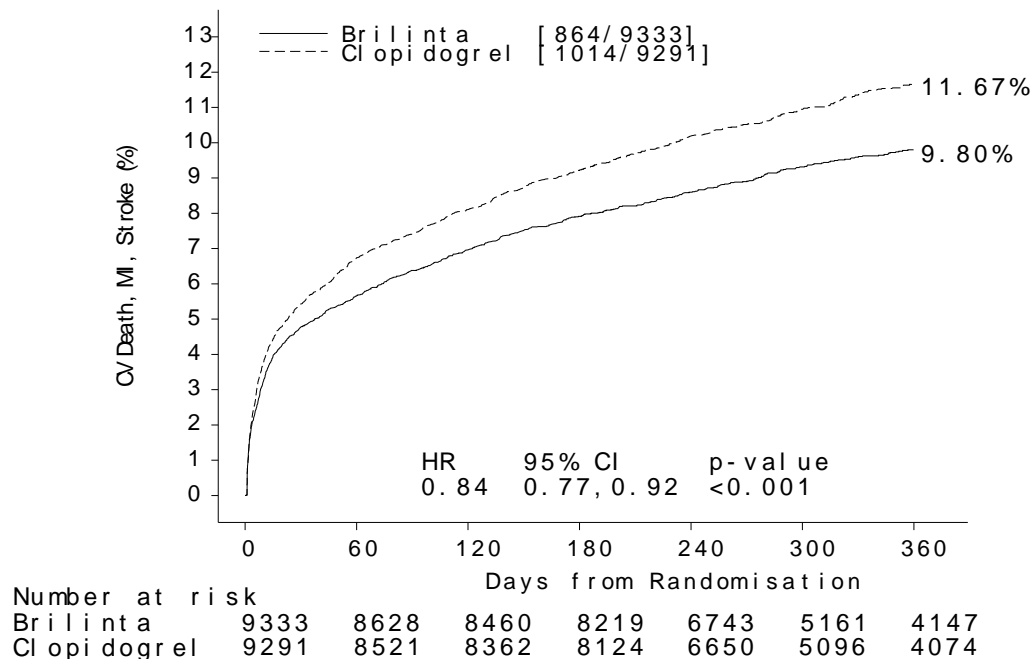
<sup>b</sup> Includes patients that could have had other non-fatal events or died

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.

**Figure 7 – Time to First Occurrence of CV death, MI, or Stroke in PLATO**

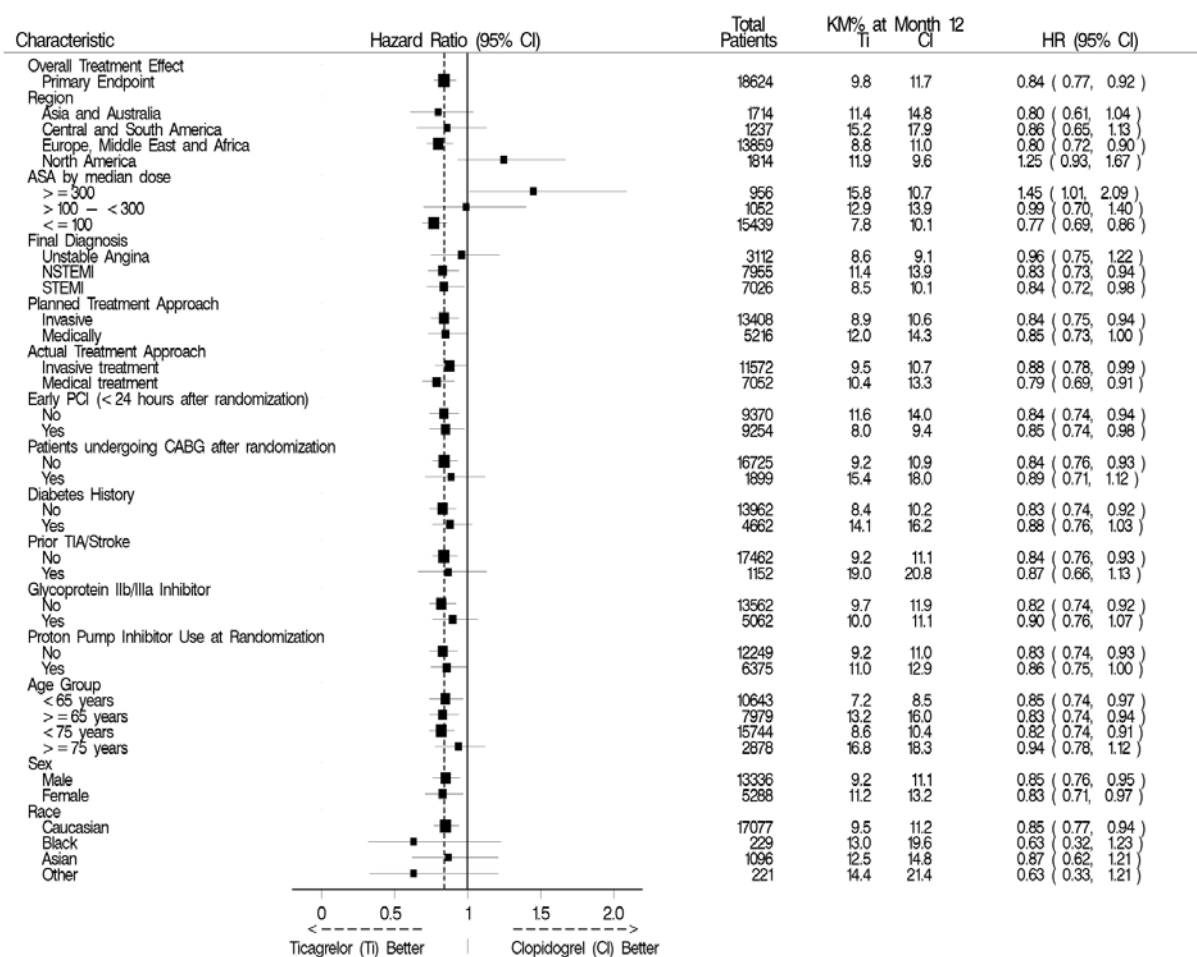


The curves separate by 30 days (RRR 12%) and continue to diverge throughout the 12 month treatment period (RRR 16%).

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 the maintenance dose of aspirin. 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.

**Figure 8 – Subgroup analyses of PLATO**



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. 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 ( $\leq 100$  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 region and dose.

**Table 5 – PLATO: CV Death, MI, Stroke by maintenance aspirin dose in the US and outside the US**

Region	ASADose (mg)	Ticagrelor		Clopidogrel		HR (95% CI)
		N	Events	N	Events	
US	$\geq 300$	324	40	352	27	1.62 (0.99, 2.64)
	$>100 < 300$	22	2	16	2	-
	$\leq 100$	284	19	263	24	0.73 (0.40, 1.33)
Non-US	$\geq 300$	140	28	140	23	1.23 (0.71, 2.14)
	$>100 < 300$	503	62	511	63	1.00 (0.71, 1.42)
	$\leq 100$	7449	546	7443	699	0.78 (0.69, 0.87)

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].

Keep BRILINTA in the container it comes in.

Keep BRILINTA tablets dry.

## **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).

Issued: July 20, 2011

BRILINTA™ is a trademark of the AstraZeneca group of companies.

**Manufactured by: AstraZeneca, AB S-151 85 Södertälje Sweden**

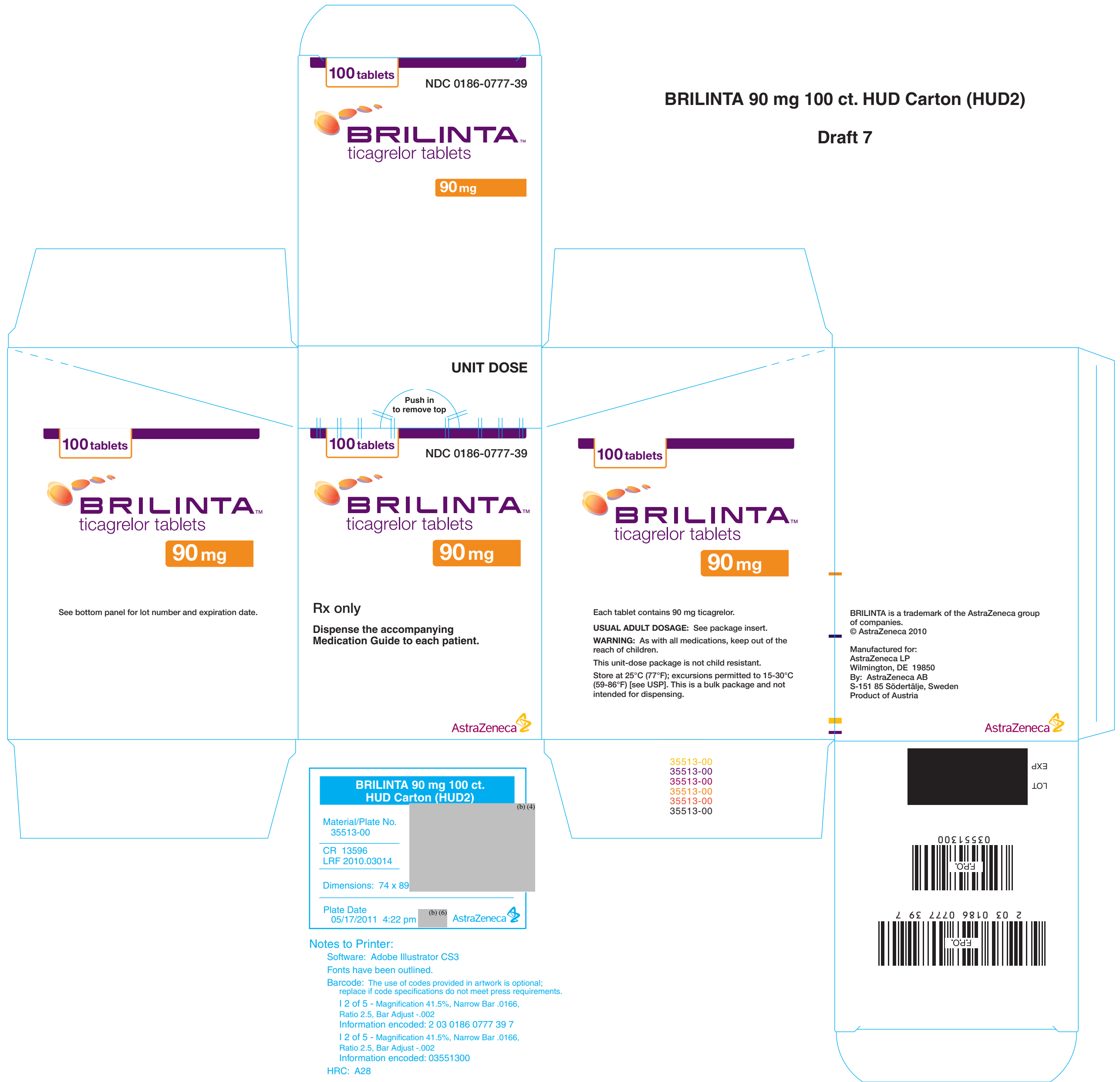
**Marketed by: AstraZeneca LP, Wilmington, DE 19850**

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BRILINTA 90 mg 100 ct. HUD Carton (HUD2)

Draft 7



100 tablets

NDC 0186-0777-39

**BRILINTA**<sup>TM</sup>  
ticagrelor tablets

90 mg

UNIT DOSE

Push in  
to remove top

100 tablets

**BRILINTA**<sup>TM</sup>  
ticagrelor tablets

90 mg

See bottom panel for lot number and expiration date.

100 tablets

NDC 0186-0777-39

**BRILINTA**<sup>TM</sup>  
ticagrelor tablets

90 mg

Rx only

Dispense the accompanying  
Medication Guide to each patient.

AstraZeneca

100 tablets

**BRILINTA**<sup>TM</sup>  
ticagrelor tablets

90 mg

Each tablet contains 90 mg ticagrelor.

**USUAL ADULT DOSAGE:** See package insert.

**WARNING:** As with all medications, keep out of the reach of children.

This unit-dose package is not child resistant.

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP]. This is a bulk package and not intended for dispensing.

BRILINTA is a trademark of the AstraZeneca group of companies.  
© AstraZeneca 2010

Manufactured for:  
AstraZeneca LP  
Wilmington, DE 19850  
By: AstraZeneca AB  
S-151 85 Södertälje, Sweden  
Product of Austria

AstraZeneca

BRILINTA 90 mg 100 ct.  
HUD Carton (HUD2)

Material/Plate No.  
35513-00

CR 13596  
LRF 2010.03014

Dimensions: 74 x 89

Plate Date  
05/17/2011 4:22 pm

AstraZeneca

35513-00  
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EXP  
LOT



Notes to Printer:

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Fonts have been outlined.

Barcode: The use of codes provided in artwork is optional; replace if code specifications do not meet press requirements.

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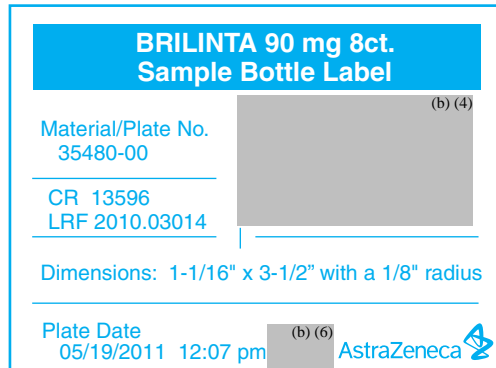
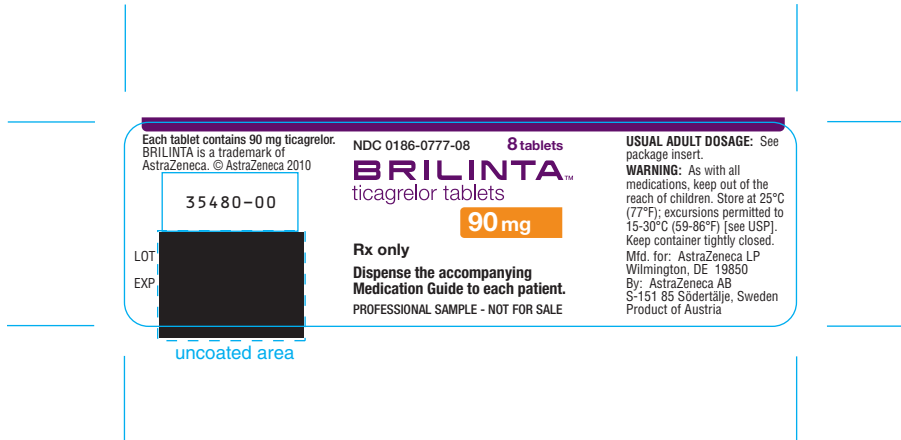
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HRC: A28

# BRILINTA 90 mg 8ct. Sample Bottle Label

Draft 6



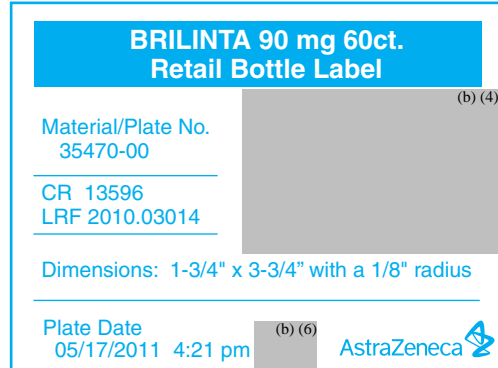
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Fonts have been outlined.

# BRILINTA 90 mg 60ct. Retail Bottle Label

Draft 6



## Notes to Printer:

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Fonts have been outlined.

Barcode: The use of codes provided in artwork is optional;  
replace if code specifications do not meet press requirements.

12-digit UPC - Magnification 100%. Bar Adjust -.002

Information encoded: 3 0186 0777 60 7

BRILINTA 90 mg 180ct. Retail Bottle Label

Draft 6

Each tablet contains 90 mg ticagrelor.  
**USUAL ADULT DOSAGE:** See package insert.  
**WARNING:** As with all medications, keep out of the reach of children. Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP]. Keep container tightly closed.

NDC 0186-0777-18 **180 tablets**

**BRILINTA™**  
ticagrelor tablets

**90 mg**

**Rx only**  
Dispense the accompanying Medication Guide to each patient.

35482-00

LOT [redacted]  
EXP [redacted]

Mfd. for: AstraZeneca LP  
Wilmington, DE 19850  
By: AstraZeneca AB  
S-151 85 Södertälje, Sweden  
Product of Austria

**AstraZeneca**

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0186-0777-18 8  
FPO.

uncoated area

**BRILINTA 90 mg 180ct.**  
**Retail Bottle Label**

(b) (4)

Material/Plate No.  
35482-00

CR 13596  
LRF 2010.03014

Dimensions: 2-5/16" x 3-3/4" with a 1/8" radius

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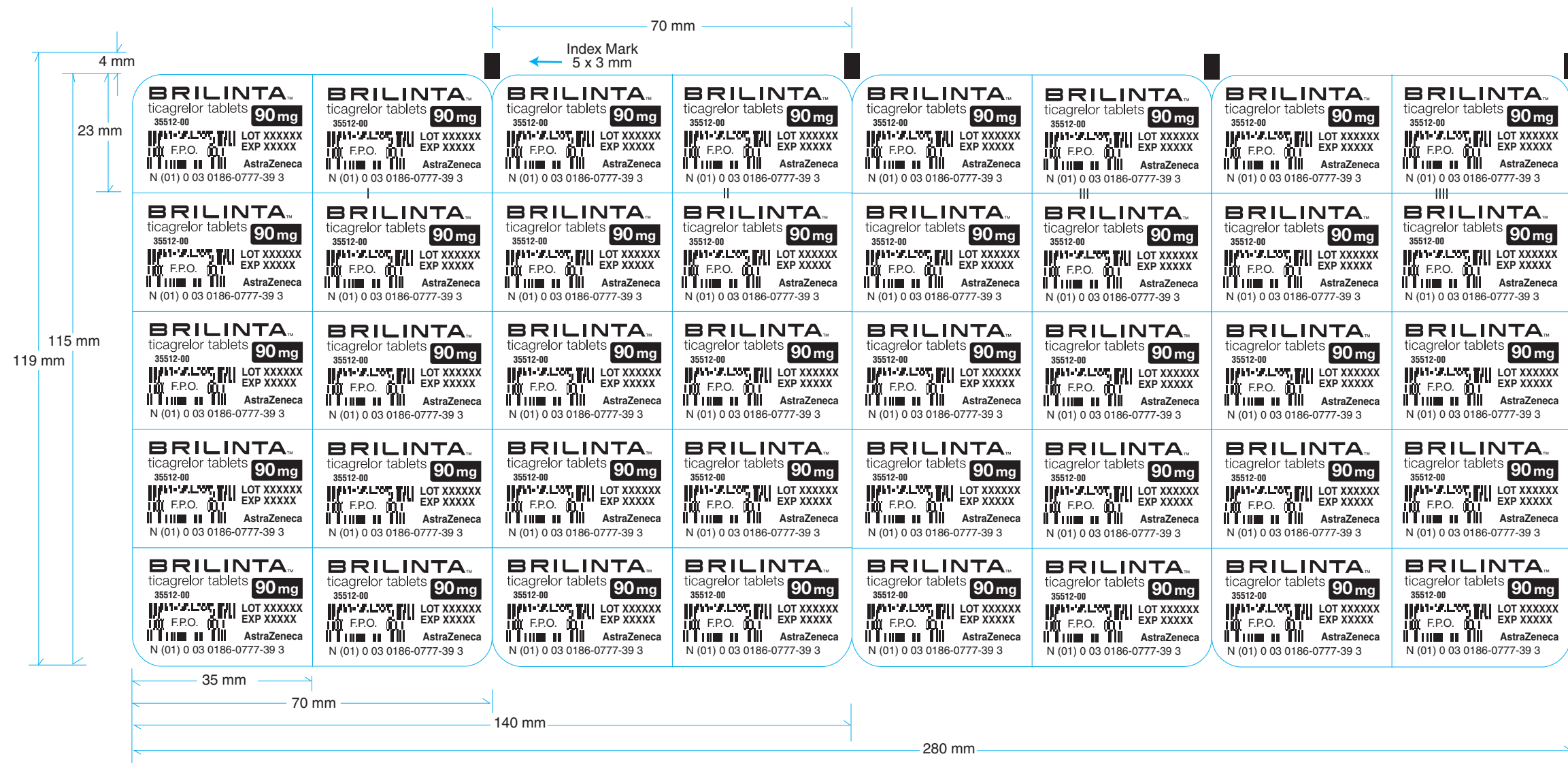
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12-digit UPC - Magnification 100%, Bar Adjust -.002

Information encoded: 3 0186 0777 18 8

# BRILINTA 90 mg Pr. Plates 100-count HUD Blister Draft 3



**BRILINTA 90 mg Pr. Plates  
10-count HUD Blister (HUD2)**

Material/Plate No. 35512-00	■ Black
CR # 13596	
Dimensions: 23 x 35 mm each	
Plate Date 08/24/2010 9:58 am	(b) (6) AstraZeneca

**Notes to Printer:**

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