BRILINTA® 90mg
(ticagrelor)

1. NAME OF MEDICINAL PRODUCT

BRILINTA® (ticagrelor), 90 mg, film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 90 mg of ticagrelor.
For excipients, see section List of excipients.

3. 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.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

BRILINTA, co-administered with acetylsalicylic acid (ASA), 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 medically, and those who are managed with percutaneous coronary intervention (PCI) or coronary artery by-pass grafting (CABG).

4.2 Posology and method of administration

In patients with 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. Treatment is recommended for at least 12 months unless discontinuation of BRILINTA is clinically indicated (see section Pharmacodynamic properties). After one year, patients with MI initiated on 90 mg may continue treatment with 60 mg without interruption if they have a high risk of an atherothrombotic event.

Patients taking BRILINTA should also take a daily low maintenance dose of acetylsalicylic acid (ASA) of 75-150 mg, unless specifically contraindicated. An initial loading dose of ASA, is recommended for patients with ACS (see section Pharmacodynamics properties).

Missed dose

Lapses in therapy should be avoided. A patient who misses a dose of BRILINTA should take their next dose at its scheduled time.

Switching

Physicians who desire to switch patients, with a prior ACS event to BRILINTA, should administer the first 90 mg dose of BRILINTA 24 hours following the last dose of other antiplatelet medication (see section Pharmacodynamic properties).

Premature discontinuation

Premature discontinuation with any antiplatelet therapy, including BRILINTA, could result in an increased risk of cardiovascular (CV) death, myocardial infarction (MI), or stroke due to the patient's underlying disease (see section Special warnings and special precautions for use).

Administration

For oral use. BRILINTA can be taken with or without food. For patients who are unable to swallow the tablet(s) whole, BRILINTA 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.

Special Populations

Paediatric patients:

Safety and efficacy in children below the age of 18 have not been established (see section Pharmacodynamic properties).

Elderly patients:

No dose adjustment is required.

Patients with renal impairment:

No dose adjustment is necessary for patients with renal impairment (see section Pharmacokinetic properties).

Patients with hepatic impairment:

No dose adjustment is necessary for patients with mild hepatic impairment. BRILINTA has not been studied in patients with severe hepatic impairment and there is limited information on treatment of patients with moderate hepatic impairment (see section Contraindications, Special warnings and special precautions for use, and Pharmacokinetic properties).

4.3 Contraindications

- Hypersensitivity to ticagrelor or any of the excipients (see section Undesirable effects).
- Active pathological bleeding.
- History of intracranial haemorrhage (see section Undesirable effects).
- Severe hepatic impairment (see section Posology and method of administration, Special warnings and special precautions for use and Pharmacokinetic properties).

- 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 (see section Special warnings and special precautions for use and Interaction with other medicinal products and other forms of interaction).

4.4 Special warnings and special precautions for use

Bleeding risk

As with other antiplatelet agents, the use of BRILINTA in patients at known increased risk for bleeding should be balanced against the benefit in terms of prevention of thrombotic events. If clinically indicated, BRILINTA should be used with caution in the following patient groups:

- Patients with a propensity to bleed (e.g. due to recent trauma, recent surgery, active or recent gastrointestinal bleeding or moderate hepatic impairment) or who are at increased risk of trauma. The use of BRILINTA is contraindicated in patients with active pathological bleeding, in those with a history of intracranial haemorrhage and severe hepatic impairment (see section Contraindications).

- Patients with concomitant administration of medicinal products that may increase the risk of bleeding (e.g. non-steroidal anti-inflammatory drugs (NSAIDS), oral anticoagulants, and/or fibrinolytics within 24 hours of BRILINTA dosing).

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

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

Surgery

- If a patient requires surgery, physicians should consider each patient's clinical profile as well as the benefits and risks of continued antiplatelet therapy when determining when discontinuation of BRILINTA treatment should occur.
- Because of the reversible binding of BRILINTA, restoration of platelet aggregation occurs faster with BRILINTA compared to clopidogrel. In the OFFSET Study, mean Inhibition of Platelet Aggregation (IPA) for BRILINTA at 72 hours post-dose was comparable to mean IPA for clopidogrel at 120 hours post-dose. The more rapid offset of effect may predict a reduced risk of bleeding complications, e.g. in settings where antiplatelet therapy must be temporarily discontinued due to surgery or trauma.

- In PLATO, patients undergoing CABG, BRILINTA had a similar rate of major bleeds compared to clopidogrel at all days after stopping therapy except Day 1 where BRILINTA had a numerically higher rate of major bleeding.
- Based on the results in PLATO, if a CABG procedure is planned the bleeding risk with BRILINTA is numerically increased compared to that seen with clopidogrel when therapy is discontinued within 96 hours prior to the procedure.
- If a patient is to undergo elective surgery and antiplatelet effect is not desired, BRILINTA should be discontinued 5 days prior to surgery. (see section Pharmacodynamic properties).

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, caution is advised for treatment beyond one year.

Patients with moderate hepatic impairment

There is limited experience with BRILINTA in patients with moderate hepatic impairment therefore, caution is advised in these patients. Use of BRILINTA is contraindicated in patients with severe hepatic impairment (see sections Posology and method of administration, Contraindications, and Pharmacokinetic properties).

Bradyarrhythmia

Holter ECG monitoring has shown an increased frequency of mostly asymptomatic ventricular pauses during treatment with ticagrelor compared with clopidogrel. In phase 3 studies evaluating the safety and efficacy of BRILINTA, bradyarrhythmic events were reported in a similar frequency for ticagrelor and comparators (placebo, clopidogrel and ASA). Patients with an increased risk of bradycardic events (e.g. patients without a pacemaker who have sick sinus syndrome, 2^{nd} or 3^{rd} degree atrioventricular (AV) block, or bradycardic-related syncope) have been excluded from BRILINTA outcome studies. Therefore, due to the limited clinical experience in these patients, caution is advised (see also section Pharmacodynamic properties).
Bradyarrhythmic events and AV blocks have been reported in the post-marketing setting in patients taking BRILINTA (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.

Dyspnoea

Dyspnoea, usually mild to moderate in intensity and often resolving without need for treatment discontinuation, is reported in patients treated with BRILINTA (see section Undesirable effects). The mechanism has not yet been elucidated. If a patient reports new,

prolonged, or worsened dyspnoea this should be investigated fully, and if not tolerated, treatment with BRILINTA should be stopped.

Central Sleep Apnoea

Central sleep apnoea including Cheyne-Stokes 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.

Thrombotic Thrombocytopenic Purpura (TTP)

Thrombotic Thrombocytopenic Purpura has been reported very rarely with the use of BRILINTA. TTP is a serious condition and requires prompt treatment.

Interference with laboratory tests

Platelet function tests to diagnose Heparin induced thrombocytopenia (HIT)

False negative results in platelet function test for heparin induced thrombocytopenia (HIT) have been reported in patients administered ticagrelor. This is related to inhibition of the $P2Y_{12}$-receptor on the healthy donor platelets in the test by ticagrelor in the patient's sera/plasma. Information on concomitant treatment with ticagrelor is required for interpretation of HIT platelet function tests.

Before considering discontinuation of ticagrelor, the benefit and risk of continued treatment should be assessed, taking both the prothrombotic state of HIT and the increased risk of bleeding with concomitant anticoagulant and ticagrelor treatment into consideration.

Other

Based on a relationship observed in the PLATO Study between maintenance ASA dose and relative efficacy of ticagrelor compared to clopidogrel, co-administration of ticagrelor and high maintenance dose ASA (>300 mg) is not recommended (see section Pharmacodynamic properties).

Co-administration of BRILINTA with strong CYP3A4 inhibitors (e.g. ketoconazole, clarithromycin, nefazadone, ritonavir, and atazanavir) is contraindicated (see section Contraindications and Interaction with other medicinal products and other forms of interaction). Co-administration may lead to a substantial increase in BRILINTA exposure (see section Interaction with other medicinal products and other forms of interaction).

Discontinuations

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

4.5 Interaction with other medicinal products and other forms of interaction

Drug-Drug Interactions

Effects of Other Drugs on BRILINTA

Medicinal Products metabolised by CYP3A4

Ketoconazole (Strong CYP3A4 Inhibitors)
Co-administration of ketoconazole with ticagrelor increased ticagrelor C_{max} and AUC equal to 2.4-fold and 7.3-fold, respectively. The C_{max} and AUC of the active metabolite were reduced by 89% and 56%, respectively. Other strong inhibitors of CYP3A4 (clarithromycin, nefazodone, ritonavir, and atazanavir) would be expected to have similar effects and their concomitant use with BRILINTA is contraindicated (see section Contraindications and Special warnings and special precautions for use).

Diltiazem (Moderate CYP3A4 inhibitors)
Co-administration of ticagrelor and diltiazem increased the C_{max} of ticagrelor by 69% and AUC by 174%, and decreased the active metabolite C_{max} by 38% and AUC was unchanged. There was no effect of ticagrelor on diltiazem plasma levels. Other moderate CYP3A4 inhibitors (e.g. amprenavir, aprepitant, erythromycin, fluconazole, and verapamil) can as well be co-administered with BRILINTA.

Rifampin and Other CYP3A Inducers
Co-administration of rifampin with ticagrelor decreased ticagrelor C_{max} and AUC by 73% and 86%, respectively. The C_{max} of the active metabolite was unchanged and the AUC was decreased by 46%, respectively. Other CYP3A4 inducers (e.g. phenytoin, carbamazepine, and phenobarbital) would be expected to decrease the exposure to ticagrelor as well and may result in reduced efficacy of BRILINTA.

Cyclosporine (PgP and CYP3A inhibitor)
Co-administration of cyclosporine (600 mg) with ticagrelor increased ticagrelor C_{max} and AUC equal to 2.3-fold and 2.8-fold, respectively. The AUC of the active metabolite was increased by 32% and C_{max} was decreased by 15% in the presence of cyclosporine. There was no effect of ticagrelor on cyclosporine blood levels.

No data are available on concomitant use of BRILINTA with other drugs that also are potent P-glycoprotein (P-gp) 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 (see section Special warnings and special precautions for use).

Others
Clinical pharmacology interaction studies showed that co-administration of ticagrelor with heparin, enoxaparin, and ASA did not have any effect on ticagrelor or the active metabolite plasma levels. Co-administration of ticagrelor and heparin had no effect on heparin based on activated partial thromboplastin time (aPTT) and activated coagulation time (ACT)

assays. Co-administration of ticagrelor and enoxaparin had no effect on enoxaparin based on factor Xa assay.

Delayed and decreased exposure to oral $P2Y_{12}$ inhibitors, including ticagrelor and its active metabolite, has been reported in patients treated with morphine (approximately 35% reduction in ticagrelor). This interaction may be related to reduced gastrointestinal motility, and therefore apply to other opioids. The clinical relevance is unknown.

Effects of BRILINTA on Other Drugs

Medicinal Products metabolised by CYP3A4

Simvastatin
Co-administration of ticagrelor with simvastatin increased simvastatin C_{max} by 81% and AUC by 56% and increased simvastatin acid C_{max} by 64% and AUC by 52% with some individual increases equal to 2 to 3-fold. Consideration of the clinical significance should be given to the magnitude and range of changes on the exposure to patients requiring greater than 40 mg of simvastatin. There was no effect of simvastatin on ticagrelor plasma levels. BRILINTA may have similar effect on lovastatin, but is not expected to have a clinically meaningful effect on other statins.

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

Medicinal Products metabolised by CYP2C9

Tolbutamide
Co-administration of ticagrelor with tolbutamide resulted in no change in the plasma levels of either drug, which suggest that ticagrelor is not a CYP2C9 inhibitor and unlikely to alter the CYP2C9 mediated metabolism of drugs like warfarin and tolbutamide.

Oral Contraceptives
Co-administration of ticagrelor and levonorgestrel and ethinyl estradiol increased ethinyl estradiol exposure by approximately 20% but did not alter the PK of levonorgestrel. No clinically relevant effect on oral contraceptive efficacy is expected when levonorgestrel and ethinyl estradiol are co-administered with BRILINTA.

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

Other Concomitant Therapy

In clinical studies, BRILINTA was commonly administered with acetylsalicylic acid, heparin, low molecular weight heparin, intravenous GpIIb/IIIa inhibitors, proton pump

inhibitors, statins, beta-blockers, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers as needed for concomitant conditions. These studies did not produce any evidence of clinically significant adverse interactions.

4.6 Fertility, pregnancy and lactation

Fertility

Ticagrelor had no effect on male or female fertility in animals (see section Preclinical safety data).

Pregnancy

No clinical study has been conducted in pregnant or lactating women. Limited clinical data on exposure to BRILINTA during pregnancy are available.

Animal studies do not indicate direct harmful effects with respect to pregnancy, embryonal/foetal development, parturition, or postnatal development. Because animal reproduction studies are not always predictive of a human response, ticagrelor should be used during pregnancy only if the potential benefit to the mother justifies any potential risks to the foetus.

Lactation

It is not known whether this medicinal product is excreted in human milk. Studies in rats have shown that ticagrelor and active metabolites are excreted in the milk. The use of BRILINTA during breastfeeding is not recommended.

4.7 Effects on ability to drive and use machines

No studies on the effects of BRILINTA on the ability to drive and use machines have been performed. BRILINTA is expected to have no or negligible influence on the ability to drive and use machines. During treatment with BRILINTA, dizziness and confusion have been reported. Therefore, patients who experience these symptoms should be cautious while driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

The safety profile of BRILINTA has been evaluated in two large phase 3 outcome trials (PLATO and PEGASUS) including more than 39,000 patients (See section Pharmacodynamic properties). The relevant adverse drug reactions observed in these studies are discussed below.

The safety of BRILINTA in patients with acute coronary syndromes (UA, NSTEMI and STEMI) was evaluated in the PLATO Study, which compared patients treated with BRILINTA 90 mg twice daily to patients treated with clopidogrel 75 mg once daily both given in combination with ASA and other standard therapies. Median treatment duration for BRILINTA was 277 days. In PLATO, patients on BRILINTA had a higher incidence of discontinuation due to adverse events than clopidogrel (7.4% vs. 5.4%).

The safety of BRILINTA in patients with history of MI (MI occurred at least one year ago) and high risk of developing a thrombotic event was evaluated in the PEGASUS Study, which compared patients treated with BRILINTA 60 mg twice daily or 90 mg twice daily combined with ASA to ASA therapy alone and other standard therapies. Median treatment duration for BRILINTA 60 mg was 29.4 months. In PEGASUS, patients on BRILINTA had a higher incidence of discontinuation due to adverse events compared to ASA therapy alone (16.1% for ticagrelor 60 mg with ASA vs. 8.5% for ASA therapy alone).

The most commonly reported adverse drug reactions in patients treated with ticagrelor were bleeding and dyspnoea (see also section Special warnings and special precautions for use).

Description of selected adverse drug reactions

Bleeding findings in PLATO

Overall outcome of bleeding events in the PLATO Study are shown in Table 1.

Table 1 Analysis of overall bleeding events, Kaplan-Meier estimate of bleeding rates by treatment at 12 months (PLATO)

Safety Endpoints	**BRILINTA 90 mg twice daily N=9235**		**Clopidogrel 75 mg once daily (%) N=9186**	***p*-value**
	KM%	**Hazard Ratio (95% CI)**	**KM%**	
PLATO-defined bleeding categories				
Primary Safety Endpoint PLATO-defined Total Major	11.6	1.04 (0.95, 1.13)	11.2	0.4336
Secondary Endpoints PLATO Fatal/Life-Threatening	5.8	1.03 (0.90, 1.16)	5.8	0.6988
PLATO Total Major or Minor	16.1	1.11 (1.03, 1.20)	14.6	0.0084
PLATO Non-CABG Major	4.5	1.19 (1.02, 1.38)	3.8	0.0264
PLATO Non-Procedural Major	3.1	1.31 (1.08, 1.60)	2.3	0.0058
PLATO Non-Procedural Major or Minor	5.9	1.39 (1.21, 1.60)	4.3	<0.0001
TIMI-defined bleeding categories				

TIMI Major	7.9	1.03 (0.93, 1.15)	7.7	0.5669
TIMI Major or Minor	11.4	1.05 (0.96, 1.15)	10.9	0.3272

Bleeding category definitions:
PLATO Major Fatal/life-threatening: Fatal bleeding, OR any intracranial bleeding, OR intrapericardial with cardiac tamponade, OR with hypovolaemic shock or severe hypotension requiring pressors/inotropes or surgery OR clinically apparent with >50 g/L decrease in haemoglobin, OR ≥4 red cell units transfused.
PLATO Major Other: Significantly disabling, OR clinically apparent with 30-50 g/L decrease in haemoglobin, OR 2-3 red cell units transfused.
PLATO Minor: Requires medical intervention to stop or treat bleeding.
TIMI Major: Fatal bleeding, OR any intracranial bleeding, OR clinically overt signs of haemorrhage associated with a drop in haemoglobin (Hgb) of ≥50 g/L, or when Hgb is not available, a fall in haematocrit (Hct) of ≥15%.
TIMI Minor: Clinically apparent with 30-50 g/L decrease in haemoglobin.

In PLATO, time to first PLATO-defined Total Major bleeding for BRILINTA did not differ significantly from that of clopidogrel. There were few fatal bleeding events in the study, 20 (0.2%) for BRILINTA 90 mg twice daily and 23 (0.3%) for clopidogrel 75 mg once daily. When minor bleeding was included, combined PLATO-defined Major and Minor bleeding events were significantly higher on BRILINTA than on clopidogrel. Overall rates of TIMI-defined bleeding events did not differ significantly between BRILINTA and clopidogrel.

CABG-related bleeding: In PLATO, 42% of the 1584 patients (12% of cohort) who underwent CABG surgery had a PLATO-defined Major Fatal/Life-threatening bleeding with no difference between the treatment groups. Fatal CABG bleeding occurred in 6 patients in each treatment group (see section Special warnings and special precautions for use).

Non-CABG related bleeding and non-procedural related bleeding: BRILINTA and clopidogrel did not differ in non-CABG PLATO-defined Major Fatal/Life-threatening bleeding, but PLATO-defined Total Major, TIMI Major, and TIMI Major + Minor bleeding were more common with ticagrelor. Similarly, when removing all procedure related bleeding, more bleeding occurred with ticagrelor than with clopidogrel (Table 1). Discontinuation of treatment due to non-procedural bleeding was more common for ticagrelor (2.9%) than for clopidogrel (1.2%; $p<0.001$).

Age, gender, weight, ethnicity, geographic region, concurrent conditions, concomitant therapy and medical history, including a previous stroke or transient ischaemic attack, all did not predict either overall or non-procedural PLATO-defined Major bleeding. Thus no particular risk group was identified at risk for any subset of bleeding.

Intracranial bleeding: There were more intracranial non-procedural bleeds with ticagrelor (n=27 bleeds in 26 patients, 0.3%) than with clopidogrel (n=14 bleeds, 0.2%), of which 11

bleeds with ticagrelor and 1 with clopidogrel were fatal. There was no difference in overall fatal bleeds. The percentage of intracranial bleeding was low in both treatment groups given the significant comorbidity and cardiovascular risk factors of the population under study.

Bleeding findings in PEGASUS

Overall outcome of bleeding events in the PEGASUS Study are shown in Table 2.

Table 2 Analysis of overall bleeding events, Kaplan-Meier estimate of bleeding rates by treatment at 36 months (PEGASUS)

	BRILINTA 60 mg twice daily with ASA N=6958		ASA alone N=6996	
Safety Endpoints	KM%	Hazard Ratio (95% CI)	KM%	*p*-value
TIMI-defined bleeding categories				
TIMI Major	2.3	2.32 (1.68, 3.21)	1.1	<0.0001
Fatal	0.3	1.00 (0.44, 2.27)	0.3	1.0000
ICH	0.6	1.33 (0.77, 2.31)	0.5	0.3130
Other TIMI Major	1.6	3.61 (2.31, 5.65)	0.5	<0.0001
TIMI Major or Minor	3.4	2.54 (1.93, 3.35)	1.4	<0.0001
TIMI Major or Minor or Requiring medical attention	16.6	2.64 (2.35, 2.97)	7.0	<0.0001
PLATO-defined bleeding categories				
PLATO Major	3.5	2.57 (1.95, 3.37)	1.4	<0.0001
Fatal/Life-threatening	2.4	2.38 (1.73, 3.26)	1.1	<0.0001
Other PLATO Major	1.1	3.37 (1.95, 5.83)	0.3	<0.0001
PLATO Major or Minor	15.2	2.71 (2.40, 3.08)	6.2	<0.0001

Bleeding category definitions:

TIMI Major: Fatal bleeding, OR any intracranial bleeding, OR clinically overt signs of haemorrhage associated with a drop in haemoglobin (Hgb) of ≥50 g/L, or when Hgb is not available, a fall in haematocrit (Hct) of ≥15%.
Fatal: A bleeding event that directly led to death within 7 days.
ICH: Intracranial haemorrhage.
Other TIMI Major: Non-fatal non-ICH TIMI Major bleeding.
TIMI Minor: Clinically apparent with 30-50 g/L decrease in haemoglobin.
TIMI Requiring medical attention: Requiring intervention, OR leading to hospitalisation, OR prompting evaluation.
PLATO Major Fatal/life-threatening: Fatal bleeding, OR any intracranial bleeding, OR intrapericardial with cardiac tamponade, OR with hypovolaemic shock or severe hypotension requiring pressors/inotropes or surgery OR clinically apparent with >50 g/L decrease in haemoglobin OR ≥4 red cell units transfused.
PLATO Major Other: Significantly disabling, OR clinically apparent with 30-50 g/L decrease in haemoglobin, OR 2-3 red cell units transfused.
PLATO Minor: Requires medical intervention to stop or treat bleeding.

In PEGASUS, TIMI Major bleeding for BRILINTA 60 mg twice daily was higher than for ASA alone. No increased bleeding risk was seen for fatal bleeding and only a minor increase was observed in intracranial haemorrhages, as compared to ASA therapy alone. There were few fatal bleeding events in the study, 11 (0.3%) for BRILINTA 60 mg and 12 (0.3%) for ASA therapy alone. The observed increased risk of TIMI Major bleeding with BRILINTA 60 mg was primarily due to a higher frequency of Other TIMI Major bleeding driven by events in the gastrointestinal SOC.

Increased bleeding patterns similar to TIMI Major were seen for TIMI Major or Minor and PLATO-defined Major and PLATO-defined Major or Minor bleeding categories (see Table 2). Discontinuation of treatment due to bleeding was more common with BRILINTA 60 mg compared to ASA therapy alone (6.2% and 1.5%, respectively). The majority of these bleedings were of less severity (classified as TIMI Requiring medical attention), e.g. epistaxis, bruising, and haematomas.

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

Intracranial bleeding: Spontaneous ICHs were reported in similar rates for BRILINTA 60 mg and ASA therapy alone (n=13, 0.2% in both treatment groups). Traumatic and procedural ICHs showed a minor increase with BRILINTA 60 mg treatment, (n=15, 0.2%) compared with ASA therapy alone (n=10, 0.1%). There were 6 fatal ICHs with BRILINTA 60 mg and 5 fatal ICHs with ASA therapy alone. The incidence of intracranial bleeding was low in both treatment groups given the significant comorbidity and cardiovascular risk factors of the population under study.

Dyspnoea

In PLATO, dyspnoea adverse events were reported in 13.8% of patients taking ticagrelor 90 mg twice daily and in 7.8% of patients taking clopidogrel 75 mg once daily. Most reported dyspnoea adverse events were mild to moderate in intensity and often resolved without the need of treatment discontinuation. Dyspnoea was usually reported in the initial phase of treatment and 87% of the patients who reported dyspnoea experienced a single episode. Dyspnoea serious adverse events were reported in 0.7% taking ticagrelor and 0.4% taking clopidogrel. Patients who reported dyspnoea tended to be older and more frequently had dyspnoea, CHF, COPD, or asthma at baseline. PLATO data do not suggest that the higher frequency with BRILINTA is due to new or worsening heart or lung disease. There was no indication of an adverse effect of BRILINTA on pulmonary function (see section Special warnings and special precautions for use).

In PEGASUS, dyspnoea was reported in 14.2% of patients taking BRILINTA 60 mg twice daily and in 5.5% of patients taking ASA alone. As in PLATO, most reported dyspnoea was mild to moderate in intensity (see section Special warnings and special precautions for use).

Tabulated list of adverse drug reactions

Adverse drug reactions from clinical studies with BRILINTA are listed by MedDRA System Organ Class (SOC) and frequency category determined by PEGASUS and PLATO trials in Table 3. Within each SOC and frequency category, adverse drug reactions are presented in order of decreasing seriousness. Frequency categories are defined according to the following conventions: Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000), Very rare (<1/10,000), Not known (cannot be estimated from the available data).

Table 3 Adverse Drug Reactions observed in clinical studies

System Organ Classification	Very Common	Common	Uncommon
Neoplasms benign, malignant and unspecified (including cysts and polyps)			Tumour bleedings[b]
Blood and lymphatic system disorders	Blood disorder bleedings[c]		
Metabolism and nutrition disorders	Hyperuricaemia[a]	Gout	
Psychiatric disorders			Confusion

System Organ Classification	Very Common	Common	Uncommon
Nervous system disorders		Dizziness, Syncope	Intracranial haemorrhage[l]
Eye disorders			Eye haemorrhage[d]
Ear and labyrinth disorders		Vertigo	Ear haemorrhage
Vascular disorders		Hypotension	
Respiratory, thoracic, and mediastinal disorders	Dyspnoea	Respiratory system bleedings[e]	
Gastrointestinal Disorders		Diarrhoea, Gastrointestinal haemorrhage[f], Nausea	Retroperitoneal haemorrhage
Skin and subcutaneous tissue disorders		Subcutaneous or dermal bleeding[g], Pruritus	
Musculoskeletal connective tissue and bone			Muscular bleedings[h]
Renal and urinary disorders		Urinary tract bleeding[i]	
Reproductive system and breast disorders			Reproductive system bleedings[j]
Investigations		Blood creatinine increased[a]	
Injury, poisoning and procedural complications		Post procedural haemorrhage, Traumatic bleedings[k]	

[a] Frequencies derived from lab observations (Uric acid increases to >ULN from baseline below or within reference range. Creatinine increases of >50% from baseline) and not crude adverse event report frequency.

[b] e.g. bleeding from bladder cancer, gastric cancer, colon cancer.
[c] e.g. increased tendency to bruise, spontaneous haematoma, haemorrhagic diathesis.
[d] e.g. conjunctival, retinal, intraocular bleeding.
[e] e.g. epistaxis, haemoptysis.
[f] e.g. gingival bleeding, rectal haemorrhage, gastric ulcer haemorrhage.
[g] e.g. ecchymosis, skin haemorrhage, petechiae.
[h] e.g. haemarthrosis, muscle haemorrhage.
i e.g. haematuria, cystitis haemorrhagic.
[j] e.g. vaginal haemorrhage, haematospermia, postmenopausal haemorrhage.
[k] e.g. contusion, traumatic haematoma, traumatic haemorrhage.
[l] i.e. spontaneous, procedure related or traumatic intracranial haemorrhage.

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.

Immune system disorders: Hypersensitivity reactions including angioedema (see section Contraindications).
Skin and subcutaneous tissue disorders: Urticaria, rash.
Blood disorders: Thrombotic Thrombocytopenic Purpura (See section Special warnings and special precautions for use).
Cardiac disorders: Bradyarrhythmia, AV block (See section Special warnings and special precautions for use).
Nervous system disorders: Central sleep apnoea including Cheyne-Stokes respiration (see section Special warnings and special precautions for use).

4.9 Overdose

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

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

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

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group (ATC code):
Pharmacotherapeutic group: Platelet aggregation inhibitors excluding heparin
ATC code: B01AC24

5.1 Pharmacodynamic properties

Mechanism of action:

BRILINTA contains ticagrelor, a member of the chemical class cyclopentyl-triazolo-pyrimidines (CPTP), which is an oral, direct acting, selective, and reversibly binding $P2Y_{12}$ receptor antagonist that prevents adenosine diphosphate (ADP)-mediated $P2Y_{12}$ dependent platelet activation and aggregation. Ticagrelor does not prevent ADP binding but when bound to the $P2Y_{12}$ receptor prevents ADP-induced signal transduction. Since platelets participate in the initiation and/or evolution of thrombotic complications of atherosclerotic disease, inhibition of platelet function has been shown to reduce the risk of cardiovascular events such as CV death, MI, or stroke.

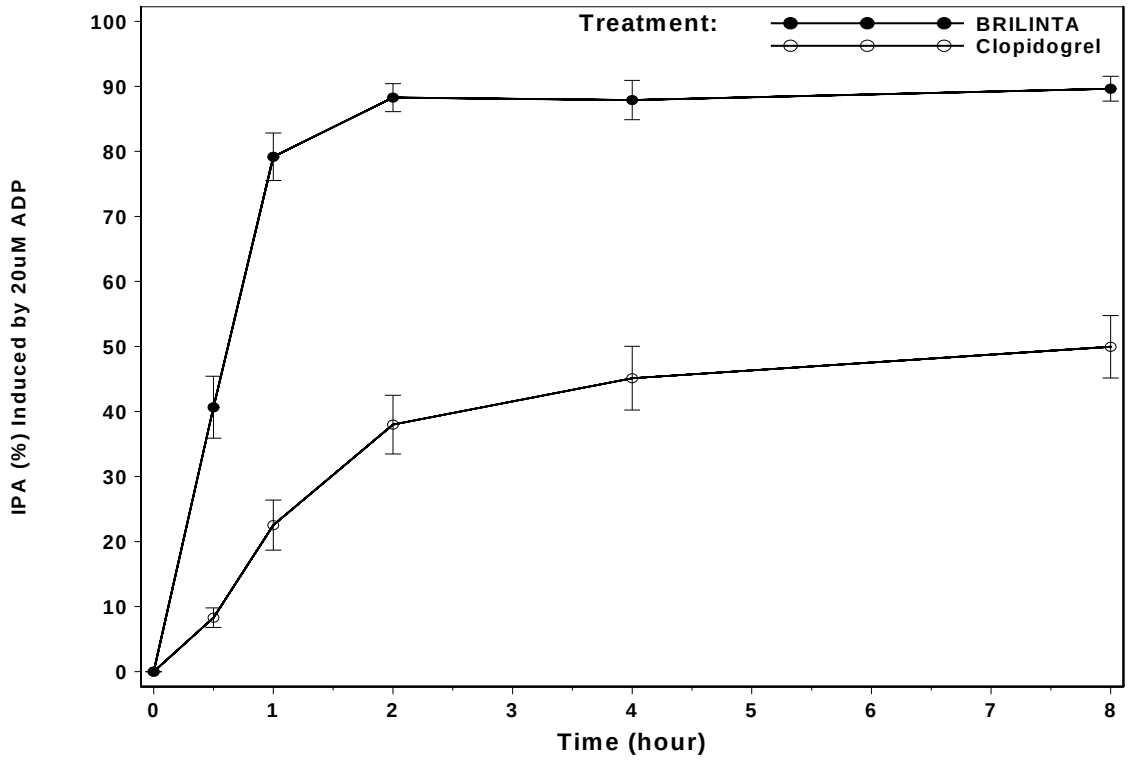
Ticagrelor has an additional mechanism of action, increasing local endogenous adenosine levels by inhibiting equilibrative nucleoside transporter-1 (ENT-1). Adenosine is formed locally at sites of hypoxia and tissue damage through degradation of released adenosine tri-phosphate (ATP) and di-phosphate (ADP). As adenosine degradation is essentially restricted to the intracellular space, inhibition of ENT-1 by ticagrelor prolongs the half-life of adenosine and thereby increases its local extracellular concentration providing enhanced local adenosine responses. Ticagrelor has no clinically significant direct effect on adenosine receptors (A_1, A_{2A}, A_{2B}, A_3) and is not metabolised to adenosine.

Ticagrelor has been documented to augment the following adenosine-induced effects in healthy subjects and in patients with ACS: vasodilation (measured by coronary blood flow increases in healthy volunteers and ACS patients; headache), inhibition of platelet function (in human whole blood *in vitro*) and dyspnoea. However, a link between the observed increases in adenosine and clinical outcomes (e.g. morbidity-mortality) has not been clearly elucidated.

Pharmacodynamic effects:

Onset of Action

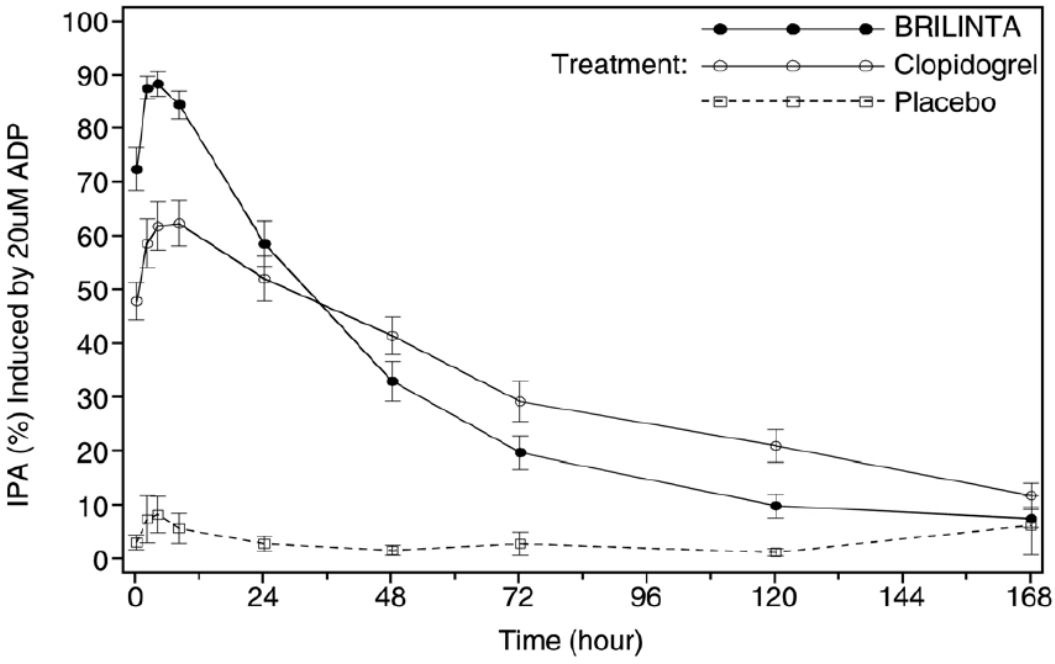
Figure 1 Mean final extent Inhibition (±SE) of Platelet Aggregation (IPA) following single oral doses of 180 mg BRILINTA or 600 mg clopidogrel in patients with stable CAD



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 in patients with stable coronary artery disease (CAD) on ASA. The onset was evaluated following a loading dose of 180 mg ticagrelor or 600 mg clopidogrel.

BRILINTA demonstrates a rapid onset of pharmacological effect as demonstrated by a mean IPA for BRILINTA at 0.5 hours after 180 mg loading dose of about 41%, with the maximum IPA effect of 87.9% to 89.6% by 2-4 hours post dose. 90% of patients had final extent IPA >70% by 2 hours post dose. The high IPA effect of BRILINTA between 87%-89% was maintained between 2-8 hours.

Figure 2 Mean final extent Inhibition (±SE) of Platelet Aggregation (IPA) following the last maintenance dose of 90 mg BRILINTA or 75 mg clopidogrel or placebo



BRILINTA	58.4%	32.8%	19.5%	9.7%	7.3%
Clopidogrel	51.8%	41.3%	29.1%	20.8%	11.6%
Placebo	2.6%	1.4%	2.6%	1.0%	6.0%

Offset of Effect

The offset was examined after 6 weeks on ticagrelor 90 mg twice daily or clopidogrel 75 mg once daily, again in response to 20 μM ADP. After the BRILINTA concentrations decline to a level less than that required for receptor saturation, IPA gradually decreases with declining plasma concentrations. Since BRILINTA binds reversibly, the recovery of platelet function does not depend on replacement of platelets. BRILINTA has a faster rate of offset of IPA as compared to clopidogrel as determined by the slope of offset from 4-72 hours after last dose (see section Special warnings and special precautions for use).

Median final extent IPA measured after the last dose of BRILINTA is approximately 20-30% higher for BRILINTA compared to clopidogrel. However, by 24 hours post-dose, %IPA is similar between BRILINTA and clopidogrel, and is lower for BRILINTA from 72 hours through 7 days compared with the clopidogrel. Mean %IPA for BRILINTA at 72 hours (Day 3) post last dose was comparable to clopidogrel at Day 5, and %IPA for BRILINTA at Day 5 was similar to clopidogrel at Day 7, which is not statistically different from placebo.

Responders to BRILINTA

IPA induced by BRILINTA has less variability at peak plasma concentrations of BRILINTA observed with the 90 mg twice daily dose compared to clopidogrel 75 mg once

daily. Patients with stable CAD predetermined to have low IPA response to clopidogrel (non-responders), and given a concomitant dose of ASA, exhibited higher mean IPA response after administration of BRILINTA as compared to clopidogrel. In non-responders to clopidogrel, the IPA response to BRILINTA was observed to be higher and more consistent. BRILINTA treatment resulted in consistently higher IPA compared with clopidogrel, and this was apparent post dose for both responders and non-responders.

Switching Data

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

Clinical efficacy:

The clinical evidence for the efficacy of BRILINTA is derived from two phase 3 trials:

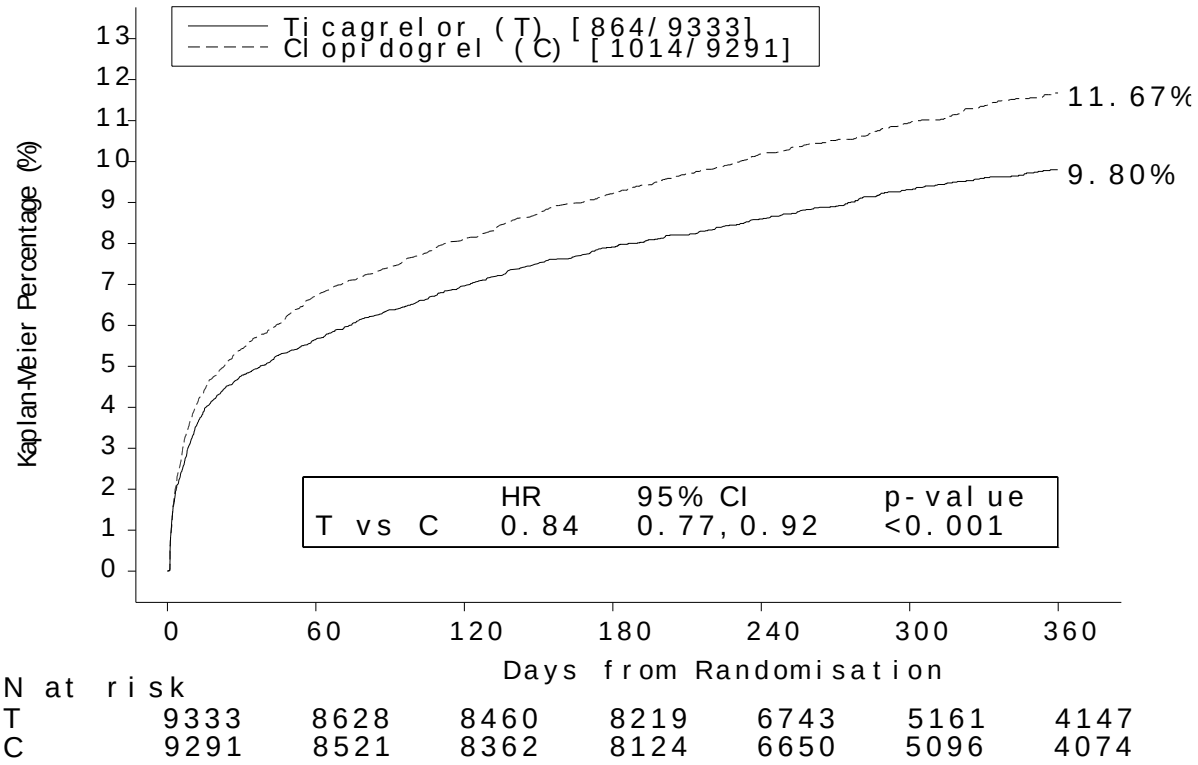
- The PLATO [PLATelet Inhibition and Patient Outcomes] Study, a comparison of BRILINTA to clopidogrel, both given in combination with ASA and other standard therapy.
- The PEGASUS TIMI-54 [PrEvention with TicaGrelor of SecondAry Thrombotic Events in High-RiSk AcUte Coronary Syndrome Patients] Study, a comparison of BRILINTA treatment combined with ASA to ASA therapy alone.

PLATO study (Acute Coronary Syndromes)

The PLATO Study was a 18,624 patient randomised, double-blind, parallel group, phase 3, efficacy and safety study of BRILINTA compared with clopidogrel for prevention of thrombotic events (CV death, MI, and stroke) in patients with ACS (unstable angina, non-ST elevation MI [NSTEMI], or ST elevation MI [STEMI]).

The Study was comprised of patients who presented within 24 hours of onset of the most recent episode of chest pain or symptoms. Patients were randomised to receive clopidogrel (75 mg once daily, with an initial loading dose of 300 mg. An additional loading dose of 300 mg was allowed at investigator discretion), or a loading dose of 180 mg of BRILINTA followed by a maintenance dose of 90 mg of BRILINTA twice daily. Patients could have been medically managed, treated with PCI or CABG.

Figure 3 Kaplan-Meier plot and analysis of the primary clinical composite endpoint of CV death, MI and stroke in PLATO (full analysis set)



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

Table 4 Analysis of primary and secondary efficacy endpoints in PLATO (full analysis set)

	Patients with Events				
Primary Endpoint	**BRILINTA 90 mg twice daily (%) N=9333**	**Clopidogrel 75 mg once daily (%) N=9291**	**Relative Risk Reduction[a] (%)**	**Hazard Ratio (95% CI)**	***p*-value**
Composite of CV Death/MI (excl. silent MI)/Stroke	9.3	10.9	16	0.84(0.77,0.92)	*p*=0.0003
CV death	3.8	4.8	21	0.79(0.69,0.91)	*p*=0.0013
MI (excl. silent MI)	5.4	6.4	16	0.84(0.75,0.95)	*p*=0.0045
Stroke	1.3	1.1	-17	1.17(0.91,1.52)	*p*=0.2249

Secondary Endpoints					
Composite of CV Death/MI (excl. silent MI)/Stroke – intent to invasively manage	8.5	10.0	16	0.84(0.75,0.94)	*p*=0.0025
Composite of all-cause mortality/MI (excl. silent MI)/Stroke	9.7	11.5	16	0.84(0.77,0.92)	*p*=0.0001
Composite of CV Death/Total MI/Stroke/SRI[b]/RI[c]/TIA[d]/Other ATE[e]	13.8	15.7	12	0.88(0.81,0.95)	*p*=0.0006
All-cause mortality	4.3	5.4	22	0.78(0.69,0.89)	*p*=0.0003**

[a]RRR = (1-Hazard Ratio) x 100%. Values with a negative relative risk reduction indicate a relative risk increase.
[b]SRI = Severe Recurrent Cardiac Ischaemia.
[c]RI = Recurrent Cardiac Ischaemia.
[d]TIA = Transient Ischaemic Attack.
[e]ATE = Arterial Thrombotic events.
**nominal *p*-value

BRILINTA is superior to clopidogrel in the prevention of thrombotic events (relative risk Reduction [RRR] 16%, absolute risk reduction [ARR] 1.9%, NNT=54) of the composite efficacy endpoint (CV death, MI, and stroke) over 12 months. The difference in treatments was driven by CV death and MI with no difference on strokes. BRILINTA demonstrated a statistically significant RRR of 16% (ARR 1.1%) for MI and a 21% relative risk reduction (ARR 1.1%) for CV death. Treating 91 patients with BRILINTA instead of clopidogrel will prevent 1 CV death.

BRILINTA showed superiority to clopidogrel in preventing the composite endpoint (CV death, MI, or stroke). This result appeared early (ARR 0.6% and RRR of 12% at 30 days), with a constant treatment effect over the entire 12-month period, yielding ARR 1.9% per year with RRR of 16%. This suggests it is appropriate to treat for at least 12 months (see section Posology and method of administration).

In PLATO, a large number of subgroup comparisons were conducted for the primary efficacy endpoint to assess the robustness and consistency of the overall benefit. The treatment effect of BRILINTA *vs*. clopidogrel appears consistent across multiple patient subgroups by demographic characteristics including weight, gender, medical history, concomitant therapy, and by final index event diagnosis (STEMI, NSTEMI, and UA).

A weakly significant treatment interaction was observed with region whereby the HR for the primary endpoint favours BRILINTA in the rest of world but favours clopidogrel in

North America, which represented approximately 10% of the overall population studied (interaction p-value=0.045).

This apparent treatment-by-region interaction observed in PLATO could plausibly be attributed to chance, at least in part. Additional analyses suggest that the efficacy of BRILINTA relative to clopidogrel is associated with ASA dose during maintenance therapy. The data show greater efficacy of ticagrelor compared to clopidogrel when used in conjunction with low maintenance dose ASA (75-150 mg). The relative efficacy of ticagrelor versus clopidogrel when used with high doses of ASA (>300 mg) is less certain. Based on this observed relationship between maintenance ASA dose and relative efficacy of ticagrelor compared to clopidogrel, it is recommended that BRILINTA is used with a low maintenance dose of ASA 75-150 mg (see section Posology and method of administration and Special warnings and special precautions for use).

The benefits associated with BRILINTA were also independent of the use of other acute and long-term cardiovascular therapies, including heparin, low molecular weight heparin (LMWH), intravenous GpIIb/IIIa inhibitors, lipid-lowering drugs, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists, and proton pump inhibitors (see section Interaction with other medicinal products and other forms of interaction).

BRILINTA demonstrated a statistically significant RRR in the composite endpoint of CV death, MI, and stroke in ACS patients planned for invasive management (RRR 16%, ARR 1.7%, p=0.0025). In an exploratory analysis, BRILINTA demonstrated an RRR of the primary composite endpoint in ACS patients intended for medical management (RRR 15%, ARR 2.3%, nominal p=0.0444). Consistent with the primary endpoint of the study, the effect in these two groups was driven by CV death and MI with no effect on stroke. In patients receiving stents, there were numerically fewer definite stent thromboses among patients treated with ticagrelor compared to clopidogrel (73 vs. 107, RRR 32%, ARR 0.6%, nominal p=0.0123).

BRILINTA demonstrated a statistically significant RRR of 16% (ARR 2.1%) for the composite of all-cause mortality, MI, and stroke compared to clopidogrel.

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

Holter Substudy

To study the occurrence of ventricular pauses and other arrhythmic episodes during PLATO, investigators performed Holter monitoring in a subset of nearly 3,000 patients, of whom approximately 2,000 had recordings both in the acute phase of their ACS and after one month. The primary variable of interest was the occurrence of ventricular pauses ≥3 seconds. More patients had ventricular pauses with BRILINTA (6.0%) than with clopidogrel (3.5%) in the acute phase; and 2.2% and 1.6%, respectively, after 1 month.

More patients had ventricular pauses with BRILINTA than with clopidogrel, however, there were no adverse clinical consequences associated with this imbalance (including pacemaker insertions) in this population of patients.

Genetic Substudy

In PLATO, 10,285 patients provided genetic samples for genotype determination of CYP2C19 and ABCB1 loci. An analysis provided these associations of genotype groupings on efficacy and safety outcomes in PLATO. The superiority of ticagrelor over clopidogrel in reducing major events was not significantly affected by patient CYP2C19 or ABCB1 genotype.

Similar to the overall PLATO Study, Total Major Bleeding did not differ between ticagrelor and clopidogrel regardless of CYP2C19 or ABCB1 genotype. Non-CABG PLATO Major bleeding was increased with ticagrelor compared to clopidogrel in patients with one or more CYP2C19 LOF allele, but was similar to clopidogrel in patients with no loss of function allele.

Combined Efficacy and Safety Composite

A combined efficacy and safety composite (CV death, MI, stroke, or PLATO-defined 'Total Major' bleeding) supports the clinical benefit of ticagrelor compared to clopidogrel (RRR 8%, ARR 1.4%, HR 0.92; p=0.0257) over 12 months after ACS events.

PEGASUS Study (History of Myocardial Infarction)

The PEGASUS TIMI-54 study was a 21,162 patient, event-driven, randomised, double blind, placebo controlled, parallel group, international multicentre study to assess the prevention of thrombotic events with ticagrelor given at 2 doses (either 90 mg twice daily or 60 mg twice daily) combined with low dose ASA (75-150 mg) compared to ASA therapy alone in patients with history of MI and additional risk factors for atherothrombosis.

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

Figure 4 Kaplan-Meier plot and analysis of primary clinical composite endpoint of CV death, MI and stroke in PEGASUS (full analysis set)

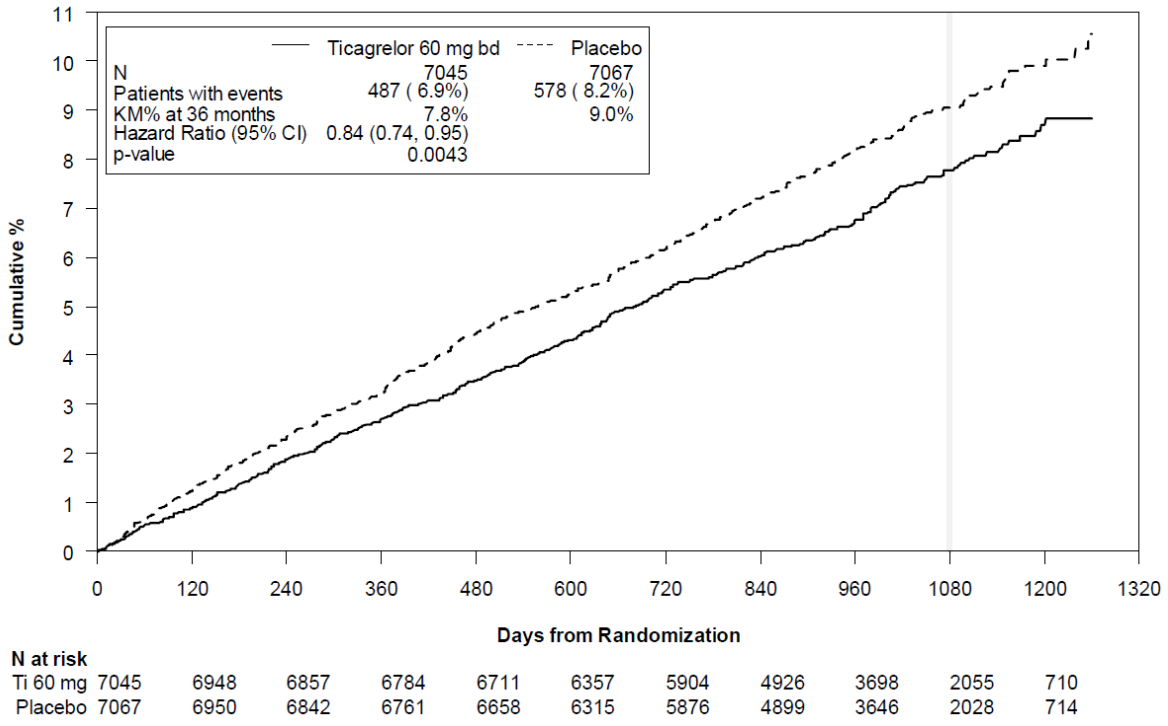


Table 5 Analysis of primary and secondary efficacy endpoints in PEGASUS (full analysis set)

	BRILINTA 60 mg twice daily + ASA N=7045			ASA alone N=7067		p-value
Characteristic	Patients with events	KM %	HR (95% CI)	Patients with events	KM %	
Primary endpoint						
Composite of CV Death/MI /Stroke	487 (6.9%)	7.8%	0.84 (0.74, 0.95)	578 (8.2%)	9.0%	0.0043 (s)
CV death	174 (2.5%)	2.9%	0.83 (0.68, 1.01)	210 (3.0%)	3.4%	0.0676
MI	285 (4.0%)	4.5%	0.84 (0.72, 0.98)	338 (4.8%)	5.2%	0.0314
Stroke	91 (1.3%)	1.5%	0.75 (0.57, 0.98)	122 (1.7%)	1.9%	0.0337
Secondary endpoint						
CV death	174 (2.5%)	2.9%	0.83 (0.68, 1.01)	210 (3.0%)	3.4%	-

All-cause mortality	289 (4.1%)	4.7%	0.89 (0.76, 1.04)	326 (4.6%)	5.2%	-

Hazard ratio and p-values are calculated separately for ticagrelor vs. ASA alone from Cox proportional hazards model with treatment group as the only explanatory variable.
Kaplan-Meier percentage calculated at 36 months.
Note: the number of first events for the components CV Death, MI and Stroke are the actual number of first events for each component and do not add up to the number of events in the composite endpoint.
(s) Indicates statistical significance.
CI = Confidence interval; CV = Cardiovascular; HR = Hazard ratio; KM = Kaplan-Meier; MI = Myocardial infarction; N = Number of patients.

Both 60 mg twice daily and 90 mg twice daily regimens of BRILINTA, in combination with ASA, were superior to ASA alone in the prevention of thrombotic events (composite endpoint: CV death, MI and stroke), with a consistent treatment effect over the entire study period, yielding a 16% RRR and 1.27% ARR for ticagrelor 60 mg and a 15% RRR and 1.19% ARR for ticagrelor 90 mg.

Although the efficacy profile of ticagrelor 90 mg and 60 mg were similar, there is evidence that the lower dose has a better tolerability and safety profile in relation to risk of the bleeding and dyspnoea. Therefore, BRILINTA 60 mg twice daily co-administered with ASA is recommended for the prevention of thrombotic events (CV death, MI 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.

Relative to ASA alone, BRILINTA 60 mg twice daily significantly reduced the primary composite endpoint of CV death, MI and stroke. Each of the components contributed to the reduction in the primary composite endpoint (CV death 17% RRR, MI 16% RRR, and stroke 25% RRR).

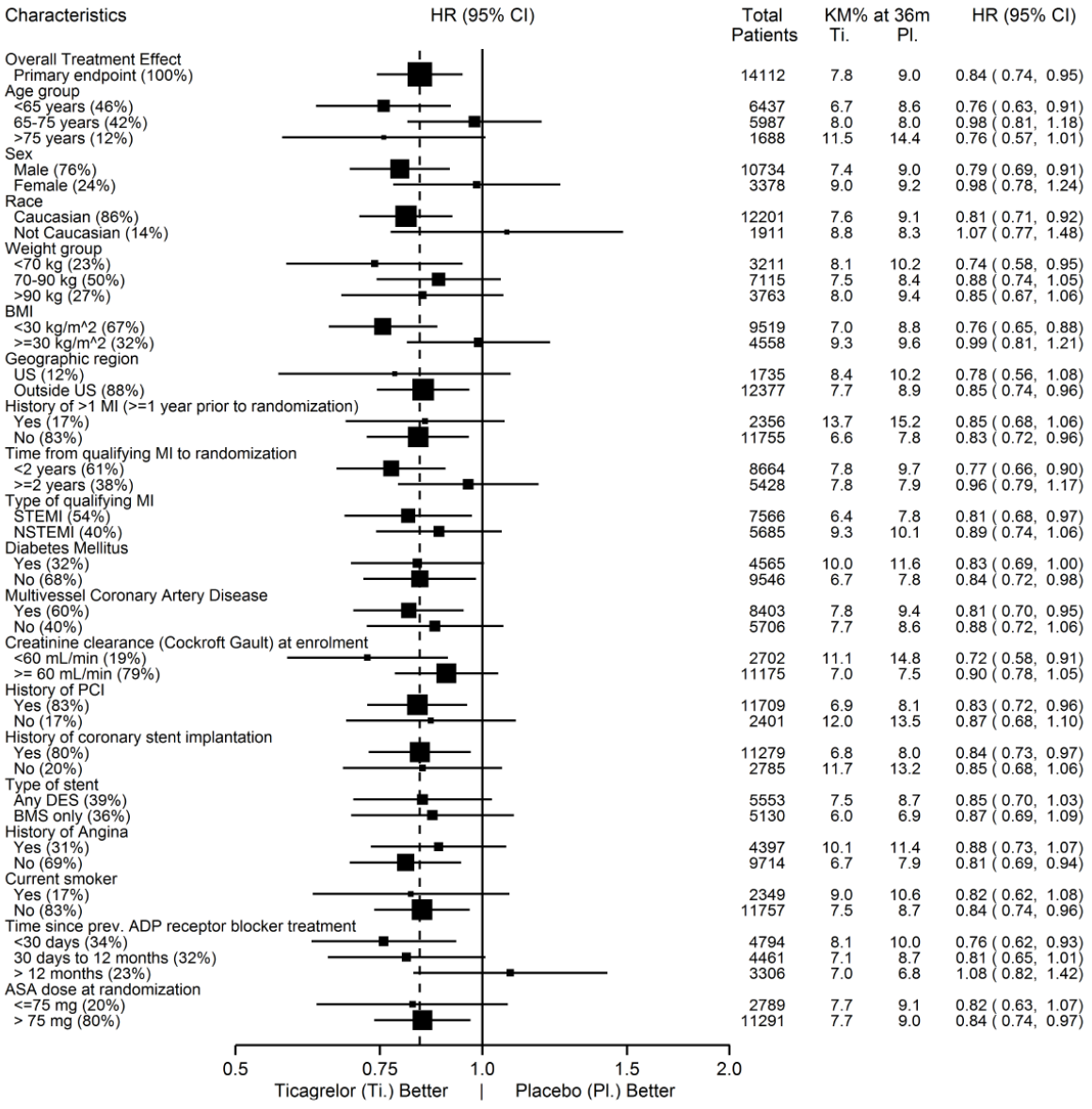
Treating 79 patients for up to 36 months with BRILINTA 60 mg twice daily in combination with ASA instead of ASA therapy alone will prevent one primary composite endpoint event.

The benefit of ticagrelor seen on the primary composite endpoint was also reflected across the two secondary endpoints, with a numerical decrease in both CV death and all-cause mortality for ticagrelor 60 mg combined with ASA compared to ASA therapy alone, but this did not reach statistical significance (see Table 5).

The RRR for the composite endpoint from 1 to 360 days (17% RRR) and from 361 days and onwards (16% RRR) was similar. This effect was consistent throughout the study, with duration up to 47 months (median 33 months). The consistency of RRR over time suggests that it is appropriate to continue treatment with ticagrelor as long as the patient remains at high risk of developing thrombotic events (see section Posology and method of administration).

The treatment effect of BRILINTA 60 mg twice daily *vs*. ASA was consistent across major subgroups, see Figure 5.

Figure 5 Hazard ratios and rates of the primary clinical composite end point of CV death, MI and stroke by patient subgroup in PEGASUS (full analysis set)



The treatment effect of BRILINTA 60 mg twice daily *vs*. ASA therapy alone was consistent across multiple patient subgroups, based on demographic characteristics including weight, gender, medical history, and region.

The benefits associated with BRILINTA were also independent of the use of other cardiovascular therapies including lipid-lowering drugs, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists, calcium channel blockers, nitrates, and proton pump inhibitors (see section Interaction with other medicinal products and other forms of interaction).

Paediatric population

In a randomised, double-blind, placebo-controlled, phase 3 trial, the primary objective of reducing the rate of vaso-occlusive crises in paediatric patients aged 2 to less than 18 years with sickle cell disease, was not met.

5.2 Pharmacokinetic properties

General:

Ticagrelor demonstrates linear pharmacokinetics and exposure to BRILINTA and the active metabolite (AR-C124910XX) are approximately dose proportional.

Absorption:

Absorption of BRILINTA is rapid with a median t_{max} of approximately 1.5 hours. The formation of the major circulating metabolite AR-C124910XX (also active) from BRILINTA is rapid with a median t_{max} of approximately 2.5 hours. The C_{max} and AUC of BRILINTA and the active metabolite increased in an approximately proportional manner with dose over the dose range studied (30-1260 mg).

The mean absolute bioavailability of BRILINTA was estimated to be 36% (range 25.4% to 64.0%). Ingestion of a high-fat meal had no effect on BRILINTA C_{max} or the AUC of the active metabolite, but resulted in a 21% increase in BRILINTA AUC and 22% decrease in the active metabolite C_{max}. These small changes are considered of minimal clinical significance; therefore, BRILINTA can be given with or without food.

Ticagrelor as crushed tablets mixed in water, given orally or administered through a nasogastric tube into the stomach, is bioequivalent to whole tablets (AUC and C_{max} within 80-125% for ticagrelor and the active metabolite). Initial exposure (0.5 and 1 hour post-dose) from crushed ticagrelor tablets mixed in water was higher compared to whole tablets, with a generally identical concentration profile thereafter (2 to 48 hours).

Distribution:

The steady state volume of distribution of BRILINTA is 87.5 L. BRILINTA and the active metabolite is extensively bound to human plasma protein (>99.0%).

Metabolism:

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

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

Excretion:

The primary route of BRILINTA elimination is via hepatic metabolism. When radiolabeled BRILINTA is administered, the mean recovery of radioactivity is approximately 84% (57.8% in faeces, 26.5% in urine). Recoveries of BRILINTA and the active metabolite in urine were both less than 1% of the dose. The primary route of elimination for the active metabolite is mostly via biliary secretion. The mean $t_{1/2}$ was approximately 6.9 hours (range 4.5-12.8 hours) for BRILINTA and 8.6 hours (range 6.5-12.8 hours) for the active metabolite.

Special populations:

Ethnicity:

Patients of Asian descent have a 39% higher mean bioavailability compared to Caucasian patients. Patients self-identified as Black had an 18% lower bioavailability of BRILINTA compared to Caucasian patients. In clinical pharmacology studies, the exposure (C_{max} and AUC) to BRILINTA in Japanese subjects was approximately 40% (20% after adjusting for body weight) higher compared to that in Caucasians.

Elderly:

Higher exposures to BRILINTA (approximately 60% for both C_{max} and AUC) and the active metabolite (approximately 50% for both C_{max} and AUC) were observed in elderly (≥65 years) subjects compared to younger subjects. These differences are not considered clinically significant (see section Posology and method of administration).

Paediatric:

BRILINTA is not indicated in a paediatric population (see section Posology and method of administration and section Pharmacodynamic properties).

Gender:

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

Renal impairment:

Exposure to BRILINTA was approximately 20% lower and exposure to the active metabolite was approximately 17% higher in patients with severe renal impairment compared to subjects with normal renal function. The IPA effect of BRILINTA was similar between the two groups, however there was more variability observed in individual response in patients with severe renal impairment.

In patients with end stage renal disease on haemodialysis AUC and C_{max} of BRILINTA 90 mg administered on a day without dialysis were 38% and 51% higher respectively, compared to subjects with normal renal function. A similar increase in exposure was observed when BRILINTA was administered immediately prior to dialysis showing that BRILINTA is not dialysable. Exposure of the active metabolite increased to a lesser extent. The IPA effect of BRILINTA was independent of dialysis in patients with end stage renal disease and similar to subjects with normal renal function.

No dosing adjustment is needed in patients with renal impairment.

Hepatic impairment:

C_{max} and AUC for BRILINTA were 12% and 23% higher in patients with mild hepatic impairment compared to matched healthy subjects, respectively, however the IPA effect of BRILINTA was similar between the two groups. No dose adjustment is needed for patients with mild hepatic impairment. BRILINTA has not been studied in patients with severe hepatic impairment and there is no pharmacokinetic information in patients with moderate hepatic impairment (see section Posology and method of administration, Contraindications and Special warnings and special precautions for use).

5.3 Preclinical safety data

Preclinical data for ticagrelor and major metabolite have not demonstrated unacceptable risk for adverse effects for humans based on conventional studies of safety pharmacology, single and repeated dose toxicity, and genotoxic potential.

Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar or above to clinical exposure levels and with possible relevance to clinical use were as follows: GI toxicity and gastrointestinal irritation.

No compound-related tumours were observed in a 2-year mouse study at oral doses up to 250 mg/kg/day (>18-fold the maximum human therapeutic exposure). There was no increase in tumours in male rats at oral doses up to 120 mg/kg/day (>15-fold the maximum human therapeutic exposure). There was an increase in uterine adenocarcinomas and hepatocellular adenomas plus adenocarcinomas and a decrease in pituitary adenomas and mammary fibroadenomas in female rats only exposed to high doses (>25-fold the maximum human therapeutic exposures). No change in tumour incidence was observed at 60 mg/kg/day (>8-fold difference to the maximum human therapeutic exposure.) The uterine tumours seen only in rats were found to be the result of a non-genotoxic endocrine effect of hormonal imbalance present in rats given high doses of ticagrelor. The benign liver tumours are considered secondary to the response by the liver to the metabolic load placed on the liver from the high doses of ticagrelor.

Ticagrelor has been tested in a range of *in vitro* and *in vivo* tests, and was not shown to be genotoxic.

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

Ticagrelor had no effect on foetal development at oral doses up to 100 mg/kg/day in rats (5.1 times the maximum human therapeutic exposure) and up to 42 mg/kg/day in rabbits (equivalent to the maximum human therapeutic exposure). Ticagrelor had no effects on parturition or postnatal development in rats at doses up to 60 mg/kg/day (4.6 times the maximum human therapeutic exposure).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core
Mannitol (E421)
Dibasic calcium phosphate
Magnesium stearate
Sodium starch glycolate
Hydroxypropyl-cellulose

Coating
Talc
Titanium dioxide (E171)
Ferric oxide yellow (E172)
Polyethylene-glycol 400
Hypromellose

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

Please refer to expiry date on the outer carton.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Standard foil blister packs in cartons of 60 and 180 tablets.
Calendar foil blister packs in cartons of 14, 56, and 168 tablets.
Perforated foil blister pack of 100x1 tablets.
Not all pack sizes may be marketed.

6.6 Instructions for use, handling and disposal

No special requirements.

Product Owner

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