

PRODUCT MONOGRAPH

PrBRILINTA[®]

ticagrelor tablets

90 mg

Platelet Aggregation Inhibitor

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TABLE OF CONTENTS

PART I: HEALTH PROFESSIONAL INFORMATION	3
SUMMARY PRODUCT INFORMATION.....	3
INDICATIONS AND CLINICAL USE	3
WARNINGS AND PRECAUTIONS	4
ADVERSE REACTIONS	8
DRUG INTERACTIONS.....	12
DOSAGE AND ADMINISTRATION	15
OVERDOSAGE.....	16
ACTION AND CLINICAL PHARMACOLOGY	17
STORAGE AND STABILITY	21
DOSAGE FORMS, COMPOSITION AND PACKAGING.....	22
PART II: SCIENTIFIC INFORMATION.....	23
PHARMACEUTICAL INFORMATION	23
CLINICAL TRIALS	24
DETAILED PHARMACOLOGY	28
TOXICOLOGY.....	30
REFERENCES.....	32
PART III: CONSUMER INFORMATION.....	33

PrBRILINTA®

ticagrelor tablets

PART I: HEALTH PROFESSIONAL INFORMATION
SUMMARY PRODUCT INFORMATION

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

INDICATIONS AND CLINICAL USE

BRILINTA (ticagrelor), co-administered with acetylsalicylic acid (ASA), is indicated for the secondary prevention of atherothrombotic events in patients with Acute Coronary Syndromes (ACS) (unstable angina [UA], non ST elevation Myocardial Infarction [NSTEMI] or ST elevation Myocardial Infarction [STEMI]) who are to be managed medically and those who are to be managed with percutaneous coronary intervention (PCI) (with or without stent) and/or coronary artery by-pass graft (CABG).

Based on a relationship observed in PLATO between maintenance ASA dose and relative efficacy of BRILINTA compared to clopidogrel, BRILINTA is recommended to be co-administered with low maintenance dose ASA (75-150 mg daily).

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, 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 WARNINGS AND PRECAUTIONS).
- Patients who are also taking strong CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin, nefazodone, ritonavir, and atazanavir), as it may lead to a substantial increase in exposure to ticagrelor (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, active or recent gastrointestinal bleeding, or moderate hepatic impairment). The use of BRILINTA is contraindicated in patients with active pathological bleeding, in those with 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).

No data exist with BRILINTA regarding a hemostatic benefit of platelet transfusions; circulating BRILINTA may inhibit transfused platelets. 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 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, nefazadone, ritonavir, and atazanavir) is contraindicated as co-administration may lead to a substantial increase in exposure to ticagrelor (see CONTRAINDICATIONS and DRUG INTERACTIONS).

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).

Cardiovascular

Patients at Risk for Bradycardic Events: Due to observations of mostly asymptomatic ventricular pauses in an earlier clinical study, the Phase III study (PLATO) excluded patients with an increased risk of bradycardic events (e.g., patients who have sick sinus syndrome, 2nd or 3rd degree AV block or bradycardic-related syncope and not protected with a pacemaker). Therefore, due to the limited clinical experience, BRILINTA should be used with caution in these patients (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 trial 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

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. BRILINTA has no or negligible influence on the ability to drive and use machines. During treatment for Acute Coronary Syndromes, dizziness and confusion 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 PLATO, approximately 13.8% of patients randomized to BRILINTA, versus 7.8% for clopidogrel, reported dyspnea, including dyspnea at rest, exertional dyspnea, paroxysmal nocturnal dyspnea, and nocturnal dyspnea. The dyspnea is usually mild to moderate in intensity and often resolves during continued BRILINTA treatment. The mechanism has not yet been elucidated.

Eighty-seven percent of patients taking BRILINTA who reported dyspnea experienced a single episode. Approximately 30% of dyspnea episodes resolved within 7 days.

PLATO data do not suggest that the higher frequency of dyspnea with BRILINTA 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 on

pulmonary function. 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).

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.

Animal studies do not indicate direct harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development. In animals, ticagrelor had no effect on male or female fertility (see TOXICOLOGY).

Because animal reproduction studies are not always predictive of a human response, BRILINTA should be used during pregnancy only if the potential benefit to the mother justifies any potential risks to the fetus.

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.

Geriatrics (≥ 65 years of age): In PLATO, 43.1% of patients were ≥ 65 years of age and 15% were ≥ 75 years of age. The relative risk of bleeding was similar in both treatment and age groups. No overall differences in safety or effectiveness were observed between these patients and younger patients.

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.

Hepatic Impairment: Use of BRILINTA is contraindicated in patients with moderate or severe hepatic impairment (see CONTRAINDICATIONS).

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).

Uric Acid Increase: In PLATO, patients on BRILINTA had a higher risk of hyperuricemia than those receiving clopidogrel. 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.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

In PLATO, a total of 6762 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 3138 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).

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.

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 – PLATO-Defined

	BRILINTA (%) N=9235	Clopidogrel (%) 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

	BRILINTA (%) N=9235	Clopidogrel (%) N=9186	p-value*
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 and 23 (0.3%) for clopidogrel. 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 vs. 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 Subgroups Patient Population: 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

	BRILINTA (%) N=9235	Clopidogrel (%) N=9186	p-value
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		
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

Adverse Event (System Organ Class)	BRILINTA (%) N=9235	Clopidogrel (%) N=9186
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		
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 ^b	6.5	5.8
Dizziness ^b	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 ($\geq 1\%$ to $< 10\%$)

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

Uncommon ($\geq 0.1\%$ 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 ($\geq 0.01\%$ to $< 0.1\%$)

- *Musculoskeletal connective tissue and bone*: hemarthrosis

Abnormal Hematologic and Clinical Chemistry Findings

Serum uric acid concentration increased to more than upper limit of normal in 22% of patients receiving BRILINTA compared to 13% of patients receiving clopidogrel. The mean increases in uric acid were approximately 15% from baseline in the BRILINTA group and approximately 7% in the clopidogrel group. Mean serum uric acid decreased after discontinuation of BRILINTA treatment to approximately 7% above baseline, but with no decrease observed for clopidogrel. The number of patients with potential uric acid-related adverse events was similar for the BRILINTA group (2.1%) compared with the clopidogrel group (1.8%).

Serum creatinine concentration increased by $> 50\%$ in 8.3% of patients receiving BRILINTA compared to 6.7% of patients receiving clopidogrel. The increases typically did not progress with ongoing treatment and often decreased with continued therapy. Evidence of reversibility on discontinuation was observed even in those with the greatest on treatment increases. Treatment groups in PLATO did not differ for renal related serious adverse events.

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). Therefore, co-administration of BRILINTA and CYP3A4/5 substrates with narrow therapeutic indices is not recommended. 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

Effects of Other Drugs on BRILINTA

Ketoconazole (Strong CYP3A4 Inhibitors): 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 (Moderate CYP3A4 inhibitors): Co-administration of diltiazem with ticagrelor increased the ticagrelor C_{max} by 69% and AUC by 174% and decreased its active metabolite C_{max} 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.

Rifampin and Other CYP3A4 Inducers: Co-administration of rifampin with ticagrelor decreased the ticagrelor C_{max} and AUC by 73% and 86%, respectively. The C_{max} of its active metabolite was unchanged and the AUC was decreased by 46%. Other CYP3A4 inducers (e.g., dexamethasone, phenytoin, carbamazepine and phenobarbital) would be expected to decrease the exposure to ticagrelor as well and may result in reduced efficacy of BRILINTA.

Others: Clinical pharmacology interaction studies showed that 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.

Effects of BRILINTA on Other Drugs

Simvastatin: 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. 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. There was no effect of simvastatin on ticagrelor plasma levels. BRILINTA may have similar effect on lovastatin, but is not expected to have a clinically meaningful effect on other statins.

Atorvastatin: Co-administration of atorvastatin and ticagrelor increased the atorvastatin acid C_{max} by 23% and AUC by 36%. Similar increases in AUC and C_{max} were observed for all atorvastatin acid metabolites. These increases are not considered clinically significant.

Tolbutamide: Co-administration of ticagrelor with tolbutamide resulted in no change in the plasma levels of either drug, which demonstrates ticagrelor is not a CYP2C9 inhibitor and unlikely to alter the metabolism of other drugs metabolized via CYP2C9.

Warfarin: 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, therefore, warfarin and BRILINTA should be co-administered with caution (see WARNINGS AND PRECAUTIONS, General).

Oral Contraceptives: Co-administration of ticagrelor and levonorgestrel and ethinyl estradiol increased the ethinyl estradiol exposure 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.

Digoxin (P-gp Substrate): Concomitant administration of ticagrelor increased the digoxin C_{max} by 75% and AUC by 28%. Therefore, appropriate clinical and/or laboratory monitoring is recommended when giving narrow therapeutic index P-gp dependent drugs like digoxin concomitantly with BRILINTA.

Other Concomitant Therapy: 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. Therefore, BRILINTA may be given with or without food.

Grapefruit Juice Interaction: A drug-drug interaction study with grapefruit juice has not been performed. Based on the pharmacokinetic data for ticagrelor, grapefruit juice is expected to increase ticagrelor exposure to a clinically insignificant extent. Therefore, BRILINTA can be taken with grapefruit juice.

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

General

The PLATO trial data suggest the efficacy of BRILINTA (ticagrelor) relative to clopidogrel 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 compared to clopidogrel, high maintenance dose ASA (> 150 mg daily) is not recommended for maintenance dual antiplatelet therapy with BRILINTA. There is no conclusive evidence regarding the underlying biological mechanism. Based on analysis of the available clinical data, it is recommended that BRILINTA be used with a daily low maintenance dose of ASA (75-150 mg) (see CLINICAL TRIALS).

Furthermore, no safety and efficacy data is available on the use of BRILINTA beyond one year treatment duration (see CLINICAL TRIALS).

Recommended Dose and Dosage Adjustment

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

Patients taking BRILINTA should also take acetylsalicylic acid (ASA) daily, unless specifically contraindicated. Following an initial loading dose of ASA, BRILINTA should be used with a daily maintenance dose of ASA of 75-150 mg.

BRILINTA may be taken orally with or without food. 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.

Switching from clopidogrel to BRILINTA: 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 to clopidogrel results in an absolute IPA decrease of 24.5%. Clinicians who desire to switch patients from clopidogrel to BRILINTA should administer the first 90 mg dose of BRILINTA 24 hours following the last dose of clopidogrel (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics).

Missed Dose

Lapses in therapy should be avoided. A patient who misses a dose of BRILINTA should take one 90 mg tablet (their next dose) at its scheduled time (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics).

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. BRILINTA has not been studied in patients with moderate or severe hepatic impairment (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions).

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) is a member of the chemical class cyclopentyltriazolopyrimidines (CPTP), characterized as being orally active, selective and reversibly bound antagonists of the adenosine diphosphate (ADP) P₂Y₁₂ receptor. BRILINTA acts on platelet P₂Y₁₂ receptors and prevents ADP-mediated platelet activation and aggregation, by interacting with a binding site different from that of ADP (noncompetitive antagonism).

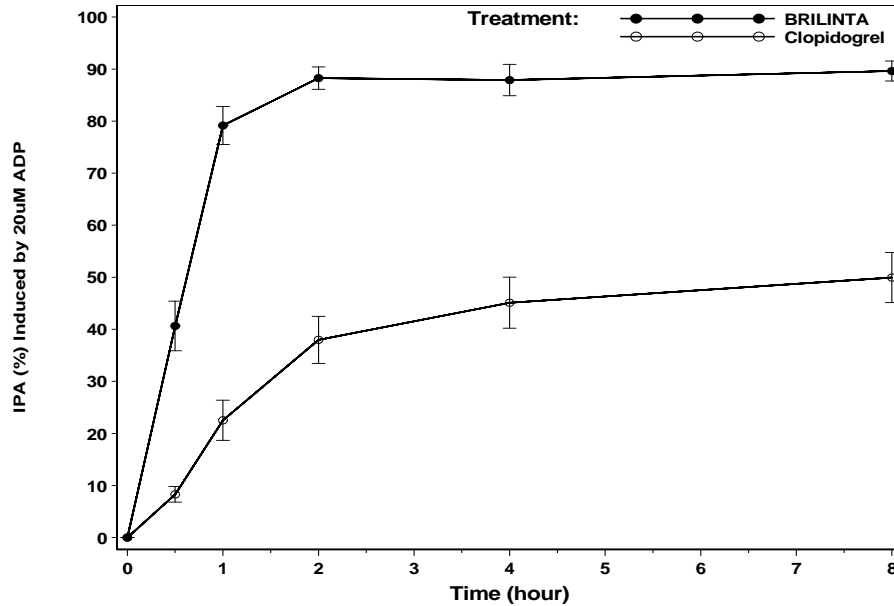
Pharmacodynamics

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 P₂Y₁₂ 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.

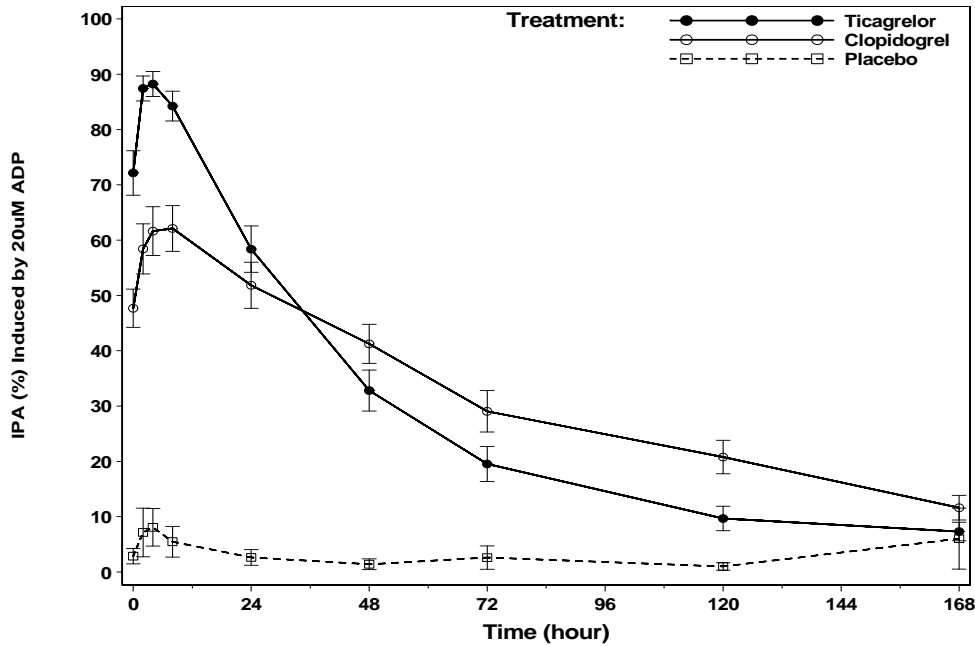
Figure 1: Mean final extent IPA (\pm SD) following single oral doses of 180 mg BRILINTA or 600 mg clopidogrel in patients with stable coronary artery disease



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 (\pm 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. 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 to BRILINTA 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)	t_{1/2} (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 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.

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 P2Y₁₂ 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 radiolabeled 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 10th or 90th 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.

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 and the active metabolite were approximately 20% lower 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. Ticagrelor has not been studied in patients with moderate or severe hepatic impairment, therefore it is contraindicated for use in this population (see CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, Special Populations 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 $\frac{90}{T}$ on one side and plain on the reverse side.

Composition

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

Packaging

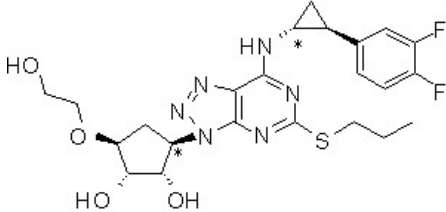
BRILINTA is available in blister compliance packs of 60 tablets (4 x 15 tablets).

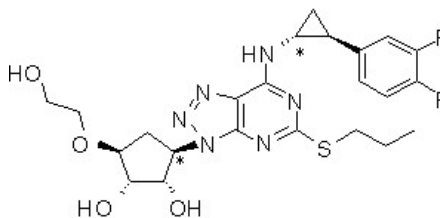
BRILINTA is available in HDPE bottles of 60 tablets for institutional use only.

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 ₂ N ₆ O ₄ S (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 clinical efficacy of BRILINTA (ticagrelor) in preventing thrombotic events in patients with Acute Coronary Syndromes (ACS) has been evaluated in a Phase III trial involving 18,624 patients, entitled the PLATO (PLATElet Inhibition and Patient Outcomes) study: a study of BRILINTA compared with clopidogrel, both given in combination with acetylsalicylic acid (ASA) and other standard therapy.

Study Design

The PLATO study was a multicentre, international, randomized, double-blind, parallel group, 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]) (Table 4).

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.

Table 4: Summary of patient demographics for PLATO trial in patients with non-ST or ST elevation ACS

Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
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=18624 BRILINTA n=9333; Clopidogrel n=9291	Mean = 62 years (19-97 years) < 65=57% ≥ 65 years=43% < 75years=85% ≥ 75 years=15%	Male 72% Female 28%

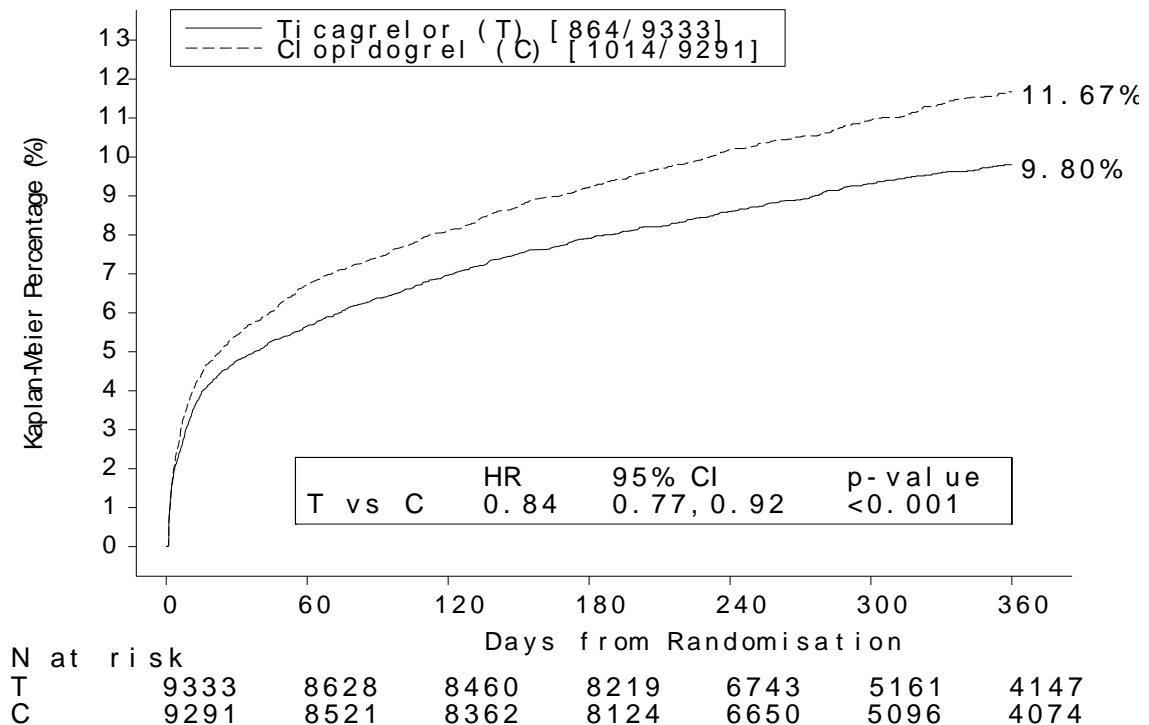
Study Results

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.

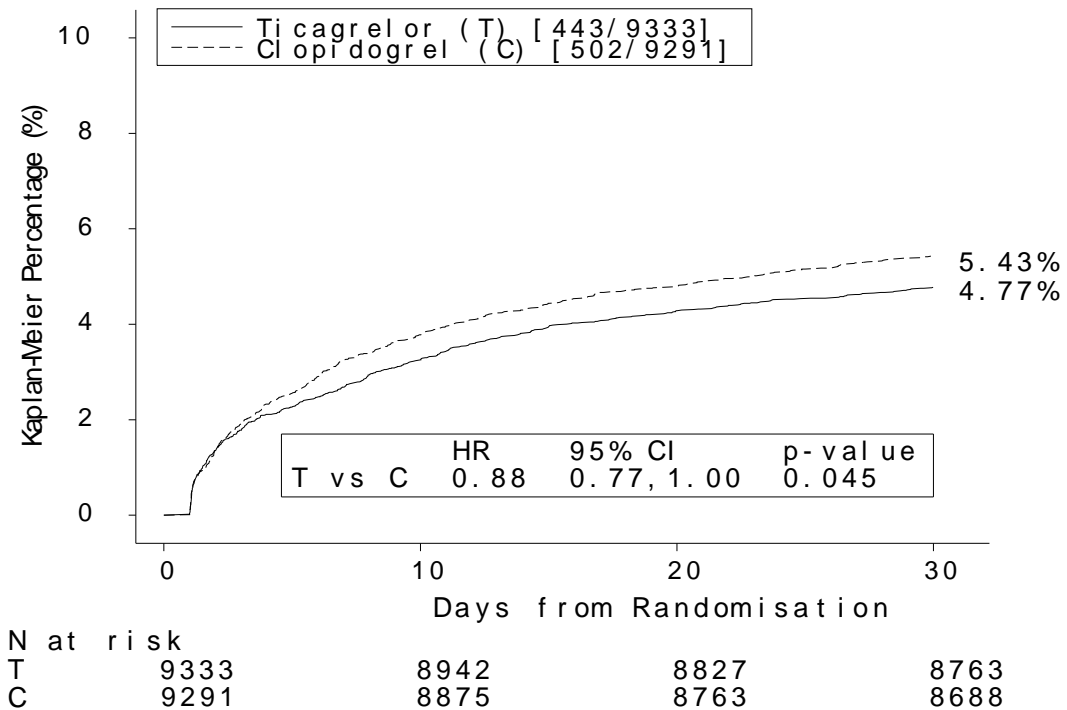
Figure 3: Time to first occurrence of CV death, MI and stroke (PLATO)



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 5).

Table 5: Patients with Outcome Events in PLATO

	Patients with Events		RRR (%)	HR (95% CI)	p-value
	BRILINTA (%) N=9333	Clopidogrel (%) N=9291			
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 over 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 3000 patients, of whom approximately 2000 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. More patients had ventricular pauses with BRILINTA than with clopidogrel. However, there were no adverse clinical consequences associated with this imbalance (including pacemaker insertions) in this population of patients.

DETAILED PHARMACOLOGY

Pharmacodynamics

Mechanism of action

The primary mechanism of action of ticagrelor is the antagonism of platelet P2Y₁₂ 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 P2Y₁₂ receptor radioligand from the P2Y₁₂ receptors on the surface of human washed platelets *in vitro*, with a K_i 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 P2Y₁₂ 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 P2Y₁₂ receptor is different from that of ADP.

Secondary Pharmacodynamics

Effects on the Adenosine System

Binding assays showed that ticagrelor has low affinities for the adenosine A₁, A_{2A} and A_{2B} receptors, but high affinity for the adenosine A₃ receptor. Moreover, functional assays characterized ticagrelor as an antagonist of the A₁ (IC₅₀: 36 µM), A_{2B} (IC₅₀: 193 µM) and A₃ (IC₅₀: 13.7 µM) receptors and as an agonist of the A_{2A} receptor (EC₅₀: 0.77 µM). Ticagrelor was also shown to inhibit the adenosine transporter (IC₅₀: 0.673µM), and thereby adenosine uptake in human MCF7 cells (IC₅₀: 61 nM) and human erythrocytes (IC₅₀: 100 nM), besides of being a weak inhibitor of the adenosine deaminase at concentrations > 10 µM. The active metabolite of ticagrelor was shown to have similar effects to that of the parent compound, although with a lesser potency. Taken together, these data suggest that ticagrelor and its active metabolite may potentiate the effects of endogenous adenosine *in vivo*. Furthermore, these mechanisms may well be one of those leading to the increased occurrence of dyspnea in patients treated with ticagrelor.

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 (K_i: 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 6β-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 human therapeutic exposure). There was no increase in tumours in male rats oral doses up to 120 mg/kg/day (>15-fold the 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 human therapeutic exposures). No change in individual tumour incidence was observed at 60 mg/kg/day (>8-fold difference to the human therapeutic dose). 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 human therapeutic exposure) and had no effect on fertility of male rats at doses up to 180 mg/kg/day (15.7 times the 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 human therapeutic exposure) and up to 42 mg/kg/day in rabbits (equivalent to the 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 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.

REFERENCES

1. Butler K, Teng R. Pharmacokinetics, pharmacodynamics, safety and tolerability of multiple ascending doses of ticagrelor in healthy volunteers. *Br J Clin Pharmacol* 2010; 70: 65-77.
2. Cannon CP, Husted S, Harrington RA, Scirica BM, Emanuelsson H, Peters G, et al. Safety, tolerability, and initial efficacy of AZD6140, the first reversible oral adenosine diphosphate receptor antagonist, compared with clopidogrel, in patients with non-ST-segment elevation acute coronary syndrome: primary results of the DISPERSE-2 trial. *J Am Coll Cardiol* 2007; 50(19): 1844-51.
3. Gurbel PA, Bliden KP, Butler K, et al. A Randomised Double-Blind Study to Assess the Onset and Offset of the Antiplatelet Effects of Ticagrelor versus Clopidogrel in Patients with Stable Coronary Artery Disease. The ONSET/OFFSET Study. *Circulation* 2009;120 (18 supplement); S1143.
4. Gurbel PA, Bliden KP, Butler K, et al. A Randomised Double-Blind Assessment of the ONSET and OFFSET of the Antiplatelet Effects of Ticagrelor versus Clopidogrel in Patients with Stable Coronary Artery Disease: the ONSET/OFFSET Study. *Circulation* 2009; 120: 2577-85.
5. Husted S, Emanuelsson H, Heptinstall S, Sandset PM, Wickens M, Peters G. Pharmacodynamics, pharmacokinetics, and safety of the oral reversible P2Y₁₂ antagonist AZD6140 with aspirin in patients with atherosclerosis: a double-blind comparison to clopidogrel. *Eur Heart J* 2006; 27: 1038-47.
6. James S, Akerblom A, Cannon CP, Emanuelsson H, Husted S, Katus H, et al. Comparison of ticagrelor, the first reversible oral P2Y₁₂ receptor antagonist, with clopidogrel in patients with acute coronary syndromes: Rationale, design, baseline characteristics of the PLATElet inhibition and patient Outcomes (PLATO) trial. *Am Heart J* 2009; 157: 599-605.
7. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held, C, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;361: 1045-57.

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:

You have been prescribed BRILINTA because you have had a heart attack or angina (chest pain). BRILINTA taken with low dose acetylsalicylic acid (aspirin) reduces the risk of:

- having a stroke
- having another heart attack
- dying from cardiovascular disease.

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 (see What the nonmedicinal ingredients are).
- You have problems with bleeding, such as bleeding in your stomach or gut from an ulcer.
- 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 yellow, hydroxypropyl cellulose, hypromellose, magnesium stearate, mannitol, polyethylene glycol 400, sodium starch glycolate, talc and titanium dioxide.

What dosage forms it comes in:

Film-coated tablets, 90 mg.

WARNINGS AND PRECAUTIONS

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

- You are taking or planning on taking any other medications (prescription and non-prescription) as certain medications can seriously affect the way other medications work (see INTERACTIONS WITH THIS MEDICATION).
- 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')
- 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 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 gouty arthritis or increased plasma uric acid level.
- You are less than 18 years old.
- You are pregnant or plan to become pregnant.
- 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.

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 than 150 mg daily) acetylsalicylic acid (aspirin).
- Digoxin.
- Rifampin, dexamethasone, phenytoin, carbamazepine and phenobarbital.

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

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: The usual dose is one tablet twice a day, 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.

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

BRILINTA is not recommended for patients under 18 years of age.

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.

Do not take a double dose (two tablets at the same time) even if you miss a dose.

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.

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

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	
Common	Bleeding such as blood in your urine or stools (black stools)		X	
	Nosebleed		X	
	Swelling of your legs or ankles		X	
	Bruising		X	
	Rash		X	
	Arrhythmia (rapid, slow or irregular heartbeat)		X	
	Chest pain		X	
	Cardiac failure (increased fatigue, swelling of legs and feet and shortness of breath)		X	
Bleeding after surgery		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	
Uncommon	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 co-ordination. •Suddenly feeling dizzy or sudden severe headache with no known cause.		X	X
	Blood in your eye		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 SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701C
Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

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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