NEW ZEALAND DATA SHEET

1. PRODUCT NAME

BRILINTA® 60 mg film-coated tablets
BRILINTA® 90 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

60 mg: each tablet contains 60 mg ticagrelor.

90 mg: each tablet contains 90 mg ticagrelor.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

90 mg - Round, biconvex, yellow, film coated tablets, 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 (aspirin), is indicated for the prevention of atherothrombotic events (cardiovascular death, myocardial infarction and stroke)

- in 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).

- in patients with a history of myocardial infarction (MI occurred at least one year ago) and a high risk of developing an atherothrombotic event.

For further information, please refer to section 5.1.

4.2 DOSE AND METHOD OF ADMINISTRATION

Acute Coronary Syndromes

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 5.1). After one year, patients initiated on 90 mg twice daily may continue treatment with 60 mg twice daily without interruption.

Patients taking BRILINTA should also take a daily low maintenance dose of aspirin of 75 -150 mg, unless specifically contraindicated. An initial loading dose of aspirin is recommended for patients with ACS (see section 5.1). Discontinuation of ASA may be considered after 3 months in patients with ACS who have undergone a PCI procedure and have an increased risk of bleeding (see section 4.4).

History of Myocardial Infarction (MI occurred at least one year ago)

In patients with a history of Myocardial Infarction (MI occurred at least one year ago) no loading dose of BRILINTA is required and the recommended dose is 60 mg twice daily.

Long term treatment is recommended unless discontinuation of BRILINTA is clinically indicated (see section 5.1).

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

Patients may start treatment with BRILINTA 60 mg twice daily, regardless of their previous anti-platelet regimen, and irrespective if there has been a lapse in therapy or not.

Patients should discontinue their current anti-platelet therapy before initiating BRILINTA with low dose aspirin at the next scheduled dose.

Patients initiated on BRILINTA 90 mg twice daily at the time of the acute event, after one year, may continue treatment with 60 mg twice daily without interruption.

Dosage Considerations

Premature discontinuation

Premature discontinuation with any antiplatelet therapy, including BRILINTA, could result in an increased risk of cardiovascular death, myocardial infarction, or stroke due to the patient's underlying disease (see section 4.4). Therefore premature discontinuation of treatment should be avoided.

Missed dose

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

Switching

In patients having an ACS event, the loading dose of 180 mg should be given as soon as possible regardless of any previous antiplatelet treatment.

Physicians who desire to switch patients with a prior ACS event, to BRILINTA should administer the first dose of BRILINTA 24 hours following the last dose of the other antiplatelet medication.

Method of administration

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

Elderly population

No dose adjustment is required in the elderly (see section 5.2).

Renal impairment

No dose adjustment is necessary for patients with renal impairment (see section 5.2).

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. Use in patients with severe hepatic impairment is therefore contraindicated (see section 4.3, 4.4 and 5.2).

Paediatric population

The safety and efficacy of BRILINTA in children below the age of 18 have not been established (see section 5.1).

4.3 CONTRAINDICATIONS

- Hypersensitivity to the ticagrelor or any of the excipients listed in section 6.1 (see section 4.8).
- Active pathological bleeding
- History of intracranial haemorrhage (see section 4.8)
- Severe hepatic impairment (see sections 4.2, 4.4 and 5.2)
- 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 sections 4.5).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Bleeding risk

In the phase 3 pivotal trial (PLATO [PLATelet Inhibition and Patient Outcomes], 18,624 patients) 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 acute coronary syndromes treated with BRILINTA and aspirin showed an increased risk of non-CABG major bleeding and also more generally in bleeds requiring medical attention i.e. Major or Minor PLATO bleeds, but not Fatal or Life-threatening bleeds (see section 4.8).

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, 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 in patients with severe hepatic impairment (see section 4.3).

- 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).

Discontinuing ASA after 3 months and continuing with BRILINTA as single antiplatelet therapy has been shown to decrease the risk of bleeding, with no observed increase in risk of major adverse cardiovascular events (MACE), in patients with ACS who have undergone a PCI procedure. The decision to discontinue ASA and continue with BRILINTA as single antiplatelet therapy in patients with an increased risk of bleeding should be based on clinical judgment considering the risk of bleeding versus the risk of thrombotic events.

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

Antifibrinolytic therapy (aminocaproic acid or tranexamic acid) and/or recombinant factor VIIa therapy may increase 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.

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 coronary artery bypass grafting (CABG), BRILINTA had more bleeding than clopidogrel when stopped within 1 day prior to surgery but a similar rate of major bleeds compared to clopidogrel after stopping therapy 2 or more days before surgery (see section 4.8).

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 5.1).

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 a 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 section 4.2, 4.3 and 5.2).

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 aspirin). Patients with an increased risk of bradycardic events (e.g. patients without a pacemaker who have sick sinus syndrome, 2nd or 3rd 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 (also see section 5.1).

Bradyarrhythmic events and AV blocks have been reported in the post-marketing setting in patients taking BRILINTA (see section 4.8), 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.

In addition, caution should be exercised when administering BRILINTA concomitantly with medicinal products known to induce bradycardia. However no evidence of clinically significant adverse reactions was observed in the PLATO trial after concomitant administration with one or more medicinal products known to induce bradycardia (e.g. 96% beta blockers, 33% calcium channel blockers diltiazem and verapamil, and 4% digoxin) (see section 4.5).

During the Holter substudy in PLATO, more patients had ventricular pauses $\geq$3 seconds with ticagrelor than with clopidogrel during the acute phase of their ACS. The increase in Holter-detected ventricular pauses with ticagrelor was higher in patients with chronic heart failure (CHF) than in the overall study population during the acute phase of ACS, but not at one month with ticagrelor or compared to clopidogrel. There were no adverse clinical consequences associated with this imbalance (including syncope or pacemaker insertion) in this patient population (see section 5.1).

Dyspnoea

Dyspnoea, usually mild to moderate in intensity and often resolving without need for treatment discontinuation, is reported in patients treated with BRILINTA. Patients with asthma/COPD may have an increased absolute risk of experiencing dyspnoea with BRILINTA (see section 4.8). Ticagrelor should be used with caution in patients with 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.

Central Sleep Apnoea

Central sleep apnoea including Cheyne-Stokes respiration has been reported in the postmarketing 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 aspirin dose and relative efficacy of ticagrelor compared to clopidogrel, co-administration of ticagrelor and high maintenance dose aspirin (>300 mg) is not recommended (see section 5.1).

Discontinuation

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 4.2).

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

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 medicinal products on BRILINTA

Medicinal products metabolised by CYP3A4

Ketaconazole (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, nefazodone, ritonavir and atazanavir) would be expected to have similar effects and therefore concomitant use with BRILINTA is contraindicated (see section 4.3).

Diltiazem (Moderate CYP3A4 inhibitors)

Co-administration of diltiazem and ticagrelor 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 and fluconazole) would be expected to have a similar effect and can as well be co-administered with BRILINTA.

Rifampicin and Other CYP3A Inducers

Co-administration of rifampicin 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 BRILINTA as well. Co-administration of ticagrelor with potent CYP3A inducers may decrease exposure and efficacy of ticagrelor therefore their concomitant use with BRILINTA is discouraged.

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.

Others

Clinical pharmacology interaction studies showed that co-administration of ticagrelor with heparin, enoxaparin, and aspirin 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.

No data are available on concomitant use of BRILINTA with other medicines 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.

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 medicinal products

<u>Medicinal products metabolised by CYP3A4</u>

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. Co-administration of ticagrelor with doses of simvastatin exceeding 40 mg daily could cause adverse effects of simvastatin and should be weighed against potential benefits. 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. The concomitant use of ticagrelor with doses of simvastatin or lovastatin greater than 40 mg is not recommended.

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.

A similar effect on other statins metabolised by CYP3A4 cannot be excluded. Patients in PLATO receiving ticagrelor took a variety of statins, with no concern of an association with statin safety among the 93% of the PLATO cohort taking these medicinal products.

Other

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

Medicinal products metabolised by CYP2C9 - Tolbutamide

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

Oral contraceptives

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

Digoxin (P-gp substrate)

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. Therefore, appropriate clinical and/or laboratory monitoring is recommended when giving narrow therapeutic index P-gp dependent medicinal products like digoxin concomitantly with ticagrelor.

Medicinal products known to induce bradycardia

Due to observations of mostly asymptomatic ventricular pauses and bradycardia, caution should be exercised when administering BRILINTA concomitantly with medicinal products known to induce bradycardia (see section 4.4). However no evidence of clinically significant adverse reactions was observed in the PLATO trial after concomitant administration with one or more medicinal products known to induce bradycardia (e.g. 96% beta blockers, 33% calcium channel blockers diltiazem and verapamil and 4% digoxin).

Rosuvastatin (BCRP substrate)

Ticagrelor has been shown to increase rosuvastatin concentrations, which may result in increased risk of myopathy. Consideration should be given to the benefits of prevention of major adverse cardiovascular events by use of rosuvastatin and the risks with increased rosuvastatin plasma concentrations.

Other concomitant therapy

In clinical studies, BRILINTA was commonly administered with aspirin, proton pump inhibitors, statins, beta-blockers, angiotensin converting enzyme inhibitors and angiotensin receptor blockers as needed for concomitant conditions for long-term and also heparin, low molecular weight heparin and intravenous GpIIb/IIIa inhibitors for short durations (see section 5.1). No evidence of clinically significant adverse interactions with these medicinal products was observed.

Co-administration of ticagrelor with heparin, enoxaparin or desmopressin had no effect on activated partial thromboplastin time (aPTT), activated coagulation time (ACT) or factor Xa assays. However, due to potential pharmacodynamic interactions, caution should be exercised with the concomitant administration of BRILINTA with medicinal products known to alter haemostasis.

Due to reports of cutaneous bleeding abnormalities with SSRIs (e.g. paroxetine, sertraline and citalopram), caution is advised when administering SSRIs with ticagrelor as this may increase the risk of bleeding.

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy

Women of childbearing potential

Women of childbearing potential should use appropriate contraceptive measures to avoid pregnancy during BRILINTA therapy.

Pregnancy

There are no or limited amount of data from the use of ticagrelor in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). BRILINTA is not recommended during pregnancy.

Breastfeeding

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

Fertility

BRILINTA had no effect on male or female fertility in animals (see section 5.3).

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 5.1). 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 acetylsalicylic acid (aspirin) 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 aspirin to aspirin 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 aspirin therapy alone (16.1% for ticagrelor 60 mg with aspirin vs. 8.5% for aspirin therapy alone).

The most commonly reported adverse drug reactions in patients treated with ticagrelor were bleeding and dyspnoea (also see section 4.4).

Tabulated summary of adverse drug reactions

Adverse drug reactions from the PLATO and PEGASUS clinical studies with BRILINTA (Table 1) are listed by MedDRA System Organ Class (SOC) and frequency category. 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 1 Adverse Drug reactions observed in PLATO and PEGASUS phase 3 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
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		Gastrointestinal haemorrhage[f] , Diarrhoea, Nausea	Retroperitoneal haemorrhage
Skin and subcutaneous tissue disorders		Subcutaneous or dermal bleeding[g], Pruritus	

System Organ Classification	Very Common	Common	Uncommon
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.

Description of selected adverse drug reactions

Bleeding findings in PLATO

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

Table 2 –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** 75mg 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 90mg twice daily and 23 (0.3%) for clopidogrel 75mg 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 coronary artery bypass graft (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 4.4).

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 bleeds, more bleeding occurred with ticagrelor than with clopidogrel (Table 2). 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 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 one 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 3.

Table 3 Analysis of Overall Bleeding Events, Kaplan-Meier estimate of bleeding rates by treatment at 36 months (PEGASUS)

Safety Endpoints	BRILINTA 60 mg twice daily with Aspirin N=6958		Aspirin alone N=6996	*p*-value
	KM%	Hazard Ratio (95% CI)	KM%	
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 aspirin alone. No increased bleeding risk was seen for fatal bleeding and only a minor increase was observed in intracranial haemorrhages, as compared to aspirin therapy alone. There were few fatal bleeding events in the study, 11 (0.3%) for BRILINTA 60 mg and 12 (0.3%) for aspirin 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 3). Discontinuation of treatment due to bleeding was more common with BRILINTA 60 mg compared to aspirin 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 aspirin 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 aspirin therapy alone (n=10, 0.1%). There were 6 fatal ICHs with BRILINTA 60 mg and 5 fatal ICHs with aspirin 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% in 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 4.4).

In PEGASUS, dyspnoea was reported in 14.2% of patients taking BRILINTA 60 mg twice daily and in 5.5% of patients taking aspirin alone. As in PLATO, most reported dyspnoea was mild to moderate in intensity (see section 4.4).

Post-marketing 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 4.3)

Skin and subcutaneous tissue disorders: Rash

Blood disorders: Thrombotic Thrombocytopenic Purpura (see section 4.4)

Cardiac disorders: Bradyarrhythmia, AV block (see section 4.4)

Nervous system disorders: Central sleep apnoea including Cheyne-Stokes respiration (see section 4.4)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via https://pophealth.my.site.com/carmreportnz/s.

4.9 OVERDOSE

There is currently no known antidote to reverse the effects of ticagrelor, and ticagrelor is not dialysable (see section 5.2). 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. Gastrointestinal 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 (see section 4.8).

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

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Platelet aggregation inhibitors excluding heparin, ATC code: B01AC24

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 CV 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. Ticagrelor has no clinically significant direct effect on adenosine receptors (A_1, A_{2A}, A_{2B}, A_3) and is not metabolised to adenosine. Adenosine has been documented to have a number of effects that include: vasodilation, cardioprotection, platelet inhibition, modulation of inflammation and induction of dyspnoea, which may contribute to the clinical profile of ticagrelor.

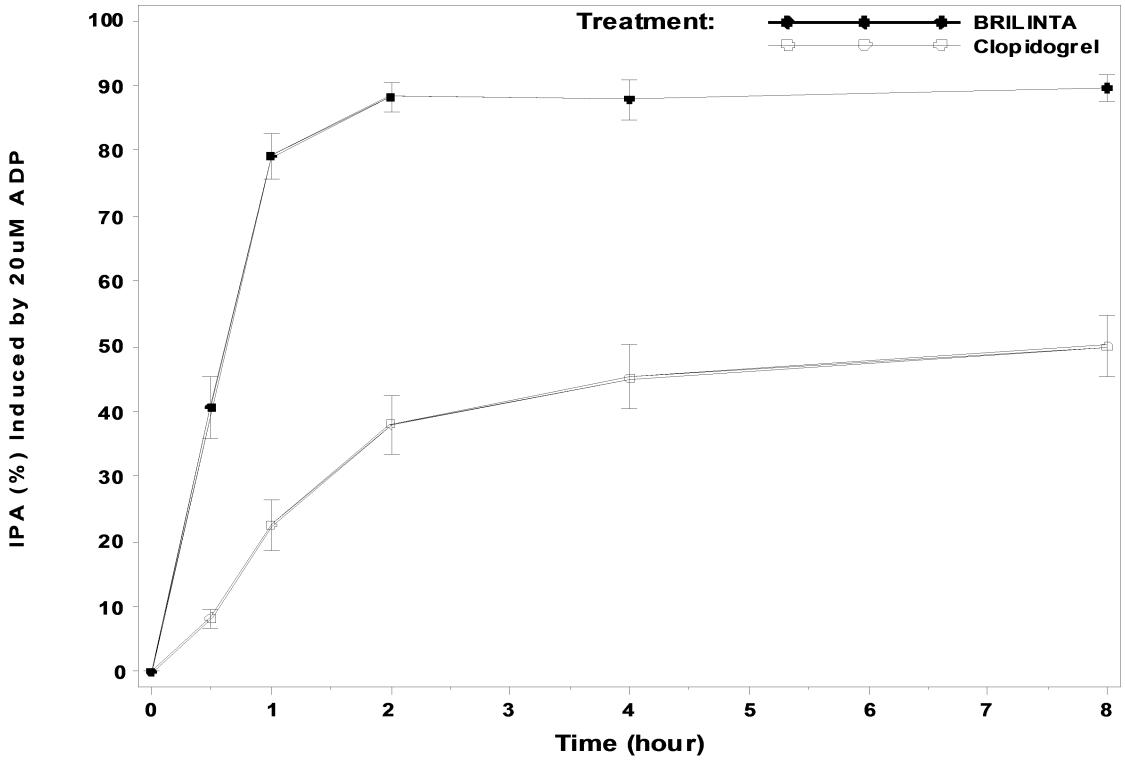
Pharmacodynamic effects

Onset of Action

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 aspirin. The onset was evaluated following a loading dose of 180 mg ticagrelor or 600 mg clopidogrel.

Ticagrelor demonstrates a rapid onset of pharmacological effect as demonstrated by a mean IPA for ticagrelor 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 ticagrelor between 87%-89% was maintained between 2-8 hours.

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



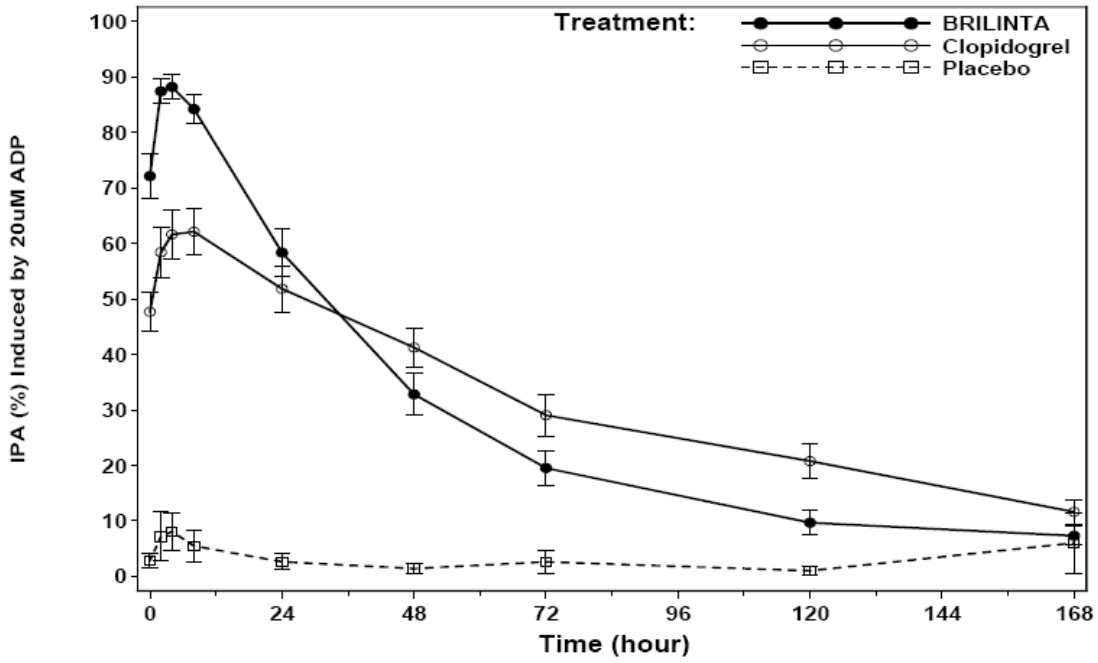
Offset of Effect

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 4.4).

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.

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%

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 aspirin, 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 anti-platelet effect (see section 4.2).

Adenosine mechanism (ENT-1)

Ticagrelor increased plasma adenosine concentrations in ACS patients and has been shown to augment several physiological responses to adenosine. Adenosine is a vasodilator; ticagrelor has been shown to augment adenosine-induced coronary blood flow increases in healthy volunteers and ACS patients. Adenosine is an endogenous platelet inhibitor;

ticagrelor has been shown to augment adenosine-mediated inhibition of platelet aggregation in addition to platelet inhibition due to its $P2Y_{12}$ antagonism. Adenosine has been linked to the cardio-protective effect of preconditioning; ticagrelor has been shown to reduce infarct size via an adenosine-mediated mechanism in a rat model of reperfusion injury. Adenosine also induces dyspnoea; ticagrelor has been shown to augment adenosine-induced dyspnoea in healthy volunteers. Thus, the dyspnoea observed in some patients taking ticagrelor (see section 4.8) may partly be mediated by adenosine.

Clinical efficacy and safety

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

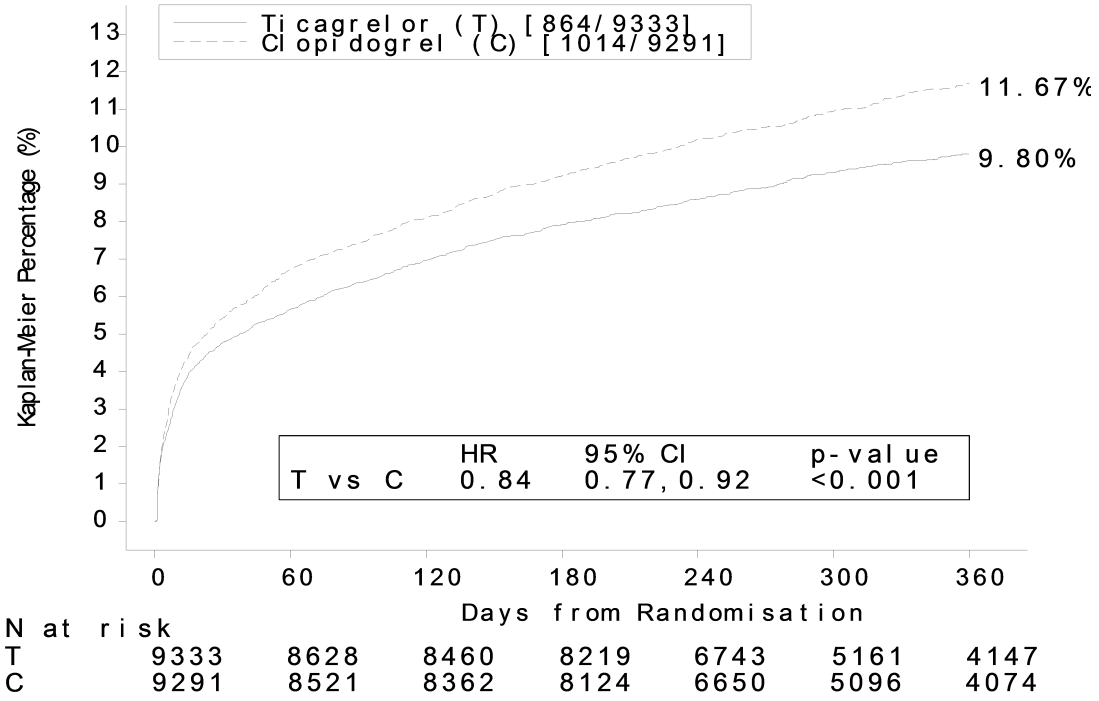
- The PLATO [PLATelet Inhibition and Patient Outcomes] study, a comparison of BRILINTA to clopidogrel, both given in combination with aspirin and other standard therapy.
- The PEGASUS TIMI-54 [PrEvention with TicaGrelor of SecondAry Thrombotic Events in High-RiSk AcUte Coronary Syndrome Patients] study,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

Primary Endpoint	Patients with Events				
	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)[a]	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[a]	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	13.8	15.7	12	0.88(0.81,0.95)	*p*=0.0006

Death/Total MI/Stroke/SRI[b]/RI[c]/TIA[d]/ Other ATE[e]					
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
**nominal *p*-value.
[b]SRI = Severe Recurrent Cardiac Ischaemia.
[c]RI = Recurrent Cardiac Ischaemia.
[d]TIA = Transient Ischemic Attack.
[e]ATE = Arterial Thrombotic events.

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 4.2).

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).

A weakly significant treatment interaction was observed with region whereby the hazard ratio 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 aspirin dose during maintenance therapy. The data show greater efficacy of ticagrelor compared to clopidogrel when used in conjunction with low maintenance dose aspirin (75-150 mg). The relative efficacy of ticagrelor versus clopidogrel when used with high doses of aspirin (>300 mg) is less certain. Based on this observed relationship between maintenance aspirin dose and relative efficacy of ticagrelor compared to clopidogrel, it is recommended that BRILINTA is used with a low maintenance dose of aspirin 75-150 mg (see sections 4.2 and 4.4).

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 4.5).

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 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 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 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 (see section 4.4). The increase in ventricular pauses in the acute phase of ACS was more pronounced in ticagrelor patients with history of 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 ticagrelor 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.

PLATO 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 CV 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 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 aspirin (75-150 mg daily) compared to aspirin therapy alone (75-150 mg daily) in patients with history of MI and additional risk factors for atherothrombosis.

Risk Factors

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
- 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)

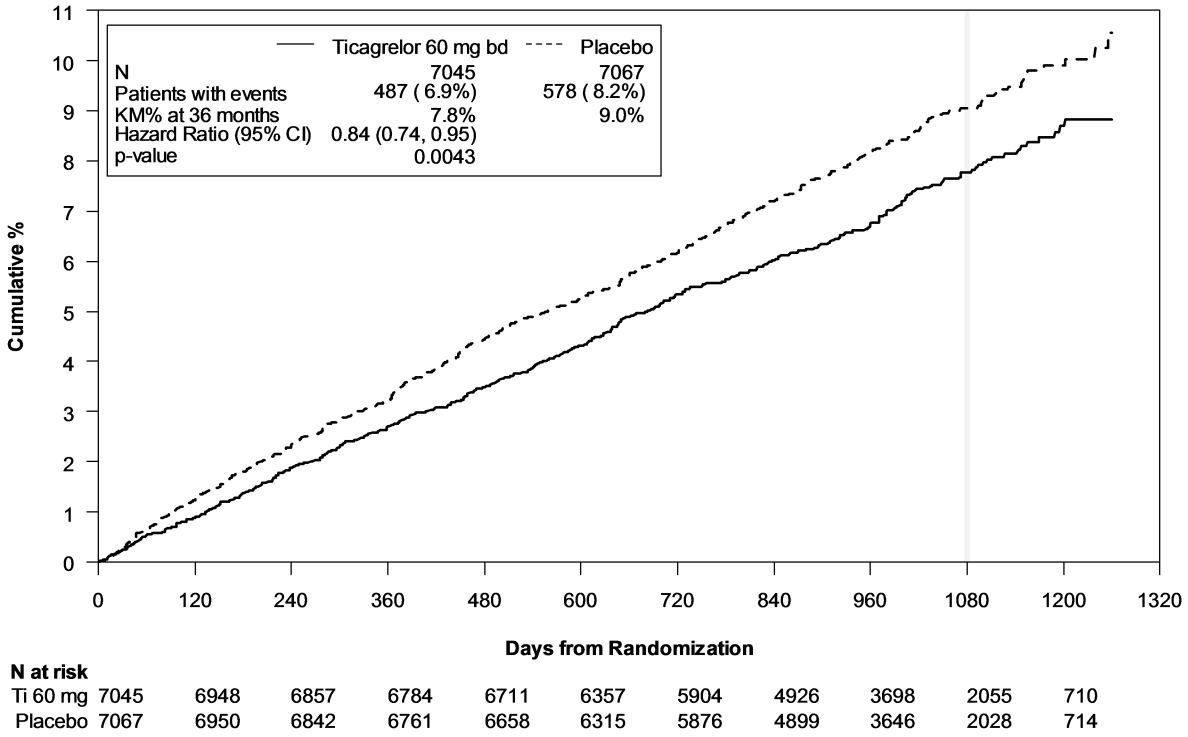


Table 5 Analysis of primary and secondary efficacy endpoints in PEGASUS (full analysis set)

	BRILINTA 60 mg twice daily+ Aspirin N = 7045			Aspirin 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. aspirin 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 aspirin, were superior to aspirin 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 aspirin 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 aspirin 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).

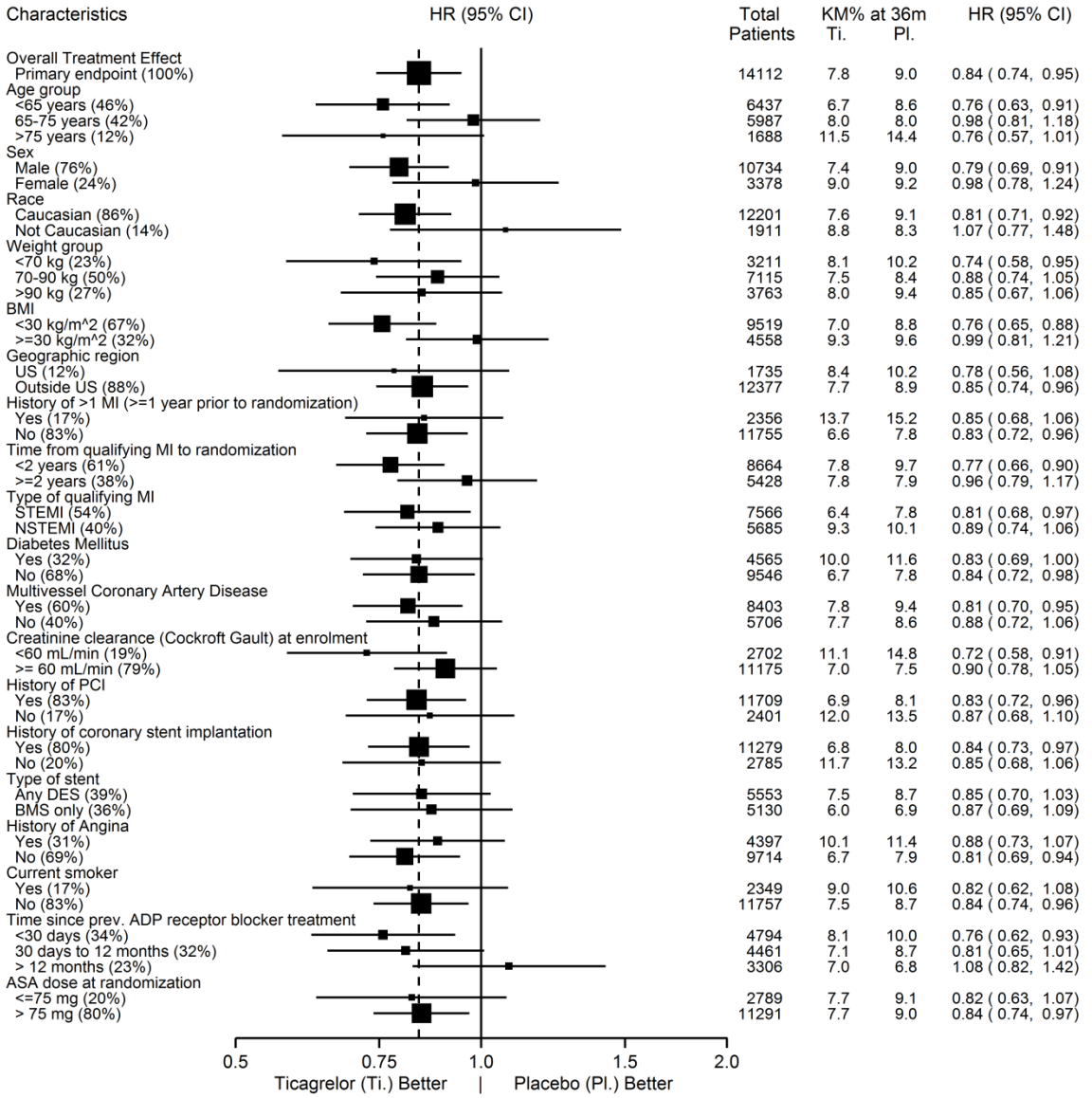
Treating 79 patients for up to 36 months with BRILINTA 60 mg twice daily in combination with aspirin instead of aspirin therapy alone will prevent one primary composite endpoint event.

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 aspirin compared to aspirin 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 48 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 4.2).

The treatment effect of BRILINTA 60 mg twice daily over aspirin 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 Stoke by patient subgroup in PEGASUS (full analysis set)



The treatment effect of BRILINTA 60 mg twice daily over aspirin 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 4.5).

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

Ticagrelor demonstrates linear pharmacokinetics and exposure to ticagrelor and the active metabolite (AR-C124910XX) are approximately dose proportional up to 1260 mg.

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. Following oral administration of ticagrelor 90 mg under fasted conditions, C_{max} is 529 ng/ml and AUC is 3451 ng*h/ml. The metabolite parent ratios are 0.28 for C_{max} and 0.42 for AUC.

The mean absolute bioavailability of ticagrelor was estimated to be 36% (range 25.4% to 64.0%). Ingestion of a high-fat meal resulted in a 21% increase in ticagrelor AUC and 22% decrease in the active metabolite C_{max} but had no effect on ticagrelor C_{max} or the AUC of the active metabolite. These small changes are considered of minimal clinical significance; therefore, ticagrelor 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 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 weak P-glycoprotein inhibitors. Ticagrelor is a BCRP inhibitor.

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 radiolabeled 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.

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 (see section 4.2).

Paediatric

BRILINTA is not indicated in a paediatric population (see section 4.2 and 5.1).

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.

Renal impairment

Exposure to ticagrelor was approximately 20% lower and exposure to the active metabolite was approximately 17% higher in patients with severe renal impairment compared to subjects with normal renal function. The IPA effect of 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 ticagrelor 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. Ticagrelor has not been studied in patients with severe hepatic impairment and there is no pharmacokinetic information in patients with moderate hepatic impairment (see section 4.2, 4.3 and 4.4).

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 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. The exposure in patients self-identified as Hispanic or Latino was similar to that in Caucasians.

5.3 PRECLINICAL SAFETY DATA

Preclinical data for ticagrelor and its 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

60 mg film coated tablet

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

Coating

Titanium dioxide (E171)
Ferric oxide black (E172)
Ferric oxide red (E172)
Polyethylene glycol 400
Hypromellose

90 mg film coated tablet

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 (E464)

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

3 years.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

PVC-PVDC/Al transparent calendar blister (with sun/moon symbols) of 14 tablets; cartons of 14 tablets (1 blister) and 56 tablets (4 blisters).

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Return unused and expired medicines to your local pharmacy for disposal.

7 MEDICINE SCHEDULE

Prescription Medicine.

8. SPONSOR

AstraZeneca Limited
PO Box 87453
Meadowbank
Auckland 1742.
Telephone: 0800 684 432

9. DATE OF FIRST APPROVAL

BRILINTA 60 mg: 18 November 2016
BRILINTA 90 mg: 18 August 2011

10. DATE OF REVISION OF THE TEXT

20 March 2024

VV-RIM-01434149 v9.0

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.5 & 5.2	Additional information is added regarding the interaction with rosuvastatin.