Proposed packaging material		
Code	Brilinta 90 60 (56s & 14s) FCT-ODT-PI-02.01	
Submission	☐NDA ☐Renewal ☒Variation change detail no.: RO-Change Event-0037319	
Code of previous version	Brilinta 90 60 (56s & 14s) FCT-ODT-PI-01.04	
Changes	Harmonization PI and PIL between THALES and ODT	
Reference	☒CDS version: 9.0 and 10.0 ☐CPIL version:N/A	☐SmPC country/version/date:USPI (2020) ☐GRL approval:N/A
Name & Date	NA (31 January 2024)	

WARNING: BLEEDING RISK

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

WARNING: ASPIRIN DOSE AND BRILINTA EFFECTIVENESS

- **Maintenance doses of aspirin above 100 mg reduce the effectiveness of BRILINTA and should be avoided. After any initial dose, use with aspirin 75-100 mg per day.**

BRILINTA™

90 mg & 60 mg

(ticagrelor) Film-coated tablets

90 mg

(ticagrelor) orodispersible tablet

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 90 mg of ticagrelor

Each tablet contains 60 mg of ticagrelor

Each orodispersable tablet contains 90 mg of ticagrelor

PHARMACEUTICAL FORM

90 mg - Round, biconvex, yellow, film-coated tablets. The tablets are marked with "90" above "T" on one side and plain on the other.

60 mg - Round, biconvex, pink, film-coated tablets. The tablets are marked with "60" above "T" on one side and plain on the other.

Orodispersible tablet - Round, flat, bevelled edged, white to pale pink, orodispersible tablets marked with '90' above 'TI' on one side and plain on the other.

INDICATIONS

BRILINTA 90 mg:

BRILINTA 90 mg co-administered with ASA 75-100 mg is indicated for the prevention of thrombotic events (cardiovascular death, myocardial infarction and stroke) in patients with acute coronary syndromes (ACS) [unstable angina, non-ST elevation myocardial infarction (NSTEMI) or ST elevation myocardial infarction (STEMI)] including patients managed with percutaneous coronary intervention (PCI) or coronary artery by-pass grafting (CABG).

BRILINTA 90 mg co-administered with acetylsalicylic acid (ASA), is indicated to reduce the risk of stroke in patients with acute ischaemic stroke (NIH Stroke Scale score ≤ 5) or high-risk transient ischaemic attack (TIA) ($ABCD_2$ score ≥ 6).

For further details see sections *Posology and Clinical Studies*.

BRILINTA 60 mg:

BRILINTA 60 mg is indicated for the prevention of thrombotic events (cardiovascular death, myocardial infarction, and stroke) in patients with a history of myocardial infarction (MI occurred at least one year ago) and a high risk of developing a thrombotic event and have at least 1 of the following risk factors:

- Age ≥ 65 years
- Diabetes mellitus requiring medication
- Documented history of a second prior presumed spontaneous MI (>1 year ago)
- Documented history of angiographic evidence of multivessel CAD (stenosis ≥50% in 2 major coronary artery territories [ie.left anterior descending, ramus intermedius, left circumflex, right coronary artery], involving the main vessel, a major branch, or a bypass graft)
- Chronic, non-end stage renal dysfunction (creatinine clearance calculated by Cockroft

Gault equation < 60 ml/min).

POSOLOGY AND METHOD OF ADMINISTRATION

Posology

Patients taking Brilinta should also take a daily low maintenance dose of ASA 75 – 100 mg, unless specifically contraindicated.

Acute coronary syndromes

Brilinta treatment should be initiated with a single 180 mg loading dose (two tablets of 90 mg) and then continued at 90 mg twice daily.

Acute ischaemic stroke or transient ischaemic attack

Treatment with Brilinta should be initiated with a single 180 mg loading dose (two tablets of 90 mg) and then continued with 90 mg twice daily for 30 days (see section Clinical Studies).

History of myocardial infarction

Brilinta 60 mg twice daily is the recommended dose when an extended treatment is required for patients with a history of MI of at least one year and a high risk of an atherothrombotic event. Treatment may be started without interruption as continuation therapy after the initial one-year treatment with Brilinta 90 mg or other adenosine diphosphate (ADP) receptor inhibitor therapy in ACS patients with a high risk of an atherothrombotic event. Treatment can also be initiated up to 2 years from the MI, or within one year after stopping previous ADP receptor inhibitor treatment. There are limited data on the efficacy and safety of Brilinta beyond 3 years of extended treatment.

Missed dose

Lapses in therapy should also be avoided. A patient who misses a dose of Brilinta should take only one tablet (their next dose) at its scheduled time.

Special populations

Elderly

No dose adjustment is required in elderly.

Renal impairment

No dose adjustment is necessary for patients with renal impairment.

Hepatic impairment

Ticagrelor has not been studied in patients with severe hepatic impairment and its use in these patients is therefore contraindicated. Only limited information is available in patients with moderate hepatic impairment. Dose adjustment is not recommended, but ticagrelor

should be used with caution. No dose adjustment is necessary for patients with mild hepatic impairment.

Paediatric population

The safety and efficacy of ticagrelor in children below the age of 18 years have not been established. No data are available.

Method of administration

For oral use.

Brilinta can be administered with or without food.

For patients who are unable to swallow the tablet(s) whole, the tablets 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.

The orodispersible tablets may be used as an alternative to BRILINTA 90 mg film-coated tablets for patients who have difficulty swallowing the tablets whole or for whom there is a preference for orodispersible tablets. The tablet should be placed on the tongue, where it will rapidly disperse in saliva. It can then be swallowed with water (maximum 150 mL) or without water. The tablet can also be dispersed in water and administered via a nasogastric tube (CH8 or greater). It is important to flush the nasogastric tube through with water after administration of the mixture. A 60 mg orodispersible tablet is not available.

CONTRAINDICATIONS

History of Intracranial Hemorrhage

BRILINTA is contraindicated in patients with a history of intracranial hemorrhage (ICH) because of a high risk of recurrent ICH in this population *(see Clinical Studies).*

Active Bleeding

BRILINTA is contraindicated in patients with active pathological bleeding such as peptic ulcer or intracranial hemorrhage *(see Warnings and Precautions and Adverse Reactions)*.

Severe Hepatic Impairment

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

Hypersensitivity

BRILINTA is contraindicated in patients with hypersensitivity (e.g. angioedema) to ticagrelor or any component of the product (*see Adverse Reactions)*.

Co-administration with strong CYP3A4 inhibitors

Co-administration of ticagrelor 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.

WARNINGS AND PRECAUTIONS

General Risk of Bleeding

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

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

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

Concomitant Aspirin Maintenance Dose

In PLATO, use of BRILINTA with maintenance doses of aspirin above 100 mg decreased the effectiveness of BRILINTA. Therefore, after the initial loading dose of aspirin (usually 325 mg), use BRILINTA with a maintenance dose of aspirin of 75-100 mg *(see Dosage and Administration and Clinical Studies).*

Moderate Hepatic Impairment

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

Dyspnea was reported in 14% of patients treated with BRILINTA and in 8% of patients taking clopidogrel. Dyspnea was usually mild to moderate in intensity and often resolved during continued treatment. If a patient develops new, prolonged, or worsened dyspnea during treatment with BRILINTA, exclude underlying diseases that may require treatment. If dyspnea is determined to be related to BRILINTA, no specific treatment is required; continue BRILINTA without interruption.

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

In THALES, dyspnea led to study drug discontinuation in 1.0% and 0.2% of patients taking ticagrelor 90 mg in combination with ASA vs. ASA alone, respectively.

Central Sleep Apnoea

Central sleep apnoea including Cheyne-Strokes respiration has been reported in the post-marketing setting in patients taking BRILINTA. If central sleep apnoea is suspected, further clinical assessment may be considered.

Discontinuation of BRILINTA

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

Strong Inhibitors of Cytochrome CYP3A

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

Cytochrome CYP3A Potent Inducers

Avoid use with potent CYP3A inducers, such as rifampin, phenytoin, carbamazepine, and phenobarbital *(see Drug Interactions and Clinical Pharmacology)*

Surgery

Patients should be advised to inform physicians and dentists that they are taking ticagrelor before any surgery is scheduled and before any new medicinal product is taken.

In PLATO patients undergoing coronary artery bypass grafting (CABG), ticagrelor had more bleeding than clopidogrel when stopped within 1 day prior to surgery but a similar rate of major bleeds compared to clopidogrel after stopping therapy 2 or more days before surgery. If a patient is to undergo elective surgery and antiplatelet effect is not desired, ticagrelor should be discontinued 5 days prior to surgery.

Patients with prior ischaemic stroke

ACS patients with prior ischaemic stroke can be treated with Brilinta for up to 12 months (PLATO study).

In PEGASUS, patients with history of MI with prior ischaemic stroke were not included. Therefore, in the absence of data, treatment beyond one year is not recommended in these patients.

Hepatic impairment

Use of ticagrelor is contraindicated in patients with severe hepatic impairment. There is limited experience with ticagrelor in patients with moderate hepatic impairment, therefore, caution is advised in these patients.

Patients at risk for bradycardic events

Holter ECG monitoring has shown an increased frequency of mostly asymptomatic ventricular pauses during treatment with ticagrelor compared with clopidogrel. Patients with an increased risk of bradycardic events (e.g., patients without a pacemaker who have sick sinus syndrome, 2nd or 3rd degree AV block or bradycardic related syncope) have been excluded from the main studies evaluating the safety and efficacy of ticagrelor. Therefore, due to the limited clinical experience, ticagrelor should be used with caution in these patients

In addition, caution should be exercised when administering ticagrelor concomitantly with medicinal products known to induce bradycardia. However, no evidence of clinically significant adverse reactions was observed in the PLATO trial after concomitant administration with one or more medicinal products known to induce bradycardia (e.g. 96% beta blockers, 33% calcium channel blockers diltiazem and verapamil, and 4% digoxin).

During the Holter sub study in PLATO, more patients had ventricular pauses ≥3 seconds with ticagrelor than with clopidogrel during the acute phase of their ACS. The increase in Holter-detected ventricular pauses with ticagrelor was higher in patients with chronic heart failure (CHF) than in the overall study population during the acute phase of ACS, but not at one month with ticagrelor or compared to clopidogrel. There were no adverse clinical consequences associated with this imbalance (including syncope or pacemaker insertion) in this patient population.

Bradyarrythmic events and AV blocks have been reported in the post-marketing setting in patients taking ticagrelor (see section Undesirable effects), primarily in patients with ACS, where cardiac ischemia and concomitant drugs reducing the heart rate or affecting cardiac conduction are potential confounders. The patient's clinical condition and concomitant medication should be assessed as potential causes prior to adjusting treatment.

Creatinine elevations

Creatinine levels may increase during treatment with ticagrelor. The mechanism has not been elucidated. Renal function should be checked according to routine medical practice. In patients with ACS, it is recommended that renal function is also checked one month after initiating the treatment with ticagrelor, paying special attention to patients ≥ 75 years, patients with moderate/severe renal impairment and those receiving concomitant treatment with an angiotensin receptor blocker (ARB).

Uric acid increase

Hyperuricaemia may occur during treatment with ticagrelor. Caution is advised in patients with history of hyperuricaemia or gouty arthritis. As a precautionary measure, the use of ticagrelor in patients with uric acid nephropathy is discouraged.

Other

Based on a relationship observed in PLATO between maintenance ASA dose and relative efficacy of ticagrelor compared to clopidogrel, coadministration of ticagrelor and high maintenance dose ASA (>300 mg) is not recommended

Premature discontinuation

Premature discontinuation with any antiplatelet therapy, including Brilinta, could result in an increased risk of cardiovascular (CV) death, MI or stroke due to the patient's underlying disease. Therefore, premature discontinuation of treatment should be avoided.

Sodium

BRILINTA contains less than 1 mmol sodium (23 mg) per doe, i.e., is essentially 'sodium-free'

Laboratory Test Interferences

False negative functional tests for Heparin Induced Thrombocytopenia (HIT)

BRILINTA has been reported to cause false negative results in platelet functional tests (to include, but may not be limited to, the heparin-induced platelet aggregation (HIPA) assay) for patients with Heparin Induced Thrombocytopenia (HIT). This is related to inhibition of the P2Y12-receptor on the healthy donor platelets in the test by ticagrelor in the affected

patient's serum/plasma. Information on concomitant treatment with BRILINTA is required for interpretation of HIT functional tests. Based on the mechanism of BRILINTA interference, BRILINTA is not expected to impact PF4 antibody testing for HIT.

ADVERSE REACTIONS

Clinical Trials Experience

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

- Bleeding [see Warnings and Precautions]
- Dyspnea [see Warnings and Precautions]

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

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

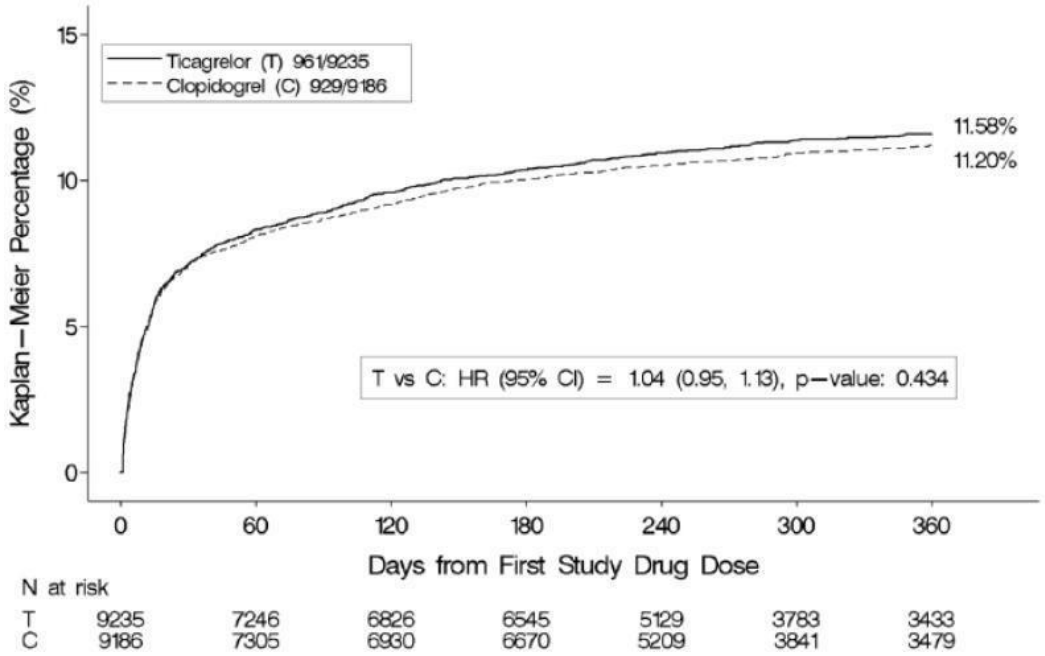
Bleeding

PLATO used the following bleeding severity categorization:

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

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

Figure 1 – Kaplan-Meier estimate of time to first PLATO-defined 'Total Major' bleeding event



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

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

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

As shown in Table 1, BRILINTA was associated with a somewhat greater risk of non-CABG bleeding than was clopidogrel. No baseline demographic factor altered the relative risk of bleeding with BRILINTA compared to clopidogrel.

In PLATO, 1584 patients underwent CABG surgery. The percentages of those patients who bled are shown in Table 2. Rates were very high but similar for BRILINTA and clopidogrel.

Table 2 – CABG bleeds (KM%)

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

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

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

Drug Discontinuation

In PLATO, the rate of study drug discontinuation attributed to adverse reactions was 7.4% for BRILINTA and 5.4% for clopidogrel. Bleeding caused permanent discontinuation of study drug in 2.3% of BRILINTA patients and 1.0% of clopidogrel patients. Dyspnea led to study drug discontinuation in 0.9% of BRILINTA and 0.1% of clopidogrel patients. In THALES, patients on ticagrelor 90 mg with ASA had a higher incidence of discontinuation due to adverse events compared to ASA therapy alone (9.7% for ticagrelor 90 mg with ASA vs. 7.6% for ASA therapy alone).

Common Adverse Events

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

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

	BRILINTA N=9235	Clopidogrel N=9185
Dyspnea[a]	13.8	7.8
Headache	6.5	5.8
Cough	4.9	4.6
Dizziness	4.5	3.9
Nausea	4.3	3.8
Atrial fibrillation	4.2	4.6
Hypertension	3.8	4.0
Non-cardiac chest pain	3.7	3.3
Diarrhea	3.7	3.3
Back pain	3.6	3.3
Hypotension	3.2	3.3
Fatigue	3.2	3.2
Chest pain	3.1	3.5

[a]Includes: dyspnea, dyspnea exertional, dyspnea at rest, nocturnal dyspnea, dyspnea paroxysmal nocturnal

Bleeding findings in THALES

Overall outcome of bleeding events in the THALES study are shown in Table 4.

Table 4 – Analysis of overall bleeding events, Kaplan-Meier estimates at 30 days (THALES)[a]

	Ticagrelor 90 mg twice daily + ASA N=5523			ASA alone N=5493		
Safety Endpoints	**Patients with events**	**KM%**	**Hazard Ratio (95% CI)**	**Patients with events**	**KM%**	***p*-value**
GUSTO-defined bleeding categories						
GUSTO Severe	28 (0.5%)	0.5%	3.99 (1.74, 9.14)	7 (0.1%)	0.1%	0.001
GUSTO Severe or Moderate	36 (0.7%)	0.6%	3.27 (1.67, 6.43)	11 (0.2%)	0.2%	<.001

[a] Full analysis set – intention-to-treat analysis: included all patients randomised irrespective of their protocol adherence and continued participation in the study.

Bleeding category definitions:

GUSTO Severe: Any one of the following: fatal bleeding, intracranial bleeding (excluding asymptomatic haemorrhagic transformations of ischaemic brain infarctions and excluding microhaemorrhages <10 mm evident only on gradient-echo magnetic resonance imaging), bleeding that caused haemodynamic compromise requiring intervention (e.g., systolic blood pressure <90 mm Hg that required blood or fluid replacement, or vasopressor/inotropic support, or surgical intervention).

GUSTO Moderate: Bleeding requiring transfusion of whole blood or packed red blood cells without haemodynamic compromise (as defined above).

In THALES, the rate of GUSTO Severe bleeding for ticagrelor 90 mg twice daily in combination with ASA was higher than for ASA alone. A similar bleeding pattern was observed for the GUSTO Severe or Moderate bleeding category (see Table 4). Due to the low number of GUSTO Severe bleeding events, no conclusion can be drawn regarding bleeding risk across subgroups. Discontinuation of treatment due to bleeding was more common with ticagrelor 90 mg with ASA compared to ASA therapy alone (2.9% and 0.6%, respectively).

Intracranial bleeding and fatal bleeding:
In total, there were 21 intracranial haemorrhages (ICHs) (19 spontaneous, 1 traumatic, 1 procedural) for ticagrelor 90 mg with ASA and 6 ICHs (3 spontaneous, 2 traumatic, 1 procedural) for ASA alone. Fatal bleedings occurred in 11 patients (10 fatal ICHs, 1 fatal gastrointestinal bleed) for ticagrelor 90 mg with ASA and in 2 patients (2 fatal ICHs) for ASA alone.

Bleeding in PEGASUS (Secondary Prevention in Patients with a History of Myocardial Infarction)
Overall outcome of bleeding events in the PEGASUS study are shown in Table 5.

Table 5– Bleeding events (PEGASUS)

	BRILINTA* + Aspirin N=6958		**Aspirin Alone N=6996**	
	n (%) patients with event	**Events / 100 pt yrs**	**n (%) patients with event**	**Events / 100 pt yrs**
TIMI Major	115 (1.7)	0.78	54 (0.8)	0.34
Fatal	11 (0.2)	0.08	12 (0.2)	0.08
Intracranial haemorrhage	28 (0.4)	0.19	23 (0.3)	0.14
TIMI Major or Minor	168 (2.4)	1.15	72 (1.0)	0.45

*60 mg BID

TIMI Major: Fatal bleeding, OR any intracranial bleeding, OR clinically overt signs of hemorrhage associated with a drop in hemoglobin (Hgb) of ≥5 g/dL, or a fall in hematocrit (Hct) of 15%. **Fatal:** A bleeding event that directly led to death within 7 days.

TIMI Minor: Clinically apparent with 3-5 g/dL decrease in hemoglobin.

The bleeding profile of BRILINTA 60 mg compared to aspirin alone was consistent across multiple pre-defined subgroups (e.g., by age, gender, weight, race, geographic region, concurrent conditions, concomitant therapy, stent, and medical history) for TIMI Major and TIMI Major or Minor bleeding events.

Other Adverse Reactions in PEGASUS

Adverse reactions that occurred in PEGASUS at rates of 3% or more are shown in Table 6.

Table 6 – Non-hemorrhagic adverse reactions reported in >3.0% of patients in the ticagrelor 60 mg treatment group (PEGASUS)

	BRILINTA* + Aspirin N=6958	Aspirin Alone N=6996
Dyspnea	**14.2**	**5.5**
Dizziness	**4.5**	**4.1**
Nausea	**3.3**	**2.5**

*60 mg BID

Bradycardia

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

PLATO and PEGASUS excluded patients at increased risk of bradycardic events (e.g., patients who have sick sinus syndrome, 2nd or 3rd degree AV block, or bradycardic-related syncope and not protected with a pacemaker).

In PLATO, syncope, pre-syncope and loss of consciousness were reported by 1.7% and 1.5% of BRILINTA 90mg and clopidogrel patients, respectively. In PEGASUS, syncope was reported by 1.2% and 0.9% of patients on BRILINTA 60 mg twice daily and aspirin alone, respectively.

Postmarketing Experience

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.

Blood and lymphatic system disorders: Thrombotic Thrombocytopenic Purpura (TTP) has been rarely reported with the use of BRILINTA. TTP is a serious condition which can occur after a brief exposure (<2 weeks) and requires prompt treatment.

Cardiovascular system: disorders: bradyarrhytmic events and AV blocks have been reported in the post-marketing setting in patients taking ticagrelor.

Immune system disorders – Hypersensitivity reactions including angioedema (see Contraindications)
Nervous system disorders – Central sleep apnoea including Cheyne-Strokes respiration (see Warnings and Precautions)
Skin and subcutaneous tissue disorders: Rash

Gynecomastia

In PLATO, gynecomastia was reported by 0.23% of men on BRILINTA and 0.05% on clopidogrel.
Other sex-hormonal adverse reactions, including sex organ malignancies, did not differ between the two treatment groups in PLATO.

Lab abnormalities

Serum Uric Acid

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

In PEGASUS, serum uric acid levels increased approximately 0,2 mg/dL from baseline on Brilinta 60 mg and no elevation was observed on aspirin alone. Gout occurred more commonly in patients on BRILINTA than in patients on aspirin alone (1.5%,1.1%). Mean serum uric acid concentrations decreased after treatment was stopped

Serum Creatinine

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

In PEGASUS, serum creatinine concentration increased by >50% in approximately 4% of patients receiving BRILINTA 60 mg, similar to aspirin alone. The frequency of renal related adverse events was similar for ticagrelor and aspirin alone regardless of age and baseline renal function

Table 7 - Adverse reactions by frequency and system organ class (SOC)

System Organ Classification	Very common	Common	Uncommon
Neoplasm benign, malignant and unspecified (including cyst and polyps			Tumour bleedings[a]
Blood and lymphatic system disorders	Blood disorder bleedings[b]		
Immune system disorders			Hypersensitivity including angiooedema[c]
Metabolism and nutrition disorders	Hyperuricaemia[d]	Gout/Gouty Arthritis	
Psychiatric disorders			Confusion
Nervous system disorders		Dizziness, Syncope, Headache	Intracranial haemorrhage
Eye disorders			Eye haemorhage[e]
Ear and labyrinth disorders		Vertigo	Ear haemorrhage
Cardiac disorders			Bradyarrhytmia AV block[c]
Vascular disorders		Hypotension	
Respiratory, thoracic and mediastinal disorder	Dyspnoea	Respiratory system bleedings[f]	
Gastrointestinal disorders		Gastrointestinal haemorrhage[g], Diarrhoea, Nausea, Dyspepsia, Constipation	Retroperitoneal haemorrhage
Skin and subcutaneous tissue disorders		Subcutaneous or dermal bleeding[h], rash, pruritus	

Muscosceletal connective tissue and bone			Muscular bleedingsi
Renal and urinary disorders		Urinary tract bleeding[j]	
Reproductive system and breast disorders			Reproductive system bleedings[k]
Investigations		Blood creatinine increased[d]	
Injury, poisoning and procedural complications		Post procedural haemorrhage. Traumatic bleedings[l]	

a e.g. bleeding from bladder cancer, gastric cancer, colon cancer

b e.g. increased tendency to bruise, spontaneous haematoma, haemorrhagic diathesis

c Identified in postmarketing experience

d Frequencies derived from lab observations (Uric acid increases to >upper limit of normal from baseline below or within reference range. Creatinine increases of >50% from baseline.) and not crude adverse event report frequency.

e e.g. conjunctival, retinal, intraocular bleeding

f e.g. epistaxis, haemoptysis

g e.g. gingival bleeding, rectal haemorrhage, gastric ulcer haemorrhage

h e.g. ecchymosis, skin haemorrhage, petechiae

i e.g. haemarthrosis, muscle haemorrhage

j e.g. haematuria, cystitis haemorrhagic

k e.g. vaginal haemorrhage, haematospermia, postmenopausal haemorrhage l

l e.g. contusion, traumatic haematoma, traumatic haemorrhage

DRUG INTERACTIONS

Effects of other drugs

Ticagrelor is predominantly metabolized by CYP3A4 and to a lesser extent by CYP3A5. Ticagrelor is also a p-glycoprotein (P-gp) substrate.

CYP3A inhibitors

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

CYP3A inducers

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

Aspirin

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

Effect of BRILINTA on other drugs

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

Simvastatin, lovastatin

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

Digoxin

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

Other Concomitant Therapy

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

Cyclosporine (Pgp and CYP3A inhibitor)

Coadministration of cyclosporine (600 mg) with ticagrelor increased ticagrelor Cmax and AUC equal to 2.3fold and 2.8 fold, respectively. The AUC of the active metabolite was increased by 32% and Cmax was decreased by 15% in the presence of cyclosporine. No data are available on concomitant use of ticagrelor with other active substances that also are potent Pgp inhibitors and moderate CYP3A4 inhibitors (e.g. verapamil, quinidine) that also may increase ticagrelor exposure. If the association cannot be avoided, their concomitant use should be made with caution.

Oral contraceptives

Coadministration of ticagrelor and levonorgestrel and ethinyl estradiol increased ethinyl estradiol exposure approximately 20% but did not alter the pharmacokinetics of levonorgestrel. No clinically relevant effect on oral contraceptive efficacy is expected when levonorgestrel and ethinyl estradiol are co-administered with ticagrelor.

Medicinal products known to induce bradycardia

Due to observations of mostly asymptomatic ventricular pauses and bradycardia, caution should be exercised when administering ticagrelor concomitantly with medicinal products known to induce bradycardia. However, no evidence of clinically significant adverse reactions

was observed in the PLATO trial after concomitant administration with one or more medicinal products known to induce bradycardia (e.g. 96% beta blockers, 33% calcium channel blockers diltiazem and verapamil, and 4% digoxin).

Others

Clinical pharmacology interaction studies showed that coadministration of ticagrelor with heparin, enoxaparin and ASA or desmopressin did not have any effect on the pharmacokinetics of ticagrelor or the active metabolite or on ADP-induced platelet aggregation compared with ticagrelor alone. If clinically indicated, medicinal products that alter haemostasis should be used with caution in combination with ticagrelor. A 2fold increase of ticagrelor exposure was observed after daily consumption of large quantities of grapefruit juice (3x 200 ml). This magnitude of increased exposure is not expected to be clinically relevant to most patients.

A delayed and decreased exposure to oral P2Y12 inhibitors, including ticagrelor and its active metabolite, has been observed in patients with ACS treated with morphine (35% reduction in ticagrelor exposure). This interaction may be related to reduced gastrointestinal motility and apply to other opioids. The clinical relevance is unknown, but data indicate the potential for reduced ticagrelor efficacy in patients co-administered ticagrelor and morphine. In patients with ACS, in whom morphine cannot be withheld and fast P2Y12 inhibition is deemed crucial, the use of a parenteral P2Y12 inhibitor may be considered.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C:

There are no adequate and well-controlled studies of BRILINTA use in pregnant women. In animal studies, ticagrelor caused structural abnormalities at maternal doses about 5 to 7 times the maximum recommended human dose (MRHD) based on body surface area. BRILINTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In reproductive toxicology studies, pregnant rats received ticagrelor during organogenesis at doses from 20 to 300 mg/kg/day. The lowest dose was approximately the same as the MRHD of 90 mg twice daily for a 60 kg human on a mg/m_2 basis. Adverse outcomes in offspring occurred at doses of 300 mg/kg/day (16.5 times the MRHD on a mg/m_2 basis) and included supernumerary liver lobe and ribs, incomplete ossification of sternebrae, displaced articulation of pelvis, and misshapen/misaligned sternebrae. At the mid-dose of 100 mg/kg/day, delayed development of liver and skeleton was seen. When pregnant rabbits received ticagrelor during organogenesis at doses from 21 to 63 mg/kg/day, fetuses exposed to the highest maternal dose of 63 mg/kg/day (6.8 times the MRHD on a mg/m_2 basis) had delayed gall bladder development and incomplete ossification of the hyoid, pubis and sternebrae occurred.

In a prenatal/postnatal study, pregnant rats received ticagrelor at doses of 10 to 100 mg/kg/day

during late gestation and lactation. Pup death and effects on pup growth were observed at 180 mg/kg/day (approximately 10 times the MRHD on a mg/m2 basis). Relatively minor effects such as delays in pinna unfolding and eye opening occurred at doses of 10 and 60 mg/kg (approximately one-half and 3.2 times the MRHD on a mg/m2 basis).

Nursing Mothers

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

Pediatric Use

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

Geriatric Use

In PLATO, 43% of patients were ≥65 years of age and 15% were ≥75 years of age.
The relative risk of bleeding was similar in both treatment and age groups.
No overall differences in safety or effectiveness were observed between these patients and younger patients. While this clinical experience has not identified differences in responses between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out.

Hepatic Impairment

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

Renal Impairment

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

OVERDOSAGE

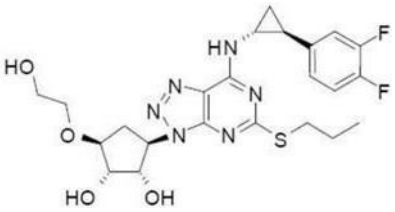
There is currently no known treatment to reverse the effects of BRILINTA, and ticagrelor is not dialyzable. Treatment of overdose should follow local standard medical practice. Bleeding is the expected pharmacologic effect of overdosing. If bleeding occurs, appropriate supportive measures should be taken.

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

Other effects of overdose may include gastrointestinal effects (nausea, vomiting, diarrhea) or ventricular pauses. Monitor the ECG.

DESCRIPTION

BRILINTA contains ticagrelor, a cyclopentyltriazolopyrimidine, inhibitor of platelet activation and aggregation mediated by the P2Y12 ADP-receptor. Chemically it is (1*S*,2*S*,3*R*,5*S*)-3-[7-{[(1*R*,2*S*)-2-(3,4-difluorophenyl) cyclopropyl] amino}-5(propylthio)-3*H*-[1,2,3]-triazolo[4,5-*d*] pyrimidin-3-yl]-5-(2hydroxyethoxy) cyclopentane-1,2-diol. The empirical formula of ticagrelor is $C_{23}H_{28}F_2N_6O_4S$ and its molecular weight is 522.57. The chemical structure of ticagrelor is:



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

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

BRILINTA 60 mg tablets for oral administration contain 60 mg of ticagrelor and the following ingredients: mannitol, dibasic calcium phosphate, sodium starch glycolate, hydroxypropyl cellulose, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol 400, ferric oxide black, and ferric oxide red.

BRILINTA 90 mg orodispersable tablets for oral administration contain 90 mg of BRILINTA and the following ingredients: Mannitol, Microcrystalline cellulose, Crospovidone, Xylitol, Anhydrous calcium hydrogen phosphate, Sodium stearyl fumarate, Hydroxypropylcellulose and Colloidal anhydrous silica.

CLINICAL PHARMACOLOGY

Mechanism of Action

Ticagrelor and its major metabolite reversibly interact with the platelet P2Y12 ADP-receptor to prevent signal transduction and platelet activation. Ticagrelor and its active metabolite are

approximately equipotent

Pharmacodynamics

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

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

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

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

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

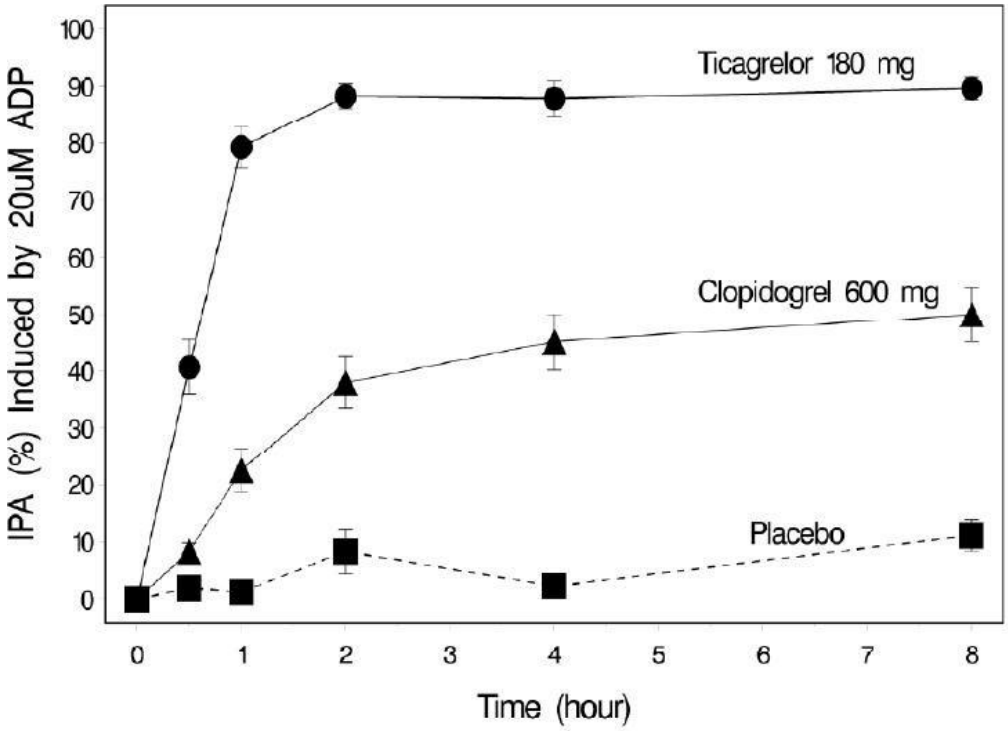
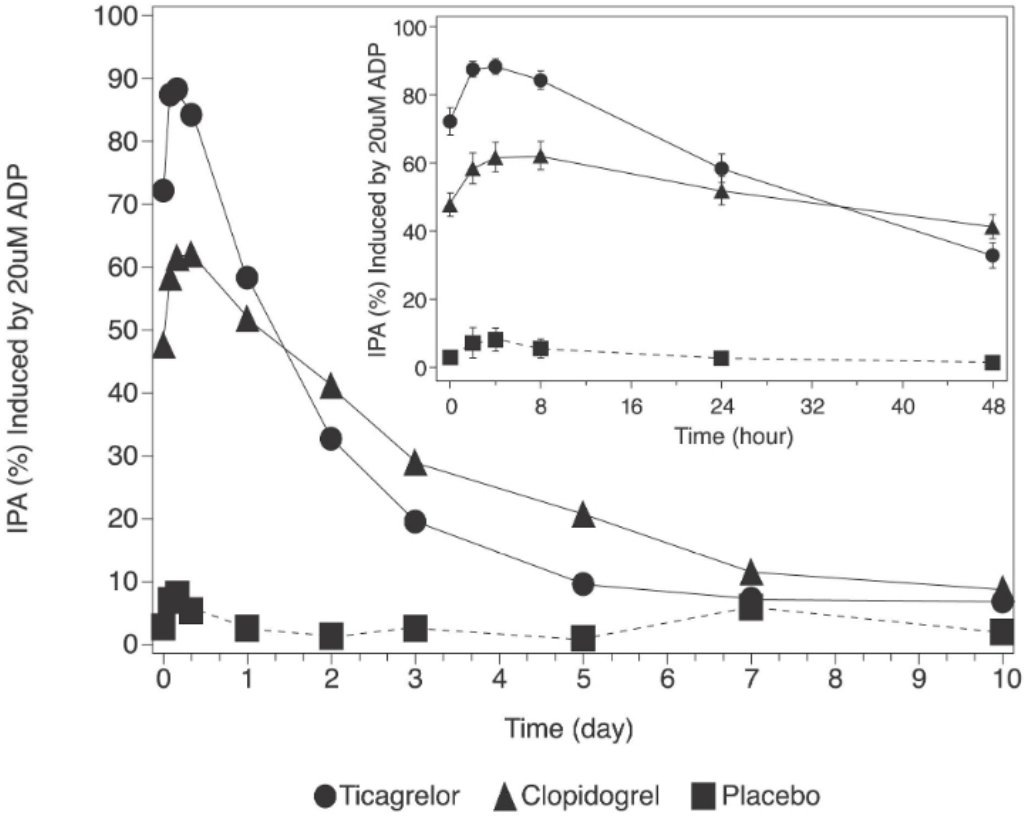


Figure 3 – Mean inhibition of platelet aggregation (IPA) following 6 weeks on placebo, ticagrelor 90 mg twice daily, or clopidogrel 75 mg daily



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

Adenosine mechanism (ENT-1)

Ticagrelor increased plasma adenosine concentrations in ACS patients and has been shown to augment several physiological responses to adenosine. Adenosine is a vasodilator; ticagrelor has been shown to augment adenosine-induced coronary blood flow increases in healthy volunteers and ACS patients. Adenosine is an endogenous platelet inhibitor; ticagrelor has been shown to augment adenosine-mediated inhibition of platelet aggregation in addition to platelet inhibition due to its P2Y12 antagonism. Adenosine has been linked to the cardioprotective effect of preconditioning; ticagrelor has been shown to reduce infarct size via an adenosine-mediated mechanism in a rat model of reperfusion injury. Adenosine also induces dyspnoea; ticagrelor has been shown to augment adenosine-induced dyspnoea in healthy volunteers. Thus, the dyspnoea observed in some patients taking ticagrelor (see section Undesirable effects) may partly or completely be mediated by adenosine.

Pharmacokinetics

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

Absorption

Absorption of ticagrelor occurs with a median tmax of 1.5 h (range 1.0–4.0). The formation of the major circulating metabolite AR-C124910XX (active) from ticagrelor occurs with a median tmax of 2.5 h (range 1.5-5.0).

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

Brilinta as crushed tablets mixed in water, given orally or administered through a nasogastric tube into the stomach, is bioequivalent to whole tablets (AUC and Cmax within 80-125% for ticagrelor and the active metabolite), with a median tmax of 1.0 hour (range 1.0 – 4.0) for ticagrelor and 2.0 hours (range 1.0 –8.0) for AR-C124910XX.

Ticagrelor orodispersible tablets, dispersed in saliva and swallowed without water or suspended in water and administered through a nasogastric tube into the stomach, were bioequivalent to film-coated whole tablets (AUC and Cmax within 80-125% for ticagrelor and the active metabolite). When the orodispersible tablet was dispersed in saliva and swallowed with water, ticagrelor AUC was similar, while Cmax was about 15% lower than for the film-coated tablet. The small difference in Cmax noted is unlikely to be of clinical relevance.

Distribution

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

Metabolism

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

Excretion

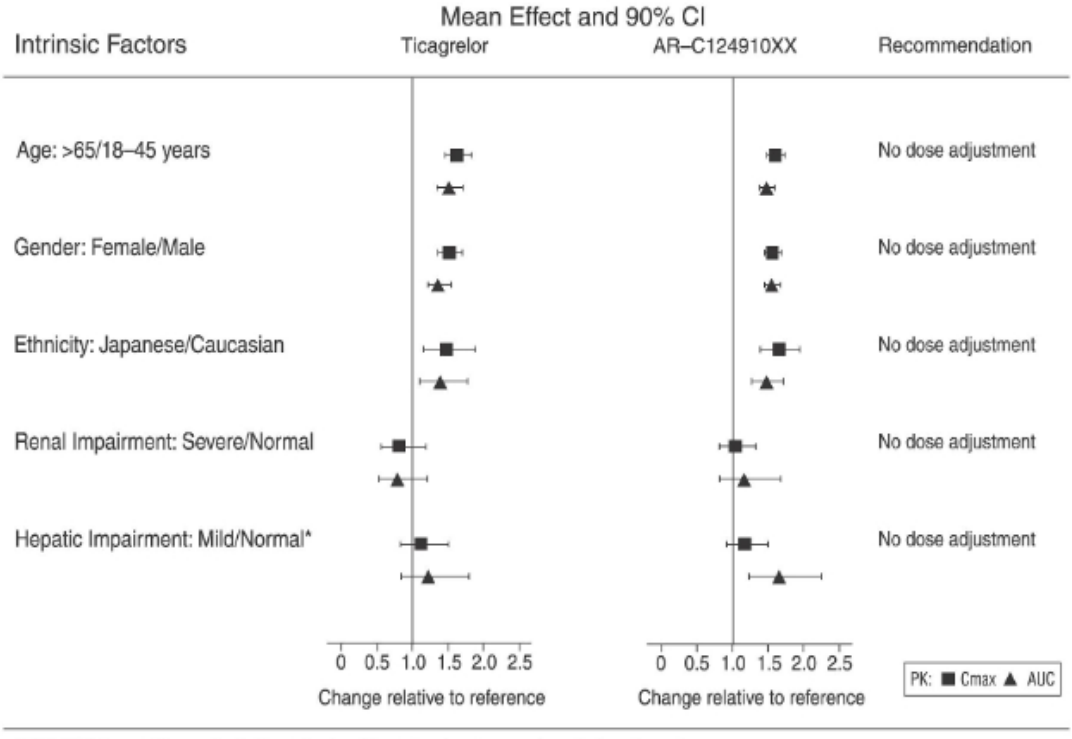
The primary route of ticagrelor elimination is hepatic metabolism. When radio-labelled ticagrelor is administered, the mean recovery of radioactivity is approximately 84% (58% in

feces, 26% in urine). Recoveries of ticagrelor and the active metabolite in urine were both less than 1% of the dose. The primary route of elimination for the major metabolite of ticagrelor is most likely to be biliary secretion. The mean t1/2 is approximately 7 hours for ticagrelor and 9 hours for the active metabolite.

Special Populations

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

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



Pediatric

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

Body Weight

No dose adjustment is necessary for ticagrelor based on weight.

Smoking

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

Renal impairment

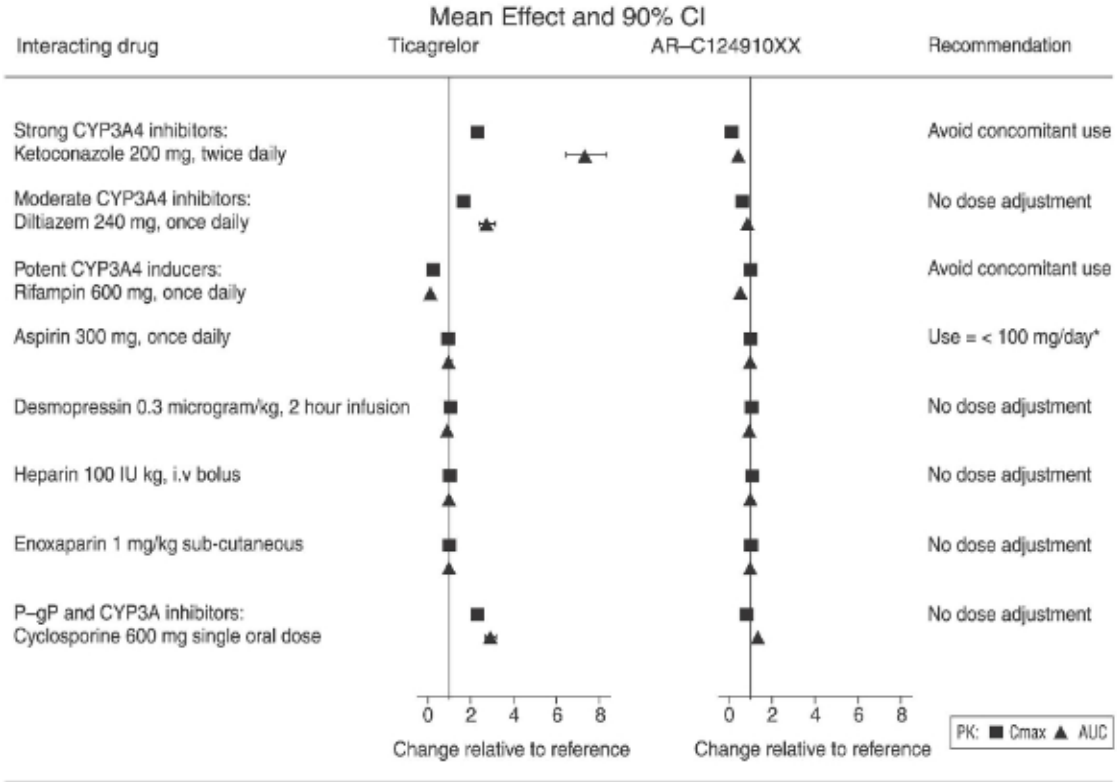
In patients with end stage renal disease on haemodialysis AUC and Cmax of ticagrelor 90

mg administered on a day without dialysis were 38% and 51% higher compared to subjects with normal renal function. A similar increase in exposure was observed when ticagrelor was administered immediately prior to dialysis (49% and 61%, respectively) showing that ticagrelor is not dialysable. Exposure of the active metabolite increased to a lesser extent (AUC 13-14% and Cmax 17-36%). The inhibition of platelet aggregation (IPA) effect of ticagrelor was independent of dialysis in patients with end stage renal disease and similar to subjects with normal renal function.

Effects of Other Drugs on BRILINTA

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

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



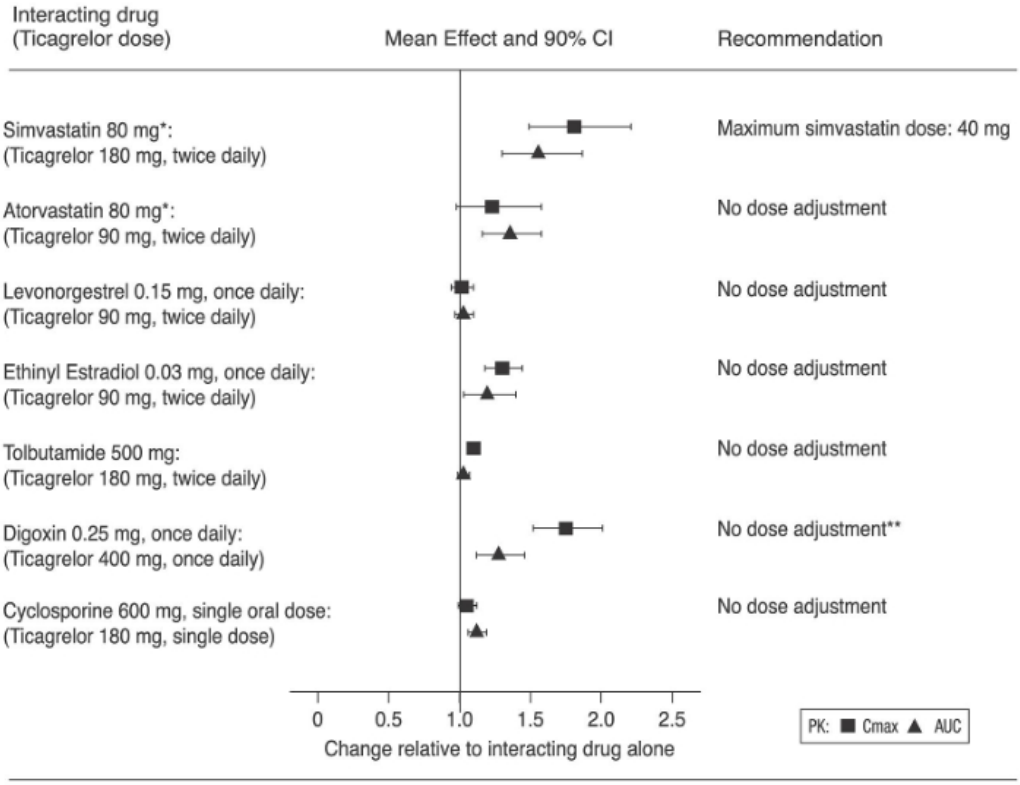
* BRILINTA has not been studied in patient with moderate or severe hepatic impairment.

Effects of BRILINTA on Other Drugs

In vitro metabolism studies demonstrate that ticagrelor and its major active metabolite are weak inhibitors of CYP3A4, potential activators of CYP3A5 and inhibitors of the P-gp transporter. Ticagrelor and AR-C124910XX were shown to have no inhibitory effect on human CYP1A2, CYP2C19, and CYP2E1 activity. For specific *in vivo* effects on the pharmacokinetics of simvastatin, atorvastatin, ethinyl estradiol, levonorgestrerol, tolbutamide,

digoxin, and cyclosporine see Figure 6.

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



*Similar increases in AUC and Cmax were observed for all metabolites

**Monitor digoxin levels with initiation of or change in BRILINTA therapy

Pharmacogenetics

In a genetic sub study cohort of PLATO, the rate of thrombotic CV events in the BRILINTA arm did not depend on CYP2C19 loss of function status**.**

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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

Mutagenesis

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

Impairment of Fertility

Ticagrelor had no effect on male fertility at doses up to 180 mg/kg/day or on female fertility at doses up to 200 mg/kg/day (>15-fold the MRHD on the basis of AUC). Doses of ≥10 mg/kg/day given to female rats caused an increased incidence of irregular duration estrus cycles (1.5-fold the MRHD based on AUC).

Clinical Studies

THALES Study (Acute Ischaemic Stroke or Transient Ischaemic Attack)

The THALES study was a 11,016 patient, event driven, randomised, double blind, placebo controlled, parallel group, international multicentre phase 3 study to test the hypothesis that ticagrelor in combination with ASA is superior to ASA alone in preventing stroke and death in patients with acute ischaemic stroke or transient ischaemic attack (TIA).

Patients were eligible to participate if they were aged 40 years or over, with non-cardioembolic acute ischaemic stroke (NIHSS score ≤ 5) or high-risk TIA (defined as $ABCD^2$ score ≥ 6 or ipsilateral atherosclerotic stenosis ≥ 50% in the internal carotid or an intracranial artery). Patients who received thrombolysis or thrombectomy within 24 hours prior to randomisation were not eligible.

The study was comprised of patients who were randomised within 24 hours of onset of an acute ischaemic stroke or TIA. Patients received ticagrelor (90 mg twice daily, with an initial loading dose of 180 mg) and ASA or ASA alone for 30 days. The recommended ASA dose was 75 - 100 mg once daily with an initial loading dose of 300 - 325 mg.

Clinical efficacy

Figure 7 - Analysis of the primary clinical composite endpoint of all stroke (including haemorragic stroke) and all death (THALES).

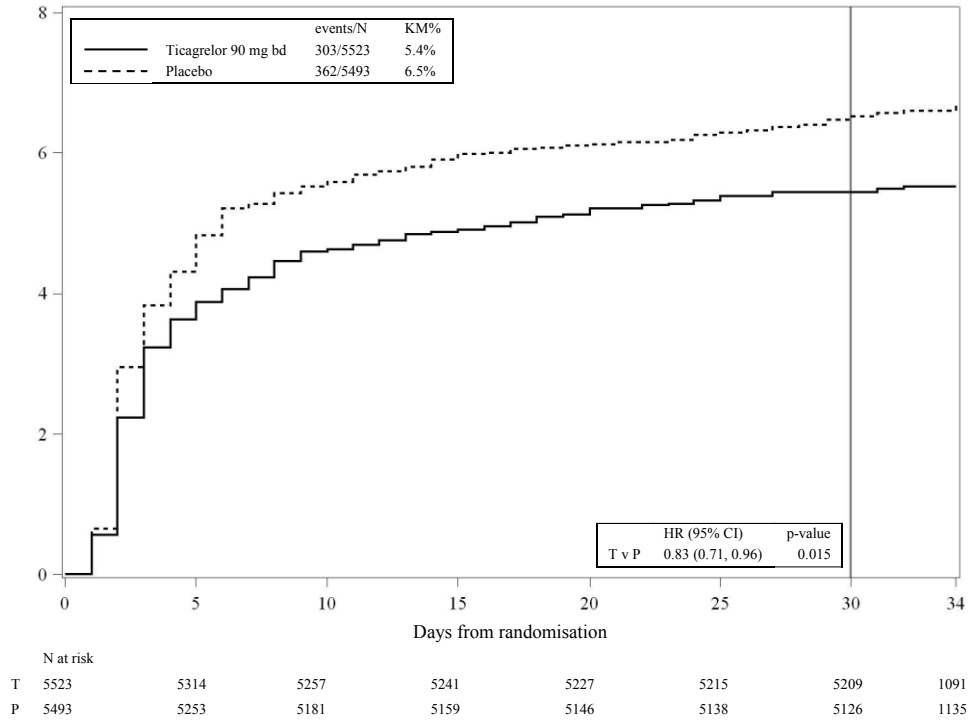


Table 8 – Analysis of primary and secondary efficacy endpoints (THALES)

	Ticagrelor 90 mg twice daily + ASA N=5523			ASA alone N=5493		*p*-value
Characteristic	Patients with events	KM%	HR (95% CI)	Patients with events	KM%	
Primary endpoint						
Composite of stroke/death	303 (5.5%)	5.4%	0.83 (0.71, 0.96)	362 (6.6%)	6.5%	0.015 (s)
Stroke	284 (5.1%)	5.1%	0.81 (0.69, 0.95)	347 (6.3%)	6.3%	0.008 (s)
Death	36 (0.7%)	0.6%	1.33 (0.81, 2.19)	27 (0.5%)	0.5%	0.264
Secondary endpoint						
Ischaemic stroke	276 (5.0%)	5.0%	0.79 (0.68, 0.93)	345 (6.3%)	6.2%	0.004 (s)

Hazard ratios and p-values are calculated for ticagrelor in combination with ASA vs. ASA alone from Cox proportional hazards model with treatment group as the only explanatory variable.

Kaplan-Meier percentage calculated at 30 days.

Note: the number of first events for the components stroke and death are the actual number of first events for each component and do not add up to the number of events in the composite endpoint.

(s) Indicates statistical significance.

CI = Confidence Interval; HR = Hazard ratio; KM = Kaplan-Meier; N = Number of patients

Brilinta 90 mg twice daily, in combination with ASA, was superior to ASA alone in prevention of the composite endpoint of stroke and death, which corresponded to a relative risk reduction (RRR) of 17% and an absolute risk reduction (ARR) of 1.1% (Table 8). The effect was driven by a reduction in the stroke component of the primary endpoint (19% RRR, 1.1% ARR).

Acute Coronary Syndromes and Secondary Prevention after Myocardial Infarction PLATO

PLATO was a randomized double-blind study comparing BRILINTA (N=9333) to clopidogrel (N=9291), both given in combination with aspirin and other standard therapy, in patients with acute coronary syndromes (ACS), who presented within 24 hours of onset of the most recent episode of chest pain or symptoms. The study's primary endpoint was the composite of first occurrence of cardiovascular death, non-fatal MI (excluding silent MI), or non-fatal stroke.

Patients who had already been treated with clopidogrel could be enrolled and randomized to either study treatment. Patients with previous intracranial hemorrhage, gastrointestinal bleeding within the past 6 months, or with known bleeding diathesis or coagulation disorder were excluded. Patients taking anticoagulants were excluded from participating and patients who developed an indication for anticoagulation during the trial were discontinued from study drug. Patients could be included whether there was intent to manage the ACS medically or invasively, but patient randomization was not stratified by this intent.

All patients randomized to BRILINTA received a loading dose of 180 mg followed by a maintenance dose of 90 mg twice daily. Patients in the clopidogrel arm were treated with an initial loading dose of clopidogrel 300 mg, if clopidogrel therapy had not already been given. Patients undergoing PCI could receive an additional 300 mg of clopidogrel at investigator discretion. A daily maintenance dose of aspirin 75-100 mg was recommended, but higher maintenance doses of aspirin were allowed according to local judgment. Patients were treated for at least 6 months and for up to 12 months.

PLATO patients were predominantly male (72%) and Caucasian (92%). About 43% of patients were >65 years and 15% were >75 years. Median exposure to study drug was 277 days. About half of the patients received pre-study clopidogrel and about 99% of the patients received aspirin at some time during PLATO. About 35% of patients were receiving a statin at baseline and 93% received a statin sometime during PLATO.

Table 9 shows the study results for the primary composite endpoint and the contribution of each component to the primary endpoint. Separate secondary endpoint analyses are

shown for the overall occurrence of CV death, MI, and stroke and overall mortality.

Table -9 – Patients with outcome events (KM%) (PLATO)

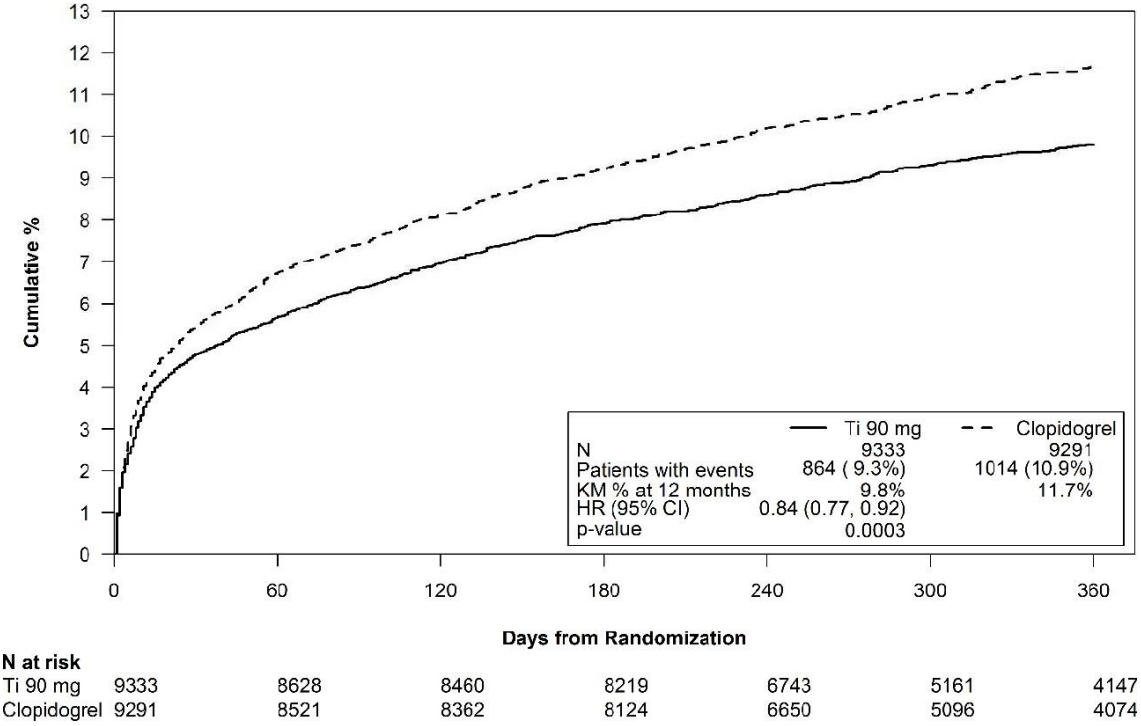
	BRILINTA[1] 90 mg N=9333	Clopidogrel 75 mg N=9291	Hazard Ratio (95% CI)	p-value
Composite of CV death, MI, or stroke	9.8	11.7	0.84 (0.77, 0.92)	0.0003
CV death	2.9	4.0	0.74	
Non-fatal MI	5.8	6.9	0.84	
Non-fatal stroke	1.4	1.1	1.24	
Secondary endpoints[2]				
CV death	4.0	5.1	0.79 (0.69, 0.91)	0.0013
MI[3]	5.8	6.9	0.84 (0.75, 0.95)	0.0045
Stroke[3]	1.5	1.3	1.17 (0.91, 1.52)	0.22
All-cause mortality	4.5	5.9	0.78 (0.69, 0.89)	0.0003

[1]Dosed at 90 mg BID

[2]Note: rates of first events for the components CV Death, MI and Stroke are the actual rates for first events for each component and do not add up to the overall rate of events in the composite endpoint

[3]Including patients who could have had other non-fatal events or died

Figure 8 – Time to first occurrence of CV death, MI, or stroke (PLATO)



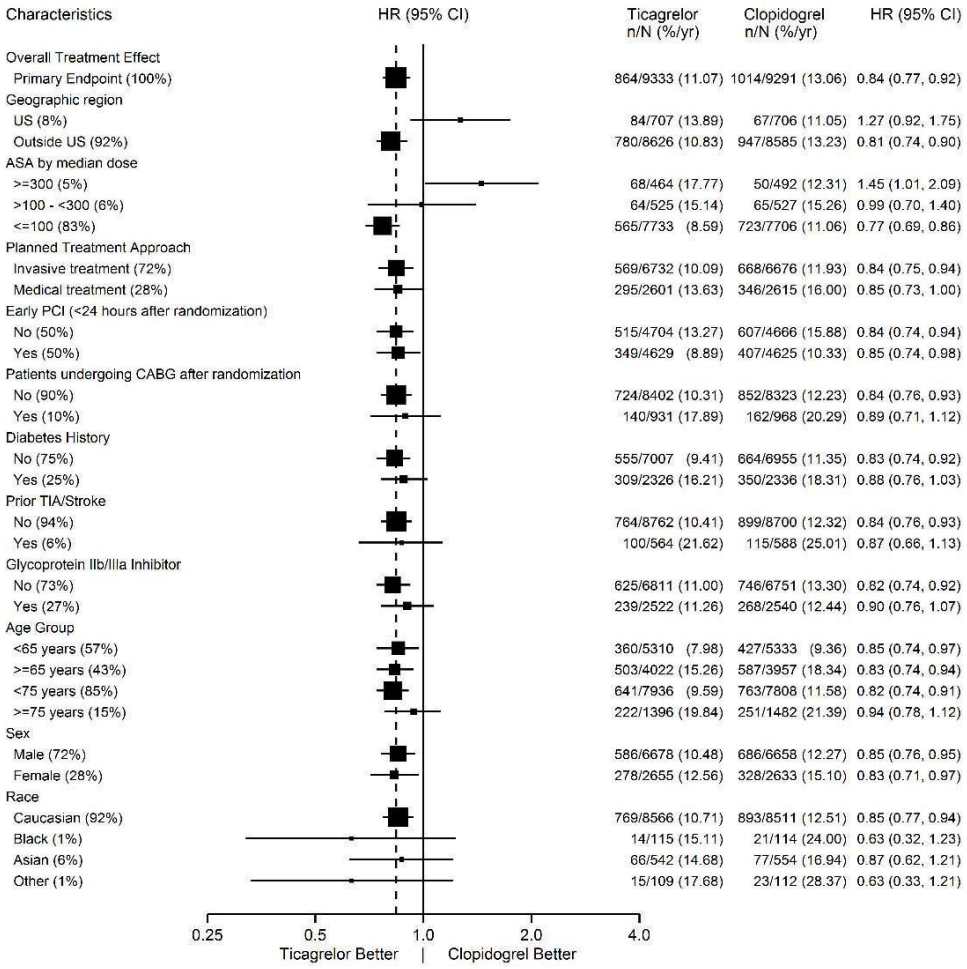
The curves separate by 30 days (RRR 12%) and continue to diverge throughout the 12-month treatment period (RRR 16%). Among 11289 patients with PCI receiving any

stent during PLATO, there was a lower risk of stent thrombosis (1.3% for adjudicated " definite") than with clopidogrel (1.9%) (HR 0.67, 95% CI 0.50-0.91; p=0.009). The results were similar for drug-eluting and bare metal stents.

A wide range of demographic, concurrent baseline medications, and other treatment differences were examined for their influence on outcome. Many of these are shown in Figure 9. Such analyses must be interpreted cautiously, as differences can reflect the play of chance among a large number of analyses. Most of the analyses show effects consistent with the overall results, but there are two marked exceptions: a finding of heterogeneity by region and a strong influence of the maintenance dose of aspirin. These are considered further below.

Most of the characteristics shown are baseline characteristics, but some reflect post-randomization determinations (e.g., final diagnosis, aspirin maintenance dose, use of PCI).

Figure 9 – Subgroup analyses of PLATO



Note: The figure above presents effects in various subgroups most of which are baseline characteristics and most of which were pre-specified. The 95% confidence limits that are shown do not take into account how many comparisons were made, nor do they reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

Regional Differences

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

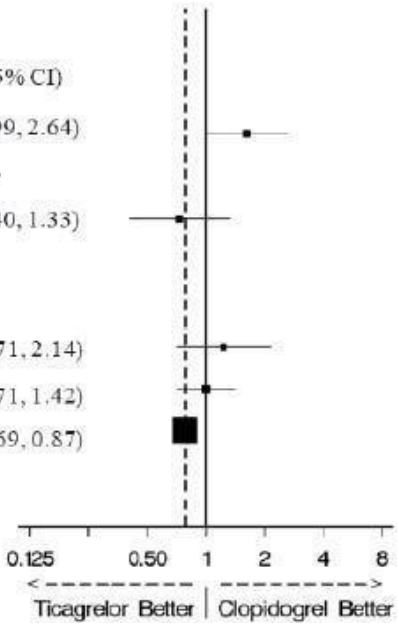
A wide variety of baseline and procedural differences between the US and non-US (including intended invasive vs. planned medical management, use of GPIIb/IIIa inhibitors, use of drug eluting vs. bare-metal stents) were examined to see if they could account for regional differences, but with one exception,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

Aspirin Dose

The PLATO protocol left the choice of aspirin maintenance dose up to the investigator and use patterns were different in US sites from sites outside of the US. About 8% of non-US investigators administered aspirin doses above 100 mg, and about 2% administered doses above 300 mg. In the US, 57% of patients received doses above 100 mg and 54% received doses above 300 mg. Overall results favored BRILINTA when used with low maintenance doses (≤100 mg) of aspirin, and results analyzed by aspirin dose were similar in the US and elsewhere. Figure 10 shows overall results by median aspirin dose. Figure 10 shows results by region and dose.

Figure 10 – CV death, MI, stroke by maintenance aspirin dose in the US and outside the US (PLATO)

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



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

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

PEGASUS

The PEGASUS TIMI-54 study was a 21162-patient, randomized, double-blind, placebo-controlled, parallel-group study. Two doses of ticagrelor, either 90 mg twice daily or 60 mg twice daily, co-administered with 75-150 mg of aspirin, were compared to aspirin therapy alone in patients with history of MI. The primary endpoint was the composite of first occurrence of CV death, non-fatal MI and non-fatal stroke. CV death and all-cause mortality were assessed as secondary endpoints.

Patients were eligible to participate if they were ≥50 years old, with a history of MI 1 to 3 years prior to randomization and had at least one of the following risk factors for thrombotic cardiovascular events: age ≥65 years, diabetes mellitus requiring medication, at least one other prior MI, evidence of multivessel coronary artery disease, or creatinine clearance <60 mL/min. Patients could be randomized regardless of their prior ADP receptor blocker therapy or a lapse in therapy. Patients requiring or who were expected to require renal dialysis during the study were excluded. Patients with any previous intracranial hemorrhage, gastrointestinal bleeding within the past 6 months, or with known bleeding diathesis or coagulation disorder were excluded. Patients taking anticoagulants were

excluded from participating and patients who developed an indication for anticoagulation during the trial were discontinued from study drug. A small number of patients with a history of stroke were included. Based on information external to PEGASUS, 102 patients with a history of stroke (90 of whom received study drug) were terminated early and no further such patients were enrolled.

Patients were treated for at least 12 months and up to 48 months with a median follow up time of 33 months.

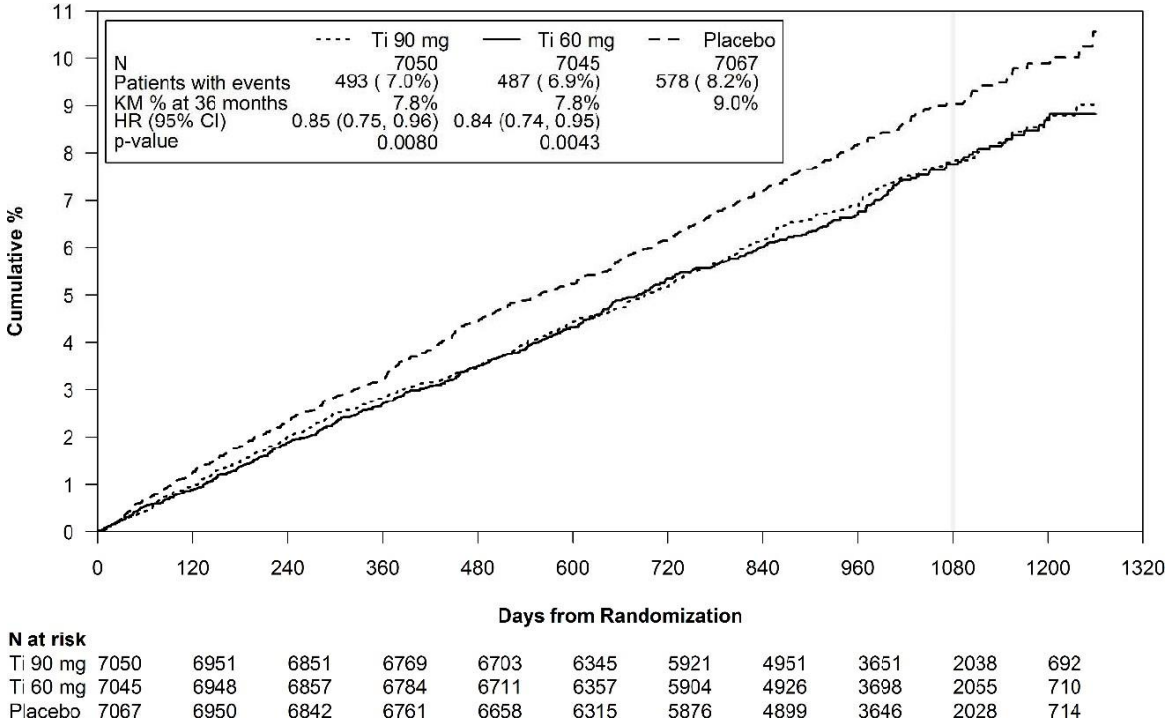
Patients were predominantly male (76%) Caucasian (87%) with a mean age of 65 years, and 99.8% of patients received prior Aspirin therapy. See Table 10 for key baseline features.

Table 11 – Baseline features (PEGASUS)

Demographic	**% Patients**
< 65 years	45%
Diabetes	32%
Multivessel disease	59%
History of > 1 MI	17%
Chronic non end stage renal disease	19%
Stent	80%
Prior P2y12 platelet inhibitor therapy	89%
Lipid lowering therapy	94%

The Kaplan-Meier curve (Figure 11) shows time to first occurrence of the primary composite endpoint of CV death, non-fatal MI or non-fatal stroke.

Figure 11 - Time to First Occurrence of CV death, MI or Stroke in PEGASUS



Ti = Ticagrelor BID, CI = Confidence interval; HR = Hazard ratio; KM = Kaplan-Meier; N = Number of patients.

Both the 60 mg and 90 mg regimens of BRILINTA in combination with aspirin were superior to aspirin alone in reducing the incidence of CV death, MI or stroke. The absolute risk reductions for BRILINTA plus aspirin vs. aspirin alone were 1.27% and 1.19% for the 60 and 90 mg regimens, respectively. Although the efficacy profiles of the two regimens were similar, the lower dose had lower risks of bleeding and dyspnea.

Table 11 shows the results for the 60 mg plus aspirin regimen vs. aspirin alone.

Table 11 – Incidences of the primary composite endpoint, primary composite endpoint components, and secondary endpoints (PEGASUS)

	BRILINTA[1] 60 mg + Aspirin N = 7045		**Aspirin Alone N = 7067**		**HR (95% CI)**	***p*-value**
	N (Patients with events)	**KM %**	**N (Patients with events)**	**KM %**		
Time to first CV death, MI, or Stroke[2]	487	7.8	578	9.0	0.84 (0.74, 0.95)	0.0043

CV Death[4]	116		128			
Myocardial infarction [4]	283		336			
Stroke [4]	88		114			
Subjects with events at any time CV death[3.5]	174	2.9	210	3.4	0.83 (0.68, 1.01)	
Myocardial infarction [5]	285	4.5	338	5.2	0.84 (0.72, 0.98)	
Stroke [5]	91	1.5	122	1.9	0.75 (0.57, 0.98)	
Secondary endpoint						
All-cause mortality	289	4.7%	326	5.2%	0.89 (0.76, 1.04)	-

CI = Confidence interval; CV = Cardiovascular; HR = Hazard ratio; KM = Kaplan-Meier; MI = Myocardial infarction; N = Number of patients.

[1] 60 mg BID

[2] Primary endpoint

[3] Secondary endpoint

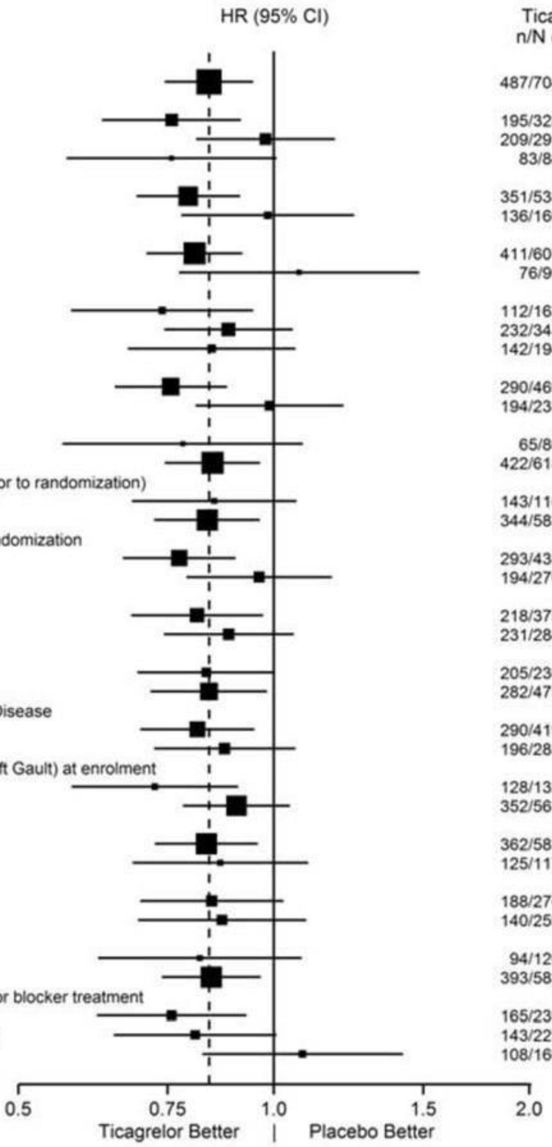
[4] For the components, the first – occurring component of the composite is included

[5] 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 the events in the composite endpoint

In PEGASUS, the RRR for the composite endpoint from 1 to 360 days (17% RRR) and from 361 days and onwards (16% RRR) was similar. The treatment effect of BRILINTA 60 mg twice daily over aspirin was consistent across pre-defined subgroups, see Figure 12

Figure 12 – Subgroup analyses of ticagrelor 60 mg (PEGASUS)

Characteristics	Ticagrelor n/N (%/yr)	Placebo n/N (%/yr)	HR (95% CI)
Overall Treatment Effect			
Primary endpoint (100%)	487/7045 (2.62)	578/7067 (3.10)	0.84 (0.74, 0.95)
Age group			
<65 years (46%)	195/3283 (2.24)	243/3154 (2.93)	0.76 (0.63, 0.91)
65-75 years (42%)	209/2913 (2.71)	225/3074 (2.76)	0.98 (0.81, 1.18)
>75 years (12%)	83/849 (3.81)	110/839 (5.01)	0.76 (0.57, 1.01)
Sex			
Male (76%)	351/5384 (2.47)	435/5350 (3.09)	0.79 (0.69, 0.91)
Female (24%)	136/1661 (3.09)	143/1717 (3.14)	0.98 (0.78, 1.24)
Race			
Caucasian (86%)	411/6077 (2.55)	509/6124 (3.13)	0.81 (0.71, 0.92)
Non-Caucasian (14%)	76/968 (3.09)	69/943 (2.90)	1.07 (0.77, 1.48)
Weight group			
<70 kg (23%)	112/1636 (2.63)	145/1575 (3.54)	0.74 (0.58, 0.95)
70-90 kg (50%)	232/3457 (2.53)	277/3658 (2.86)	0.88 (0.74, 1.05)
>90 kg (27%)	142/1941 (2.74)	155/1822 (3.23)	0.85 (0.67, 1.06)
BMI			
<30 kg/m^2 (67%)	290/4692 (2.35)	391/4827 (3.07)	0.76 (0.65, 0.88)
>=30 kg/m^2 (32%)	194/2335 (3.13)	186/2223 (3.18)	0.99 (0.81, 1.21)
Geographic region			
US (12%)	65/863 (2.93)	82/872 (3.67)	0.78 (0.56, 1.08)
Outside US (88%)	422/6182 (2.58)	496/6195 (3.03)	0.85 (0.74, 0.96)
History of >1 MI (>=1 year prior to randomization)			
Yes (17%)	143/1168 (4.66)	168/1188 (5.43)	0.85 (0.68, 1.06)
No (83%)	344/5876 (2.21)	410/5879 (2.64)	0.83 (0.72, 0.96)
Time from qualifying MI to randomization			
<2 years (61%)	293/4331 (2.60)	375/4333 (3.34)	0.77 (0.66, 0.90)
>=2 years (38%)	194/2704 (2.65)	202/2724 (2.74)	0.96 (0.79, 1.17)
Type of qualifying MI			
STEMI (54%)	218/3757 (2.19)	268/3809 (2.68)	0.81 (0.68, 0.97)
NSTEMI (40%)	231/2842 (3.09)	262/2843 (3.47)	0.89 (0.74, 1.06)
Diabetes Mellitus			
Yes (32%)	205/2308 (3.38)	239/2257 (4.03)	0.83 (0.69, 1.00)
No (68%)	282/4736 (2.25)	339/4810 (2.67)	0.84 (0.72, 0.98)
Multivessel Coronary Artery Disease			
Yes (60%)	290/4190 (2.64)	355/4213 (3.23)	0.81 (0.70, 0.95)
No (40%)	196/2852 (2.57)	223/2854 (2.92)	0.88 (0.72, 1.06)
Creatinine clearance (Cockroft Gault) at enrolment			
<60 mL/min (19%)	128/1320 (3.75)	184/1382 (5.09)	0.72 (0.58, 0.91)
>=60 mL/min (79%)	352/5610 (2.36)	383/5565 (2.60)	0.90 (0.78, 1.05)
History of PCI			
Yes (83%)	362/5874 (2.34)	430/5835 (2.79)	0.83 (0.72, 0.96)
No (17%)	125/1170 (4.03)	148/1231 (4.61)	0.87 (0.68, 1.10)
Type of stent			
Any DES (39%)	188/2769 (2.63)	222/2784 (3.08)	0.85 (0.70, 1.03)
BMS only (36%)	140/2598 (2.00)	156/2532 (2.29)	0.87 (0.69, 1.09)
Current smoker			
Yes (17%)	94/1206 (2.99)	108/1143 (3.64)	0.82 (0.62, 1.08)
No (83%)	393/5838 (2.54)	469/5919 (3.00)	0.84 (0.74, 0.96)
Time since prev. ADP receptor blocker treatment			
<30 days (34%)	165/2391 (2.70)	216/2403 (3.52)	0.76 (0.62, 0.93)
30 days to 12 months (32%)	143/2231 (2.41)	175/2230 (2.98)	0.81 (0.65, 1.01)
>12 months (23%)	108/1661 (2.39)	100/1645 (2.21)	1.08 (0.82, 1.42)



Note: The figure above presents effects in various subgroups all of which are baseline characteristics and most of which were pre-specified. The 95% confidence limits that are shown do not take into account how many comparisons were made, nor do they reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted

List of excipients

<u>90 mg film coated tablet</u>:

<u>Core</u>

Mannitol (E421)

Dibasic calcium phosphate

Magnesium stearate

Sodium starch glycolate

Hydroxypropyl cellulose

<u>Coating</u>

Talc

Titanium dioxide (E171)

Ferric oxide yellow (E172)

Polyethylene glycol 400

Hypromellose

60 mg film coated-tablet:

Core

Mannitol (E421)

Dibasic calcium phosphate

Magnesium stearate

Sodium starch glycolate

Hydroxypropyl cellulose

Coating

Titanium dioxide (E171)

Ferric oxide black (E172)

Ferric oxide red (E172)

Polyethylene glycol 400

Hypromellose

90 mg orodispersable tablet

Mannitol (E421)

Microcrystalline cellulose (E460)

Crospovidone (E1202)

Xylitol (E967)

Anhydrous calcium hydrogen phosphate (E341)

Sodium stearyl fumarate

Hydroxypropylcellulose (E463)

Colloidal anhydrous silica

Incompatibilities

Not applicable

Shelf Life

Please refer to expiry date on the blister strip or outer carton.

Special precautions for storage

Do not store above 30°C.

90 mg BRILINTA tablet: Box of 4 blisters @ 14 film-coated tablets
(Reg. No : DKI1635301117A1)
60 mg BRILINTA tablet: Box of 4 blisters @ 14 film-coated tablets
(Reg.No : DKI1751303217A1)
90 mg BRILINTA orodispersible tablet: Box of 7 blisters @ 8 orodispersible tablets
(Reg. No : DKI2351304481A1)

HARUS DENGAN RESEP DOKTER

BRILINTA 60 mg
Manufactured and Packed by
AstraZeneca AB
Gartunavagen SE-152 57 Södertälje
Sweden

BRILINTA 90 mg
Manufactured by
AstraZeneca AB
Gartunavagen SE-152 57 Södertälje
Sweden

Packed and released by
AstraZeneca Pharmaceutical Co., Ltd
No.2 Huangshan Road. Wuxi, Jiangsu
China

BRILINTA 90 mg orodispersible tablet
Manufactured, Packed and released by
AstraZeneca AB
Gartunavagen SE-152 57 Södertälje
Sweden

Imported by
PT AstraZeneca Indonesia
Cikarang, Bekasi – Indonesia

DISETUJUI OLEH BPOM : 20/06/2024

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EREG100422VR12300112
EREG100422VR12300332

Date of revision of text:

31 January 2024

Doc ID: Doc ID-005315900

DISETUJUI OLEH BPOM : 20/06/2024

ID : EREG100422VR12300111
EREG100422VR12300112
EREG100422VR12300332

Proposed packaging material		
Code	Brilinta 90 60 (56s & 14s) FCT-ODT-PIL-02.01	
Submission	☐NDA ☐Renewal ☒Variation change detail no.: RO-Change Event-0037319	
Code of previous version	Brilinta 90 60 (56s & 14s) FCT-PIL-01.06	
Changes	Harmonization PI and PIL between THALES and ODT	
Reference	☐CDS version: N/A ☒CPIL version:16 Apr 2020	☐SmPC country/version/date:USPI (2020) ☐GRL approval:N/A
Name & Date	NA (31 January 2024)	

PERHATIAN: RISIKO PERDARAHAN

- **BRILINTA, seperti obat antiplatelet lainnya, dapat menyebabkan perdarahan yang signifikan, terkadang fatal.**
- **BRILINTA tidak boleh digunakan pada pasien yang sedang dalam kondisi perdarahan atau memiliki riwayat perdarahan di otak.**
- **Jangan menggunakan BRILINTA pada pasien yang berencana untuk menjalani operasi *coronary artery bypass graft* (CABG). Jika memungkinkan, hentikan penggunaan BRILINTA minimal 5 hari sebelum melakukan semua jenis tindakan operasi.**
- **Masih terdapat risiko perdarahan pada pasien dengan kondisi tekanan darah rendah yang baru saja menjalani operasi *coronary angiography, percutaneous coronary intervention (PCI), CABG*, atau tindakan operasi lainnya yang menggunakan BRILINTA sebelumnya.**
- **Jika memungkinkan, atasi perdarahan tersebut tanpa menghentikan penggunaan BRILINTA karena dapat meningkatkan risiko kejadian kardiovaskular lainnya.**

PERHATIAN: DOSIS ASPIRIN DAN KEGUNAAN BRILINTA

- **Dosis pemeliharaan Aspirin di atas 100 mg dapat mengurangi efek BRILINTA dan harus dihindari. Setelah menggunakan Aspirin sebagai dosis awal pada dosis berapa pun, lanjutkan dengan Aspirin 75 – 100 mg sehari.**

Informasi untuk Pasien

BRILINTA™ 60 mg & 90 mg

Tablet Salut Selaput

Tablet Orodispersible

Ticagrelor

Bacalah seluruh isi leaflet ini dengan seksama sebelum Anda mulai menggunakan obat ini karena leaflet ini berisi informasi penting bagi Anda.

- Simpan leaflet ini, Anda mungkin memerlukannya di kemudian hari.
- Apabila Anda memiliki pertanyaan lebih lanjut, hubungi dokter, apoteker, atau perawat Anda.
- Obat ini hanya diresepkan untuk Anda. Dilarang memberikan obat ini untuk orang lain. Hal ini dapat membahayakan orang lain, bahkan jika tanda penyakit yang mereka derita sama dengan penyakit Anda.
- Apabila Anda mengalami efek samping, komunikasikan dengan dokter, apoteker atau perawat Anda. Hal ini termasuk efek samping yang mungkin timbul yang tidak terdaftar dalam leaflet ini. Lihat bagian 4 dari leaflet ini.

Informasi yang terkandung dalam leaflet ini

1. Apa itu Brilinta dan apa kegunaannya

Brilinta mengandung substansi aktif ticagrelor. Obat ini tergolong dalam kelompok obat antiplatelet.

Kegunaan Brilinta 60 mg

Brilinta digunakan untuk pencegahan kejadian trombotik (infark miokard, stroke, dan kematian kardiovaskular) pada pasien dengan sejarah infark miokard yang pernah muncul setidaknya satu tahun yang lalu dan pasien dengan risiko tinggi mengalami kejadian trombosis dan memiliki setidaknya 1 dari faktor risiko berikut:

- Berumur lebih dari 65 tahun
- Diabetes mellitus yang memerlukan pengobatan
- Riwayat tertulis dugaan munculnya infark miokard spontan kedua (lebih dari 1 tahun yang lalu)
- Riwayat tertulis berupa bukti angiografi dari *Multivessel CAD* (stenosis ≥50% pada 2 area mayor arteri coroner [seperti anterior kiri bawah, *ramus intermedius*, *circumflex* kiri, arteri koroner kanan], meliputi pembuluh darah utama, pembuluh darah cabang mayor, atau *bypass graft*)
- Disfungsi ginjal kronis (*non-end stage)* dengan klirens kreatinin < 60 ml/min (dihitung berdasarkan *Cockroft Gault equation*)

Kegunaan Brilinta 90 mg

Brilinta 90 mg yang diberikan bersama dengan ASA 75-100 mg diindikasikan untuk pencegahan kejadian trombotik (kematian kardiovaskular, infark miokard dan stroke) pada pasien dengan *Acute Coronary Syndromes* (ACS) [angina tidak stabil, *Non-ST Elevation Myocardial Infarction* (NSTEMI) atau *ST Elevation Myocardial Infarction* (STEMI) termasuk pasien yang ditangani dengan *Percutaneous Coronary Intervention* (PCI) atau *Coronary Artery By-pass Grafting* (CABG).

Brilinta 90 mg yang diberikan bersama dengan asam asetilsalisilat (ASA), diindikasikan untuk mengurangi risiko stroke pada pasien dengan stroke iskemik akut (dengan *NIH Stroke Scale score ≤ 5*) atau berisiko tinggi mengalami serangan iskemik transien (TIA) dengan ABCD^2 *score* ≥ 6.

Brilinta 90 mg mengurangi kemungkinan Anda mengalami serangan jantung, stroke, atau kematian karena penyakit yang berhubungan dengan jantung atau pembuluh darah Anda.

Cara Kerja Brilinta

Brilinta mempengaruhi sel yang dikenal dengan sebutan 'platelet' (atau trombosit). Sel darah yang sangat kecil ini membantu menghentikan perdarahan dengan menggumpal bersama untuk menyumbat lubang kecil pada pembuluh darah yang sobek atau rusak.

Meskipun demikian, platelet dapat membentuk sumbatan pada pembuluh darah yang sakit pada jantung dan otak. Hal ini sangat berbahaya karena:

- Sumbatan dapat menghentikan aliran darah secara total; hal ini dapat menyebabkan serangan jantung (infark myocardium) atau stroke, atau
- Sumbatan dapat menghentikan sebagian aliran darah; hal ini mengurangi aliran darah ke jantung dan menyebabkan nyeri dada yang hilang timbul (disebut sebagai 'angina tidak stabil')
- Sumbatan darah dapat memutus suplai darah di pembuluh darah ke otak sepenuhnya; hal ini dapat menyebabkan stroke, atau
- Sumbatan darah dapat memutus sementara atau sebagian pembuluh darah sehingga mengurangi aliran darah ke otak dan menyebabkan gejala seperti stroke, seperti stroke iskemik akut atau berisiko tinggi mengalami serangan iskemik transient (TIA)

Brilinta membantu menghentikan penggumpalan platelet. Hal ini menurunkan risiko pembentukan gumpalan yang dapat menyebabkan berkurangnya aliran darah.

2. Hal yang perlu Anda ketahui sebelum mengkonsumsi Brilinta

Jangan gunakan Brilinta

- Apabila Anda adalah pasien dengan hipersentivitas (sebagai contoh : angioedema) terhadap ticagrelor atau bahan lain yang terkandung dalam obat ini (lihat bagian isi kemasan obat dan informasi).
- Apabila Anda adalah pasien dengan pendarahan patologis aktif seperti ulkus peptik atau perdarahan intrakranial.
- Apabila Anda adalah pasien dengan riwayat perdarahan intrakranial (*Intracarnial Haemorrhage*) karena dapat berisiko tinggi terjadinya *Intracarnial Haemorrhage*

berulang.

- Apabila Anda adalah pasien dengan gangguan hati berat
- Apabila Anda mengkonsumsi obat-obatan berikut ini:
    - Ketokonozole (digunakan untuk mengobati infeksi jamur)
    - Clarithromycin (digunakan untuk mengobati infeksi bakteri)
    - Nefazodone (sebagai antidepresan)
    - Ritonavir atau atazanavir (digunakan untuk mengobati infeksi HIV dan AIDS).

Jangan gunakan Brilinta apabila Anda mengalami hal tersebut diatas. Apabila Anda tidak yakin, bicarakan dengan dokter atau apoteker sebelum menggunakan obat ini.

Peringatan dan pencegahan

Komunikasikan terhadap dokter atau apoteker Anda sebelum menggunakan Brilinta apabila:

- Anda memiliki risiko tinggi perdarahan karena:
    - Baru-baru ini mengalami cedera serius
    - Baru-baru ini menjalani tindakan operasi (termasuk operasi gigi, tanyakan kepada dokter gigi Anda mengenai hal ini)
    - Anda mengidap penyakit yang berhubungan dengan pembekuan darah
    - Baru-baru ini anda mengalami pendarahan di lambung atau usus (seperti usus lambung atau polip usus)
- Anda dijadwalkan menjalani operasi (termasuk operasi gigi) selama menggunakan Brilinta. Hal ini dikarenakan peningkatan risiko perdarahan. Dokter Anda mungkin dapat menghentikan penggunaan obat ini sejak 7 hari sebelum operasi.
- Denyut jantung Anda rendah tidak normal (biasanya lebih rendah dari 60 denyut per menit) dan Anda belum memiliki alat pacu jantung terpasang pada jantung Anda.
- Anda mengidap asma atau penyakit paru lainnya atau kesulitan bernafas.
- Anda memiliki masalah pada hati Anda atau sebelumnya pernah menderita penyakit yang mempengaruhi hati Anda.
- Anda memiliki hasil periksa darah yang menunjukkan kadar asam urat yang tidak lazim

Apabila Anda mengalami/memiliki kondisi tersebut diatas (atau Anda tidak yakin), bicarakan dengan dokter atau apoteker sebelum menggunakan obat ini.

Anak-anak dan remaja

Brilinta tidak direkomendasikan untuk anak dan remaja di bawah usia 18 tahun.

Brilinta dan obat-obatan lain

Komunikasikan kepada dokter atau apoteker Anda apabila Anda sedang, pernah, atau akan mengkonsumsi obat-obatan lain. Hal ini dikarenakan Brilinta dapat mempengaruhi cara kerja beberapa jenis obat-obatan lain, begitu juga obat-obatan lain dapat mempengaruhi cara kerja Brilinta.

Anda harus memberitahukan dokter atau apoteker Anda apabila Anda sedang mengkonsumsi obat-obatan sebagai berikut:

- Simvastatin atau lovastastin dengan dosis lebih dari 40 mg per hari
- Rifampicin (antibiotik)
- Fenitoin, carbamazepine, dan fenobarbital (digunakan untuk mengendalikan kejang)
- Digoxin (digunakan untuk mengobati gagal jantung)
- Siklosporin (digunakan untuk melemahkan pertahanan tubuh Anda)
- Diltiazem (digunakan untuk mengobati ritme jantung tidak normal)
- Penghambat beta (digunakan untuk mengobati tekanan darah tinggi)
- Morphine (digunakan untuk analgesik atau antinyeri)

Secara khusus, beritahukan dokter atau apoteker Anda apabila Anda sedang mengkonsumsi obat-obatan yang meningkatkan risiko perdarahan sebagai berikut:

- Antikoagulan oral yang sering dikenal dengan sebutan ‘pengencer darah’ termasuk warfarin
- Obat anti inflamasi non-steroid (OAINS) yang sering digunakan sebagai penghilang nyeri seperti ibuprofen atau naproxen
- Obat-obatan lain seperti ketokonazole (digunakan untuk mengobati infeksi jamur), clarithromycin (digunakan untuk mengobati infeksi bakteri), nefazodone (sebuah antidepresan), ritonavir dan atazanavir (digunakan untuk mengobati infeksi HIV dan AIDS)

Komunikasikan dengan dokter Anda bahwa karena Anda mengkonsumsi Brilinta, Anda memiliki peningkatan risiko perdarahan apabila dokter memberikan Anda obat fibrinolitik, atau yang sering disebut ‘penghilang gumpalan’, seperti streptokinase atau alteplase.

Kehamilan dan menyusui

Penggunaan Brilinta pada ibu hamil atau wanita yang berencana untuk hamil tidak direkomendasikan. Wanita harus menggunakan alat kontrasepsi yang sesuai selama mengkonsumsi Brilinta.

Bicarakan dengan dokter Anda apabila Anda berencana menyusui selama mengkonsumsi Brilinta. Dokter Anda akan mendiskusikan dengan Anda keuntungan dan risiko mengkonsumsi Brilinta pada masa menyusui tersebut.

Apabila Anda sedang hamil atau menyusui, mungkin hamil, atau berencana untuk hamil, mintalah anjuran dari dokter atau apoteker Anda sebelum mengkonsumsi obat ini.

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Mengemudi dan penggunaan mesin

Brilinta tidak banyak mempengaruhi kemampuan Anda mengemudi dan menggunakan mesin. Apabila Anda merasa pusing atau kebingungan selama mengkonsumsi obat ini, berhati-hatilah dalam mengemudi dan menggunakan mesin.

3. Cara menggunakan Brilinta

Selalu gunakan obat ini persis seperti yang diinstruksikan dokter Anda. Apabila Anda tidak yakin, periksa ulang dengan dokter, apoteker, atau perawat Anda.

Berapa banyak yang harus dikonsumsi

Brilinta 60 mg :

- Dosis yang lazim diberikan adalah satu buah tablet 60 mg dua kali sehari. Teruskan penggunaan Brilinta sesuai instruksi dokter.
- Gunakan obat ini pada waktu yang sama setiap harinya (contohnya satu tablet di pagi hari dan satu tablet di malam hari).

Brilinta 90 mg :

Jika Anda pernah mengalami serangan jantung atau angina tidak stabil (angina atau nyeri dada yang tidak terkontrol dengan baik):

- Dosis awal sejumlah 2 tablet pada saat yang bersamaan (dosis *loading* 180 mg). Dosis ini akan diberikan pada Anda di rumah sakit
- Setelah dosis awal, dosis lazim yang diberikan adalah 90 mg dua kali sehari selama 12 bulan kecuali dokter Anda mengatakan lain
- Gunakan obat ini pada waktu yang sama setiap harinya (contohnya satu tablet di pagi hari dan satu tablet di malam hari).

Jika Anda pernah mengalami stroke iskemik akut (NIH Stroke Scale score ≤ 5) atau berisiko tinggi mengalami serangan iskemik transien (TIA, dengan *$ABCD_2$ score* ≥ 6):

- Dosis awal sejumlah 2 tablet 90 mg sekaligus (dosis loading 180 mg).
- Setelah dosis awal, dosis lazim yang diberikan adalah satu tablet 90 mg dua kali sehari yang diberikan selama 30 hari kecuali dokter Anda mengatakan lain.
- Gunakan obat ini pada waktu yang sama setiap harinya (contohnya satu tablet di pagi hari dan satu tablet di malam hari).

Penggunaan Brilinta dengan obat-obatan lain untuk pembekuan darah

Dokter Anda biasanya akan menganjurkan Anda meminum asam asetilsalisilat. Asam

asetilsalisilat terkandung dalam berbagai macam obat yang digunakan untuk mencegah pembekuan darah. Dokter Anda akan menganjurkan dosis yang tepat untuk Anda (biasanya sekitar 75-100 mg sehari).

Cara menggunakan Brilinta

- Anda dapat meminum tablet dengan atau tanpa makanan.
- Anda dapat memeriksa apakah Anda sudah meminum obat dengan cara melihat blister. Terdapat lambang matahari (untuk pagi hari) dan bulan (untuk malam hari). Informasi ini dapat mengingatkan apakah Anda sudah meminum dosis obat.
- Tablet orodispersible – Anda dapat meletakkan tablet di atas lidah dimana tablet akan cepat tersebar dan terlarut dalam air liur, dapat ditelan baik dengan air (maksimal 150 mL) atau tanpa air.

Apabila Anda mengalami kesulitan menelan tablet

Apabila Anda kesulitan menelan tablet, Anda dapat menghaluskan tablet dan mencampurnya sebagai berikut:

- Hancurkan tablet hingga menjadi serbuk halus
- Tuangkan serbuk ke dalam setengah gelas air
- Aduk dan minum segera
- Untuk memastikan tidak ada serbuk yang tertinggal dalam gelas, bilas gelas dengan setengah gelas air dan habiskan airnya

Apabila Anda menggunakan Brilinta dalam jumlah lebih dari yang seharusnya

Apabila Anda mengkonsumsi lebih banyak tablet Brilinta dari yang seharusnya, segera bicarakan dengan dokter Anda atau segera pergi ke rumah sakit terdekat. Anda dapat mengalami peningkatan risiko perdarahan.

Apabila Anda lupa menggunakan Brilinta

- Apabila Anda lupa mengkonsumsi Brilinta, minumlah dosis berikutnya seperti biasa.
- Jangan pernah mengkonsumsi dosis ganda untuk mengganti dosis yang terlupa. Jangan pernah mengkonsumsi dua tablet dalam satu hari.

Apabila Anda berhenti menggunakan Brilinta

Jangan berhenti menggunakan Brilinta tanpa konsultasi ke dokter terlebih dahulu. Gunakan obat ini setiap hari dan selama yang diresepkan oleh dokter Anda. Apabila Anda menghentikan penggunaan Brilinta, Anda dapat mengalami peningkatan risiko serangan jantung ulang atau stroke atau kematian akibat penyakit yang berhubungan dengan jantung.

dan pembuluh darah.

Apabila Anda memiliki pertanyaan lebih lanjut mengenai obat ini, tanyakan pada dokter atau apoteker Anda.

4. Efek samping yang mungkin terjadi

Seperti semua obat-obatan, obat ini dapat mengakibatkan efek samping, yang tidak dialami oleh setiap orang.

Brilinta mempengaruhi pembekuan darah, sehingga sebagian besar efek sampingnya berkaitan dengan perdarahan. Perdarahan dapat terjadi pada bagian tubuh manapun. Beberapa perdarahan lazim terjadi (seperti memar dan mimisan). Perdarahan berat jarang terjadi, namun dapat mengancam nyawa.

Segera temui dokter apabila Anda merasakan gejala-gejala berikut ini – Anda mungkin memerlukan penanganan medis segera:

- Perdarahan pada otak atau intrakranial adalah efek samping yang jarang terjadi, dan menimbulkan tanda dan gejala stroke seperti:
    - Rasa kesemutan atau kelemahan pada lengan, kaki, wajah, terutama pada salah satu sisi tubuh Anda
    - Kebingungan, kesulitan berbicara dan memahami orang lain yang timbul secara mendadak
    - Kesulitan berjalan, kehilangan keseimbangan atau koordinasi yang muncul mendadak
    - Rasa pusing atau nyeri kepala hebat yang muncul secara mendadak tanpa sebab yang jelas
- Tanda perdarahan seperti:
    - Perdarahan derajat berat yang tidak dapat dikontrol
    - Perdarahan yang tidak terduga atau perdarahan yang berlangsung lama
    - Air seni berwarna merah jambu, merah, atau coklat
    - Muntah berwarna merah darah atau muntah berwarna hitam seperti bubuk kopi
    - Tinja berwarna merah atau hitam seperi ter
    - Batuk atau muntah gumpalan darah
- Pingsan (sinkop)
    - Kehilangan kesadaran sementara karena penurunan tekanan darah secara mendadak (sering)

Diskusikan dengan dokter Anda apabila Anda merasakan hal-hal berikut:

- **Rasa sulit bernafas – hal ini sangat sering terjadi**. Hal ini mungkin disebabkan oleh penyakit jantung Anda atau sebab lain, atau hal ini dapat merupakan efek samping Brilinta. Rasa sulit bernafas akibat Brilinta biasanya ringan dan disertai oleh sensasi 'lapar udara' secara tiba-tiba yang muncul saat istirahat yang muncul pada minggu pertama terapi dan akan menghilang pada kebanyakan orang. Apabila Anda merasakan kesulitan bernafas yang bertambah parah atau bertahan dalam waktu lama, hubungi dokter Anda. Dokter Anda akan menentukan apakah Anda memerlukan investigasi lebih lanjut.

Efek samping lain yang mungkin terjadi

Sangat sering (dapat mempengaruhi lebih dari 1 dari 10 orang)

- Kadar asam urat yang tinggi dalam darah (diketahui melalui pemeriksaan laboratorium)
- Perdarahan yang disebabkan oleh gangguan perdarahan

Sering (mempengaruhi sampai 1 dari 10 orang)

- Memar
- Nyeri kepala
- Pusing atau sensasi ruangan berputar
- Diare atau maag
- Mual
- Konstipasi
- Ruam
- Gatal
- Nyeri hebat atau pembengkakan sendi – ini merupakan tanda asam urat
- Rasa pusing atau melayang atau pandangan kabur – ini merupakan tanda tekanan darah rendah
- Mimisan
- Perdarahan setelah operasi atau dari luka cukur atau luka lain yang tidak normal
- Perdarahan dari dinding lambung (ulkus)
- Gusi berdarah

Tidak sering (dapat mempengaruhi sampai 1 dari 100 orang)

- Reaksi alergi - ruam, gatal, pembengkakan pada wajah, bibir, atau lidah dapat merupakan tanda reaksi alergi
- Kebingungan
- Gangguan penglihatan yang disebabkan oleh darah dalam mata Anda
- Perdarahan vagina yang lebih berat, atau terjadi di luar jadwal menstruasi Anda

- Perdarahan pada sendi dan otot yang menyebabkan pembengkakan yang nyeri
- Perdarahan organ dalam, hal ini dapat menyebabkan rasa pusing atau melayang
- Gangguan darah dan sistem limfatik: *Thrombotic Thrombocytopenic Purpura*

Frekuensi belum dapat ditetapkan dari data yang tersedia

- Detak jantung rendah yang tidak normal (biasanya lebih rendah dari 60 detak jantung per menit).

Pelaporan efek samping

Apabila Anda mengalami efek samping, hubungi dokter, apoteker, atau perawat Anda. Hal ini termasuk efek samping yang mungkin terjadi yang tidak disebutkan dalam leaflet ini.

5. Cara penyimpanan Brilinta

Jauhkan obat ini dari penglihatan dan jangkauan anak-anak.

Jangan gunakan obat ini setelah lewat tanggal kadaluarsa, yang tercantum pada label dan kertas karton setelah 'EXP'. Tanggal kadaluarsa menunjukkan tanggal terakhir dari bulan tersebut.

Jangan disimpan pada suhu di atas 30°C.

Jangan buang obat apapun ke saluran pembuangan air atau tempat pembuangan sampah rumah tangga. Tanyakan apoteker Anda tentang cara pembuangan obat yang sudah tidak digunakan lagi. Perilaku ini membantu melindungi lingkungan.

6. Isi paket obat dan informasi lainnya

Brilinta 60 mg mengandung

- Zat aktif ticagrelor. Setiap tablet salut selaput mengandung ticagrelor 60 mg
- Komposisi lainnya adalah
  - Tablet Inti: mannitol (E421), dihidrat kalsium hidrogen fosfat, *sodium starch glycolate type A*, hidroksipropilselulosa (E463), Magnesium Stearate (E470b).
  - Selaput salut: hypromellose (E464), titanium dioxide (E171), talc, macrogol 400, iron oxide black (E172), and iron oxide red (E172)

Brilinta 90 mg mengandung

- Zat aktif ticagrelor. Setiap tablet salut selaput mengandung ticagrelor 90 mg
- Komposisi lainnya adalah
  - Tablet Inti: mannitol (E421), dihidrat kalsium hidrogen fosfat, *sodium starch glycolate type A*, hidroksipropilselulosa (E463), Magnesium Stearate (E470b).
  - Selaput salut: hypromellose (E464), titanium dioxide (E171), talc, macrogol 400, and iron oxide yellow (E172).

Brilinta 90 mg orodispersible tablet mengandung

- Zat aktif ticagrelor. Setiap tablet orodispersible mengandung ticagrelor 90 mg

- Komposisi lainnya adalah :
  mannitol, Microcrystalline cellulose, Crospovidone, Xylitol, Anhydrous calcium hydrogen phosphate, Sodium stearyl fumarate, Hydroxypropylcellulose, Colloidal anhydrous silica.

Bagaimana bentuk Brilinta dan isi paket obat

60 mg - tablet salut selaput berbentuk bulat, bikonveks, merah jambu, ditandai dengan “60” di atas “T” pada satu sisinya

90 mg - tablet salut selaput berbentuk bulat, bikonveks, kuning, ditandai dengan “90” di atas “T” pada satu sisinya

Brilinta tersedia dalam blister standar (dengan simbol matahari dan bulan) dalam karton berisi 56 tablet (4 blister @ 14 tablets)

90 mg tablet orodispersible - tablet orodispersible berbentuk bulat, datar, tepi miring, putih sampai merah muda pucat, ditandai dengan '90' di atas 'TI' di satu sisi dan polos di sisi lain.

Brilinta tersedia dalam blister standar dalam karton berisi 56 tablet (7 blister @ 8 tablet orodispersible)

Pemegang Hak Pemasaran dan Produsen

Brilinta 60 mg

Diproduksi oleh:
AstraZeneca AB
Gartunavagen SE-152 57 Södertälje
Sweden

Brilinta 90 mg

Diproduksi oleh:
AstraZeneca AB
Gartunavagen SE-152 57 Södertälje
Sweden

Dikemas dan dirilis oleh:
AstraZeneca Pharmaceutical. Co. Ltd
Wuxi, Cina

Brilinta 90 mg orodispersible tablet

Diproduksi oleh:

AstraZeneca AB

Gartunavagen SE-152 57 Södertälje

Sweden

Diimpor oleh:

PT AstraZeneca Indonesia

Cikarang,

Bekasi – Indonesia

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