BRILINTA®
ticagrelor

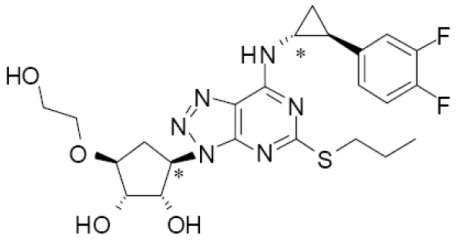
PRODUCT INFORMATION

NAME OF THE MEDICINE

Ticagrelor

Chemical Name (IUPAC): (1*S*,2*S*,3*R*,5*S*)-3-[7-{[(1*R*,2*S*)-2-(3,4-Difluorophenyl)cyclopropyl]amino}-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl]-5-(2-hydroxyethoxy)cyclopentane-1,2-diol

The chemical structure of ticagrelor is:



CAS number: 274693-27-5

Molecular weight: 522.57

DESCRIPTION

Ticagrelor is a white or off-white to pale pink crystalline powder. The log P (octanol/water) has been measured to >4.0 at pH 7.4. The molecule has no pKa values within physiological range and does not demonstrate pH dependent solubility. It is non-hygroscopic, exhibiting no significant increase in water content after exposure at 40°C/75% RH.

Each tablet contains 90mg of ticagrelor. The tablets also include the following excipients - mannitol, calcium hydrogen phosphate, sodium starch glycollate, hydroxypropyl cellulose, magnesium stearate, hypromellose, titanium dioxide, purified talc, macrogol 400, iron oxide yellow. BRILINTA does not contain gluten.

PHARMACOLOGY

Mechanism of action

BRILINTA contains ticagrelor, a member of the chemical class cyclopentyltriazolopyrimidines (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 death, myocardial infarction 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- and di-phosphate (ATP and 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. However, a link between the observed increases in adenosine and clinical outcomes (e.g.: morbidity-mortality) has not been clearly elucidated. Ticagrelor has no clinically significant direct effect on adenosine receptors (A_1, A_{2A}, A_{2B}, A_3) and is not metabolised to adenosine.

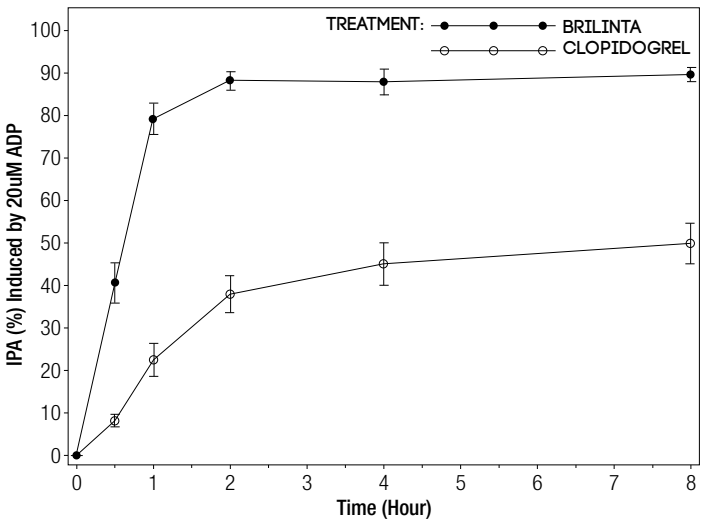
Pharmacodynamic effects

Onset of Action

In patients with stable coronary artery disease on acetylsalicylic acid (ASA), ticagrelor demonstrates a rapid onset of pharmacological effect as demonstrated by a mean Inhibition of Platelet Aggregation (IPA) for ticagrelor at 0.5 hours after 180mg loading dose of about 41%, with the maximum IPA effect of 87.9% to 89.6% by 2-4 hours post dose, see Figure 1. 90% of patients had final extent IPA >70% by 2 hours post dose. The high IPA effect of ticagrelor between 87%-89% was maintained between 2-8 hours.

Figure 1

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



Offset of Effect

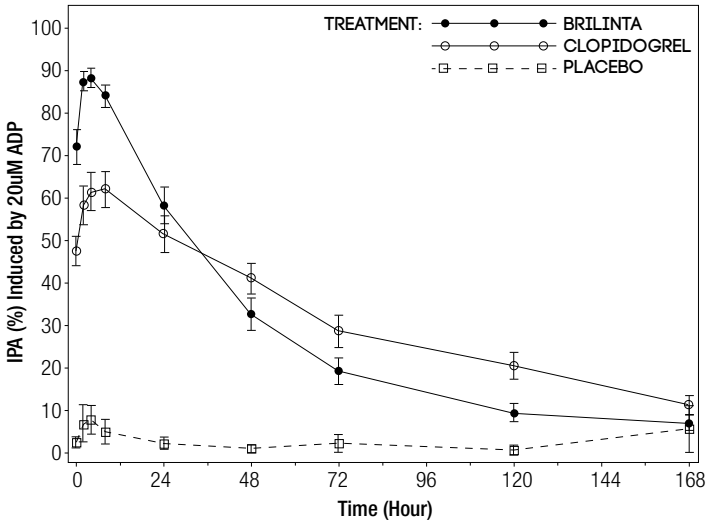
After the ticagrelor and the active metabolite concentrations decline to a level less than that required for receptor saturation, IPA gradually decreases with declining plasma concentrations. Since ticagrelor binds reversibly, the recovery of platelet function does not depend on replacement of platelets.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

Median final extent IPA measured after the last dose of BRILINTA is approximately 20-30% higher for ticagrelor compared to clopidogrel. However, by 24 hours post-dose, %IPA is similar between ticagrelor

and clopidogrel, indicating that patients who miss a dose of BRILINTA would have an IPA level comparable to those treated with once daily clopidogrel. In addition, %IPA is lower for ticagrelor from 72 hours through 7 days compared with clopidogrel. Mean %IPA for ticagrelor at 72 hours (Day 3) post last dose was comparable to clopidogrel at Day 5, and %IPA for ticagrelor at Day 5 was similar to clopidogrel at Day 7, which is not statistically different from placebo, see Figure 2.

Figure 2

Mean final extent Inhibition of Platelet Aggregation (IPA) (±SE) following the last maintenance dose of 90mg twice daily BRILINTA or 75mg clopidogrel once daily 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%

Responders to ticagrelor

The IPA induced by ticagrelor has less variability at peak plasma concentrations of ticagrelor and the active metabolite at peak plasma concentrations observed with the 90mg bd dose compared to clopidogrel. Patients with stable coronary artery disease predetermined to have low IPA response to clopidogrel (non-responders), and given a concomitant dose of ASA, exhibited higher mean IPA response after administration of BRILINTA as compared to clopidogrel. In non-responders to clopidogrel, the IPA response to ticagrelor 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

Patients can be switched from clopidogrel to BRILINTA without interruption of anti-platelet effect. Patients switching from clopidogrel to BRILINTA results in an absolute IPA increase of 26.4% and switching from BRILINTA to clopidogrel results in an absolute IPA decrease of 24.5% (also refer to DOSAGE AND ADMINISTRATION). Switching from prasugrel to BRILINTA has not been investigated.

Adenosine mechanism (ENT-1)

Ticagrelor increased plasma adenosine concentrations in 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 $P2Y_{12}$ antagonism. Adenosine has been linked to the cardio-protective effect of preconditioning. Ticagrelor has been shown to augment adenosine-induced dyspnoea in healthy volunteers.

Pharmacokinetics

Ticagrelor demonstrates linear pharmacokinetics. Exposure to ticagrelor and active metabolite AR-C124910XX are approximately dose proportional.

Absorption

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

The mean absolute bioavailability of ticagrelor was estimated to be 36%, (range 25.4% to 64.0%). Ingestion of a high-fat meal had no effect on ticagrelor C_{max} or the AUC of the active metabolite, but resulted in a 21% increase in ticagrelor AUC and 22% decrease in the active metabolite C_{max}. These 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). Compared to whole tablets, the geometric least-squares (LS) mean concentrations of ticagrelor were higher at 0.5 hour and 1 hour following administration of crushed tablets suspended in water and dispersed tablets suspended in water administered via NGT, respectively. At two hours post-dose the geometric LS mean concentrations following administration of the crushed tablet suspended in water and the dispersed tablet suspended in water administered via NGT were similar to the geometric LS mean concentration following administration of the whole tablet. The geometric LS mean concentrations of the major metabolite of ticagrelor, AR-C124910XX, were higher, compared with whole tablets, following administration of crushed tablets suspended in water at 0.5 hour and 1 hour post-dose, respectively, and higher at 0.5 hour, 1 hour and 2 hours post-dose respectively following administration of dispersed tablets suspended in water administered via a NGT.

Distribution

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

Metabolism

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

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

Excretion

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

Clearance of ticagrelor

The systemic clearance of ticagrelor is 14.2 L/h.

Special populations

Elderly

Higher exposures to ticagrelor (approximately 60% for both C_{max} and AUC) and the active metabolite (approximately 50% for both C_{max} and AUC) were observed in elderly (≥65 years) subjects compared to younger subjects. These differences are not considered clinically significant. No dose adjustment is needed for elderly patients.

Paediatric

BRILINTA has not been evaluated in a paediatric population.

Gender

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

Body weight

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

Smoking

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

Renal impairment

Exposure to ticagrelor was approximately 20% lower and exposure to the active metabolite was approximately 17% higher as measured by AUC in patients with severe renal impairment compared to subjects with normal renal function. The IPA effect of ticagrelor was similar between the two groups, however there was more variability observed in individual response in patients with severe renal impairment. These differences are not considered clinically significant. No dosing adjustment is needed in patients with renal impairment.

No information is available concerning treatment of patients on renal dialysis.

Hepatic impairment

The C_{max} and AUC for ticagrelor were 12% and 23% higher in patients with mild hepatic impairment compared to matched healthy subjects, respectively, however the IPA effect of ticagrelor was similar between the two groups. These differences are not considered clinically significant. No dose adjustment is needed for patients with mild hepatic impairment.

BRILINTA has not been studied in patients with moderate or severe hepatic impairment (refer to CONTRAINDICATIONS)

Race

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

CLINICAL TRIALS

The clinical evidence for the efficacy of BRILINTA is derived from the PLATO [PLATelet Inhibition and Patient Outcomes] study, a randomised, double-blind comparison of BRILINTA to clopidogrel, both given in combination with ASA and other standard therapy.

The PLATO study was a Phase III randomised, double-blind, parallel group, efficacy and safety study with 18,624 patients comparing BRILINTA with clopidogrel for prevention of vascular events in patients with acute coronary syndromes (unstable angina, non ST elevation Myocardial Infarction [NSTEMI] or ST elevation Myocardial Infarction [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 could have been medically managed, treated with percutaneous coronary intervention (PCI) (with or without stent) or coronary artery bypass graft (CABG).

Patients were excluded from participation in the study for any of the following: 1) Active bleeding, history of previous intracranial bleed, gastrointestinal (GI) bleed within the past 6 months, major surgery within 30 days. 2) Moderate or severe liver disease. 3) Patient required dialysis. 4) Oral anticoagulation therapy that could not be stopped. 5) Fibrinolytic therapy in the 24 hours prior to randomisation, or planned fibrinolytic treatment following randomisation. 6) Known clinically important anaemia or thrombocytopenia. 7) Increased risk of bradycardic events unless treated with a pacemaker. 8) A need for chronic concomitant oral strong CYP3A inhibitors, CYP3A substrates with narrow therapeutic indices, or strong CYP3A inducers.

Patients were randomised to receive a loading dose of 180mg of BRILINTA followed by a maintenance dose of 90mg of BRILINTA twice daily or clopidogrel 75mg once daily, with an initial loading dose of 300mg if previous thienopyridine therapy had not been given; an additional loading dose of 300mg was allowed at investigator discretion. Patients were to receive concomitant ASA 75-100mg daily. For patients not previously on ASA a loading dose of 160mg to 500mg was allowed.

The patient population was 92% Caucasian, 28% female, 42% greater than 65 years of age with 15% greater than 75 years of age. Concomitant medications taken post-randomization included beta-blockers (86%), lipid-lowering agents (93%) and ACE inhibitors (79%).

Planned treatment duration was a minimum of 6 months to a maximum of 12 months. Mean exposure to study drug in PLATO was 246 days for ticagrelor; median exposure was 276 days (interquartile range 177-365 days). Patients who prematurely discontinued study drug, but did not withdraw from the study, continued to be followed for study endpoint events. Study visits were scheduled 1, 3, 6, 9 and 12 months following randomization. Enrolment was stopped based on primary endpoint projections. To ensure 6 months minimum treatment, patients continued on-trial until their next scheduled visit at 6, 9 or 12 months, which became their final visit. Of the randomised patients, 18062 (98%) completed the study. Patients were considered to have completed the study if they had a final visit (81.9% for ticagrelor, 81.2% for clopidogrel) died (4.4% for ticagrelor, 5.6% for clopidogrel), or were followed up/alive (vital status collected when contacted, but patient did not want to continue participation in the study (10.4% for ticagrelor, 10.5% for clopidogrel). The most common reason for premature termination of study participation was withdrawal of informed consent (2.9%).

There were 2 patients on the ticagrelor arm (none on clopidogrel) for whom vital status was unknown at the end of the study period.

The primary endpoint was time to first occurrence of any event from the composite of death from vascular causes, MI and stroke. Planned accrual of 1780 primary endpoint events in PLATO provided 90% power to detect a relative risk reduction of 13.5% with ticagrelor compared with clopidogrel over a 12-month period given an event rate of 11% in the clopidogrel group at 12 months.

BRILINTA reduced the occurrence of the primary composite endpoint compared to clopidogrel in both the UA/NSTEMI and STEMI population (Figure 3 and Table 1). Primary and Secondary efficacy endpoints were hierarchically tested in the sequence shown in Table 1.

Figure 3

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

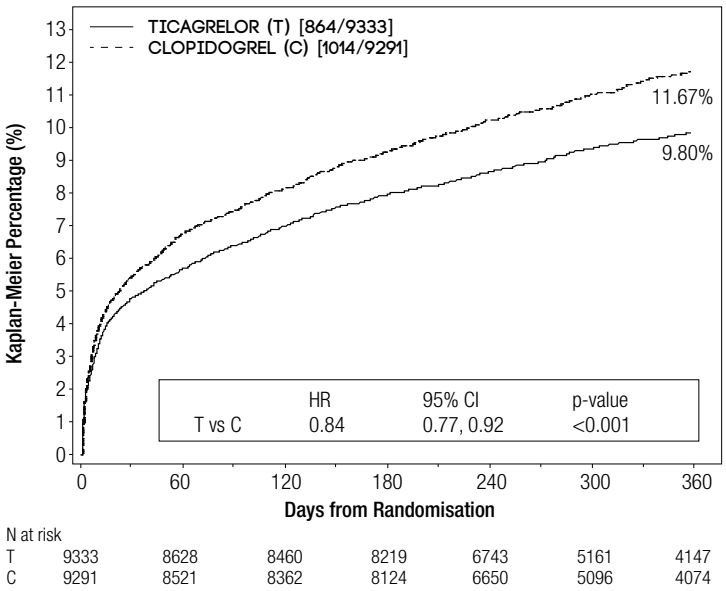


Table 1

Outcome Events in PLATO

Primary Endpoints	Ticagrelor (+ASA) % N=9333 % Patients with events (KM %/ Year[b])	Clopidogrel (+ASA) % N=9291 % Patients with events (KM %/ Year[b])	Absolute Risk Reduction %	Relative Risk Reduction[a] %	Hazard Ratio (95% CI)	p-value
Composite of CV Death/MI (excl. silent MI)/Stroke	9.3 (9.8)	10.9 (11.7)	1.9	16	0.84 (0.77, 0.92)	p=0.0003
Secondary Endpoints						
Composite of CV Death/MI (excl. silent MI)/Stroke – intent to invasively manage	8.5 (8.9)	10.0 (10.6)	1.7	16	0.84 (0.75, 0.94)	p=0.0025
Composite of all-cause mortality/ MI (excl. silent MI)/ Stroke	9.7 (10.2)	11.5 (12.3)	2.1	16	0.84 (0.77, 0.92)	p=0.0001
Composite of CV Death/ Total MI/ Stroke/ SRI/RI/ TIA/Other ATE	13.8 (14.6)	15.7 (16.7)	2.1	12	0.88 (0.81, 0.95)	p=0.0006
Each component of primary efficacy endpoints:						
• MI (excl. silent MI)	5.4 (5.8)	6.4 (6.9)	1.1	16	0.84 (0.75, 0.95)	p=0.0045
• CV death	3.8 (4.0)	4.8 (5.1)	1.1	21	0.79 (0.69, 0.91)	p=0.0013
• Stroke	1.3 (1.5)	1.1 (1.3)	-0.2	-17	1.17 (0.91, 1.52)	p=0.2249
All-cause mortality	4.3 (4.5)	5.4 (5.9)	1.4	22	0.78 (0.69, 0.89)	**

a RRR = (1-Hazard Ratio) x 100%. Values with a negative relative risk reduction indicate a relative risk increase.

b Kaplan-Meier percentages calculated at 12 months

** Formal hierarchical statistical testing of secondary endpoints concluded after stroke; all-cause mortality was evaluated for completeness resulting in a nominal p-value of p=0.0003

BRILINTA is superior to clopidogrel in the prevention of thrombotic events (RRR 16%, ARR 1.9%, NNT=54) of the composite efficacy endpoint (cardiovascular (CV) death, myocardial infarction (MI) or stroke) over 12 months. The difference in treatments was driven by cardiovascular death and myocardial infarction with no significant difference in the rate of strokes (1.5% on ticagrelor vs 1.3% on clopidogrel). BRILINTA demonstrated a statistically significant relative risk reduction 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.

The superiority of BRILINTA over clopidogrel 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. Figure 3 reveals that the estimate of the risk to the first occurrence of any event in the composite efficacy endpoint for BRILINTA and clopidogrel continues to diverge at 12 months.

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

Patients ≥65 years or ≥75 years of age had a higher rate of major CV events in both treatment arms. For patients ≥75 years of age, the rate of major CV events was 15.9% on ticagrelor vs 16.9% on clopidogrel.

For patients <75 years of age, the rate of major CV events was 8.1% on ticagrelor vs 9.8% on clopidogrel. Similar differences were seen in patients ≥65 years compared with those <65 years.

In addition, patients weighing <60kg had a higher rate of major CV events in both treatment arms. For patients weighing <60kg, the rate of major CV events was 12.4% on ticagrelor vs 16.4% on clopidogrel. For patients weighing ≥60kg, the rate of major CV events was 9.0% on ticagrelor vs 10.4% on clopidogrel.

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). The explanation for this apparent treatment-by-region interaction observed in PLATO is uncertain. It could be due to chance, however 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 BRILINTA compared to clopidogrel when used in conjunction with low maintenance dose ASA (75-150mg). The relative efficacy of BRILINTA versus clopidogrel when used with high doses of ASA (>300mg) 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 75-150mg (refer to DOSAGE AND ADMINISTRATION and PRECAUTIONS).

BRILINTA demonstrated a statistically significant relative risk reduction (RRR) in the primary composite endpoint (cardiovascular (CV) death, myocardial infarction (MI) or stroke) in acute coronary syndromes (ACS) patients planned for invasive management (RRR 16%, absolute risk reduction (ARR) 1.7%, p=0.0025). In a pre-specified, exploratory analysis, BRILINTA demonstrated a 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 fewer definite stent thromboses among patients treated with BRILINTA compared to clopidogrel (73 vs. 107, RRR 32%, ARR 0.6%; nominal p=0.0123).

BRILINTA demonstrated a statistically significant RRR of 16% (p=0.0001, ARR 2.1%) for the composite of all-cause mortality, MI and stroke compared to clopidogrel.

Holter Substudy

To study the occurrence of ventricular pauses and other arrhythmic episodes during PLATO, investigators performed Holter monitoring in a subset of nearly 3000 patients, of whom approximately 2000 had recordings both in the acute phase of their ACS and after one month. The primary variable of interest was the occurrence of ventricular pauses ≥3 seconds. More patients had ventricular pauses with BRILINTA (6.0%) than with clopidogrel (3.5%) in the acute phase, and 2.2% and 1.6% respectively after 1 month.

The increase in ventricular pauses in the acute phase of ACS was more pronounced in BRILINTA patients with history of congestive heart failure (CHF) (9.2% versus 5.4% in patients without CHF history; for clopidogrel patients, 4.0% in those with versus 3.6% in those without CHF history). This imbalance did not occur at one month: 2.0% versus 2.1% for BRILINTA patients with and without CHF history respectively; and 3.8% versus 1.4% with clopidogrel. There were no adverse clinical consequences associated with this imbalance (including pacemaker insertions) in this population of patients.

Genetic Substudy

In the PLATO genotyping substudy of 10,285 patients ticagrelor findings were consistent with overall PLATO findings. Ticagrelor was more efficacious than clopidogrel in reducing major CV events irrespective of CYP2C19 and ABCB1 polymorphisms. Similar to the overall PLATO study, total PLATO 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 clopidogrel in patients with one or more CYP2C19 loss of function alleles, but similar to clopidogrel in patients with no loss of function allele.

Renal

The PLATO study included 15,202 ACS patients who had serum creatinine levels available at baseline. Of these patients, 3237 (21.2%) had chronic kidney disease (CKD) (defined as Creatinine Clearance <60mL/min by the Cockroft-Gault equation). In patients with CKD, treatment with ticagrelor resulted in a statistically significant reduction in major CV events compared with clopidogrel and absolute risk reduction with ticagrelor increased as renal function declined. No significant difference in major bleeding was observed between ticagrelor and clopidogrel irrespective of renal function, while numerically more non-procedure related bleeding was observed with ticagrelor.

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 BRILINTA compared to clopidogrel (RRR 8%, ARR 1.4%, HR 0.92; p=0.0257) over 12 months after ACS events.

INDICATIONS

BRILINTA, in combination with aspirin, is indicated for the prevention of atherothrombotic events (cardiovascular death, myocardial infarction and stroke) in adult patients with acute coronary syndromes (unstable angina [UA], 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).

CONTRAINDICATIONS

- Hypersensitivity to ticagrelor or any of the excipients (refer to ADVERSE EFFECTS)
- Active pathological bleeding
- History of intracranial haemorrhage
- Moderate to severe hepatic impairment
- 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 (refer to PRECAUTIONS)

PRECAUTIONS

Bleeding risk

In the PLATO study, the key exclusion criteria included an increased risk for bleeding, clinically important thrombocytopenia or anaemia, previous intracranial bleed, gastrointestinal bleed within the past 6 months or major surgery within the past 30 days. Patients with ACS treated with BRILINTA and ASA showed an increased risk of non-CABG major bleeding and also more generally in bleeds requiring medical attention i.e. Major + Minor PLATO bleeds, but not Fatal or Life-threatening bleeds (refer to ADVERSE EFFECTS).

As with other anti-platelet agents, BRILINTA prolongs bleeding time and should be used with caution in patients who may be at risk of increased bleeding. Therefore, the use of BRILINTA in patients at known increased risk for bleeding should be balanced against the benefit in terms of prevention of atherothrombotic 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, coagulation disorders or active or recent gastrointestinal bleeding). The use of BRILINTA is contraindicated in patients with active pathological bleeding in those with a history of intracranial haemorrhage, and in patients with moderate to severe hepatic impairment (refer to CONTRAINDICATIONS).
- Patients with concomitant administration of drugs that may increase the risk of bleeding (e.g. non-steroidal anti-inflammatory drugs (NSAIDS), oral anticoagulants (eg. warfarin) and/or fibrinolytics/ thrombolytics 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

Patients should be advised to inform physicians and dentists that they are taking BRILINTA before any surgery is scheduled and before any new medicinal product is taken. 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 (refer to Pharmacodynamic effects) study, mean 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, eg, in settings where antiplatelet therapy must be temporarily discontinued due to surgery or trauma.

In patients undergoing coronary bypass grafting (CABG) in PLATO, those on BRILINTA had a non-statistically significant higher rate of major bleeding compared with those on clopidogrel when the drug was stopped within 1 day prior to surgery but a similar rate of major bleeds compared with those on clopidogrel after stopping therapy 2 or more days before surgery.

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.

Renal Dialysis

As there is no safety and efficacy data for BRILINTA in patients undergoing renal dialysis, caution should be used with these patients as ticagrelor is not expected to be dialyzable.

Patients at risk for bradycardic events

Due to observations of mostly asymptomatic ventricular pauses in an earlier clinical study, 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) were excluded from the main study evaluating the safety and efficacy of BRILINTA. Therefore, due to the limited clinical experience in these patients, caution is advised.

In addition, caution should be exercised when administering BRILINTA concomitantly with drugs 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 drugs known to induce bradycardia (e.g. 96% beta blockers, 33% calcium channel blockers diltiazem and verapamil, and 4% digoxin).

During the Holter substudy 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 congestive 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 was no adverse clinical consequences associated with this imbalance (including syncope or pacemaker insertion) in this patient population (refer to CLINICAL TRIALS/Holter Study).

Dyspnoea

Dyspnoea, usually mild to moderate in intensity and often resolving without need for treatment discontinuation, is reported by 13.8% in patients treated with BRILINTA in PLATO and by 7.8% treated with clopidogrel. Discontinuations due to dyspnoea were reported in 0.9% of patients taking BRILINTA and 0.1% of patients taking clopidogrel (refer to ADVERSE EVENTS).

Patients with asthma/ chronic obstructive pulmonary disorder (COPD) may have an increased absolute risk of experiencing dyspnoea with BRILINTA. BRILINTA should be used with caution in patients with a history of asthma and/or COPD. The mechanism has not 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.

Creatinine Elevations

Creatinine levels may increase during treatment with ticagrelor (see ADVERSE EFFECTS/Lab Abnormalities/Creatinine Elevations). The mechanism has not been elucidated. Renal function should be checked after one month and thereafter according to routine medical practice paying special attention to patients ≥75 years and patients with moderate/severe renal impairment and those receiving concomitant treatment with an Angiotensin II Receptor Blocker (ARB).

Uric Acid Increase

In the PLATO study, patients on ticagrelor had a higher risk of hyperuricaemia than those patients receiving clopidogrel. Caution should be exercised when administering ticagrelor to 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 the relationship observed in PLATO between maintenance ASA dose and relative efficacy of BRILINTA compared to clopidogrel, co-administration of BRILINTA and high dose maintenance dose ASA (>300mg) is not recommended (refer to CLINICAL TRIALS).

In PLATO, patients weighing <60kg were at greater risk of cardiovascular events and slightly higher risk of major bleeding compared with patients weighing ≥60kg (refer to CLINICAL TRIALS and ADVERSE EFFECTS).

Discontinuations

Patients who require discontinuation of BRILINTA are at increased risk for cardiac events. Premature discontinuation of treatment should be avoided. If BRILINTA must be temporarily stopped due to an adverse event(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.

Effects on fertility

Ticagrelor was found to have no effect on fertility of female rats at oral doses up to 200mg/kg per day (approximately 20 times the human therapeutic exposure) and had no effect on fertility of male rats at doses up to 180mg/kg/day (about 16 times the human therapeutic exposure).

Ticagrelor had no effect on fetal development at oral doses up to 100mg/kg per day in rats (about 5 times the recommended human therapeutic exposure) and up to 42mg/kg per day in rabbits (equivalent to the human therapeutic exposure). Ticagrelor had no effects on parturition or postnatal development in rats at doses up to 60mg/kg/day (just under 5 times the human therapeutic exposure).

Use in pregnancy – category B1

No clinical data on exposed pregnancies are available for ticagrelor.

Animal studies do not indicate direct harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development. Because animal reproduction studies are not always predictive of a human response, ticagrelor is not recommended for use during pregnancy.

Use in lactation

It is not known whether ticagrelor 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.

Paediatric use

The safety and efficacy of BRILINTA has not been established in patients under 18 years of age.

Use in the elderly

Higher exposures to ticagrelor and the active metabolite were observed in elderly (≥65 years) subjects compared to younger subjects. These differences are not considered clinically significant. No dose adjustment is needed for elderly patients.

In PLATO, patients ≥65 years or ≥75 years of age were at greater risk of cardiovascular events and slightly higher risk of major bleeding compared with younger patients (refer to CLINICAL TRIALS and ADVERSE EFFECTS).

Carcinogenicity

No compound-related tumours were observed in a 2-year mouse study at oral doses up to 250mg/kg/day (*ca.*18-fold the human therapeutic exposure to ticagrelor). There was no increase in tumours in male rats oral doses up to 120mg/kg/day (*ca.* 15-fold the human therapeutic exposure). Increases in uterine adenocarcinomas and hepatocellular adenomas /adenocarcinomas and decreases in pituitary adenomas and mammary fibroadenomas were observed in female rats at more than 25 times the human therapeutic exposure to ticagrelor, with no change in tumour incidence seen at around 8 times the human therapeutic exposure. The uterine tumours seen only in rats were hypothesized to result from a 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.

Genotoxicity

Ticagrelor showed no genotoxic potential in assays for gene mutations (bacterial reverse mutation, mouse lymphoma TK) and chromosomal damage (rat micronucleus *in vivo*).

INTERACTIONS WITH OTHER MEDICINES

Ticagrelor is primarily a CYP3A4 substrate and a mild inhibitor of CYP3A4. Ticagrelor is also a P-gp substrate and a weak P-gp inhibitor and may increase the exposure of P-gp substrates.

Effects of Other Drugs on BRILINTA

Drugs metabolised by CYP3A4

Ketoconazole and other strong CYP3A4 inhibitors

Co-administration of ketoconazole with ticagrelor increased the ticagrelor C_{max} and AUC equal to 2.4-fold and 7.3-fold, respectively. The C_{max} and AUC of the active metabolite were reduced by 89% and 56%, respectively. Other strong inhibitors of CYP3A4 (clarithromycin, nefazadone, ritonavir and atanazavir) would be expected to have similar effects and their concomitant use with BRILINTA is contraindicated.

Diltiazem and other moderate CYP3A4 inhibitors

Co-administration of ticagrelor with diltiazem increased the ticagrelor C_{max} 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) would be expected to have a similar effect as diltiazem leading to increased exposure to ticagrelor, therefore caution is advised.

Rifampin and other CYP3A4 inducers

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

Cyclosporin (PgP and CYP3A inhibitor)

Co administration of cyclosporin (600mg dose) with ticagrelor (180mg) as a single oral dose in healthy male volunteers 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 33% and C_{max} was decreased by 15% in the presence of cyclosporin. Caution is advised when cyclosporin and ticagrelor are coadministered.

Effects of BRILINTA on Other Drugs

Drugs metabolised by CYP3A4

Simvastatin

Co-administration of ticagrelor with simvastatin increased the simvastatin C_{max} by 81% and AUC by 56% and increased simvastatin acid C_{max} by 64% and AUC by 52% with some individual increases equal to 2 to 3 fold. There was no effect of simvastatin on ticagrelor

plasma levels. There is the potential for an increase in simvastatin-related adverse events such as myopathy and rhabdomyolysis with co-administration; no cases of rhabdomyolysis were reported when ticagrelor was co-administered with simvastatin 40mg daily or lower. Therefore concomitant use of ticagrelor with doses of simvastatin greater than 40mg daily is not recommended.

A similar effect on other statins metabolised by CYP3A4 cannot be excluded.

Atorvastatin

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

BRILINTA is not expected to have a clinically meaningful effect on other statins which are not metabolised by CYP3A4.

Other

Ticagrelor is a mild CYP3A4 inhibitor. Co-administration of BRILINTA and CYP3A4 substrates with narrow therapeutic indices (i.e. ergot alkaloids) is not recommended, as ticagrelor may increase the exposure to these drugs.

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

P-glycoprotein (P-gp) substrates (including digoxin and cyclosporin)

Concomitant administration of ticagrelor increased the digoxin C_{max} by 75% and AUC by 28%. The mean trough digoxin levels were increased about 30% with ticagrelor co-administration with some individual maximum increases to 2 fold. In the presence of digoxin, the C_{max} and AUC of ticagrelor and its active metabolite were not affected. Concomitant administration of ticagrelor had a minor effect on the AUC (Gmean ratio 1.12 [90%CI; 105.75-119.20]) and C_{max} (Gmean ratio 1.05 [90%CI; 98.67-111.81] of cyclosporin. Appropriate clinical and/or laboratory monitoring is recommended when giving narrow therapeutic index P-gp dependent drugs like digoxin and cyclosporin concomitantly with BRILINTA.

No data are available on concomitant use of BRILINTA with potent P-gp inhibitors (e.g. verapamil, quinidine) that may increase ticagrelor exposure.

Other Concomitant Therapy

In clinical studies, BRILINTA was commonly administered with ASA, heparin, low molecular weight heparin, intravenous GpIIb/IIIa inhibitors, proton pump inhibitors, statins, beta-blockers, angiotensin converting enzyme inhibitors and angiotensin receptor blockers as needed for concomitant conditions. These studies did not produce any evidence of clinically significant adverse interactions. Due to potential pharmacodynamic interactions, caution should be exercised with the concomitant administration of BRILINTA and medicinal products known to alter haemostasis.

Adenosine: Based on the mechanism of action of ticagrelor, patients may transiently experience increased dyspnoea in association with a bolus dose of adenosine while taking ticagrelor (see PHARMACOLOGY/Mechanism of Action).

Aspirin: Clinical pharmacology interaction studies showed that co-administration of ticagrelor with ASA did not have any effect on ticagrelor or its active metabolite plasma levels.

Heparin and enoxaparin: Clinical pharmacology interaction studies showed that co-administration of ticagrelor with heparin did not have any effect on ticagrelor or its active metabolite plasma levels. Co-administration of ticagrelor and heparin had no effect on heparin based on activated partial thromboplastin time (aPTT) and activated coagulation time (ACT) assays. Co administration of ticagrelor and heparin had no effect on enoxaparin based on factor Xa assay.

Non Steroidal Anti-Inflammatory Drugs (NSAIDS)

Concomitant administration with chronic NSAIDs has not been studied. Because of the potential for increased risk of bleeding, chronic NSAIDs and ticagrelor should be co-administered with caution (refer to PRECAUTIONS/Bleeding Risk).

Clopidogrel and Prasugrel

Ticagrelor and clopidogrel or prasugrel should not be co-administered.

Concomitant administration with clopidogrel has not been studied. Switching from clopidogrel to ticagrelor results in an absolute IPA increase of 26.4% and switching from ticagrelor to clopidogrel results in an absolute IPA decrease of 24.5%. Patients can be switched from clopidogrel to BRILINTA without interruption of anti-platelet effect (refer to PHARMACOLOGY/Switching Data).

Switching from prasugrel to BRILINTA has not been investigated.

Drugs known to induce bradycardia: Due to observations of mostly asymptomatic ventricular pauses and bradycardia, caution should be exercised when administering BRILINTA concomitantly with drugs 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 drugs known to induce bradycardia (e.g. 96% beta blockers, 33% calcium channel blockers diltiazem and verapamil, and 4% digoxin).

Selective Serotonin Reuptake Inhibitors (SSRIs)

Due to reports of cutaneous bleeding abnormalities with SSRIs, caution is advised when administering SSRIs with BRILINTA as this may increase the risk of bleeding. In PLATO, there was no increase in major bleeding in patients taking BRILINTA concomitantly with SSRIs.

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 for ACS, dizziness and confusion have been reported. Therefore, patients who experience these symptoms should be cautious while driving or using machines.

ADVERSE EFFECTS

The safety profile of BRILINTA in patients with ACS (UA, NSTEMI and STEMI) was evaluated in PLATO study, which compared patients treated with BRILINTA (loading dose of 180mg of BRILINTA and a maintenance dose of 90mg bd) to patients treated with clopidogrel (300-600mg loading dose followed by 75mg od maintenance dose) both given in combination with ASA and other standard therapies.

Median treatment duration for BRILINTA was 276 days (of the 9333 ticagrelor patients, 6762 patients were treated for greater than 6 months and 3138 were treated for greater than 12 months).

The most commonly reported adverse events in patients treated with ticagrelor were dyspnoea, headache, and epistaxis and these events occurred at higher rates than in the clopidogrel treatment group. Serious adverse events were reported in a similar frequency between BRILINTA (20.2%) and clopidogrel (20.3%) treated patients. The most frequent serious adverse events observed were cardiac failure (1.1% vs 1.0%), non-cardiac chest pain (0.9% vs 0.9%) and dyspnoea (0.7% vs 0.4%).

Discontinuation

The ticagrelor group had a higher discontinuation rate due to AEs than clopidogrel (7.4% vs. 5.4%). The difference was driven mainly by dyspnoea (0.9% vs. 0.1%) and epistaxis (0.4% vs. 0.1%). The ticagrelor and clopidogrel groups had a similar discontinuation rate due to other AEs.

The discontinuation rate due to serious adverse events was 2.8% for ticagrelor and 2.4% for clopidogrel.

Bleeding Events

The following bleeding definitions were used in the PLATO study:

'Major Fatal/Life-threatening': fatal, or intracranial, or intrapericardial bleed with cardiac tamponade, or hypovolaemic shock or severe hypotension due to bleeding and requiring pressors or surgery, or clinically overt or apparent bleeding associated with a decrease in haemoglobin of more than 50 g/L, or transfusion of 4 or more units (whole blood or PRBCs) for bleeding.

'Major Other': Significantly disabling (e.g. intraocular with permanent vision loss), or clinically overt or apparent bleeding associated with a decrease in haemoglobin of 30 to 50 g/L, or transfusion of 2-3 units (whole blood or PRBCs) for bleeding.

'Minor': Requires medical intervention to stop or treat bleeding (e.g. epistaxis requiring visit to medical facility for packing).

Minimal bleeds included all other bleeds not requiring intervention or treatment (eg. bruising, bleeding gums, oozing from injection sites, etc); these were collected but not adjudicated.

The primary safety endpoint in the PLATO study was the composite endpoint of 'Total Major' bleeding, which consisted of the components of 'Major Fatal/Life-threatening' and 'Major Other'. In PLATO, the rate of 'Total Major' bleeding did not significantly differ for BRILINTA compared to clopidogrel (Figure 4).

Overall outcome of bleeding events in the PLATO study are shown in Table 2.

Bleeding events reported in PLATO were also mapped to the TIMI (Thrombolysis in Myocardial Infarction) scale, to facilitate comparison with other similar studies. The following TIMI bleeding definitions were used:

- **TIMI Major:** Clinically overt bleeding associated with a fall in haemoglobin >50 g/L, or intracranial haemorrhage.
- **TIMI Minor:** Overt bleeding associated with a fall in haemoglobin of ≥30 g/L but ≤50 g/L.

PLATO definitions are more inclusive when compared to TIMI definitions of bleeding. Compared to TIMI, the PLATO definitions feature lower thresholds to capture bleeding events during both acute and chronic phases of ACS.

Figure 4

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

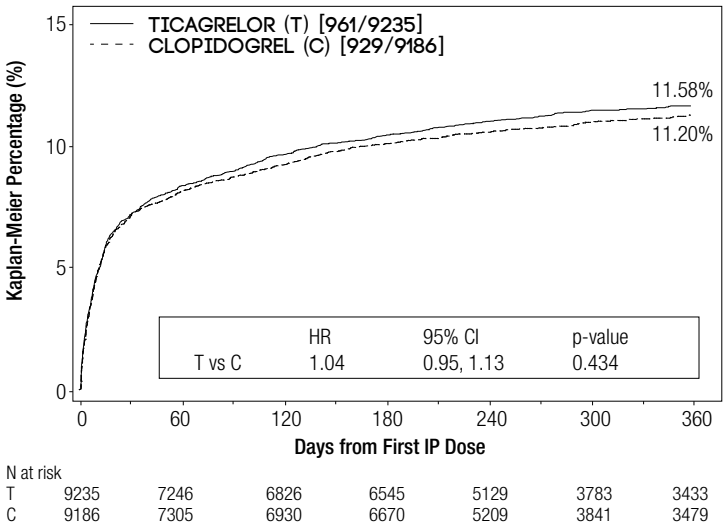


Table 2

Analysis of Overall Bleeding Events

	Ticagrelor (+ASA) (%) N=9235	Clopidogrel (+ASA) (%) N=9186	p-value*
Primary Safety Endpoint Total Major	11.6	11.2	0.4336
Secondary Endpoints Major Fatal/Life-Threatening	5.8	5.8	0.6988
Combined Total Major + Minor	16.1	14.6	0.0084
Non-CABG Total Major	4.5	3.8	0.0264
Non-Procedural Major	3.1	2.3	0.0058
Non-Procedural Major + Minor	5.9	4.3	<0.0001
TIMI-defined bleeding category TIMI-defined Major	7.9	7.7	0.5669
TIMI-defined Major + Minor	11.4	10.9	0.3272

*Nominal p-value not corrected for multiple testing

In PLATO, time to first PLATO-defined 'Total Major' bleeding for BRILINTA did not differ significantly from that of clopidogrel. The event rate for bleeding was higher for both treatment arms during the first 30 days compared to the remainder of the study; most events occurred during this period. There were few fatal bleeding events in the study, 20 (0.2%) for BRILINTA and 23 (0.3%) for clopidogrel. When minor bleeding was included, combined PLATO-defined Major and Minor bleeding events were significantly higher on BRILINTA than on clopidogrel. Minimal bleeding rates on BRILINTA were higher than on clopidogrel. Overall rates of TIMI-defined bleeding events did not differ significantly between BRILINTA and clopidogrel. Refer to the bleeding definitions under the subheading Bleeding Events.

CABG-related bleeding: In PLATO, 1584 patients (12%) underwent coronary artery bypass graft (CABG) surgery. 'Major Fatal/Life-threatening' bleeding was approximately 42% in both treatment groups. There was no difference between the treatment groups with respect to risk of 'Major Fatal/Life-threatening' CABG bleeding relative to time of last dose before the procedure. Fatal CABG bleeding occurred uncommonly, 6 patients in each treatment group (0.8% and 0.7% of CABG patients on BRILINTA and clopidogrel, respectively).

Non-CABG related bleeding: When CABG bleeding is removed from the analysis (Table 3), the absolute bleeding rates for all categories are lower. The groups 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 was more common with BRILINTA.

Table 3

Non-CABG Related PLATO-defined Major Bleeding Events and TIMI-defined Bleeding Events

	Ticagrelor (+ASA) (%) N=9235	Clopidogrel (+ASA) (%) N=9186	p-value
PLATO-defined bleeding category Total Major	4.5	3.8	0.0264
Major Fatal/Life-Threatening	2.1	1.9	0.2516
TIMI-defined bleeding category TIMI-defined Major	2.8	2.2	0.0246
TIMI-defined Major + Minor	4.5	3.6	0.0093

Bleeding unrelated to any procedure: As shown in Table 2 PLATO-defined 'Major' and 'Major + Minor' non-procedural bleeding was more frequent with BRILINTA. Discontinuation of treatment due to non-procedural bleeding was more common for BRILINTA (2.9%) than for clopidogrel (1.2%; p<0.001). Clinically important locations for 'Major + Minor' bleeding in rank order by frequency were (BRILINTA vs clopidogrel): intracranial (27 vs 14 events), pericardial (11 vs 11), retroperitoneal (3 vs 3), intraocular (2 vs 4) and intra-articular (2 vs 1). Other common locations were in rank order of frequency: gastrointestinal (170 vs 135 events), epistaxis (116 vs 61), urinary (45 vs 37), subcutaneous/dermal (43 vs 38) and haemoptysis (13 vs 7).

There was no difference with BRILINTA compared to clopidogrel for fatal non-procedural bleeding.

Intracranial bleeding: There were more intracranial non-procedural bleeds with BRILINTA (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.

Among ticagrelor-treated patients in PLATO, there were similar rates of haemorrhagic stroke between those with a history of prior TIA or ischaemic stroke and those without prior TIA or ischaemic stroke: 2/564 (0.35%) vs 21/8762 (0.24%).

Gastrointestinal bleeding and Fatal gastrointestinal bleeding: Total major GI bleeding was higher on ticagrelor than clopidogrel (1.3% vs 1%) however fatal/life threatening GI bleeding rates were similar and fatal GI bleeding events were less on ticagrelor (0 vs 5 events).

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

Patients ≥65 or ≥75 years of age had a slightly higher rate of major bleeding in both treatment arms. For patients ≥75 years of age, the rate of major bleeding was 12.1% on ticagrelor vs 11.8% on clopidogrel. For patients <75 years of age, the rate of major bleeding was 10.1% on ticagrelor vs 9.8% on clopidogrel. Similar differences were seen in patients ≥65 years compared with those <65 years.

In addition, patients weighing <60kg had a slightly higher rate of major bleeding in both treatment arms. For patients weighing <60kg, the rate of major bleeding was 11.2% on ticagrelor vs 13.3% on clopidogrel. For patients weighing ≥60kg, the rate of major bleeding was 10.3% on ticagrelor vs 9.9% on clopidogrel.

Dyspnoea

Dyspnoea is reported by patients treated with BRILINTA. Dyspnoea adverse events (AEs) (dyspnoea, dyspnoea at rest, dyspnoea exertional, dyspnoea paroxysmal nocturnal, and nocturnal dyspnoea), when combined, were reported in 13.8% of patients taking BRILINTA and in 7.8% taking clopidogrel in the PLATO study. The study did not exclude patients with underlying CHF, COPD or asthma. Most of the dyspnoea AEs were mild to moderate in intensity. Dyspnoea Serious Adverse Events were reported in 0.7% taking BRILINTA and 0.4% taking clopidogrel. More patients taking BRILINTA 0.9% discontinued study drug than did patients taking clopidogrel 0.1% due to dyspnoea. Dyspnoea was usually reported in the initial phase of treatment; the time to the first dyspnoea AE was numerically shorter with ticagrelor (median of 20 days) than with clopidogrel (median of 33 days) during treatment with study medication.

Eighty-seven percent of patients taking BRILINTA that reported dyspnoea experienced a single episode.

Compared with clopidogrel, patients with asthma/COPD treated with ticagrelor may have an increased risk of experiencing non-serious dyspnoea (3.29% ticagrelor versus 0.53% clopidogrel) and serious dyspnoea (0.38% ticagrelor versus 0.00% clopidogrel).

Approximately 30% of all dyspnoea resolved within 7 days. 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 of dyspnoea with BRILINTA is due to new or worsening heart or lung disease.

In patients who underwent pulmonary function testing in the clinical program, there was no indication of an adverse effect of BRILINTA on pulmonary function.

In PLATO, the CV benefit of BRILINTA was maintained in patients who reported dyspnoea.

Lab Abnormalities

Uric acid elevations: In PLATO, serum uric acid concentration increased to more than upper limit of normal in 22% of patients receiving BRILINTA compared to 13% of patients receiving clopidogrel. Mean serum uric acid concentration increased approximately 15% with BRILINTA compared to approximately 7.5% with clopidogrel and after treatment was stopped, decreased to approximately 7% on BRILINTA but with no decrease observed for clopidogrel. The hyperuricaemia AEs reported were 0.5% for BRILINTA vs. 0.2% for clopidogrel. Of these AEs 0.05% for BRILINTA vs. 0.02% for clopidogrel were considered causally related by investigators. For gouty arthritis, the AEs reported were 0.2% for BRILINTA vs 0.1% for clopidogrel; none of these adverse events were assessed as causally related by investigators.

Creatinine elevations: In PLATO, serum creatinine concentration significantly increased by >30% in 25.5% of patients receiving BRILINTA compared to 21.3% of patients receiving clopidogrel and by >50% in 8.3% of patients receiving BRILINTA compared to 6.7% of patients receiving clopidogrel. Creatinine elevations by >50% were more pronounced in patients >75 years (BRILINTA 13.6% versus clopidogrel 8.8%), in patients with severe renal impairment at baseline (BRILINTA 17.8% versus clopidogrel 12.5%) and in patients receiving concomitant treatment with ARBs (BRILINTA 11.2% versus clopidogrel 7.1%). The increases typically did not progress with ongoing treatment and often decreased with continued therapy. Signs of reversibility on discontinuation were observed even in those with the greatest on

treatment increases. Treatment groups in PLATO did not differ for related serious adverse events. Within these subgroups renal-related serious adverse events and adverse events leading to discontinuation of study drug were similar between treatment groups. The totality of renal AEs reported were 4.9% for BRILINTA vs. 3.8% for clopidogrel, however a similar percent of patients reported events considered by the investigators as causally related to treatment; 54 (0.6%) for BRILINTA and 43 (0.5%) for clopidogrel.

The following adverse events have been identified following studies with BRILINTA (see Table 4).

Table 4

Treatment Emergent Adverse Events Reported by at Least 2.5% of Patients in Either Group[a]

	% Incidence[b]	% Incidence[b]
SYSTEM ORGAN CLASS EVENT	**Ticagrelor (+ASA)**	**Clopidogrel (+ASA)**
Cardiac Disorders		
Atrial Fibrillation	4.2	4.6
Bradycardia	2.9	2.9
Cardiac Failure	2.3	2.6
Gastrointestinal Disorders		
Nausea[c]	4.3	3.8
Diarrhea[c]	3.7	3.3
Vomiting[c]	2.5	2.3
Constipation[c]	2.2	2.6
General Disorders and Administration Site Conditions		
Non-cardiac chest pain	3.7	3.3
Fatigue	3.2	3.2
Chest pain	3.1	3.5
Pyrexia	2.9	2.8
Oedema peripheral	2.3	2.5
Musculoskeletal and Connective Tissue Disorders		
Back pain	3.6	3.3
Nervous System Disorders		
Headache[c]	6.5	5.8
Dizziness[c]	4.5	3.9
Respiratory, Thoracic and Mediastinal Disorders		
Dyspnoea[c,d]	13.8	7.8
Epistaxis	6.0	3.4
Cough	4.9	4.6
Skin and subcutaneous tissue disorders		
Contusion	3.9	2.0
Vascular Disorders		
Hypertension	3.8	4.0
Hypotension	3.2	3.3

a These adverse events are from the PLATO study
b Very common: ≥1/10 (≥10%); Common: ≥1/100 (≥1%) and <1/10 (<10%)
c These events are considered causally related to ticagrelor.
d Several MedDRA PT combined

Additional adverse reactions that were reported in the PLATO study as possibly or probably related to BRILINTA are listed below by body system. Frequency categories are defined according to the following conventions: Very common (≥1/10), Common (≥1/100, <1/10), Uncommon (≥1/1000, <1/100), Rare (≥1/10,000, <1/1000)

Eye disorders:

- *uncommon:* eye haemorrhage (intraocular, conjunctival, retinal)

Ear and labyrinth disorders:

- *common:* vertigo
- *uncommon:* ear haemorrhage

Nervous system disorders:

- *uncommon:* intracranial hemorrhage (includes the following related terms: cerebral heamorrhage, haemorrhage intracranial, haemorrhagic stroke), confusion, paraesthesia

Gastrointestinal disorders:

- *common:* abdominal pain, dyspepsia, gastrointestinal haemorrhage (includes the following related terms: rectal heamorrhage, intestinal haemorrhage, malaena, occult blood).
- *uncommon:* retroperitoneal haemorrhage, gastritis, haematemesis, gastrointestinal ulcer haemorrhage (includes the following related terms: gastric ulcer haemorrhage, duodenal ulcer haemorrhage, peptic ulcer haemorrhage),haemorrhoidal haemorrhage, oral haemorrhage (including gingival bleeding), retroperitoneal haemorrhage

Injury, poisoning and procedural complications:

- *common:* post-procedural hemorrhage, procedural site haemorrhage (includes the following related terms: vessel puncture site haemorrhage, vessel puncture site haematoma, injection site haemorrhage, puncture site haemorrhage, catheter site haemorrhage), haemorrhage
- *uncommon:* wound haemorrhage, traumatic haemorrhage

Investigations:

- *common:* blood creatinine increased

Renal and urinary disorders:

- *common:* urinary tract bleeding (includes the following related terms: haematuria, blood urine present, haemorrhage urinary tract).

Respiratory, thoracic and mediastinal disorders:

- *uncommon:* haemoptysis

Reproductive system and breast disorders

- *uncommon:* vaginal bleeding (including metrorrhagia)

Musculoskeletal connective tissue and bone disorders:

- *rare:* haemarthrosis

Skin and subcutaneous tissue disorders:

- *common:* rash, pruritus, subcutaneous or dermal bleeding or bruising (includes the following related terms: subcutaneous haemotoma, skin haemorrhage, haemorrhage subcutaneous, petechiae, haematoma, ecchymosis, increased tendency to bruise, traumatic haemotoma)

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 (refer to CONTRAINDICATIONS)

Skin and subcutaneous tissue disorders - Rash

DOSAGE AND ADMINISTRATION

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

For oral use. BRILINTA can be taken with or without food. Patients taking BRILINTA should take ASA daily unless specifically contraindicated. Following an initial dose of ASA, BRILINTA should be used with a

recommended maintenance dose of ASA 100mg daily. If required, the ASA maintenance dose may vary from 75-150mg according to clinical need.

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

Physicians who desire to switch patients from clopidogrel to BRILINTA should administer the first 90mg dose of BRILINTA 24 hours following the last dose of clopidogrel. Switching from prasugrel to BRILINTA has not been investigated.

Treatment is recommended for at least 12 months unless discontinuation of BRILINTA is clinically indicated. In patients with ACS, premature discontinuation with any antiplatelet therapy, including BRILINTA, could result in an increased risk of cardiovascular death, or myocardial infarction due to the patient's underlying disease.

Administration of crushed tablets

For patients who are unable to swallow the tablet(s) whole, Brilinta tablets (90mg and 2x90mg) can be crushed to a fine powder and mixed in water to be administered orally or via a large syringe through a nasogastric tube (CH8 or greater).

For oral administration, crush Brilinta tablets using a mortar and pestle or a similar device. Adding approximately 100 mL of water to the mortar/crushing device and stir for approximately 1 minute before transferring the dispersion to a glass/dosing cup and administer. Add another 100 mL of water to the mortar/crushing device and stir for approximately ½ minute to ensure that all the remaining powder is dispersed before transferring this to the glass/dosing cup. Stir the contents of the glass again for approximately ½ minute and administer the remaining water/dispersed tablet.

For administration via a nasogastric tube, crush the tablets as stated above and use approximately 50 mL of water to disperse the crushed powder before withdrawing the dispersion into a suitable syringe. Then administer the full contents of the syringe via the nasogastric tube. Add another 50 mL to the mortar/crushing device and stir for approximately ½ minute to ensure that all the remaining powder is dispersed, before withdrawing the dispersion into the syringe and administering via the nasogastric tube. Refill the syringe with approximately 25 mL of water and shake before flushing any remaining contents from the nasogastric tube into the stomach.

Special Populations

Elderly:

No dose adjustment is required.

Patients with renal impairment:

No dose adjustment is necessary for patients with renal impairment. No information is available concerning treatment of patients on renal dialysis and therefore BRILINTA is not recommended in these patients.

Patients with hepatic impairment:

No dose adjustment is necessary for patients with mild hepatic impairment. BRILINTA has not been studied in patients with moderate or severe hepatic impairment (refer to CONTRAINDICATIONS).

OVERDOSAGE

BRILINTA is well tolerated in single doses up to 900mg. 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.

There is currently no known antidote to reverse the effects of BRILINTA, and BRILINTA is not expected to be dialysable. 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.

Contact the Poisons Information Centre on 131126 for advice on management.

PRESENTATION AND STORAGE CONDITIONS

BRILINTA tablets are presented as round, biconvex, yellow, film-coated tablets. The tablets are marked with "90" above "T" on one side and plain on the other.

Calendar blister in cartons of 14 (1x14 tablets sample pack) and 56 (4x14 tablets),

Storage conditions

Store below 30°C.

NAME AND ADDRESS OF SPONSOR

AstraZeneca Pty Ltd
ABN 54 009 682 311
Alma Road
NORTH RYDE NSW 2113

POISON SCHEDULE OF THE MEDICINE

Prescription only medicine (Schedule 4)

DATE OF FIRST INCLUSION ON THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS

21 June 2011

DATE OF MOST RECENT AMENDMENT

18 December 2015