PRODUCT MONOGRAPH

Pr BRILINTA®

ticagrelor tablets

60 and 90 mg

Platelet Aggregation Inhibitor

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ticagrelor tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Oral	Tablet 60 mg and 90 mg	Dibasic calcium phosphate, ferric oxide black (60 mg coating), ferric oxide red (60 mg coating), ferric oxide yellow (90 mg coating), hydroxypropyl cellulose, hypromellose, magnesium stearate, mannitol, polyethylene glycol 400, sodium starch glycolate, talc (90 mg coating) and titanium dioxide.

INDICATIONS AND CLINICAL USE

BRILINTA (ticagrelor), co-administered with low-dose acetylsalicylic acid (ASA: 75-150 mg), is indicated for the secondary prevention of atherothrombotic events in:

- Patients with Acute Coronary Syndromes (ACS)
- Patients with a history of myocardial infarction (MI occurred at least one year ago) and a high risk of developing an atherothrombotic event

(see CLINICAL TRIALS and DOSAGE AND ADMINISTRATION).

Geriatrics (≥65 years): No overall differences in safety or efficacy were observed between these patients and younger patients with acute coronary syndrome (PLATO) or a history of MI (≥one year) (PEGASUS) (see ADVERSE REACTIONS and CLINICAL TRIALS).

Pediatrics (< 18 years of age): The safety and efficacy of BRILINTA in pediatric patients below the age of 18 have not been established. Therefore, BRILINTA is not recommended in this population.

CONTRAINDICATIONS

BRILINTA (ticagrelor) is contraindicated in:

- Patients who are hypersensitive to this medication or to any ingredient in the formulation. For a complete listing of ingredients, see DOSAGE FORMS, COMPOSITION AND PACKAGING.
- Patients who have active pathological bleeding such as peptic ulcer or intracranial hemorrhage (see WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS).
- Patients with a history of intracranial hemorrhage (see WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS).
- Patients with moderate to severe hepatic impairment (see DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY).
- Patients who are also taking strong CYP3A4 inhibitors (e.g. ketoconazole, clarithromycin, nefazodone, ritonavir, and atazanavir) (see WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS).

WARNINGS AND PRECAUTIONS

General

Bleeding Risk: As with other antiplatelet agents, the use of BRILINTA (ticagrelor) in patients at known increased risk for bleeding should be balanced against the benefit in terms of prevention of thrombotic events (see ADVERSE REACTIONS).

If clinically indicated, BRILINTA should be used with caution in the following patient groups:

- Patients with a propensity to bleed (e.g. due to recent trauma, recent surgery, coagulation disorders, or recent gastrointestinal bleeding). The use of BRILINTA is contraindicated in patients with active pathological bleeding, in those with a history of intracranial hemorrhage, and moderate to severe hepatic impairment (see CONTRAINDICATIONS).
- Patients requiring oral anticoagulants (e.g. warfarin, see DRUG INTERACTIONS) and/or fibrinolytics agents (within 24 hours of BRILINTA dosing). Such agents confer an independent bleeding risk as they function in a distinct and complementary mechanism of hemostasis compared to BRILINTA. The combination of BRILINTA with either of these classes of drugs has not been studied.
  - **Warfarin Therapy**: Due to an increased propensity to bleed, caution is advised in patients taking warfarin during BRILINTA therapy. A specific

drug-drug interaction study with warfarin has not been performed (see DRUG INTERACTIONS).

- Patients with concomitant administration of medicinal products that may increase the risk of bleeding, e.g. non-steroidal anti-inflammatory drugs (NSAIDs).

Platelet transfusion did not reverse the antiplatelet effect of BRILINTA in healthy volunteers and is unlikely to be of clinical benefit in patients with bleeding. Since co-administration of BRILINTA with desmopressin did not decrease template bleeding time, desmopressin is unlikely to be effective in managing clinical bleeding events.

Antifibrinolytic therapy (aminocaproic acid or tranexamic acid) and/or recombinant factor VIIa therapy may augment hemostasis. BRILINTA may be resumed after the cause of bleeding has been identified and controlled.

Maintenance Dose Acetylsalicylic Acid (ASA): Based on a relationship observed in PLATO between maintenance ASA dose and relative efficacy of BRILINTA compared to clopidogrel, co-administration of BRILINTA and high maintenance dose ASA (> 150 mg daily) is not recommended (see INDICATIONS and DOSAGE AND ADMINISTRATION).

Cytochrome P450 3A4 Strong Inhibitors: Co-administration of BRILINTA with strong CYP3A4 inhibitors (e.g. ketoconazole, clarithromycin, nefazodone, ritonavir, and atazanavir) is contraindicated as co-administration may lead to a substantial increase in exposure to ticagrelor (see CONTRAINDICATIONS and DRUG INTERACTIONS).

Premature Discontinuations: Patients who require discontinuation of BRILINTA are at increased risk for cardiac events. Premature discontinuation of treatment should be avoided. If BRILINTA must be temporarily stopped due to an adverse event, it should be re-initiated as soon as possible when the benefits outweigh the risks of the adverse event or when the adverse event has come to resolution (see DOSAGE AND ADMINISTRATION).

Uric Acid Increase: In PLATO, patients on BRILINTA had a higher risk of hyperuricemia than those receiving clopidogrel. In PEGASUS, a greater incidence of gout, gouty arthritis and hyperuricemias were reported in patients on BRILINTA compared to aspirin alone. Caution should be exercised when administering BRILINTA to patients with history of hyperuricemia or gouty arthritis. As a precautionary measure, the use of BRILINTA in patients with uric acid nephropathy is discouraged.

Cardiovascular

Patients at Risk for Bradyarrhythmia: Holter ECG monitoring conducted during clinical trials has shown an increased frequency of mostly asymptomatic ventricular pauses during treatment with ticagrelor compared with clopidogrel. In Phase 3 studies (PLATO and PEGASUS) evaluating the safety and efficacy of BRILINTA, patients with history of sick sinus syndrome, second and third degree AV block or bradycardic-related syncope and not protected with a pacemaker were excluded. The incidence of bradyarrhythmic events in these studies were reported in a similar frequency for ticagrelor and comparators (i.e., clopidogrel or

placebo). Bradyarrhythmic events have been reported in the post-marketing setting. Therefore, BRILINTA should be used with caution in patients at risk of bradyarrhythmia and these patients should be closely monitored (see CLINICAL TRIALS).

In addition, caution should be exercised when administering BRILINTA concomitantly with drugs known to induce bradycardia. However no evidence of clinically significant adverse interactions was observed in the PLATO and the PEGASUS trials during concomitant administration with one or more drugs known to induce bradycardia. In PLATO, 96% of patients took beta blockers, 33% took diltiazem or verapamil (calcium channel blockers), and 4% took digoxin.

Neurologic

Patients with Prior Ischemic Stroke: ACS patients with prior ischemic stroke can be treated with BRILINTA 90 mg for up to 12 months (PLATO). In PEGASUS, patients with a history of MI (≥one year) with prior ischemic stroke were excluded because previous studies have shown that combination use of antiplatelet agents (not ticagrelor) is associated with increased risks of intracranial hemorrhage. Therefore, in the absence of data BRILINTA treatment beyond one year in patients with ischemic stroke is not recommended.

Effects on Ability to Drive and Use Machines: No studies on the effects of BRILINTA on the ability to drive and use machines have been performed. During treatment with BRILINTA, dizziness, confusion and syncope have been reported. Therefore, patients who experience these symptoms should be cautious while driving or using machines (see ADVERSE REACTIONS).

Peri-Operative Considerations

Surgery: If a patient requires surgery, clinicians should consider each patient's clinical profile as well as the benefits and risks of continued antiplatelet therapy when determining when discontinuation of BRILINTA treatment should occur.

In PLATO patients undergoing CABG, BRILINTA had a similar rate of major bleeds compared to clopidogrel at all days after stopping therapy except Day 1 where BRILINTA had a higher rate of major bleeding (see ADVERSE REACTIONS).

Because of the reversible binding of BRILINTA, restoration of platelet aggregation occurs faster with BRILINTA compared to clopidogrel.

In the OFFSET study, mean Inhibition of Platelet Aggregation (IPA) for ticagrelor at 72 hours post-dose was comparable to mean IPA for clopidogrel at 120 hours post-dose. The more rapid offset of effect may predict a reduced risk of bleeding complications, e.g. in settings where antiplatelet therapy must be temporarily discontinued due to surgery or trauma (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics).

To minimize the risk of bleeding, if a patient is to undergo elective surgery and antiplatelet effect is not desired, BRILINTA should be discontinued 5 days prior to surgery.

Respiratory

Dyspnea: In clinical trials, approximately 14% of patients randomized to BRILINTA 90 mg or 60 mg twice daily reported dyspnea, including dyspnea at rest, exertional dyspnea, paroxysmal nocturnal dyspnea, and nocturnal dyspnea (see ADVERSE REACTIONS). The patients experienced a single episode in eighty-five percent of the cases. The dyspnea is usually mild to moderate in intensity and often resolves during continued BRILINTA treatment. Ticagrelor should be used with caution in older patients and in patients with history of asthma and/or chronic obstructive pulmonary disease. If a patient reports new, prolonged or worsened dyspnea this should be investigated fully and if not tolerated, treatment with BRILINTA should be stopped (see ADVERSE REACTIONS). The mechanism has not yet been elucidated.

PLATO data do not suggest that the higher frequency of dyspnea with BRILINTA 90 mg is due to new or worsening heart or lung disease. In patients who underwent pulmonary function testing in the clinical program, there was no indication of an adverse effect of BRILINTA 90 mg on pulmonary function.

Special Populations

Pregnant Women: The safety of BRILINTA during pregnancy has not been established, as no clinical study has been conducted in pregnant women and limited clinical data on exposure to BRILINTA during pregnancy are available. Women of child bearing potential should use appropriate contraceptive measures to avoid pregnancy.

Nursing Women: It is not known whether this drug is excreted in human milk, as no clinical study has been conducted in lactating women. Studies in rats have shown that ticagrelor and its active metabolites are excreted in milk (see DETAILED PHARMACOLOGY, Pharmacokinetics). Therefore, the use of BRILINTA during breastfeeding is not recommended.

Pediatrics (< 18 years of age): The safety and efficacy of BRILINTA in pediatric patients below the age of 18 have not been established. Therefore, BRILINTA is not recommended in this population.

Renal Impairment: No dose adjustment is necessary for patients with renal impairment. No clinical study has been conducted in patients on renal dialysis. Ticagrelor is not thought to be dialyzable. Appropriate caution should be used in patients requiring renal replacement therapy. Creatinine levels may increase during treatment with BRILINTA. The mechanism has not been identified. Renal function should be monitored in the course of patient management (see ADVERSE REACTIONS and ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The safety profile of BRILINTA has been evaluated in two large phase 3 outcome trials (PLATO and PEGASUS) including more than 39,000 patients.

Acute Coronary Syndrome

In PLATO, a total of 6,762 patients with Acute Coronary Syndromes (UA, NSTEMI and STEMI) were exposed to BRILINTA (180 mg loading dose followed by a 90 mg twice daily maintenance dose) for at least 6 months and up to 12 months for 3,138 of them.

The commonly reported adverse events in patients treated with BRILINTA (ticagrelor) were dyspnea, headache and epistaxis and these events occurred at higher rates than in the clopidogrel treatment group (see Table 3).

Serious adverse events were reported in a similar frequency between BRILINTA (20.2%) and clopidogrel (20.3%) treated patients. The most frequent serious adverse events observed were cardiac failure (1.1% vs. 1.0%), non-cardiac chest pain (0.9% vs. 0.9%) and dyspnea (0.7% vs. 0.4%).

The rate of study drug discontinuation because of adverse events was 7.4% for BRILINTA and 5.4% for clopidogrel. Dyspnea was the most common adverse events leading to study drug discontinuation for BRILINTA (0.9% for BRILINTA and 0.1% for clopidogrel).

History of Myocardial Infarction (≥One Year)

The safety of BRILINTA in patients with a history of spontaneous MI (MI occurred at least one year ago) and high risk of developing an atherothrombotic event was evaluated in the PEGASUS study, which compared patients treated with BRILINTA 60 mg twice daily (N=6,958) or 90 mg twice daily combined with low dose ASA (75-150 mg) (N=6,988) to low dose ASA (75-150 mg) therapy alone (N=6,996). The BRILINTA 60 mg dose is the only dose approved for this indication. Median treatment duration for BRILINTA 60 mg was 29.4 months (see CLINICAL TRIALS).

The commonly reported adverse events in this patient population on BRILINTA were dyspnea, epistaxis, increased tendency to bruise and contusion, and these events occurred at higher rates with BRILINTA than on ASA alone (see Table 6).

The proportion of patients who had serious adverse events was similar across the treatment groups (21.5% for BRILINTA 60 mg and 21.6% for ASA alone). The most common serious adverse events more frequently reported with BRILINTA were atrial fibrillation, syncope, dyspnea, iron deficiency anemia and epistaxis.

In PEGASUS patients on BRILINTA had a higher incidence of discontinuation due to adverse events compared to ASA alone (16.1% for BRILINTA 60 mg and 8.5% for ASA therapy alone). The most common adverse events leading to study discontinuation reported at higher rates with BRILINTA than on ASA alone were dyspnea, increased tendency to bruise, epistaxis and spontaneous hematoma.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Acute Coronary Syndrome

Bleeding Events

The primary safety endpoint in the PLATO study was the composite endpoint of 'Total Major' bleeding, which consisted of the components of 'Major Fatal/Life-threatening' and 'Major Other'. Table 1 shows the 12 month rates of patients experiencing bleeding events in the PLATO study (PLATO defined).

Table 1: Analysis of overall bleeding events, Kaplan-Meier estimate of bleeding rates by treatment at 12 months – PLATO-defined

	BRILINTA 90 mg twice daily (%) N=9235	**Clopidogrel 75 mg once daily (%) N=9186**	**p-value***
Primary Safety Endpoint			
Total Major	11.6	11.2	0.4336
Secondary Safety Endpoints			
Major Fatal/Life-Threatening	5.8	5.8	0.6988
Combined Total Major + Minor	16.1	14.6	0.0084
Non-Procedural Major	3.1	2.3	0.0058
Non-Procedural Major + Minor	5.9	4.3	<0.0001
Non-CABG Total Major	4.5	3.8	0.0264
Non-CABG Major Fatal/Life-threatening	2.1	1.9	0.2516

* Nominal p-value not corrected for multiple testing.
Major Fatal/Life-threatening: Clinically apparent with > 50 g/L decrease in hemoglobin or ≥ 4 red cell units transfused; or fatal; or intracranial; or intrapericardial with cardiac tamponade; or with hypovolemic shock or severe hypotension requiring pressors or surgery.
Major Other: Clinically apparent with 30-50 g/L decrease in hemoglobin or 2-3 red cell units transfused; or significantly disabling.
Minor: Requires medical intervention to stop or treat bleeding.

There were few fatal bleeding events in the study, 20 (0.2%) for BRILINTA 90 mg twice daily and 23 (0.3%) for clopidogrel 75 mg once daily. When minor bleeding was included,

combined PLATO-defined Major and Minor bleeding events were significantly higher on BRILINTA than on clopidogrel.

Location of 'Total Major + Minor' Bleeding (BRILINTA versus clopidogrel): intracranial 0.3% vs. 0.2%, pericardial 0.1% vs. 0.1%, retroperitoneal 0.03% vs. 0.03%, intraocular 0.02% vs. 0.04% and intra-articular 0.02% vs. 0.01%. Other common locations were in rank order of event frequency: gastrointestinal 1.8% vs. 1.5%, epistaxis 1.3% vs. 0.7%, urinary 0.5% vs. 0.4%, subcutaneous/dermal 0.5% vs. 0.4% and hemoptysis 0.1% vs. 0.08%.

Non-procedural Fatal Bleeding: There was no difference with BRILINTA compared to clopidogrel for overall non-procedural fatal bleeding. There were numerically more 'Major Fatal/Life-threatening' intracranial non-procedural bleeding events with BRILINTA (n=27 events, 0.3%) than with clopidogrel (n=14 events, 0.2%). Of the intracranial non-procedural bleeding events, 11 bleeding events with BRILINTA and 1 with clopidogrel were fatal. 'Major Fatal/Life-threatening' gastrointestinal bleeding was the same with BRILINTA and clopidogrel, with numerically more fatal events for clopidogrel (5) than for BRILINTA (none).

Bleeding in Patient Subpopulations: Baseline characteristics including age, gender, weight, race, geographic region, medical history, concurrent conditions and concomitant therapy were assessed to explore any increase in risk of bleeding with BRILINTA. No particular risk group was identified for any subset of bleeding.

Table 2 shows the overall rates of TIMI-defined bleeding events.

Table 2: Analysis of overall bleeding events – TIMI-defined

	BRILINTA (%) N=9235	**Clopidogrel (%) N=9186**	**p-value**
Major	7.9	7.7	0.5669
Major + Minor	11.4	10.9	0.3272
Non-CABG Major	2.8	2.2	0.0246
Non-CABG Major + Minor	4.5	3.6	0.0093

TIMI Major: Clinically apparent with ≥ 50 g/L decrease in hemoglobin or intracranial hemorrhage.
TIMI Minor: Clinically apparent with 30 to ≤ 50 g/L decrease in haemoglobin.

Other Adverse Events

The incidence of adverse events (regardless of causality) reported for ≥ 1% of patients treated with BRILINTA and clopidogrel in the PLATO study are presented in Table 3.

Table 3: Summary of adverse events (regardless of causality) reported for ≥ 1% of patients in either group (PLATO)

Adverse Event (System Organ Class)	**BRILINTA (%) N=9235**	**Clopidogrel (%) N=9186**
Blood and Lymphatic System Disorders		

Adverse Event (System Organ Class)	BRILINTA (%) N=9235	Clopidogrel (%) N=9186
Anaemia	1.9	1.7
Cardiac Disorders		
Atrial fibrillation	4.2	4.6
Bradycardia[a]	2.9	2.9
Cardiac failure	2.3	2.6
Ventricular tachycardia	2.0	2.1
Palpitations	1.2	1.1
Angina pectoris	1.2	1.1
Sinus bradycardia	1.1	0.8
Ventricular extrasystoles	1.1	1.1
Ventricular fibrillation	0.8	1.0
Ear and Labyrinth Disorders		
Vertigo[b]	1.5	1.3
Gastrointestinal Disorders		
Nausea[b]	4.3	3.8
Diarrhea[b]	3.7	3.3
Vomiting[b]	2.5	2.3
Constipation[b]	2.2	2.6
Dyspepsia[b]	2.0	1.8
Abdominal pain upper	1.9	2.0
Abdominal pain[b]	1.5	1.2
General Disorders and Administration Site Conditions		
Non-cardiac chest pain	3.7	3.3
Fatigue	3.2	3.2
Chest pain	3.1	3.5
Pyrexia	2.9	2.8
Edema peripheral	2.3	2.5
Asthenia	2.0	2.1
Hemorrhages or bleeding		
Epistaxis[b]	6.0	3.4
Contusion	3.9	2.0
Hematoma	2.2	1.3
Post-procedural hemorrhage[b]	2.1	2.0
Vessel puncture site hematoma	1.7	1.1
Ecchymosis	1.5	0.6
Infections and Infestations		
Urinary tract infection	2.0	1.8
Hematuria	1.9	1.6
Nasopharyngitis	1.8	1.6
Pneumonia	1.4	1.9
Bronchitis	1.3	1.4
Metabolism and Nutrition Disorders		
Diabetes mellitus	1.2	1.1
Dyslipidaemia	1.0	1.0
Hypercholesterolaemia	1.0	0.9
Hypokalaemia	1.6	1.5
Musculoskeletal and Connective Tissue Disorders		

Adverse Event (System Organ Class)	BRILINTA (%) N=9235	Clopidogrel (%) N=9186
Back pain	3.6	3.3
Pain in extremity	2.1	2.3
Musculoskeletal chest pain	1.5	1.4
Musculoskeletal pain	1.5	1.5
Arthralgia	1.5	1.4
Myalgia	1.4	1.6
Nervous System Disorders		
Headache	6.5	5.8
Dizziness	4.5	3.9
Syncope	1.1	0.8
Psychiatric Disorders		
Anxiety	2.2	1.9
Insomnia	1.7	2.0
Depression	1.1	1.1
Renal and Urinary Disorders		
Renal failure	1.0	0.7
Respiratory Disorders		
Dyspnea[a, b]	12.0	6.5
Cough	4.9	4.6
Dyspnea Exertional	1.9	1.4
Skin and Subcutaneous Tissue Disorders		
Rash[b]	1.8	1.7
Pruritus[b]	1.0	1.0
Vascular Disorders		
Hypertension	3.8	4.0
Hypotension	3.2	3.3

[a] Several MedDRA PT combined.

[b] These events have also been reported as Adverse Drug Reactions (possibly or probably related to BRILINTA).

Additional clinical Adverse Drug Reactions that were reported as possibly or probably related to BRILINTA are listed below by body system:

Common (≥ 1% to < 10%)

- *Skin and subcutaneous tissue disorders:* subcutaneous or dermal bleeding
- *Gastrointestinal disorders:* gastrointestinal hemorrhages
- *Renal and urinary disorders:* urinary tract bleeding

Uncommon (≥ 0.1% to < 1%)

- *Nervous system disorders:* intracranial hemorrhage (may be fatal or life threatening), confusion, paraesthesia
- *Gastrointestinal disorders:* gastritis, retroperitoneal hemorrhage
- *Eye disorders:* eye hemorrhage (intraocular, conjunctival, retinal)
- *Respiratory, thoracic and mediastinal disorders:* hemoptysis

Rare (≥ 0.01% to < 0.1%)

- *Musculoskeletal connective tissue and bone:* hemarthrosis

History of Myocardial Infarction (≥One Year)

Bleeding Events

The primary safety endpoint in the PEGASUS study was the 'TIMI Major bleeding'. The safety analysis included: time to first TIMI Major bleeding event following the first dose of study drug, time to first TIMI Major or Minor bleeding event and time to first PLATO Major bleeding event.

Table 4 shows the 36-month rates of patients experiencing bleeding events in the 'on treatment' analysis of the PEGASUS study (TIMI defined).

Table 4: Analysis of overall bleeding events, Kaplan-Meier estimate of bleeding rates by treatment at 36 months (PEGASUS) – TIMI-defined

	BRILINTA 60 mg twice daily with ASA (%) N=6958	**ASA alone (%) N=6996**	**p-value**
Primary Safety Endpoint			
TIMI Major bleeding*	2.3	1.1	<0.0001
Other Safety Endpoints			
Fatal	0.3	0.3	1.0000
ICH	0.6	0.5	0.3130
Other Major	1.6	0.5	<0.0001
TIMI Major or Minor	3.4	1.4	<0.0001
TIMI Major or Minor or Requiring medical attention	16.6	7.0	<0.0001

***TIMI Major**: Fatal bleeding OR any intracranial bleeding OR clinically overt signs of hemorrhage associated with a drop in haemoglobin (Hgb) of ≥50 g/L, or when Hgb is not available, a fall in hematocrit (Hct) ≥15%.
Fatal: A bleeding event that directly led to death within 7 days.
ICH: Intracranial hemorrhage.
Other TIMI Major: Non-fatal non-ICH TIMI Major bleeding.
TIMI Minor: Clinically apparent with 30 to <50 g/L decrease in hemaglobin, or when Hgb is not available, a fall in hematocrit (Hct) of 9 to <15%.
TIMI Requiring medical attention: Requiring intervention, OR leading to hospitalization, OR prompting evaluation.

In PEGASUS, TIMI Major bleeding for BRILINTA 60 mg twice daily was higher than for ASA alone. No increased bleeding risk was seen for fatal bleeding and a small increase was observed in intracranial haemorrhages, as compared to ASA therapy alone. The number of fatal bleeding events in the study was, 11 (0.3%) for BRILINTA 60 mg and 12 (0.3%) for ASA therapy alone and most of these events involved cases of intracranial and gastrointestinal bleedings. The observed increased risk of TIMI Major bleeding with BRILINTA 60 mg was primarily due to a higher frequency of Other TIMI Major bleeding driven by events in the system organ class (SOC) gastrointestinal disorders; and injury, poisoning and procedural complications. The majority of TIMI major bleeding was reported as spontaneous.

Increased bleeding patterns similar to TIMI Major were seen for TIMI Major or Minor (see Table 4) and PLATO-defined Major and PLATO-defined Major or Minor bleeding categories (see Table 5). Discontinuation of treatment due to bleeding was more common with BRILINTA 60 mg compared to ASA therapy alone (6.2% and 1.5%, respectively). The majority of these bleedings were classified as TIMI Requiring medical attention, e.g. epistaxis, bruising and spontaneous hematomas. The most common causes of discontinuation due to a TIMI major bleeding event were gastrointestinal and traumatic intracranial hemorrhage.

Table 5 shows the overall rates of PLATO-defined bleeding events.

Table 5: Analysis of overall bleeding events –PLATO-defined

	BRILINTA 60 mg bd N=6958	**ASA alone (%) N=6996**	**p-value**
PLATO Major bleeding*	3.5	1.4	<0.0001
Fatal/life-threatening	2.4	1.1	<0.0001
Other PLATO Major	1.1	0.3	<0.0001
PLATO Major or Minor	15.2	6.2	<0.0001

***PLATO Major Fatal/life-threatening**: Fatal bleeding, OR any intracranial bleeding, OR intrapericardial with cardiac tamponade, OR with hypovolemic shock or severe hypotension requiring pressors/inotropes or surgery OR clinically apparent with ≥50 g/L decrease in hemoglobin or when Hgb is not available, a fall in hematocrit (Hct) ≥15%) OR ≥4 red cell units transfused.
PLATO Major Other: Significantly disabling, OR clinically apparent with 30 to <50 g/L decrease in haemoglobin (or when Hgb is not available, a fall in hematocrit (Hct) of 9 to <15%), OR 2-3 red cell units transfused.
PLATO Minor: Requires medical intervention to stop or treat bleeding.

Intracranial bleeding: Spontaneous ICHs were reported in similar rates for BRILINTA 60 mg and ASA therapy alone (0.2% in both treatment groups). Traumatic and procedural ICHs showed an increase with BRILINTA 60 mg treatment, (n=15, 0.2%) compared with ASA therapy alone (n=10, 0.1%). There were 6 fatal ICHs with BRILINTA 60 mg and 5 with ASA therapy alone.

Bleeding in Patient Subpopulations: The bleeding profile of BRILINTA 60 mg was generally consistent across multiple pre-defined subgroups (e.g. by age, gender, weight, ethnicity, geographic region, concurrent conditions, concomitant therapy, and medical history) for TIMI Major, TIMI Major or Minor and PLATO Major Bleeding events.

Common bleeding Adverse Drug Reactions (≥1% to <10%) with BRILINTA by body system:

Blood and lymphatic system disorders: blood disorder bleedings (increased tendency to bruise, spontaneous hematoma, hemorrhagic diathesis)
Gastrointestinal disorders: gastrointestinal hemorrhages (gingival, rectal, hemorrhoidal, gastrointestinal ulcer)
Injury, poisoning and procedural complications: post procedural hemorrhage, traumatic bleedings

Respiratory, thoracic and mediastinal disorders: respiratory system bleedings (epistaxis, hemoptysis)

Renal and urinary disorders: urinary tract bleeding (hematuria, cystitis hemorrhage)

Skin and subcutaneous tissue disorders: subcutaneous or dermal bleeding (ecchymosis, skin hemorrhage, petechiae)

Other Adverse Events

The incidence of adverse events (regardless of causality) reported for ≥ 1% of patients treated with BRILINTA 60 mg combined with ASA or ASA alone in the PEGASUS study are presented in Table 6.

Table 6: Summary of adverse events (regardless of causality) reported for ≥ 1% of patients in the different treatment groups and at a greater incidence with BRILINTA combined with ASA than ASA alone (PEGASUS)

Adverse Event (System Organ Class)	BRILINTA 60 mg (%) N=6958	Placebo – ASA alone (%) N=6996
Blood and Lymphatic System Disorders		
Increased tendency to bruise[b]	6.0	0.9
Spontaneous hematoma[b]	3.1	0.6
Cardiac Disorders		
Atrial fibrillation	2.8	2.5
Palpitations	1.0	0.9
Ear and Labyrinth Disorders		
Vertigo[b]	1.1	1.0
Gastrointestinal Disorders		
Diarrhea[b]	3.3	2.5
Nausea[b]	2.1	1.9
Dyspepsia	1.8	1.8
Abdominal pain	1.3	1.2
Infections and Infestations		
Bronchitis	2.7	2.6
Urinary tract infection	2.1	1.9
Sinusitis	1.1	1.0
Injury, Poisoning and Procedural Complications		
Contusion[b]	5.0	1.5
Traumatic hematoma[b]	2.3	0.6
Fall	1.1	1.0
Investigations		
Blood pressure increased	1.0	0.8
Metabolism and Nutrition Disorders		
Gout/gouty arthritis/gouty tophus[b]	1.5	1.1
Nervous System Disorders		
Dizziness[b]	4.2	3.7
Syncope[b]	1.2	0.9
Psychiatric Disorders		

Adverse Event (System Organ Class)	BRILINTA 60 mg (%) N=6958	Placebo – ASA alone (%) N=6996
Anxiety	1.4	1.2
Insomnia	1.2	1.0
Renal and Urinary Disorders		
Hematuria[b]	2.2	1.1
Reproductive System and Breast Disorders		
Benign prostatic hyperplasia	1.4	1.3
Respiratory, Thoracic and Mediastinal Disorders		
Dyspnea[a,b]	14.4	5.5
Epistaxis[b]	6.1	2.2
Cough	2.8	2.5
Skin and Subcutaneous Tissue Disorders		
Ecchymosis[b]	1.5	0.2
Pruritus[b]	1.0	0.9
Vascular Disorders		
Hypotension	1.4	1.0

[a] includes events of dyspnea, dyspnea exertional and dyspnea at rest.

[b] These events have also been reported as Adverse Drug Reactions (possibly or probably related to BRILINTA).

Less Common Clinical Trial Adverse Drug Reactions (<1%)

History of Myocardial Infarction (≥ One Year)

Blood and lymphatic system disorders: anemia

Nervous system disorders: intracranial hemorrhage (may be fatal or life threatening), loss of consciousness

Gastrointestinal disorders: gastritis erosive

Eye disorders: eye hemorrhage (intraocular, conjunctival, retinal)

Ear and labyrinth disorders: ear hemorrhage

Musculoskeletal connective tissue and bone: muscular bleedings (hemarthrosis, muscle hemorrhage)

Neoplasms benign, malignant and unspecified (including cysts and polyps): Tumour bleedings (bleeding from bladder cancer, gastric cancer, colon cancer)

Psychiatric disorders: confusion

Renal and urinary disorders: nephrolithiasis and urinary calculus (bladder, ureteric, urethral)

Reproductive system and breast disorders: reproductive system bleedings (vaginal hemorrhage, hematospermia, postmenopausal hemorrhage)

Respiratory, thoracic and mediastinal disorders: pulmonary fibrosis, pulmonary hypertension

Skin and subcutaneous tissue disorders: purpura

Abnormal Hematologic and Clinical Chemistry Findings

Acute Coronary Syndrome

Number (%) of patients with blood creatinine increased and hyperuricemia (PLATO)

	Number (%) of patients	
Abnormal Clinical Chemistry Findings	**Ticagrelor 90 mg bd (N=9235)**	**Clopidogrel 75 mg od (N=9186)**
Blood creatinine increased[a]	335 (8.3%)	271 (6.7%)
Hyperuricemia[b]	889 (22.1%)	537 (13.3%)

Derived from lab observations.

[a] creatinine increased: >50% from baseline in patients with lab data [ticagrelor 90 mg bd (N=4031); clopidogrel 75 mg od (N=4035)]

[b] hyperuricemia: uric acid increase from ≤ ULN at baseline to > ULN in patients with lab data [ticagrelor 90 mg bd (N=4031); clopidogrel 75 mg od (N=4035)]

Upper limit normal (ULN), provided by central lab, is:

8.0 mg/dl for male (age ≤90), 8.3 mg/dl for male (age >90)

6.9 mg/dl for female (age ≤65), 7.3 mg/dl for female (age 66-90), 7.7 mg/dl for female (age >90)

History of Myocardial Infarction (≥ One Year)

Number (%) of patients with blood creatinine increased, hyperuricemia and hemoglobin decreased (PEGASUS)

	Number (%) of patients	
Abnormal Clinical Chemistry Findings	**Ticagrelor 60 mg bd (N=6958)**	**ASA alone (N=6996)**
Blood creatinine increased[a]	243 (3.9%)	234 (3.6%)
Hyperuricemia[b]	444 (9.1%)	296 (5.7%)
Hemoglobin decreased[c]	637 (11.4%)	460 (7.7%)

Derived from lab observations.

[a] creatinine increased: >50% from baseline in patients with lab data [ticagrelor 60 mg (N=6240); ASA alone (N=6543)]

[b] hyperuricemia: uric acid increase from ≤ ULN at baseline to > ULN in patients with lab data [ticagrelor 60 mg (N=4857); ASA alone (N=5229)]

Upper limit normal (ULN), provided by central lab, is:

8.0 mg/dl for male (age ≤90), 8.3 mg/dl for male (age >90)

6.9 mg/dl for female (age ≤65), 7.3 mg/dl for female (age 66-90), 7.7 mg/dl for female (age >90)

[c] ≥ LLN at baseline and any on-treatment value < LLN: the denominator is patients with hemoglobin at baseline and at least one on-treatment [ticagrelor 60 mg (N=5595); ASA alone (N=5976)]

Lower limit normal (LLN), provided by central lab is:

130 g/L for male (age ≤65); 126 g/L for male (age >65)

116 g/L for female (age ≤65); 110 g/L for female (age >65)

Post-Market Adverse Drug Reactions

The following adverse reactions have been identified during post-approval use of BRILINTA. Because these reactions are reported voluntarily from a population of an unknown size, it is not always possible to reliably estimate their frequency.

Immune system disorders: hypersensitivity reactions, including angioedema (see CONTRAINDICATIONS)

Skin and subcutaneous tissue disorders: urticaria, rash

DRUG INTERACTIONS

Overview

Cytochrome P450 (CYP) 3A4/5 are the major enzymes responsible for the metabolism of BRILINTA (ticagrelor) and the formation of the active metabolite. Clinical pharmacology and in vitro data show that there is a complex interaction between ticagrelor and CYP3A4/5. Indeed, depending on the substrate, ticagrelor and its active metabolite are shown to weakly inhibit or weakly activate CYP3A4/5 (see DETAILED PHARMACOLOGY, Pharmacokinetics). CYP enzymes 1A2, 2C19, and 2E1 do not contribute meaningfully *in vitro* to ticagrelor metabolism. Ticagrelor is also a p-glycoprotein (P-gp) substrate and a weak inhibitor of P-gp.

Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 7 Established or Potential Drug-Drug Interactions

Proper Name	Reference	Effect	Clinical Comment
Ketoconazole, a strong CYP3A4 inhibitors	CT	Co-administration of ketoconazole with ticagrelor increased the ticagrelor C_{max} and AUC equal to 2.4-fold and 7.3-fold, respectively. The C_{max} and AUC of ticagrelor's active metabolite were reduced by 89% and 56%, respectively.	Other strong inhibitors of CYP3A4 (clarithromycin, nefazodone, ritonavir, and atazanavir) would be expected to have similar effects and are contraindicated with BRILINTA (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS, General).
Diltiazem, a moderate CYP3A4 inhibitor	CT	Co-administration of diltiazem with ticagrelor increased the ticagrelor Cmax by 69% and AUC by 174% and decreased its active metabolite Cmax by 38% and AUC was unchanged. There was no effect of ticagrelor on diltiazem plasma levels.	Other moderate CYP3A4 inhibitors (e.g., amprenavir, aprepitant, erythromycin, fluconazole, and verapamil) would be expected to have similar effects. These exposure changes are not considered clinically significant, and therefore, can as well be co- administered with BRILINTA.
CYP3A4 inducers, including	CT	Co-administration of rifampin with ticagrelor decreased the ticagrelor	Other strong CYP3A4 inducers (e.g., phenytoin, carbamazepine and phenobarbital) and potentially also

Proper Name	Reference	Effect	Clinical Comment
Rifampin		Cmax and AUC by 73% and 86%, respectively. The Cmax of its active metabolite was unchanged and the AUC was decreased by 46%.	weak to moderate inducers (e.g., dexamethasone) would be expected to decrease the exposure to ticagrelor as well and may result in reduced efficacy of BRILINTA. Alternative treatments should be considered.
Cyclosporine, a P-gp and CYP3A4 inhibitor	CT	Co-administration of cyclosporine (600 mg) with ticagrelor increased ticagrelor Cmax and AUC equal to 2.3-fold and 2.8-fold, respectively. The AUC of the active metabolite of ticagrelor was increased by 32% and Cmax was decreased by 15%. There was no effect of ticagrelor on cyclosporine blood levels.	If the association cannot be avoided, use concomitantly with caution.
Heparin, enoxaparin, acetylsalicylic acid (ASA)	CT	Co-administration of ticagrelor with heparin, enoxaparin and acetylsalicylic acid (ASA) did not have any effect on ticagrelor or its active metabolite plasma levels. Co-administration of ticagrelor and heparin had no effect on heparin based on activated partial thromboplastin time (aPTT) and activated coagulation time (ACT) assays. Co-administration of ticagrelor and enoxaparin had no effect on enoxaparin based on factor Xa assay.	
CY P3A4/5 substrates with narrow therapeutic	CT	Ticagrelor and its active metabolite have the capacity to weakly inhibit or weakly activate	Co-administration of BRILINTA with CYP3A4/5 substrates with narrow therapeutic indices is not recommended. BRILINTA treatment should be

Proper Name	Reference	Effect	Clinical Comment
indices		CYP3A4/5.	interrupted and resumed when therapy with the CYP3A4/5 substrate is no longer required.
Simvastatin	CT	Co-administration of ticagrelor with simvastatin increased the simvastatin C_{max} by 81% and AUC by 56% and increased simvastatin acid C_{max} by 64% and AUC by 52% with some individual increases equal to 2 to 3 fold. There was no effect of simvastatin on ticagrelor plasma levels.	Consideration of the clinical significance should be given to the magnitude and range of changes on the exposure to patients requiring greater than 40 mg of simvastatin. BRILINTA may have similar effect on lovastatin, but is not expected to have a clinically meaningful effect on other statins.
Atorvastatin	CT	Co-administration of atorvastatin and ticagrelor increased the atorvastatin acid Cmax by 23% and AUC by 36%. Similar increases in AUC and Cmax were observed for all atorvastatin acid metabolites.	These increases are not considered clinically significant.
Tolbutamide, a CYP2C9 substrate	CT	Co-administration of ticagrelor with tolbutamide resulted in no change in the plasma levels of either drug.	Ticagrelor is not a CYP2C9 inhibitor and unlikely to alter the metabolism of other drugs metabolized via CYP2C9.
Warfarin	T	A drug-drug interaction study with warfarin has not been performed. As with other oral antiplatelet therapy, there is a potential for increased risk of bleeding.	Warfarin and BRILINTA should be co-administered with caution (see WARNINGS AND PRECAUTIONS, General).
Oral Contraceptives	CT	Co-administration of ticagrelor and levonorgestrel and ethinyl estradiol increased the ethinyl estradiol exposure by approximately 20% but did not alter the PK of levonorgestrel.	No clinically relevant effect on oral contraceptive efficacy is expected when levonorgestrel and ethinyl estradiol are co-administered with BRILINTA.

Proper Name	Reference	Effect	Clinical Comment
Digoxin (P-gp Substrate)	CT	Concomitant administration of ticagrelor increased the digoxin Cmax by 75% and AUC by 28%.	Appropriate clinical and/or laboratory monitoring is recommended when giving narrow therapeutic index P-gp-dependent drugs like digoxin concomitantly with BRILINTA.

Legend: CS = Case Study; CT = Clinical Trial; T = Theoretical

In clinical studies, BRILINTA was commonly administered with ASA, heparin, low molecular weight heparin, intravenous GpIIb/IIIa inhibitors, proton pump inhibitors, statins, beta-blockers, angiotensin converting enzyme inhibitors and angiotensin receptor blockers as needed for concomitant conditions. These studies did not produce any evidence of clinically significant adverse interactions.

Drug-Food Interactions

In a study of healthy subjects, ingestion of a high-fat meal had no effect on ticagrelor C_{max} or the AUC of the active metabolite, but resulted in a 21% increase in ticagrelor AUC and 22% decrease in the active metabolite C_{max}. These changes are considered of minimal clinical significance. BRILINTA was administered without regard to food in PLATO and PEGASUS. Therefore, BRILINTA may be given with or without food.

Grapefruit Juice Interaction: Ingestion of 600 mL of grapefruit juice for four days was shown to increase ticagrelor C_{max} by 65% and AUC by 121% and to decrease its active metabolite C_{max} by 45% and AUC by 14%. Elimination half-life of ticagrelor was prolonged from 6.7 to 7.2 h and of its active metabolite from 8.2 to 12 h. These exposure changes, despite slightly delaying the recovery of platelet reactivity, are not expected to substantially increase bleeding risk in most patients. See WARNINGS AND PRECAUTIONS**,** Peri-Operative Considerations, Surgery for stopping BRILINTA and bleeding risk with respect to surgery.

Drug-Herb Interactions

Interactions with herbal products have not been studied.

Drug-Laboratory Tests Interactions

Interactions with laboratory tests have not been studied.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Patients taking BRILINTA should also take a daily low maintenance dose of ASA 75-150 mg, unless specifically contraindicated.

The PLATO trial data suggest the efficacy of BRILINTA (ticagrelor) 90 mg bid relative to clopidogrel 75 mg od is associated with ASA dose during maintenance therapy. Patients receiving a low maintenance dose of ASA benefit more than those receiving a high maintenance dose of ASA. Because the data from patients receiving high maintenance dose ASA (> 300 mg daily) do not provide conclusive evidence of the efficacy of BRILINTA 90 mg bid compared to clopidogrel 75 mg od, high maintenance dose ASA (> 150 mg daily) is not recommended for maintenance dual antiplatelet therapy with BRILINTA 90 mg. There is no conclusive evidence regarding the underlying biological mechanism (see CLINICAL TRIALS).

Recommended Dose and Dosage Adjustment

Acute Coronary Syndrome

BRILINTA 90 mg therapy should be initiated with a single 180 mg oral loading dose (two 90 mg tablets) and then continued at 90 mg twice daily.

Switching from clopidogrel to BRILINTA 90 mg:

Patients can be switched from clopidogrel to BRILINTA without interruption of antiplatelet effect. This results in an absolute inhibition of platelet aggregation (IPA) increase of 26.4%. Conversely, switching from BRILINTA 90 mg twice daily to clopidogrel 75 mg results in an absolute IPA decrease of 24.5%. Clinicians who desire to switch patients, with a prior ACS event, from clopidogrel to BRILINTA should administer the first dose of BRILINTA 24 hours following the last dose of clopidogrel (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics).

History of Myocardial Infarction (≥One Year)

BRILINTA 60 mg twice daily is the recommended dose when an extended treatment is required for patients with a history of spontaneous MI of at least one year and at high risk of developing an atherothrombotic event. No loading dose of BRILINTA is required. The BRILINTA 90 mg dose should not be used for this indication (see CLINICAL TRIALS).

BRILINTA 60 mg may be started without interruption after the initial one-year treatment with BRILINTA 90 mg or other adenosine diphosphate (ADP) receptor antagonist therapy in ACS patients at high risk of an atherothrombotic event.

Treatment can also be initiated up to two years from the spontaneous myocardial infarction, or within one year after stopping previous ADP receptor antagonist treatment (see CLINICAL TRIALS).

Treatment with BRILINTA should be continued in patients with a history of MI for as long as the patient remains at high risk of an atherothrombotic event for a duration up to three years.

Efficacy and safety data are insufficient to establish whether the benefits of BRILINTA still outweigh the risks after three years of extended treatment.

Switching from another $P2Y_{12}$ receptor antagonist to BRILINTA 60 mg:

Physicians who desire to switch patients with history of MI to BRILINTA should administer the first dose of BRILINTA 24 hours following the last dose of the other $P2Y_{12}$ receptor antagonist.

Dosing Considerations in Special Populations

Geriatrics (≥ 65 years of age)*:* No dosage adjustment is required in elderly (≥ 65 years) patients (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions).

Patients with Renal Insufficiency: No dosage adjustment is required in patients with renal impairment. No clinical study has been conducted in patients on renal dialysis. Ticagrelor is not thought to be dialyzable. Appropriate caution should be used in patients requiring renal replacement therapy (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions).

Patients with Hepatic Insufficiency: No dosage adjustment is required in patients with mild hepatic impairment. No studies have specifically been conducted for BRILINTA in patients with moderate or severe hepatic impairment. There is only limited information on the treatment of patients with moderate hepatic impairment. Therefore, use in patients with moderate or severe hepatic impairment is contraindicated (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions).

Timing of administration of a dose with respect to food
BRILINTA may be taken orally with or without food, may be given without regard to meals. In a study of healthy subjects, ingestion of a high-fat meal had no effect on ticagrelor C_{max} or the AUC of the active metabolite, but resulted in a 21% increase in ticagrelor AUC and 22% decrease in the active metabolite C_{max}. These changes are considered of minimal clinical significance. BRILINTA was administered without regard to food in PLATO (90 mg) and PEGASUS (60 mg).

Missed Dose

Lapses in therapy should be avoided. A patient who misses a dose of BRILINTA should take their next dose at its scheduled time (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics).

Premature Discontinuation

Premature discontinuation with any antiplatelet therapy, including BRILINTA, could result in an increased risk of cardiovascular (CV) death or MI due to the patient's underlying disease (see WARNINGS AND PRECAUTIONS).

Alternate Methods of Administration

For patients who are unable to swallow the tablet(s) whole, BRILINTA tablets (90 mg) can be crushed to a fine powder and mixed in half a glass of water and drunk immediately. The glass should be rinsed with a further half glass of water and the contents drunk. The mixture can also be administered via a nasogastric tube (CH8 or greater). It is important to flush the nasogastric tube through with water after administration of the mixture.

OVERDOSAGE

For management of suspected drug overdose, contact your regional Poison Control Centre.

Treatment

There is currently no known antidote to reverse the effects of BRILINTA (ticagrelor), and ticagrelor is not expected to be dialyzable. Treatment of overdose should follow local standard medical practice. The expected effect of excessive BRILINTA dosing is prolonged duration of bleeding risk associated with platelet inhibition. If bleeding occurs, appropriate supportive measures should be taken (see WARNINGS AND PRECAUTIONS, General).

Signs and Symptoms

Ticagrelor is well tolerated in single doses up to 900 mg. Gastrointestinal toxicity was dose-limiting in a single ascending dose study. Other clinically meaningful adverse effects which may occur with overdose include dyspnea and ventricular pauses.

Single oral doses of ticagrelor to mice caused no observable effects at doses up to 2000 mg/kg. Single oral doses of 500 and 2000 mg/kg ticagrelor to rats caused a transient reduction in body weight with no other observable effects.

In the event of overdose, observe for these potential adverse effects and consider ECG monitoring.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

BRILINTA (ticagrelor), a member of the chemical class cyclopentyl-triazolo-pyrimidines (CPTP), is an oral, direct acting, selective and reversibly binding $P2Y_{12}$ receptor antagonist that prevents adenosine diphosphate (ADP)-mediated $P2Y_{12}$ dependent platelet activation and aggregation. Ticagrelor does not prevent ADP binding but when bound to the $P2Y_{12}$ receptor

prevents ADP-induced signal transduction. Since platelets participate in the initiation and/or evolution of thrombotic complications of atherosclerotic disease, inhibition of platelet function has been shown to reduce the risk of cardiovascular events such as death, myocardial infarction or stroke.

There is also evidence that ticagrelor reduces cellular uptake of adenosine and prolongs this nucleotide half-life, thereby increasing local endogenous adenosine levels, via an inhibitory action of equilibrative nucleoside transporter type I (ENT-1). Whether the ticagrelor-induced increase in adenosine is clinically relevant to the safety and efficacy of BRILINTA remains to be demonstrated.

Pharmacodynamics

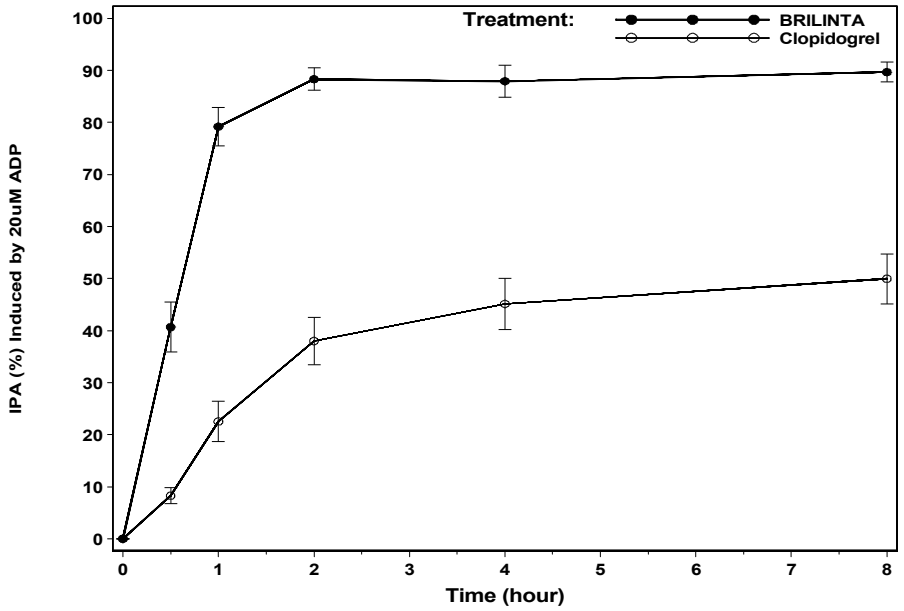
Inhibition of platelet aggregation mediated by ticagrelor increases with increasing plasma concentrations of ticagrelor and its active metabolite (AR-C124910XX), until almost complete inhibition is attained. The Inhibition of Platelet Aggregation (IPA) gradually decreases with declining plasma ticagrelor and active metabolite concentrations, as the IPA mediated by ticagrelor is reversible. Since ticagrelor reversibly binds to the $P2Y_{12}$ receptor, the recovery of platelet function is expected to be dependent on the plasma concentrations of ticagrelor and the active metabolite and not on the replacement of irreversibly inhibited platelets as with thienopyridine antiplatelet agents.

The IPA of ticagrelor is generally independent of factors such as race, hepatic or renal disease or co-administered ASA, heparin and enoxaparin.

Onset of Action

In patients with stable coronary artery disease on ASA, ticagrelor demonstrates a rapid onset of IPA effect (Figure 1). Mean IPA for ticagrelor at 0.5 hours after 180 mg loading dose is about 41%, which is similar to clopidogrel's (600 mg) maximum effect of 50% observed at 8 hours. Ninety percent of patients had final extent IPA > 70% by 2 hours post dose versus 16% for clopidogrel. Ticagrelor's maximum IPA effect of approximately 88% is reached at around 2 hours, and the IPA between 87%-89% was maintained from 2-8 hours.

Figure 1: **Mean final extent IPA (±SD) following single oral doses of 180 mg BRILINTA or 600 mg clopidogrel in patients with stable coronary artery disease**

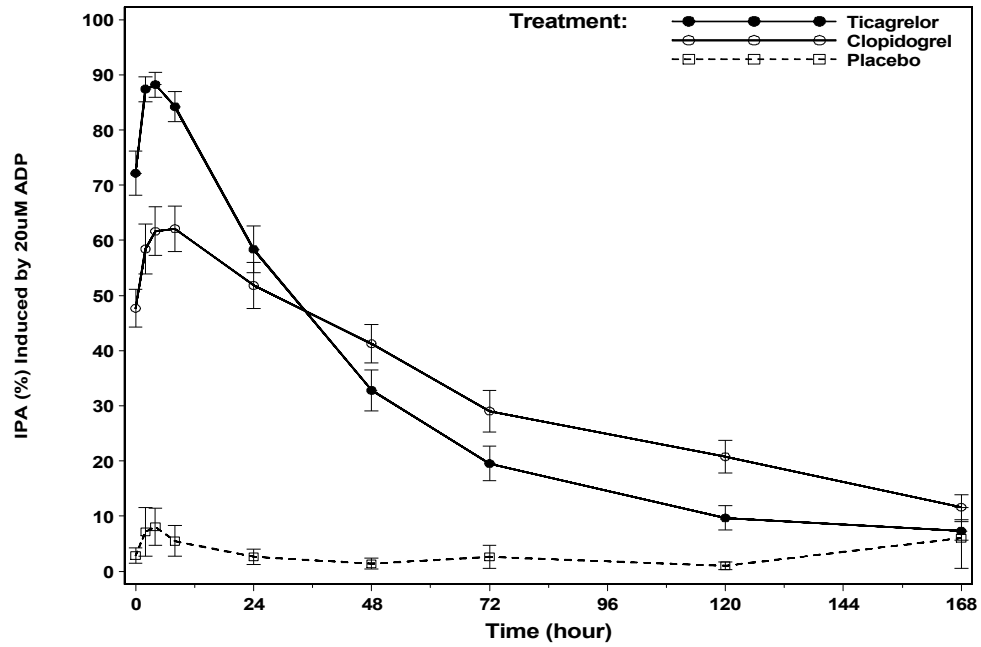


Offset of Effect

After ticagrelor and its active metabolite concentrations decline to a level less than that required for receptor saturation, IPA gradually decreases with declining plasma concentrations. Since ticagrelor binds reversibly, the recovery of platelet function does not depend on replacement of platelets. Ticagrelor has a faster rate of offset of IPA as compared to clopidogrel as determined by the slope of offset from 4-72 hours after last dose (see WARNINGS AND PRECAUTIONS, Peri-Operative Considerations).

Final extent IPA during the 90 mg twice daily-dosing interval is approximately 20%-30% (absolute difference) higher for ticagrelor compared to clopidogrel (75 mg, once daily). However, by 24 hours following the last maintenance dose, the IPA is similar between ticagrelor (58%) and clopidogrel (52%), indicating that patients who miss a dose of ticagrelor would have an IPA level comparable to those treated with once daily clopidogrel (Figure 2).

Figure 2: **Mean final extent IPA (±SE) following the last maintenance dose of 90 mg twice daily BRILINTA or 75 mg clopidogrel once daily or placebo**



Responders to BRILINTA

The IPA induced by BRILINTA has less variability with the 90 mg twice daily dose compared to clopidogrel 75 mg once daily. Patients with stable coronary artery disease predetermined to have low IPA response to clopidogrel (non-responders), and given a concomitant dose of ASA, exhibited higher mean IPA response after administration of BRILINTA as compared to clopidogrel.

Switching Data

Switching from clopidogrel 75 mg once daily to BRILINTA 90 mg twice daily results in an absolute IPA increase of 26.4% and switching from BRILINTA to clopidogrel results in an absolute IPA decrease of 24.5%. Patients can be switched from clopidogrel to BRILINTA without interruption of antiplatelet effect (see DOSAGE AND ADMINISTRATION).

Pharmacokinetics

Ticagrelor demonstrates linear pharmacokinetics. Exposure to ticagrelor and its active metabolite are approximately dose proportional.

The main pharmacokinetic parameters for ticagrelor are presented in the table below.

	C_{max} (ng/mL)	t½ (h)	Clearance (L/hr)*	Volume of distribution (L)*
Single oral dose mean (90 mg)	500	6.9	14.2	87.5

* Following a single intravenous dose of 15 mg ticagrelor.

Absorption: Absorption of ticagrelor is rapid with a median t_{max} of approximately 1.5 hours. The formation of the major circulating metabolite AR-C124910XX (also active) from ticagrelor is rapid with a median t_{max} of approximately 2.5 hours. The C_{max} and AUC of ticagrelor and the active metabolite increased in an approximately proportional manner with dose over the dose range studied (30-1260 mg). The pharmacokinetics of ticagrelor and AR-C124910XX in patients with a history of MI (> one year) were generally similar to that in the ACS population. Based on a population pharmacokinetic analysis of the PEGASUS study the median ticagrelor Cmax was 391 ng/ml and AUC was 3801 ng*h/ml at steady state for ticagrelor 60 mg. For ticagrelor 90 mg Cmax was 627 ng/ml and AUC was 6255 ng*h/ml at steady state.

The mean absolute bioavailability of ticagrelor was estimated to be 36%, (range 25.4%-64.0%). In a study of healthy subjects, ingestion of a high-fat meal had no effect on ticagrelor C_{max} or the AUC of the active metabolite, but resulted in a 21% increase in ticagrelor AUC and 22% decrease in the active metabolite C_{max}. These changes are considered of minimal clinical significance. BRILINTA was administered without regard to food in PLATO. Therefore, BRILINTA may be given with or without food.

Ticagrelor as crushed tablets mixed in water, given orally or administered through a nasogastric tube into the stomach to 36 healthy volunteers, is bioequivalent to whole tablets. Ticagrelor and the active metabolite (AUC and Cmax are well within the 80-125% range required to demonstrate bioequivalence. Initial exposure (0.5 and 1 hour post-dose) from crushed ticagrelor tablets mixed in water was higher compared to whole tablets, with a generally identical concentration profile thereafter (2 to 48 hours).

Distribution: The steady state volume of distribution of ticagrelor is 87.5 L. Ticagrelor and the active metabolite are extensively bound to human plasma proteins (> 99%).

Metabolism: The major metabolite of ticagrelor is AR-C124910XX, which is also active as assessed by *in vitro* binding to the platelet $P2Y_{12}$ ADP-receptor. The systemic exposure to the active metabolite is approximately 30-40% of that obtained for ticagrelor.

CYP3A is the major enzyme responsible for ticagrelor metabolism and the formation of the active metabolite and their interactions with other CYP3A substrates ranges from activation through to inhibition. Ticagrelor and the active metabolite are weak p-glycoprotein inhibitors.

Excretion: The primary route of ticagrelor elimination is via hepatic metabolism. When radiolabelled ticagrelor is administered, the mean recovery of radioactivity is approximately 84% (57.8% in feces, 26.5% 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 active metabolite is most likely via biliary secretion. The mean $t_{1/2}$ was approximately 6.9 hours (range 4.5-12.8 hours) for ticagrelor and 8.6 hours (range 6.5-12.8 hours) for the active metabolite.

Special Populations and Conditions

Pediatrics (< 18 years of age): Ticagrelor has not been evaluated in a pediatric population.

Geriatrics (≥ 65 years of age): Higher exposures to ticagrelor (approximately 60% for both C_{max} and AUC) and the active metabolite (approximately 50% for both C_{max} and AUC) were observed in elderly (≥ 65 years) subjects compared to younger (18-45 years) subjects. These differences are not considered clinically significant. No dose adjustment is needed for elderly patients (see WARNINGS AND PRECAUTIONS, Special Populations and DOSAGE AND ADMINISTRATION, Dosing Consideration in Special Populations).

Gender: Higher exposures to ticagrelor (approximately 52% and 37% for C_{max} and AUC, respectively) and the active metabolite (approximately 50% for both C_{max} and AUC) were observed in women compared to men. These differences are not considered clinically significant.

Body Weight: Body weight was determined to have less than a 20% change in the population mean clearance for both ticagrelor and the active metabolite at the 10^{th} or 90^{th} percentile of the body weight distribution compared to the population mean clearance at the median. This small effect on the clearance is not considered clinically relevant. Accordingly, no dose adjustment is necessary for ticagrelor based on weight.

Ethnicity: Patients of Asian descent have a 39% higher bioavailability compared to Caucasian patients. Patients self-identified as Black had an 18% lower bioavailability of ticagrelor compared to Caucasian patients. In clinical pharmacology studies, the exposure (C_{max} and AUC) to ticagrelor in Japanese subjects was approximately 40% (20% after adjusting for body weight) higher compared to that in Caucasians. These differences are not considered clinically relevant. The exposure in patients self-identified as Hispanic or Latino was similar to that in Caucasian.

Smoking: Habitual smoking increased population mean clearance of ticagrelor by approximately 22%. This effect on the clearance is not considered clinically relevant.

Renal Insufficiency: Exposure to ticagrelor was approximately 20% lower and exposure to the active metabolite was approximately 17% higher in patients with severe renal impairment compared to subjects with normal renal function. The IPA effect of ticagrelor was similar between the two groups, however there was more variability observed in individual response in patients with severe renal impairment. No dose adjustment is needed for patients with renal impairment. No clinical study has been conducted in patients on renal dialysis. Ticagrelor is not thought to be dialyzable. Appropriate caution should be used in patients requiring renal

replacement therapy (see WARNINGS AND PRECAUTIONS, Special Populations and DOSAGE AND ADMINISTRATION, Dosing Consideration in Special Populations).

Hepatic Insufficiency: The C_{max} and AUC for ticagrelor were 12% and 23% higher in patients with mild hepatic impairment compared to matched healthy subjects, respectively, however the IPA effect of ticagrelor was similar between the two groups. No dose adjustment is needed for patients with mild hepatic impairment. No studies have specifically been conducted with ticagrelor in patients with moderate or severe hepatic impairment. Only limited information is available in patients with moderate hepatic impairment. Therefore it is contraindicated for use in patients with moderate or severe hepatic impairment (see CONTRAINDICATIONS and DOSAGE AND ADMINISTRATION, Dosing Consideration in Special Populations).

STORAGE AND STABILITY

Store between 2-30°C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms

BRILINTA (ticagrelor) is available as 90 mg film-coated tablets which are round, biconvex, yellow, and intagliated with $^{90}_{T}$ on one side and plain on the reverse side.

BRILINTA (ticagrelor) is available as 60 mg film-coated tablets which are round, biconvex, pink, and intagliated with $^{60}_{T}$ on one side and plain on the reverse side.

Composition

Each tablet contains either 60 mg or 90 mg of ticagrelor. Each tablet also contains the following non-medicinal ingredients: dibasic calcium phosphate, ferric oxide black (60 mg coating), ferric oxide red (60 mg coating), ferric oxide yellow (90 mg coating), hydroxypropyl cellulose, hypromellose, magnesium stearate, mannitol, polyethylene glycol 400, sodium starch glycolate, talc (90 mg coating) and titanium dioxide.

Packaging

BRILINTA 90 mg is available in blister compliance packs of 60 tablets (4 x 15 tablets).

BRILINTA 90 mg is available in HDPE bottles of 60 tablets for institutional use only.

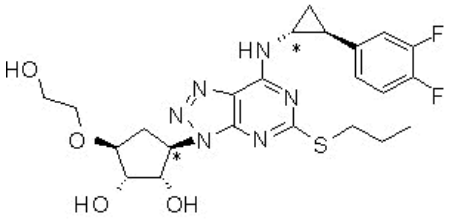
BRILINTA 60 mg is available in blister compliance packs of 60 tablets (4 x 15 tablets).

BRILINTA 60 mg is available in HDPE bottles of 60 tablets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Common Name:	Ticagrelor
Chemical Name:	(1S,2S,3R,5S)-3-[7-{[(1R,2S)-2-(3,4-Difluorophenyl)cyclopropyl]amino}-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl]-5-(2-hydroxyethoxy)cyclopentane-1,2-diol
Molecular Formula and Molecular Mass:	$C_{23}H_{28}F_2N_6O_4S$ (522.57)
Structural Formula:	
Physicochemical Properties:	Ticagrelor is a crystalline powder with an aqueous solubility of approximately 10µg/mL at room temperature. Ticagrelor exhibits no pKa value within the physiological range. Ticagrelor does not exhibit pH dependent solubility and is defined as 'low solubility' under the Biopharmaceutics Classification System. There are 4 non-solvated polymorphs (denoted Polymorph I, II, III and IV) and a number of solvated crystalline modifications of ticagrelor as distinguishable by X-Ray Powder Diffraction. Melting Point: About 140°C to 142°C as measured by differential scanning calorimetry. Partition Coefficient: Ticagrelor exhibits a log P (octanol/water) of >4.0 measured according to the OECD test guideline 107. Optical Rotation: The specific optical rotation of 1% w/v ticagrelor in ethanol is approximately -52°.

CLINICAL TRIALS

The safety and efficacy of BRILINTA in preventing atherothrombotic events has been evaluated in two large double-blind trials involving more than 39,000 patients: the PLATO study (BRILINTA 90 mg b.i.d. vs. Clopidogrel 75 mg o.d. both given in combination with acetylsalicylic acid (ASA) and other standard therapy in patients with acute coronary syndrome); and the PEGASUS TIMI-54 study (BRILINTA 90 mg b.i.d. and 60 mg b.i.d. both combined with ASA vs. ASA alone in patients with history of spontaneous MI (reported at least 1 year ago) and at risk of an atherothrombotic event).

Study Demographics and Trial Design

Table 8 Summary of patient demographics for clinical trials in specific indication

Study	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
PLATO	International, randomised, double-blind, parallel-group study comparing BRILINTA to clopidogrel	Dosage: BRILINTA (90 mg twice daily) or clopidogrel (75 mg once daily), in combination with ASA; Administration: oral; Duration: up to one year	N=18,624 BRILINTA n=9,333; Clopidogrel n=9,291	Mean = 62 years (19-97 years) < 65=57% ≥ 65 years=43% < 75years=85% ≥ 75 years=15%	Male 72% Female 28%
PEGASUS	Randomized, double-blind, placebo-controlled, parallel-group study	Dosage: 90 mg bid, 60 mg bid, or placebo bid on a background of ASA (75-150 mg od) Administration: Oral Maximum duration: 47 months Event rates calculated at 36 months	N=21,162 90 mg: 7,050 60 mg: 7,045 Placebo: 7,067	Mean = 65 years (50-95 years) < 65 years=46% 65-75 years=42% >75 years=12%	Male 76% Female 24%

PLATO – ACUTE CORONARY SYNDROME

Study Design

The PLATO study was a Phase III efficacy and safety study of BRILINTA compared with clopidogrel for the prevention of vascular events in patients with ACS (unstable angina [UA], non ST elevation Myocardial Infarction [NSTEMI] or ST elevation Myocardial Infarction [STEMI]).

Patients were randomized to receive BRILINTA (a loading dose of 180 mg followed by a maintenance dose of 90 mg twice daily) or clopidogrel (75 mg once daily, with an initial

loading dose of 300 mg if previous thienopyridine therapy had not been given. An additional loading dose of 300 mg was allowed at investigator discretion).

The study was comprised of patients who presented within 24 hours of onset of the most recent episode of chest pain or symptoms. The initiation of treatment in PLATO occurs shortly after symptom onset, prior to the assessment of coronary anatomy by angiography. Patients could have been medically managed, treated with percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG). Patients were treated for at least 6 months and up to 12 months duration, and patients were followed to study termination, irrespective of whether study drug had been discontinued. The baseline characteristics, medical history, electrocardiographic changes, and drug therapy were similar for both treatment groups.

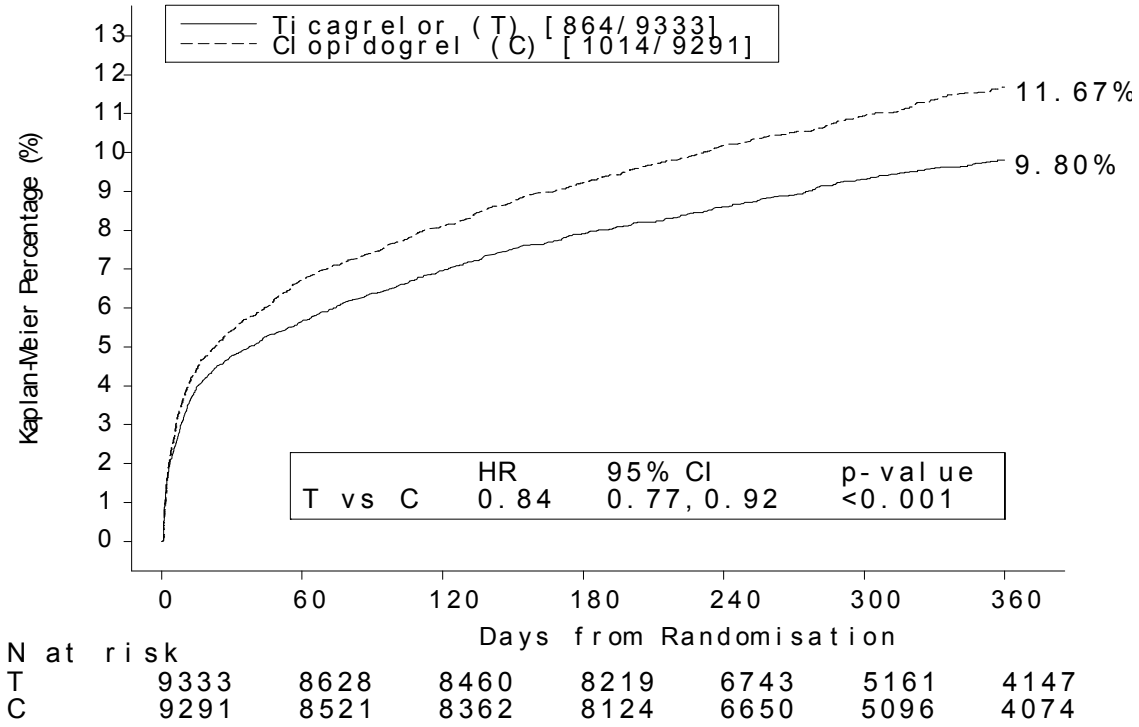
Study Results

BRILINTA was superior to clopidogrel in the prevention of thrombotic events (relative risk reduction [RRR] of 16%, absolute risk reduction [ARR] of 1.9%, number needed to treat [NNT] of 54) in the composite efficacy endpoint (primary endpoint) of CV death, MI, and stroke over 12 months in patients with ACS events (UA, NSTEMI and STEMI population) (hazard ratio [HR] 0.84; p=0.0003) (Figure 3). The difference in treatments was driven by CV death and MI with no difference on strokes. BRILINTA demonstrated a statistically significant RRR of 21% (ARR 1.1%) for CV death and a RRR of 16% (ARR 1.1%) for MI, as compared to clopidogrel (Table 5). Treating 91 patients with BRILINTA instead of clopidogrel will prevent 1 CV death.

BRILINTA reduced the occurrence of the primary composite endpoint compared to clopidogrel in both the UA/NSTEMI and STEMI population.

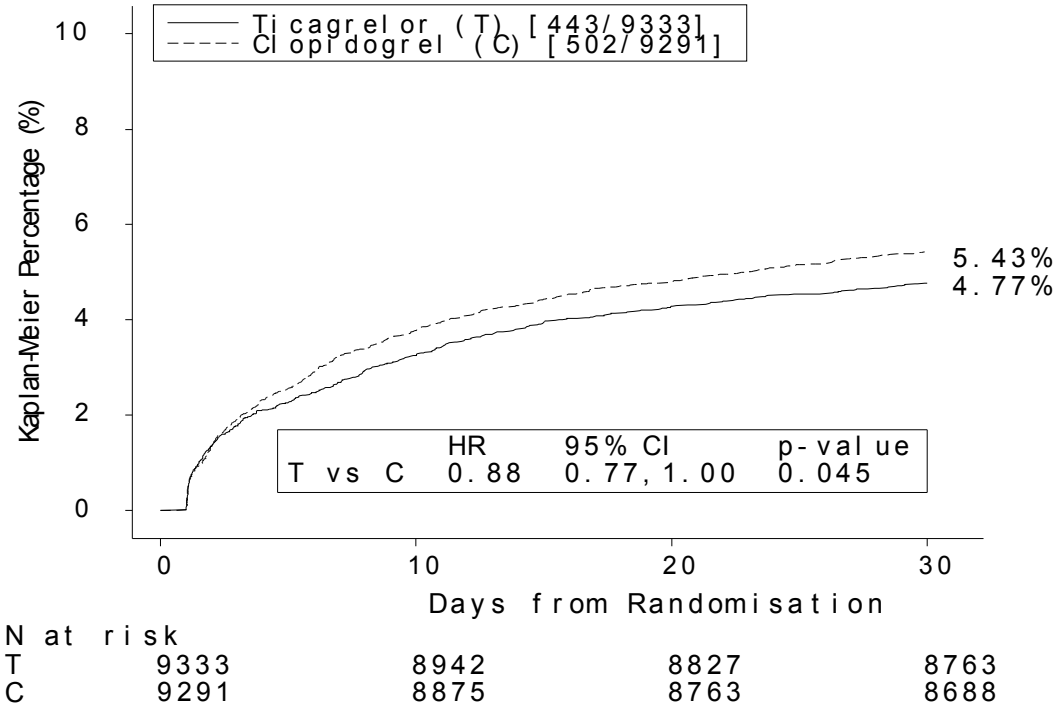
The Kaplan Meier curve (Figure 3) shows the primary composite endpoint of CV death, MI and Stroke in the UA/NSTEMI and STEMI populations. The treatment effect of BRILINTA was apparent in the first 30 days and the degree of benefit continued to increase throughout the 12 month follow-up.

Figure 3: Time to first occurrence of CV death, MI and stroke (PLATO)



Within the first 30 days of treatment (Figure 4), BRILINTA shows a statistically significant early benefit (ARR 0.6%, RRR 12%), with a constant treatment effect over the entire 12 month period, yielding ARR 1.9% per year with RRR of 16%. Together, these findings demonstrate that the benefit of BRILINTA treatment continues to accrue over 1 to 12 months, and suggests that it is appropriate to treat ACS patients with BRILINTA for at least 12 months.

Figure 4: **Primary clinical endpoint by consistency of treatment effect over time at 1-30 days**



The final secondary endpoint (all-cause mortality) was evaluated. BRILINTA demonstrated a RRR of 22% for all-cause mortality compared to clopidogrel at a nominal significance level of p=0.0003 and an ARR of 1.4% (Table 9).

Table 9: **Analysis of primary and secondary efficacy endpoints in PLATO (full analysis set)**

	Patients with Events				
	BRILINTA 90 mg twice daily (%) N=9333	Clopidogrel 75 mg once daily (%) N=9291	RRR (%)	HR (95% CI)	p-value
Primary Endpoint					
Composite of CV Death/MI (excl. silent MI)/Stroke	9.3	10.9	16	0.84 (0.77,0.92)	0.0003
Each component of primary efficacy endpoint:					
CV death	3.8	4.8	21	0.79 (0.69, 0.91)	0.0013

MI (excl. silent MI)	5.4	6.4	16	0.84 (0.75, 0.95)	0.0045
Stroke	1.3	1.1	-17	1.17 (0.91, 1.52)	0.2249
Secondary Endpoints					
Composite of CV death/MI (excl. silent MI)/stroke intent to invasively manage	8.5	10.0	16	0.84 (0.75, 0.94)	0.0025
Composite of all-cause mortality/MI (excl. silent MI)/stroke	9.7	11.5	16	0.84 (0.77, 0.92)	0.0001
Composite of CV Death/Total MI/Stroke/SRI/RI/TIA/Other ATE	13.8	15.7	12	0.88 (0.81, 0.95)	0.0006
All-cause mortality	4.3	5.4	22	0.78 (0.69, 0.89)	0.0003*

Note: A single event may be counted in more than 1 row.
ATE Arterial thrombotic events; excl. Excluding; HR Hazard ratio; RI Recurrent cardiac ischaemia; SRI Severe recurrent cardiac ischaemia; TIA Transient ischaemic attack.
* Nominal p-value.

Subgroup Analyses: In PLATO, a large number of subgroup comparisons were conducted for the primary efficacy endpoint to assess the robustness and consistency of the overall benefit. The treatment effect of BRILINTA versus clopidogrel appears consistent across multiple patient subgroups by demographic characteristics including age, gender, weight, diabetes mellitus, planned treatment approach (medically managed or invasive), prior TIA or stroke, medical history, concomitant therapy, and by final index event diagnosis (UA, NSTEMI and STEMI).

A marginally significant treatment interaction was observed with region whereby the HR for the primary endpoint favours BRILINTA in the rest of world but favours clopidogrel in North America, which represented approximately 10% of the overall population studied (interaction p-value=0.045). This apparent treatment-by-region interaction observed in PLATO could plausibly be attributed to chance, at least in part. Additional analyses suggest that the efficacy of BRILINTA relative to clopidogrel is associated with ASA dose during maintenance therapy. The data show greater efficacy of ticagrelor compared to clopidogrel when used in conjunction with low maintenance dose ASA (75-150 mg daily). The relative efficacy of ticagrelor versus clopidogrel when used with high doses of ASA (> 300 mg daily) is less certain. Based on this observed relationship between maintenance ASA dose and relative efficacy of ticagrelor compared to clopidogrel, it is recommended that BRILINTA is used with a daily low maintenance dose of ASA 75-150 mg (see INDICATIONS, WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION).

The benefits associated with BRILINTA were also independent of the use of other acute and long-term cardiovascular therapies, including heparin, low molecular weight heparin (LMWH), intravenous GpIIb/IIIa inhibitors, lipid-lowering drugs, beta-blockers, angiotensin-

converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists, and proton pump inhibitors (PPIs). The use of oral anticoagulants, and non-study antiplatelet drugs was not allowed in PLATO (see DRUG INTERACTIONS).

Holter Substudy: To study the occurrence of ventricular pauses and other arrhythmic episodes during PLATO, investigators performed Holter monitoring in a subset of nearly 3,000 patients, of whom approximately 2,000 had recordings both in the acute phase of their ACS and after one month. The primary variable of interest was the occurrence of ventricular pauses ≥ 3 seconds. More patients had ventricular pauses with BRILINTA (6.0%) than with clopidogrel (3.5%) in the acute phase; and 2.2% and 1.6% respectively after 1 month. However, there were no adverse clinical consequences associated with this imbalance (including pacemaker insertions) in this population of patients.

PLATO *Genetic Substudy*

CYP2C19 genotyping of 10,285 patients in PLATO provided associations of genotype groups with the efficacy and safety outcomes. The effects of BRILINTA compared to clopidogrel on major CV events and bleeding were not significantly affected by *CYP2C19* genotype. The efficacy and safety results of the substudy were consistent with the main PLATO study.

PEGASUS TIMI-54 – PATIENTS WITH HISTORY OF MYOCARDIAL INFARCTION (≥One Year)

Study Design

The PEGASUS study assessed the prevention of atherothrombotic events with BRILINTA given at 2 doses (either 90 mg twice daily or 60 mg twice daily) combined with low dose ASA (75-150 mg) compared to ASA therapy alone, in patients with history of spontaneous MI and additional risk factors for atherothrombosis.

Patients were eligible to participate if they were aged 50 years of over, with a history of spontaneous MI (1 to 3 years prior to randomisation), and had at least one of the following risk factors for atherothrombosis: age ≥65 years, diabetes mellitus requiring medication, a second prior MI, evidence of multivessel CAD, and/or chronic non-end-stage renal dysfunction.

Patients were ineligible if there was planned use of ADP receptor antagonist, dipyridamole, cilostazol, or needed chronic anticoagulant therapy; if they had a bleeding disorder or a history of an ischemic stroke or intracranial bleeding, a central nervous system tumour, or an intracranial vascular abnormality; if they had had intracranial or spinal cord surgery within the previous 5 years; if they had had gastrointestinal bleeding within the previous 6 months or major surgery within the previous 30 days.

The PEGASUS study was conducted for a duration up to 47 months with mean (median) duration of exposure to ticagrelor 60 mg of 25.3 months (29.4 months): 5, 481 patients (79%) were exposed for at least 12 months; 4, 505 patients (65%) for at least 24 months; and 1, 620

patients (23%) for at least 36 months of extended treatment. Patients were followed to study termination, irrespective of whether study drug had been discontinued.

Study Results

Although the efficacy profile of BRILINTA 90 mg twice daily and 60 mg twice daily were similar, there is evidence that the lower dose has a better tolerability and safety profile in relation to the risk of bleeding and dyspnea. Therefore, BRILINTA 60 mg twice daily co-administered with ASA is the approved dose for the prevention of atherothrombotic events (CV death, MI and stroke) in patients with a history of spontaneous myocardial infarction (MI occurred at least one year ago) and a high risk of developing an atherothrombotic event.

BRILINTA 60 mg twice daily, in combination with ASA, was superior to ASA alone in the prevention of atherothrombotic events (composite endpoint: CV death, MI and stroke), with a consistent treatment effect over the entire study period, yielding a 16% relative risk reduction [RRR] and 1.27% absolute risk reduction [ARR] (number needed to treat [NNT] of 79) after 36 months of treatment (Table 10). Each of the components contributed to the reduction in the primary composite endpoint (CV death 17% RRR, MI 16% RRR and stroke 25% RRR). Treating 189 patients for up to 36 months with BRILINTA 60 mg twice daily in combination with ASA instead of ASA therapy alone will prevent one CV death.

The benefit of ticagrelor seen on the primary composite endpoint was also reflected across the two secondary endpoints, with a numerical decrease in both CV death and all-cause mortality for ticagrelor 60 mg combined with ASA compared to ASA therapy alone, but this did not reach statistical significance (see Table 10).

Table 10: Analysis of primary and secondary efficacy endpoints in PEGASUS (full analysis set)

	BRILINTA 60 mg twice daily + ASA N= 7045	**ASA alone N = 7067**	**RRR%**	**HR (95% CI)**	***p*-value**
Characteristic	**Patients with events**	**Patients with events**			
Primary endpoint					
Composite of CV Death/MI/stroke	487 (6.9%)	578 (8.2%)	16%	0.84 (0.74, 0.95)	0.0043
CV death	174 (2.5%)	210 (3.0%)	17%	0.83 (0.68, 1.01)	0.0676
MI	285 (4.0%)	338 (4.8%)	16%	0.84 (0.72, 0.98)	0.0314

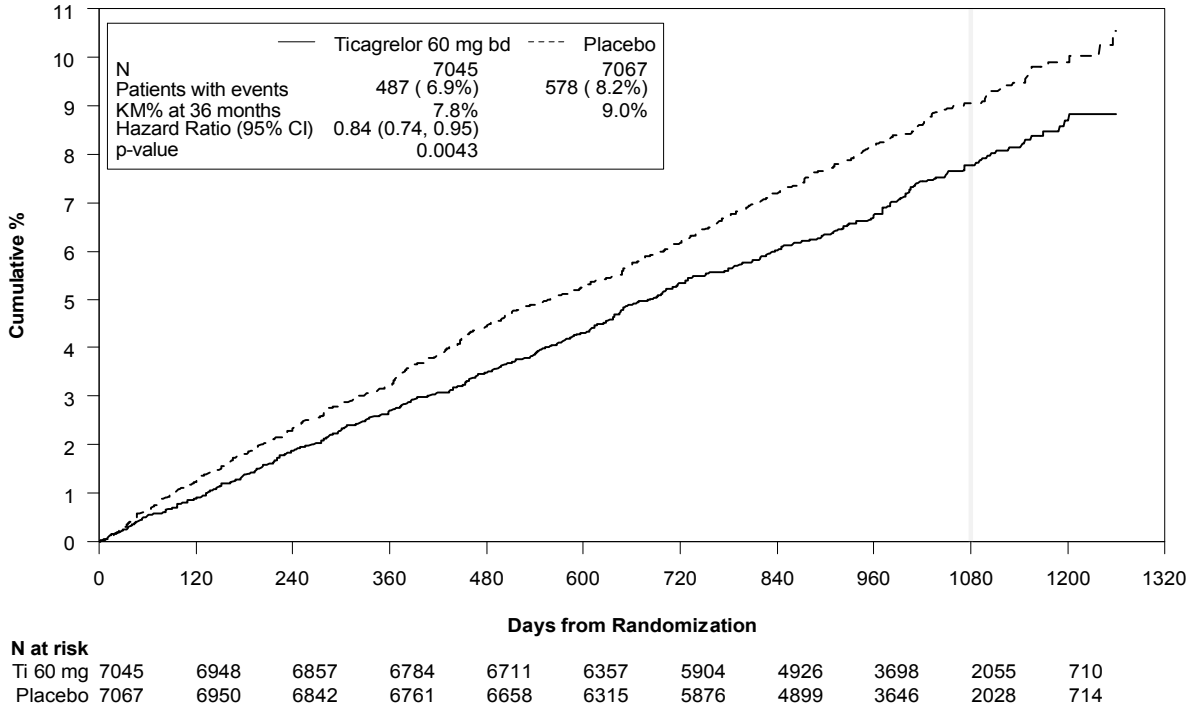
	BRILINTA 60 mg twice daily + ASA N= 7045	**ASA alone N = 7067**	**RRR%**	**HR (95% CI)**	***p*-value**
Characteristic	**Patients with events**	**Patients with events**			
Stroke	91 (1.3%)	122 (1.7%)	25%	0.75 (0.57, 0.98)	0.0337
Secondary endpoint					
CV death	174 (2.5%)	210 (3.0%)	17%	0.83 (0.68, 1.01)	-
All-cause mortality	289 (4.1%)	326 (4.6%)	11%	0.89 (0.76, 1.04)	-

Hazard ratio and p-values are calculated separately for ticagrelor versus ASA alone from Cox proportional hazards model with treatment group as the only explanatory variable.
Note: the number of first events for the components CV Death, MI and Stroke are the actual number of first events for each component and do not add up to the number of events in the composite endpoint.
CI = Confidence interval; CV = Cardiovascular; HR = Hazard ratio; MI = Myocardial infarction; N = Number of patients.

The RRR for the composite endpoint from 1 to 360 days (17% RRR) and from 361 days and onwards (16% RRR) was similar. The Kaplan-Meier plot (Figure 5) shows the analysis of the primary clinical composite endpoint of CV death, MI and stroke.

Treatment with BRILINTA should be continued in patients with a history of spontaneous MI for as long as the patient remains at high risk of an atherothrombotic event for a duration up to three years. Efficacy and safety data are insufficient to establish whether the benefits of BRILINTA still outweigh the risks after three years of extended treatment (see DOSAGE AND ADMINISTRATION).

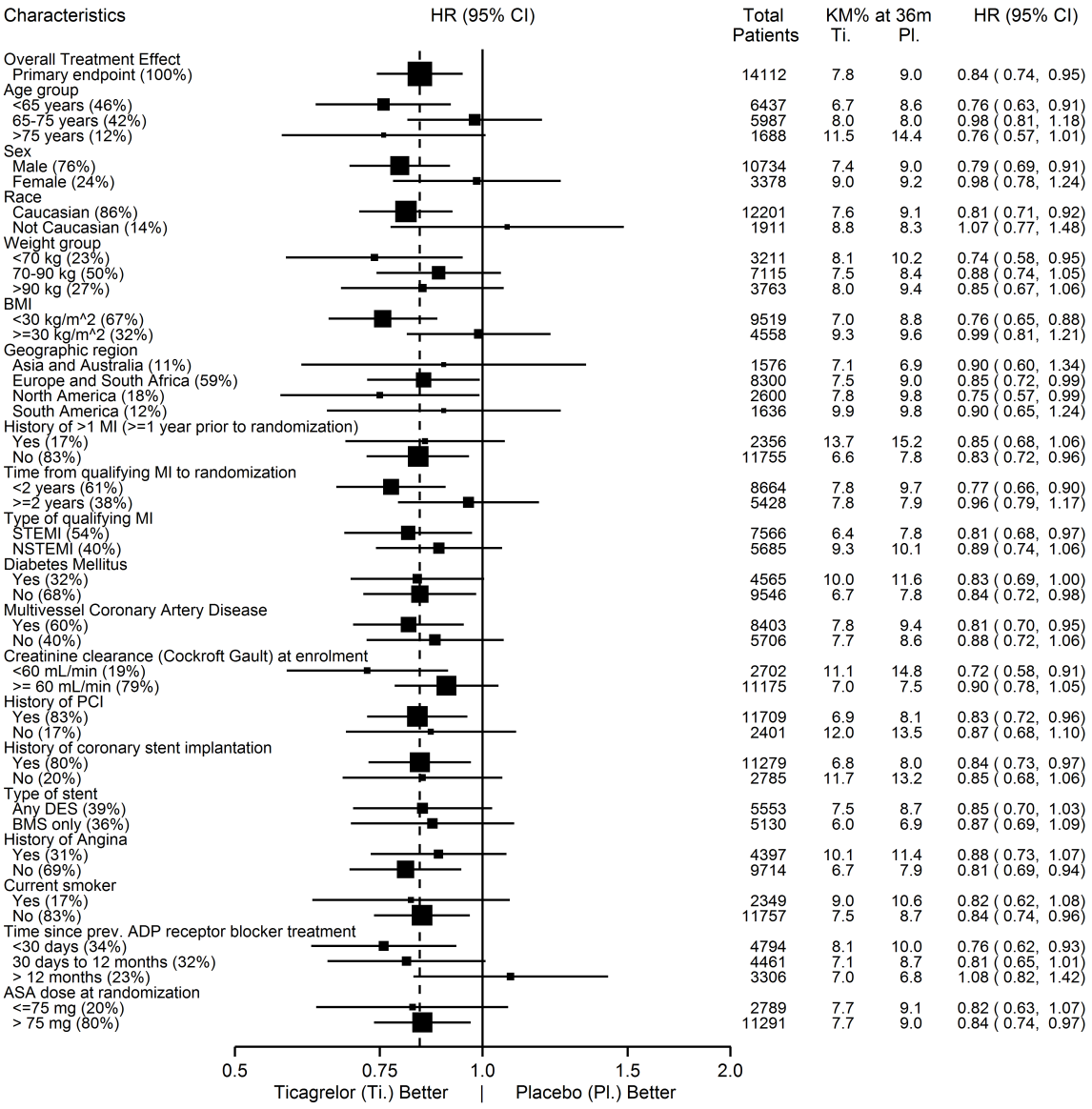
Figure 5: Primary clinical composite endpoint of CV death, MI and stroke in PEGASUS (full analysis set)



Analysis of patient subgroups

The treatment effect of BRILINTA 60 mg twice daily versus ASA across major subgroups is presented in Figure 6. There was no evidence of benefit (no reduction in the primary composite endpoint of CV death, MI and stroke), but an increase in major bleedings when ticagrelor 60 mg twice daily was introduced in clinically stable patients more than 2 years after the qualifying MI, or more than one year after stopping previous ADP receptor antagonist treatment. This also resulted in numerical increases in CV death and all-cause mortality (see DOSAGE AND ADMINISTRATION).

Figure 6: Hazard ratios and rates of the primary clinical composite endpoint of CV death, MI and stroke by patient subgroup in PEGASUS (full analysis set)



DETAILED PHARMACOLOGY

Pharmacodynamics

Mechanism of action

The primary mechanism of action of ticagrelor is the antagonism of platelet $P2Y_{12}$ receptors resulting in the inhibition of adenosine diphosphate (ADP)-induced platelet aggregation. Indeed, ticagrelor and its active metabolite AR-C124910XX were shown to similarly displace a specific $P2Y_{12}$ receptor radioligand from the $P2Y_{12}$ receptors on the surface of human washed platelets *in vitro*, with a Ki of 2.0 nM and 2.5 nM, respectively. Ticagrelor concentration-dependently inhibited ADP-induced platelet aggregation in suspensions of human and rat washed platelets. It also inhibited ADP-induced platelet aggregation in human platelet rich plasma as well as in marmoset and human whole blood. The ADP-induced platelet aggregation measured *ex vivo* as well as dynamic arterial thrombosis in the damaged femoral artery were also reduced following i.v. administration of ticagrelor in anaesthetised male Beagle dogs. The major circulating metabolite of ticagrelor, O-deethylated AR-C124910XX, showed pharmacological activity comparable to that of the parent molecule.

Therefore, ticagrelor is a selective, reversibly bound and orally active $P2Y_{12}$ receptor antagonist that prevents ADP-mediated platelet activation and aggregation. It is also characterised as a noncompetitive antagonist since its binding site on the platelet $P2Y_{12}$ receptor is different from that of ADP.

Effects on the Adenosine System

Ticagrelor has been shown to potently, concentration dependently and reversibly inhibit ENT-1. The affinity of ticagrelor for ENT-1 has been documented to be 41 nM. The main circulating metabolite of ticagrelor, AR-C124910XX, that has been reported to have a similar affinity for $P2Y_{12}$ as ticagrelor, only has weak affinity for ENT-1, 330 nM.

Effect on the uric acid uptake

Ticagrelor, AR-C124910 (active metabolite) and AR-C133913 (inactive metabolite) were shown to have an inhibitory effect on the OAT-3-dependent uric acid uptake (Ki: AZD6140: 4.9 μM; AR-C124910: 16.3 μM; and AR-C133913: 13.4 μM). They also have a weak inhibitory effect on the URAT1-mediated uric acid uptake. These results suggest that ticagrelor and its metabolites may interfere with the renal transport of uric acid which is consistent with the observation that patients on BRILINTA had a higher risk of hyperuricemia.

Pharmacokinetics

Ticagrelor was found to be widely distributed in rat tissues and the major organs identified were those associated with metabolism and excretion (liver, pancreas and kidney) as well as glandular tissues (adrenal and pituitary glands), but no accumulation seemed to occur. The

metabolic pathways for ticagrelor were found to be qualitatively similar across species and no human specific metabolites were detected.

There is a complex interaction between ticagrelor and CYP3A4/5, depending on the substrate used. *In vitro*, ticagrelor weakly inhibits testosterone 6ß-hydroxylation, moderately inhibits midazolam 4-hydroxylation and weakly activates nifedipine oxidation and midazolam 1-hydroxylation.

A study performed with pregnant female rats, demonstrated that peak placental concentrations of ticagrelor after i.v. administration were noted at 5 min post-dose, but no significant transfer to the fetus was observed. Moreover, following oral administration of ticagrelor in lactating rats, the maximum milk concentration of ticagrelor and/or its metabolites were found at 4 h post-dose. The observation that the mean concentration in milk was higher than in maternal plasma at all time-points indicates that ticagrelor and its metabolites are easily transferred into milk. The analysis of suckling young animals suggests that these molecules were well absorbed and widely distributed in the pups.

TOXICOLOGY

Acute toxicity

The acute toxicity of ticagrelor is considered low. The results of single dose studies in CD-1 mice and Sprague-Dawley rats showed that ticagrelor was well tolerated when given orally by gavage following doses up to 2000 mg/kg (the highest dose tested). This dose represents approximately 550 times the recommended human daily dose on a mg/kg basis.

Chronic toxicity

Repeat-dose studies were conducted in mice, rats and marmosets. Consistent observations across species in repeat dose studies were seen primarily in the gastrointestinal tract, but were inconsistent with respect to the location, severity, and type of the observations. Indications of subclinical bleeding were also observed across species.

Increased liver weight at high doses occurred in rodents. In rats, this was accompanied by centrilobular hypertrophy and induction of cytochrome P450 liver enzymes, and was reversible upon withdrawal of treatment.

Adrenal weights increased at higher doses in the repeat dose studies in rodents, and were reversible upon withdrawal of treatment.

Carcinogenesis

No ticagrelor-related tumours were observed in a 2-year mouse study at oral doses up to 250 mg/kg/day (>18-fold the maximum human therapeutic exposure). There was no increase in tumours in male rats at oral doses up to 120 mg/kg/day (>15-fold the maximum human therapeutic exposure). There was an increase in uterine adenocarcinomas and hepatocellular adenomas plus adenocarcinomas and a decrease in pituitary adenomas and mammary fibroadenomas in female rats only exposed to high doses (>25-fold the maximum human

therapeutic exposures). No change in individual tumour incidence was observed at 60 mg/kg/day (8-fold difference to the maximum human therapeutic exposure). When ovarian sex cord/stromal tumors were combined, there was a small, but statistically significant (Peto analysis) increase for the low- and high-dose female rats, but not for the mid-dose females. A treatment-related effect on combined ovarian sex cord/stromal tumors is uncertain due to the low incidence values, but cannot definitively be ruled out. Plasma exposures for the low dose females were 1.5 times greater than therapeutic exposures in humans. The uterine tumours seen only in rats were found to be the result of a non-genotoxic endocrine effect of hormonal imbalance triggered by inhibition of prolactin secretion in rats given high doses of ticagrelor. This mechanism of uterine tumour formation in rats is not relevant to humans. The benign liver tumours are considered likely related to the pleiotropic response that included increased liver weight, hepatocellular hypertrophy, and microsomal enzyme induction.

Mutagenesis

Ticagrelor and the active metabolite AR-C124910XX do not demonstrate any genotoxic potential in bacterial, *in vitro* mouse lymphoma L5178Y $TK^{+/-}$ 3.7.2C cell, and *in vivo* rat bone marrow micronucleus assays. The active metabolite AR-C124910XX was not genotoxic in the same *in vitro* assays.

Reproduction and development

Ticagrelor was found to have no effect on fertility of female rats at oral doses up to 200 mg/kg/day (approximately 20 times the maximum human therapeutic exposure) and had no effect on fertility of male rats at doses up to 180 mg/kg/day (15.7 times the maximum human therapeutic exposure).

Ticagrelor given during the period of organogenesis had no effect on fetal development at oral doses up to 100 mg/kg/day in rats (5.1 times the maximum human therapeutic exposure) and up to 42 mg/kg/day in rabbits (equivalent to the maximum human therapeutic exposure). Fetal effects that were considered to be developmental variants or delays were seen in fetuses from female rats given 300 mg/kg (decreased body weight, 27 pre-pelvic vertebral arches, extra 14th ribs, and incomplete ossification of various skeletal structures), that may have resulted from maternal toxicity, and fetal developmental delays were also seen in rabbits given 63 mg/kg (increased incidences of clear gall bladder contents, incompletely ossified hyoid and pubis, one or more incomplete ossification of various skeletal structures), at which there was no overt maternal toxicity.

Ticagrelor had no effects on parturition or postnatal development in rats at doses up to 60 mg/kg/day (4.6 times the maximum human therapeutic exposure), but did cause maternal (reduced body weight gain and food consumption) and developmental toxicity in pups (reduced post-natal viability, lower birth weight, and delayed growth and physical development) at 180 mg/kg.

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PART III:
CONSUMER INFORMATION

Pr BRILINTA®

ticagrelor tablets

This leaflet is part III of a three-part "Product Monograph" published when BRILINTA® was approved for sale in Canada and is designed specifically for Consumers/Care givers. This leaflet is a summary and will not tell you everything about BRILINTA. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

BRILINTA is used in combination with low dose acetylsalicylic acid (aspirin) to reduce the risk of:

- having a stroke
- having another heart attack
- dying from a disease related to the heart or blood vessels.

BRILINTA 90 mg is given to patients who have had a heart attack or angina (chest pain).

BRILINTA 60 mg is given to patients who had a heart attack over a year ago.

What it does:

BRILINTA contains a medicine called ticagrelor. This belongs to a group of medicines called antiplatelet agents.

Platelets are small fragments circulating in your blood. Platelets help stop bleeding. When a blood vessel is damaged, they clump together to help form a blood clot, which stops bleeding. However, clots can also form inside a damaged blood vessel. This can be very dangerous because:

- the clot can cut off the blood supply completely - this can cause a heart attack or stroke.
- the clot can partly block the blood vessels to the heart - this can cause chest pain which comes and goes (angina).

BRILINTA helps stop the clumping of platelets. This reduces the chance of a blood clot forming that can block a blood vessel.

When it should not be used:

- You are allergic (hypersensitive) to ticagrelor or any of the ingredients of BRILINTA.
- You have active bleeding such as bleeding in your stomach or gut from an ulcer or bleeding in your brain.
- You have moderate to severe liver disease.
- You have had a stroke caused by bleeding in the brain.
- You are taking medication known as strong CYP3A4 inhibitors such as ketoconazole, clarithromycin, nefazodone, ritonavir and atazanavir.

What the medicinal ingredient is:

Ticagrelor

What the nonmedicinal ingredients are:

Dibasic calcium phosphate, ferric oxide black (60 mg coating), ferric oxide red (60 mg coating), ferric oxide yellow (90 mg coating), hydroxypropyl cellulose, hypromellose, magnesium stearate, mannitol, polyethylene glycol 400, sodium starch glycolate, talc (90 mg coating) and titanium dioxide.

What dosage forms it comes in:

Film-coated tablets, 60 mg and 90 mg.

WARNINGS AND PRECAUTIONS

BEFORE you take BRILINTA talk to your doctor, pharmacist or dentist if:

- You have an increased risk of bleeding because of:
  - a recent serious injury
  - recent surgery (including dental procedures)
  - recent bleeding from your stomach or gut (such as a stomach ulcer or colon 'polyps')
  - a blood clotting disorder
- You have an increased risk of bleeding because you take any of the following:
  - blood thinners such as warfarin
  - fibrinolytic drugs that help dissolve blood clots
  - nonsteroidal anti-inflammatory drugs such as ibuprofen, and naproxen
  - high dose acetylsalicylic acid (aspirin)
  - drugs such as ketoconazole, clarithromycin, nefazodone, ritonavir, atazanavir
- You are due to have surgery (including dental procedures) at any time while taking BRILINTA. Your doctor may want you to stop taking BRILINTA for a short time to reduce the risk of bleeding.
- You had a stroke in the past.
- You are taking drugs to reduce the heart rate or if you have a condition that puts you at risk of having episodes of slow heart rate.
- You have a history of asthma or other breathing problems.
- You have a history of gouty arthritis or increased plasma uric acid levels.
- You are less than 18 years old.
- You are pregnant or plan to become pregnant. If you are of child-bearing age, use appropriate birth control to avoid pregnancy.
- You are breast-feeding.

While you are on BRILINTA it is important that you do not take any medicine other than that prescribed by your doctor.

If you should see another doctor or a dentist, you should inform them that you are using BRILINTA.

Driving or using machines
If you feel dizzy or confusion while taking BRILINTA, be careful when driving or using machines.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor and pharmacist about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. This is because BRILINTA can affect the way some medicines work and some medicines can have an effect on BRILINTA.

Tell your doctor or pharmacist if you are taking any of the following medicines:
- 'Oral anticoagulants' often referred to as "blood thinners" which include warfarin.
- 'Fibrinolytics' often referred to as "clot-dissolvers" which include streptokinase and alteplase.
- Other medicines to prevent or treat blood clots.
- Non-steroidal anti-inflammatory drugs (NSAIDs).
- Ketoconazole, clarithromycin, nefazodone, ritonavir and atazanavir.
- High dose (greater than150 mg daily) acetylsalicylic acid (aspirin).
- More than 40 mg daily of either simvastatin or lovastatin.
- Digoxin.
- Cyclosporine.
- Rifampin, phenytoin, carbamazepine, phenobarbital and dexamethasone.

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

PROPER USE OF THIS MEDICATION

For BRILINTA 60 mg and 90 mg:
- Take BRILINTA with or without food.
- Swallow the BRILINTA tablet whole with some water.
- Take one in the morning and one in the evening at around the same time every day.
- Your doctor will also tell you to take low dose aspirin (acetylsalicylic acid) (between 75 mg and 150 mg) once a day.
- Your doctor will tell you how long you should take BRILINTA. Do not stop taking BRILINTA without first talking to your doctor.

Usual dose:
Adults – 90 mg
If you had a recent heart attack or unstable angina, the usual dose is one 90 mg tablet twice a day.

When you arrived at the hospital, you received 180 mg (two 90 mg tablets) of BRILINTA. This is different than the **Usual 90 mg dose** that is prescribed to you. Always follow your doctor's instructions.

After one year your doctor may continue your treatment with a lower dose of one 60 mg tablet twice a day.

Adults – 60 mg
If you had a heart attack over a year ago, the usual dose is one tablet of 60 mg twice a day.

If you have trouble swallowing the tablet(s)
Follow the steps below to crush the BRILINTA tablet(s). This will help make sure that all of the crushed tablet(s) will be transferred to the drinking glass.

Steps
- use a mortar and pestle or a similar device to crush the tablet(s)
- add a small amount of water (100 mL) to the mortar and pestle/device and stir for 1 minute
- transfer the water and crushed tablet mixture to a drinking glass
- add more water (100 mL) to the mortar and pestle/device and stir for 30 seconds
- transfer the water and crushed tablet mixture to the same drinking glass
- stir the contents of the drinking glass and drink it right away

How to use the blister (4x15 tablets) pack:
BRILINTA comes in a blister pack with the time of day printed on the back of the blister (to help you keep track of your doses).

There are 15 tablets in each blister: 14 are labelled with the time of day (AM or PM), one is labelled as "Start Here AM/PM". All 15 tablets are exactly the same. Use the following dosing instructions:

First dose for each blister pack:
- Start with the tablet that is labelled **"Start Here AM/PM"**,

Second dose (one tablet) from the blister pack:
- Take your second tablet (about 12 hours later) that matches the time of day (AM or PM),

Next doses from the blister pack:
- Continue to take one tablet alternating morning (AM) and evening (PM), until they are all finished.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

If you take more BRILINTA tablets than you should, you may be at increased risk of bleeding.

Missed dose:

If you forget to take your scheduled dose of BRILINTA, take your next dose at its scheduled time. Do not take a double dose (two tablets at the same time) to make up for the forgotten tablet.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, BRILINTA may have unwanted effects on some people.

BRILINTA affects blood clotting, so most side effects are related to bleeding. Bleeding may occur in any part of the body. Some bleeding is common (like bruising and nose bleeds). Severe bleeding is uncommon, but can be life threatening.

The most common side effects of BRILINTA are:

- Headache
- Feeling dizzy or like the room is spinning
- Abdominal pain, constipation, diarrhea or indigestion
- Nausea or vomiting
- Itching
- Confusion
- A tingling feeling
- Inflamed stomach lining
- Fatigue, muscle weakness
- Anxiety
- Cough
- Severe pain and swelling in your joints (signs of gout)
- Feeling dizzy or lightheaded, or having blurred vision (signs of low blood pressure)
- Bleeding from your stomach lining (ulcer)
- Bleeding gums

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency help
	Only if severe	In all cases	
Very Common			
Feeling short of breath		X	
An increase in the level of uric acid in the blood (possible red, swollen, hot and painful joint)		X	
Bleeding caused by blood disorder		X	
Common			
Bleeding: blood in your urine (pink, red or brown urine) or stools (red or black stools – looks like tar), vomiting blood, coughing up blood, nosebleed, bruising or bleeding into the skin, bleeding more than normal after surgery or cuts or wounds, bleeding that is severe or that lasts a long time		X	
Swelling of your legs or ankles		X	
Heart problems: rapid, slow or irregular heartbeat or increased fatigue, swelling of legs and feet and shortness of breath		X	
Chest pain		X	
Fainting (syncope): temporary loss of consciousness due to sudden drop in blood flow to the brain		X	
Signs of a stroke including: •sudden numbness or weakness of your arm, leg or face, especially if only on one side of the body. •sudden confusion, difficulty speaking or understanding others. •sudden difficulty in walking or loss of balance or coordination. •suddenly feeling dizzy or sudden severe headache with no known cause.			X
Sleeplessness		X	
Uncommon			
Bleeding: blood in your eye, ear or tumour, heavier vaginal bleeding or bleeding at different times than normal menstrual bleeding, bleeding into joints and muscles causing painful swelling, internal bleeding that may cause dizziness or light-headedness		X	
Confusion		X	
Anemia: shortness of breath, paleness, weakness		X	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency help
	Only if severe	In all cases	
Kidney stones: pain when urinating, severe pain in the side and back, below the ribs		X	
Lung fibrosis: shortness of breath, dry cough, fatigue, aching muscles and joints, unexplained weight loss		X	
High blood pressure in the lungs: shortness of breath, dizziness, fatigue, racing pulse		X	
Unknown			
Allergic Reaction: rash, hives, itching, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			X
Rash		X	

This is not a complete list of side effects. For any unexpected effects while taking BRILINTA, contact your doctor or pharmacist.

HOW TO STORE IT

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

Store your BRILINTA tablets between 2-30°C.

The expiry date of this medicine is printed on the package label. Do not use the medicine after this date.

REPORTING SIDE EFFECTS

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for more information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

NOTE: This CONSUMER INFORMATION leaflet provides you with the most current information at the time of printing.

This document plus the full Product Monograph, prepared for health professionals, can be found at: www.astrazeneca.ca or by contacting AstraZeneca Canada Inc., at:
Customer Inquiries – 1 (800) 668-6000,
Renseignements – 1 (800) 461-3787.

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