

NEW ZEALAND DATA SHEET

1. NAME OF MEDICINE

BRILINTA™
90 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 90 mg ticagrelor.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet). Round, biconvex, yellow tablets marked with '90' above 'T' on one side and plain on the other.

4. CLINICAL PARTICULARS

4.1 INDICATIONS

BRILINTA, co-administered with acetylsalicylic acid (aspirin), is indicated for the prevention of atherothrombotic events in adult patients with Acute Coronary Syndromes (unstable angina, non ST elevation Myocardial Infarction [NSTEMI] or ST elevation Myocardial Infarction [STEMI]); including patients managed medically, and those who are managed with percutaneous coronary intervention (PCI) or coronary artery by-pass grafting (CABG).

For further information, please refer to section 5.1.

4.2 DOSAGE AND ADMINISTRATION

Dosage

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.

Patients taking BRILINTA should also take aspirin daily, unless specifically contraindicated. Following an initial dose of aspirin, BRILINTA should be used with a maintenance dose of aspirin of 75-150 mg (see section 5.1).

Treatment is recommended for up to 12 months unless discontinuation of BRILINTA is clinically indicated (see section 5.1). Experience beyond 12 months is limited.

In patients with Acute Coronary Syndromes (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 (see section 4.4). Therefore premature discontinuation of treatment should be avoided.

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

Patients treated with clopidogrel can be directly switched to BRILINTA if needed (see section 5.1). Switching from prasugrel to BRILINTA has not been investigated.

Special populations

Elderly population

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

Renal impairment

No dose adjustment is necessary for patients with renal impairment (see section 5.2). No information is available concerning treatment of patients on renal dialysis and therefore BRILINTA is not recommended in these patients.

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. Its use in patients with moderate to 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 in the approved adult indication has not been established. No data are available (see section 5.1 and 5.2).

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 (90 mg and 2x90 mg) 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.

4.3 CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients (see section 4.8).
- Active pathological bleeding
- History of intracranial haemorrhage (see section 4.8)
- Moderate to severe hepatic impairment (see section 4.3, 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 section 4.4 and 4.5).

4.4 WARNINGS AND PRECAUTIONS

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 + 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). 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 (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.

No data exist with BRILINTA regarding a haemostatic benefit of platelet transfusions; circulating BRILINTA may inhibit transfused platelets. Since co-administration of BRILINTA with desmopressin did not decrease template-bleeding time, desmopressin is unlikely to be effective in managing clinical bleeding events (see section 4.5).

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

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 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 PLATO study evaluating the safety and efficacy of BRILINTA. Therefore, due to the limited clinical experience, BRILINTA should be used with caution in these patients (see section 5.1).

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 ≥ 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 was reported by 13.8% of patients treated with BRILINTA and by 7.8% of patients treated with clopidogrel. In 2.2% of patients, investigators considered the dyspnoea causally related to treatment with BRILINTA. It is usually mild to moderate in intensity and often resolves without need for treatment discontinuation. 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.

Creatinine elevations

Creatinine levels may increase during treatment with BRILINTA (see section 4.8). 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, patients with moderate/severe renal impairment and those receiving concomitant treatment with an ARB.

Uric acid increase

In the PLATO study, patients on ticagrelor had a higher risk of hyperuricaemia than those patients receiving clopidogrel (see section 4.8). 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 a relationship observed in PLATO between maintenance aspirin dose and relative efficacy of ticagrelor compared to clopidogrel, co-administration of BRILINTA and high maintenance dose aspirin (>300 mg) is not recommended (see section 5.1).

Co-administration of BRILINTA with strong CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin, nefazodone, ritonavir and atazanavir) is contraindicated (see section 4.3 and 4.5). Co-administration may lead to a substantial increase in BRILINTA exposure (see section 4.5).

Co-administration of ticagrelor with strong CYP3A4 inducers (e.g. rifampicin, phenytoin, carbamazepine and phenobarbital) is discouraged, as co-administration may lead to a decrease in exposure and efficacy of ticagrelor (see section 4.5).

Co-administration of BRILINTA and CYP3A4 substrates with narrow therapeutic indices (i.e., cisapride and ergot alkaloids) is not recommended, as ticagrelor may increase the exposure to these medicinal products (see section 4.5). The concomitant use of BRILINTA with doses of simvastatin or lovastatin greater than 40 mg is not recommended (see section 4.5).

Close clinical and laboratory monitoring is recommended when giving digoxin concomitantly with BRILINTA (see section 4.5).

No data are available on concomitant use of BRILINTA with potent P-glycoprotein (P-gp) inhibitors (e.g. verapamil, quinidine, cyclosporin) that may increase ticagrelor exposure. If the association cannot be avoided, their concomitant use should be made with caution (see section 4.5).

4.5 INTERACTIONS

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

CYP3A4 inhibitors

- 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 their concomitant use with BRILINTA is contraindicated (see section 4.3 and 4.4).
- Moderate CYP3A4 inhibitors – Co-administration of diltiazem with ticagrelor increased the ticagrelor C_{max} by 69% and AUC to 2.7 fold 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.

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 CYP3A 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 (see section 4.4).

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 or desmopressin did not have any effect on the pharmacokinetics of ticagrelor or the active metabolite or on ADP-induced platelet aggregation compared with ticagrelor alone. If clinically indicated, medicinal products that

alter haemostasis should be used with caution in combination with BRILINTA (see section 4.4).

No data are available on concomitant use of BRILINTA with potent P-gp inhibitors (e.g. verapamil, quinidine, cyclosporin) that may increase ticagrelor exposure. If clinically indicated, their concomitant use should be made with caution (see section 4.4).

Effects of BRILINTA on other medicinal products

Medicinal products metabolised by CYP3A4

- *Simvastatin* – Co-administration of ticagrelor with simvastatin increased simvastatin C_{max} by 81% and AUC by 56% and increased simvastatin acid C_{max} by 64% and AUC by 52% with some individual increases equal to 2 to 3 fold. 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. The concomitant use of BRILINTA with doses of simvastatin or lovastatin greater than 40 mg is not recommended (see section 4.4).
- *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.

Ticagrelor is a mild CYP3A4 inhibitor. Co-administration of BRILINTA 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 (see section 4.4).

Medicinal products metabolised by CYP2C9

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

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

Concomitant administration of BRILINTA 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 or cyclosporin concomitantly with BRILINTA (see section 4.4).

Other concomitant therapy

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).

In the PLATO study, 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 BRILINTA 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 (see section 4.4).

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

4.6 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

Available pharmacodynamic/toxicological data in animals have shown excretion of ticagrelor and its active metabolites in milk (see section 5.3). A risk to newborns/infants cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from BRILINTA therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Fertility

Ticagrelor 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 has no or negligible influence on the ability to drive and use machines.

4.8 ADVERSE EFFECTS

Summary of safety profile

The safety of BRILINTA in patients with acute coronary syndromes (UA, NSTEMI and STEMI) was evaluated in the pivotal large phase 3 PLATO ([PLA]Telet Inhibition and Patient Outcomes] study, 18,624 patients), which compared patients treated with BRILINTA (loading dose of 180 mg of BRILINTA and a maintenance dose of 90 mg twice daily) to patients treated with clopidogrel (300-600 mg loading dose followed by 75 mg once daily maintenance dose) both given in combination with acetylsalicylic acid (aspirin) and other standard therapies.

The most commonly reported adverse reactions in patients treated with ticagrelor were dyspnoea, contusion and epistaxis and these reactions occurred at higher rates than in the clopidogrel treatment group.

Tabulated summary of adverse reactions

The following adverse reactions have been identified following studies with BRILINTA (Table 1).

Adverse reactions are classified according to frequency and System Organ Class. Frequency categories are defined according to the following conventions: Very common ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1,000$ to $< 1/100$), Rare ($\geq 1/10,000$ to $< 1/1,000$), Very rare ($< 1/10,000$), Not known (cannot be estimated from the available data)

Table 1 Adverse reactions by frequency and System Organ Class (SOC)				
System Class	Organ	Common	Uncommon	Rare
<i>Metabolism and nutrition disorders</i>				Hyperuricaemia ^a
<i>Psychiatric disorders</i>				Confusion
<i>Nervous system disorders</i>			Intracranial haemorrhage ^b , Dizziness, Headache	Paraesthesia
<i>Eye disorders</i>			Eye haemorrhage (intraocular, conjunctival, retinal)	
<i>Ear and labyrinth disorders</i>				Ear haemorrhage, Vertigo
<i>Respiratory, thoracic and mediastinal disorders</i>		Dyspnoea ^c , Epistaxis	Haemoptysis	

Table 1 Adverse reactions by frequency and System Organ Class (SOC)				
System Class	Organ	Common	Uncommon	Rare
<i>Gastrointestinal disorders</i>		Gastrointestinal haemorrhage ^d	Haematemesis, Gastrointestinal ulcer haemorrhage ^e , Haemorrhoidal haemorrhage, Gastritis, Oral haemorrhage (including gingival bleeding), Vomiting, Diarrhoea, Abdominal pain, Nausea, Dyspepsia	Retroperitoneal haemorrhage, Constipation
<i>Skin and subcutaneous tissue disorders</i>		Subcutaneous or dermal bleeding ^f , Bruising ^g	Rash, Pruritus	
<i>Musculoskeletal and connective tissue disorders</i>				Haemarthrosis [#]
<i>Renal and urinary disorders</i>			Haemorrhage urinary tract ^h	
<i>Reproductive system and breast disorders</i>			Vaginal bleeding (including metrorrhagia)	
<i>Investigations</i>				Blood creatinine increased
<i>Injury, poisoning and procedural complications</i>		Procedural site haemorrhage ⁱ	Post procedural haemorrhage, Haemorrhage	Wound haemorrhage, Traumatic haemorrhage

Multiple related adverse reaction terms have been grouped together in the table and include medical terms as described below:

^a Hyperuricaemia, Blood uric acid increased

^b Cerebral haemorrhage, Haemorrhage intracranial, Haemorrhagic stroke,

^c Dyspnoea, Dyspnoea exertional, Dyspnoea at rest, Nocturnal dyspnoea

^d Gastrointestinal haemorrhage, Rectal haemorrhage, Intestinal haemorrhage, Melaena, Occult blood

^e Gastrointestinal ulcer haemorrhage, Gastric ulcer haemorrhage, Duodenal ulcer haemorrhage, Peptic ulcer haemorrhage

^f Subcutaneous haematoma, Skin haemorrhage, Haemorrhage subcutaneous, Petechiae

^g Contusion, Haematoma, Ecchymosis, Increased tendency to bruise, Traumatic haematoma

^h Haematuria, Blood urine present, Haemorrhage urinary tract

ⁱ Vessel puncture site haemorrhage, Vessel puncture site haematoma, Injection site haemorrhage, Puncture site haemorrhage, Catheter site haemorrhage

[#] There were no reported ADRs of haemarthrosis reported in the ticagrelor arm (n=9235) of the PLATO study, the frequency has been calculated using the upper limit of the 95% confidence interval for the point estimate (based on 3/X, where X represents the total sample size e.g. 9235). This is calculated as 3/9235 which equates to a frequency category of 'rare'

Description of selected adverse reactions

Bleeding

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

Table 2 –Kaplan-Meier estimate of bleeding rates by treatment

	BRILINTA (%/year) N=9235	Clopidogrel (%/year) N=9186	P
PLATO Total Major	11.6	11.2	0.4336
PLATO Major Fatal/Life-Threatening	5.8	5.8	0.6988
Non-CABG PLATO Major	4.5	3.8	0.0264
Non-Procedural PLATO Major	3.1	2.3	0.0058
PLATO Total Major + Minor	16.1	14.6	0.0084
Non-Procedural PLATO Major + Minor	5.9	4.3	<0.0001
TIMI-defined Major	7.9	7.7	0.5669
TIMI-defined Major + Minor	11.4	10.9	0.3272

Bleeding category definitions:

Major Fatal/Life-threatening Bleed: Clinically apparent with >50 g/l decrease in haemoglobin or ≥4 red cell units transfused; or fatal; or intracranial; or intrapericardial with cardiac tamponade; or with hypovolaemic shock or severe hypotension requiring pressors or surgery.

Major Other: Clinically apparent with 30-50 g/l decrease in haemoglobin or 2-3 red cell units transfused; or significantly disabling.

Minor Bleed: Requires medical intervention to stop or treat bleeding.

TIMI Major Bleed: Clinically apparent with >50 g/l decrease in haemoglobin or intracranial haemorrhage.

TIMI Minor Bleed: Clinically apparent with 30-50 g/l decrease in haemoglobin.

BRILINTA and clopidogrel did not differ in rates of PLATO Major Fatal/Life-threatening bleeding, PLATO total Major bleeding, TIMI Major bleeding, or TIMI Minor bleeding (Table 2). However, more PLATO combined Major + Minor bleeding occurred with ticagrelor compared with clopidogrel. Few patients in PLATO had fatal bleeds: 20 (0.2%) for ticagrelor and 23 (0.3%) for clopidogrel (see section 4.4).

Age, sex, weight, race, 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 Major bleeding. Thus no particular group was identified at risk for any subset of bleeding.

CABG-related bleeding: In PLATO, 42% of the 1584 patients (12% of cohort) who underwent coronary artery bypass graft (CABG) surgery had a PLATO Major Fatal/Life-threatening bleeding with no difference between 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).

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.

Dyspnoea

Dyspnoea, a sensation of breathlessness, is reported by patients treated with BRILINTA. Dyspnoea adverse reactions (ADRs) (dyspnoea, dyspnoea at rest, dyspnoea exertional,

dyspnoea paroxysmal nocturnal and nocturnal dyspnoea), when combined, was reported by 13.8% of patients treated with ticagrelor and by 7.8% of patients treated with clopidogrel. In 2.2% of patients taking ticagrelor and by 0.6% taking clopidogrel investigators considered the dyspnoea causally related to treatment in the PLATO study and few were serious (0.14% ticagrelor; 0.02% clopidogrel), (see section 4.4). Most reported symptoms of dyspnoea were mild to moderate in intensity, and most were reported as a single episode early after starting treatment.

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). In absolute terms, this risk was higher than in the overall PLATO population. Ticagrelor should be used with caution in patients with history of asthma and/or COPD (see section 4.4).

About 30% of episodes resolved within 7 days. PLATO included patients with baseline congestive heart failure, chronic obstructive pulmonary disease, or asthma; these patients, and the elderly, were more likely to report dyspnoea. For BRILINTA, 0.9% of patients discontinued study drug because of dyspnoea compared with 0.1% taking clopidogrel. The higher incidence of dyspnoea with BRILINTA is not associated with new or worsening heart or lung disease (see section 4.4). BRILINTA does not affect tests of pulmonary function.

Investigations

Creatinine elevations: In PLATO, serum creatinine concentration significantly increased by >30% in 25.5% of patients receiving ticagrelor compared to 21.3% of patients receiving clopidogrel and by >50% in 8.3% of patients receiving ticagrelor compared to 6.7% of patients receiving clopidogrel. Creatinine elevations by >50% were more pronounced in patients > 75 years (ticagrelor 13.6% versus clopidogrel 8.8%), in patients with severe renal impairment at baseline (ticagrelor 17.8% versus clopidogrel 12.5%) and in patients receiving concomitant treatment with ARBs (ticagrelor 11.2% versus clopidogrel 7.1%). 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 ticagrelor 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 ticagrelor and 43 (0.5%) for clopidogrel.

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

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of BRILINTA. Because these reactions are reported voluntarily from a population of an unknown size, it is not always possible to reliably estimate their frequency.

Immune system disorders – Hypersensitivity reactions including angioedema (see section 4.3)

4.9 OVERDOSE

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 reactions 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

There is currently no known antidote to reverse the effects of BRILINTA, and BRILINTA is not expected to be dialysable (see section 4.4). 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.

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 P2Y₁₂ receptor antagonist that prevents adenosine diphosphate (ADP)-mediated P2Y₁₂ dependent platelet activation and aggregation. Ticagrelor does not prevent ADP binding but when bound to the P2Y₁₂ 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. Ticagrelor has no clinically significant direct effect on adenosine receptors (A₁, A_{2A}, A_{2B}, A₃) 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

In patients with stable coronary artery disease on aspirin, 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 180 mg loading dose of about 41%, with the maximum IPA effect of 89% by 2-4 hours post dose, and maintained between 2-8 hours. 90% of patients had final extent IPA >70% by 2 hours post dose.

Offset of Action

If a CABG procedure is planned, ticagrelor bleeding risk is increased compared to clopidogrel when discontinued within less than 96 hours prior to procedure.

Switching data

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 ticagrelor without any interruption of antiplatelet 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 P2Y₁₂ 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 ADVERSE EFFECTS) may partly or completely be mediated by adenosine.

Clinical efficacy and safety

The PLATO study included 18,624 patients who presented within 24 hours of onset of symptoms of unstable angina (UA), non ST elevation myocardial infarction (NSTEMI) or ST elevation myocardial infarction (STEMI), and were initially managed medically, or with percutaneous coronary intervention (PCI), or with coronary artery bypass grafting (CABG) (see section 4.1).

On a background of daily aspirin, ticagrelor 90 mg twice daily showed superiority to 75 mg daily clopidogrel in preventing the composite endpoint of cardiovascular [CV] death, myocardial infarction [MI], or stroke, with the difference driven by CV death and MI. Patients received a 300 mg loading dose of clopidogrel (600 mg possible if having PCI) or 180 mg of ticagrelor.

The result appeared early (absolute risk reduction [ARR] 0.6% and Relative Risk Reduction [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 patients with ticagrelor for up to 12 months (see section 4.2). Treating 54 ACS patients with ticagrelor instead of clopidogrel will prevent 1 atherothrombotic event; treating 91 will prevent 1 CV death (see Figure 1 and Table 3).

The treatment effect of ticagrelor over clopidogrel appears consistent across many subgroups, including weight; sex; medical history of diabetes mellitus, transient ischaemic attack or non-haemorrhagic stroke, or revascularisation; concomitant therapies including heparins, GpIIb/IIIa inhibitors and proton pump inhibitors (see section 4.5); final index event diagnosis (STEMI, NSTEMI, or UA); and treatment pathway intended at randomisation (invasive or medical).

A weakly significant treatment interaction was observed with region whereby the HR for the primary endpoint favours ticagrelor 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).

Exploratory analyses suggest a possible association with aspirin dose such that reduced efficacy was observed with ticagrelor with increasing aspirin doses. Chronic daily aspirin doses to accompany BRILINTA should be 75-150 mg (see section 4.2 and 4.4).

Figure 1 shows the estimate of the risk to the first occurrence of any event in the composite efficacy endpoint.

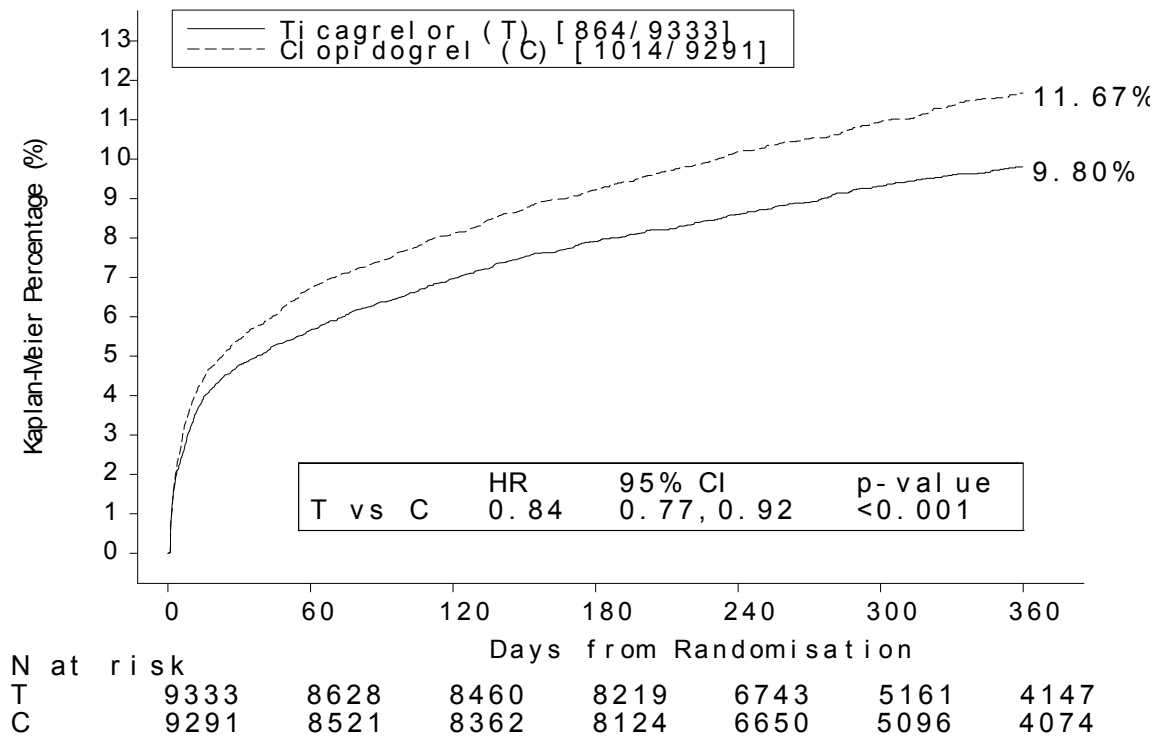


Figure 1 – Time to first occurrence of CV death, MI and Stroke (PLATO)

BRILINTA reduced the occurrence of the primary composite endpoint compared to clopidogrel in both the UA/NSTEMI and STEMI population (Table 3).

Table 3 -Outcome Events in PLATO

	BRILINTA (% patients with event) N=9333	Clopidogrel (% patients with event) N=9291	ARR^a (%/yr)	RRR^a (%) (95% CI)	P
CV death, MI (excl. silent MI) or stroke	9.3	10.9	1.9	16 (8, 23)	0.0003
Invasive intent	8.5	10.0	1.7	16 (6, 25)	0.0025
Medical intent	11.3	13.2	2.3	15 (0.3, 27)	0.0444 ^d
CV death	3.8	4.8	1.1	21 (9, 31)	0.0013
MI (excl. silent MI) ^b	5.4	6.4	1.1	16 (5, 25)	0.0045
Stroke	1.3	1.1	-0.2	-17 (-52, 9)	0.2249
All cause mortality, MI (excl. silent MI), or stroke	9.7	11.5	2.1	16 (8, 23)	0.0001
CV death, total MI, stroke, SRI, RI, TIA, or other ATE ^c	13.8	15.7	2.1	12 (5, 19)	0.0006
All-cause mortality	4.3	5.4	1.4	22 (11, 31)	0.0003 ^d
Definite stent thrombosis	1.2	1.7	0.6	32 (8, 49)	0.0123 ^d

^aARR = absolute risk reduction; RRR = relative risk reduction = (1-Hazard ratio) x 100%. A negative RRR indicates a relative risk increase.

^bexcluding silent myocardial infarction.

^cSRI = serious recurrent ischaemia; RI = recurrent ischaemia; TIA = transient ischaemic attack; ATE = arterial thrombotic event. Total MI includes silent MI, with date of event set to date when discovered.

^dnominal significance value; all others are formally statistically significant by pre-defined hierarchical testing.

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 ticagrelor (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

CYP2C19 and ABCB1 genotyping of 10,285 patients in PLATO provided associations of genotype groups with PLATO outcomes. 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 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.

Combined efficacy and safety composite

A combined efficacy and safety composite (CV death, MI, stroke, or PLATO-defined 'Total Major' bleeding) indicates that the benefit in efficacy of BRILINTA compared to clopidogrel is

not offset by the major bleeding events (ARR 1.4%, RRR 8%, HR 0.92; $p=0.0257$) over 12 months after ACS.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with BRILINTA in all subsets of the paediatric population in the granted indication (see section 4.2 and 5.2).

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%. 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).

Ticagrelor as well as the active metabolite are P-gp substrates.

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%).

Biotransformation

CYP3A4 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.

The major metabolite of ticagrelor is AR-C124910XX, which is also active as assessed by *in vitro* binding to the platelet P2Y₁₂ ADP-receptor. The systemic exposure to the active metabolite is approximately 30-40% of that obtained for ticagrelor.

Elimination

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 most likely via biliary secretion. The mean $t_{1/2}$ was approximately 7 hours for ticagrelor and 8.5 hours for the active metabolite.

Special populations

Elderly

Higher exposures to ticagrelor (approximately 25% for both C_{\max} and AUC) and the active metabolite were observed in elderly (≥ 75 years) ACS patients compared to younger patients by the population pharmacokinetic analysis. These differences are not considered clinically significant (see section 4.2).

Paediatric

Ticagrelor has not been evaluated in a paediatric population (see section 4.2 and 5.1).

Gender

Higher exposures to ticagrelor and the active metabolite 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 (creatinine clearance <30 ml/min) compared to subjects with normal renal function (see section 4.2).

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 (see section 4.2). Ticagrelor has not been studied in patients with moderate or severe hepatic impairment and its use in these patients is contraindicated (see section 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.

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.

Gastrointestinal irritation was observed in several animal species at clinical relevant exposure levels (see section 4.8).

In female rats, ticagrelor at high dose showed an increased incidence of uterine tumours (adenocarcinomas) and an increased incidence of hepatic adenomas. The mechanism for uterine tumours is likely hormonal imbalance which can lead to tumours in rats. The mechanism for the hepatic adenomas is likely due to a rodent-specific enzyme induction in the liver. Thus, the carcinogenicity findings are considered unlikely to be relevant for humans.

In rats minor developmental anomalies were seen at a maternal toxic dose (safety margin of 5.1). In rabbits a slight delay in hepatic maturity and skeletal development was seen in foetuses from dams at high dose without showing maternal toxicity (safety margin of 4.5).

Studies in rats and rabbits have shown reproductive toxicity, with slightly reduced maternal body weight gain and reduced neonatal viability and birth weight, with delayed growth.

Ticagrelor produced irregular cycles (mostly extended cycles) in female rats, but did not affect overall fertility in male and female rats. Pharmacokinetic studies performed with radio-labeled ticagrelor have shown that the parent compound and its metabolites are excreted in the milk of rats (see section 4.6).

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Core

Mannitol (E421)
Dibasic calcium phosphate
Magnesium stearate (E470b)
Sodium starch glycolate
Hydroxypropyl-cellulose (E463)

Coating

Talc
Titanium dioxide (E171)
Ferric oxide yellow (E172)
Polyethylene-glycol 400
Hypromellose (E464)

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE AND STORAGE CONDITION

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 MEDICINE CLASSIFICATION

Prescription Medicine.

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8. DATE OF PREPARATION

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CDS March 2014

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