PROFESSIONAL INFORMATION

SCHEDULING STATUS: S3

1 NAME OF THE MEDICINE

BRILINTA® 90 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 90 mg of ticagrelor.

Contains sugar: mannitol 126 mg.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated Tablets

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

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

BRILINTA is indicated for the prevention of thrombotic events (cardiovascular death, myocardial infarction and stroke) in patients with Acute Coronary Syndromes (ACS) (unstable angina, non-ST elevation Myocardial Infarction [NSTEMI] or ST elevation Myocardial Infarction [STEMI]) including patients managed medically, and those who are managed with percutaneous coronary intervention (PCI) or coronary artery by-pass grafting (CABG).

4.2 Posology and method of administration

BRILINTA treatment should be initiated with a single 180 mg loading dose (2 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.

Patients taking BRILINTA should also use 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 daily (see section 4.4 and 5.1).

Missed dose

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

Premature discontinuation

Premature discontinuation with any antiplatelet therapy, including BRILINTA, could result in an increased risk of cardiovascular (CV) death, MI or stroke due to the patient's underlying disease (see section 4.4).

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.

Medical practitioners who desire to switch patients with a prior ACS event from clopidogrel to BRILINTA should administer the first 90 mg dose of BRILINTA 24 hours following the last dose of clopidogrel. There is no data on switching patients from other ADP receptor inhibitors to BRILINTA.

Special populations

Paediatric patients:

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

Elderly patients:

No dose adjustment is required.

Patients with renal impairment:

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

Patients with hepatic impairment:

Although the delay in elimination of BRILINTA was statistically significant in patients with mild hepatic impairment (Child Pugh A), no dose adjustment is necessary in these patients. BRILINTA has not been studied in patients with severe hepatic impairment (see section 4.3, 4.4 and 5.2).

Administration

For oral use. BRILINTA can be taken with or without food.

For patients who are unable to swallow the tablet(s) whole, BRILINTA tablets (90 mg and 2 x 90 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 ticagrelor (BRILINTA) or any of its excipients listed in section 6.1.
- Active bleeding.
- Inherited bleeding disorders.
- Severe hepatic impairment.
- History of intracranial haemorrhage.
- Strong CYP3A4 inhibitors (such as ketoconazole, clarithromycin, itraconazole, ritonavir and atazanavir).
- CYP3A4 inducers (such as rifampicin, phenytoin, carbamazepine and phenobarbitone).

4.4 Special warnings and precautions for use

Bleeding risk:

The use of BRILINTA in patients at known increased risk for bleeding should be balanced against the benefit in terms of prevention of thrombotic events.

Consideration should be given to the following:

- Patients with a propensity to bleed (e.g., due to recent trauma, recent surgery, active or recent gastrointestinal bleeding or moderate hepatic impairment) or who are at increased risk of trauma. The use of BRILINTA is contraindicated in patients with active pathologic bleeding, inherited bleeding disorders and in those with a history of intracranial haemorrhage and severe hepatic impairment (see section 4.3).

- Concomitant administration of medicinal products that may increase the risk of bleeding including non-steroidal anti-inflammatory drugs (NSAIDs), oral anticoagulants and/or fibrinolytics within 24 hours of BRILINTA dosing.

- The safe co-administration of BRILINTA with warfarin has not been established.

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.

CABG-related bleeding: In the phase 3 study, 12 % underwent coronary artery bypass graft (CABG) surgery. 'Major Fatal/Life-threatening' bleeding occurred in approximately 42 % of patients and fatal CABG bleeding occurred in 6 patients.

Surgery:

- If a patient requires surgery, medical practitioners should consider each patient's clinical profile as well as the benefits and risks of continued antiplatelet therapy when determining when discontinuation of BRILINTA treatment should occur.

- In a clinical study, mean Inhibition of Platelet Aggregation (IPA) for BRILINTA at 24, 48, 72 and 120 hours post-dose was 58,4 %, 32,8 %, 19,5 % and 9,7 % respectively.

- **If a patient is to undergo elective surgery and antiplatelet effect is not desired, BRILINTA should be discontinued 5 days prior to surgery.**

- There are no data available in regard to major regional block techniques and neuraxial blocks. Caution is advised in patients with increased risk of bleeding such as those undergoing spinal anaesthesia, epidural anaesthesia and lumbar puncture.

- Neurological monitoring for neuraxial haematoma is recommended consistent with standard of care, during peri-operative and post- operative care.

- BRILINTA should be discontinued 5 days prior to surgery or for any procedure in which antiplatelet effect is not desired.

Patients at risk for bradyarrhythmia:

Holter ECG monitoring has shown an increased frequency of ventricular pauses during treatment with ticagrelor compared with clopidogrel. In phase 3 studies evaluating the safety and efficacy of BRILINTA, bradyarrhythmic events were reported in a similar frequency for ticagrelor and comparators (placebo, clopidogrel and ASA). Patients with an increased risk of bradycardic events (e.g., patients without a pacemaker who have sick sinus syndrome, 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 (see also 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 a Holter sub-study, 6 % of patients on BRILINTA developed ventricular pauses of $\geq$ 3 seconds.

Dyspnoea:

Dyspnoea commonly occurs in patients treated with BRILINTA and may resolve during continued BRILINTA treatment. The mechanism has not yet been elucidated but may be related to potentiation of

adenosine. If a patient develops new, prolonged or worsened dyspnoea during treatment with BRILINTA this should be investigated fully and if not tolerated, treatment with BRILINTA should be stopped (see section 4.8).

Central Sleep Apnoea

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

Thrombotic Thrombocytopenic Purpura (TTP):

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

Interference with laboratory tests:

Platelet function tests to diagnose Heparin-induced thrombocytopenia (HIT):

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

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

Other:

Based on a relationship observed in the PLATO Study between maintenance aspirin dose and relative efficacy of ticagrelor compared to clopidogrel, co-administration of BRILINTA and high maintenance dose of aspirin (300 mg) is not recommended (see section 4.2 and 5.1).

Co-administration of BRILINTA with strong CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin, ritonavir and atazanavir) should be avoided as co-administration may lead to a substantial increase in

exposure to BRILINTA (see section 4.3 and 4.5).

Co-administration of BRILINTA and simvastatin increased mean simvastatin C_{max} by 81 % and AUC by 56 % and increased simvastatin acid C_{max} by 64 % and AUC by 52 %, which may be associated with increased adverse events related to increased simvastatin exposure. The concomitant use of BRILINTA with doses of simvastatin or lovastatin > 40 mg is not recommended.

Concomitant administration of BRILINTA increased digoxin C_{max} by 75 % and AUC by 28 % (see section 4.5). Digoxin levels should be monitored in patients using BRILINTA and digoxin.

Discontinuations:

Patients who require discontinuation of BRILINTA are at increased risk for cardiac events or stroke. Premature discontinuation of treatment should be avoided. If BRILINTA must be temporarily stopped due to an adverse event(s), it should be re-initiated as soon as possible when the benefits outweigh the risks of the adverse event or when the adverse event has come to resolution (see section 4.2).

No data are available for treatment longer than 12 months.

4.5 Interaction with other medicines and other forms of interaction

Effects of other medicines on BRILINTA:

Medicinal products metabolised by CYP3A4:

Ketoconazole *(strong CYP3A4 inhibitors):*

Co-administration of ketoconazole with BRILINTA increased ticagrelor C_{max} and AUC equal to 2,4-fold and 7,3-fold, respectively. The C_{max} and AUC of the active metabolite were reduced by 89 % and 56 % respectively. Other strong inhibitors of CYP3A4 (clarithromycin, itraconazole, ritonavir and atazanavir) would be expected to have similar effects and should not be given concomitantly with BRILINTA (see section 4.3).

Diltiazem *(moderate CYP3A4 inhibitors):*

Co-administration of BRILINTA and diltiazem increased the C_{max} of ticagrelor by 69 % and AUC by 174 %

and decreased the active metabolite C_{max} by 38 % and AUC was unchanged. There was no effect of BRILINTA on diltiazem plasma levels. Other moderate CYP3A4 inhibitors (e.g., amprenavir, erythromycin, fluconazole and verapamil) may probably be co-administered with BRILINTA.

Rifampicin and other CYP3A4 inducers:

Co-administration of rifampicin with BRILINTA 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 phenobarbitone) would be expected to decrease the exposure to BRILINTA as well and may result in reduced efficacy of BRILINTA (see section 4.3).

Ciclosporin (P-gp and CYP3A inhibitor)

Co-administration of ciclosporin (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 ciclosporin. There was no effect of ticagrelor on ciclosporin blood levels.

Others:

Clinical pharmacology interaction studies showed that co-administration of BRILINTA with heparin, enoxaparin and aspirin did not have any effect on ticagrelor or the active metabolite plasma levels.

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 medicines:

Medicinal products metabolised by CYP3A4:

Simvastatin:

Co-administration of BRILINTA 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 2-3 fold. The concomitant use of BRILINTA with a dose of simvastatin or lovastatin > 40 mg is not recommended.

***Atorvastatin*:**

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

Medicinal products metabolised by CYP2C9:

Tolbutamide

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

Oral Contraceptives:

Co-administration of BRILINTA and levonorgestrel and ethinyl estradiol increased ethinyl estradiol 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 estradiol are co-administered with BRILINTA.

Digoxin (Pg-p substrate):

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy has not been established.

Breastfeeding

The use of BRILINTA during breastfeeding is not recommended.

4.7 Effects on ability to drive and use machines

No studies on the effects of BRILINTA on the ability to drive and use machines have been performed. During treatment for Acute Coronary Syndromes, dizziness and confusion have been reported. Therefore, patients who experience these symptoms should be cautious while driving or using machines.

4.8 Undesirable effects

a. **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.

The safety of BRILINTA in patients with acute coronary syndromes (unstable angina, NSTEMI and STEMI) was evaluated in the PLATO Study. Median treatment duration for BRILINTA was 277 days. BRILINTA had a 7,4 % incidence of discontinuation due to adverse events.

The most commonly reported adverse reactions in patients treated with BRILINTA were bleeding and dyspnoea.

b. **Tabulated summary of adverse reactions**

Adverse reactions are classified according to frequency and System Organ Class. Frequency categories are defined according to the following conventions: Very common (≥ 1/10), Common (≥ 1/100, < 1/10), Uncommon (≥ 1/1 000, < 1/100), Rare (≥ 1/10 000, < 1/1 000).

The following adverse reactions have been identified following studies with BRILINTA:

Table 1 – Adverse Reactions by System Organ Class (SOC) and by Adverse Event Frequency

System Organ Classification	Very Common	Common	Uncommon
Neoplasms benign, malignant and			Tumour

unspecified (including cysts and polyps)			bleeding[b]
Blood and lymphatic system disorders	Blood disorder bleeding[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 bleeding[e]	
Gastrointestinal disorders		Gastrointestinal haemorrhage[f] Diarrhoea, Nausea	Retroperitoneal haemorrhage
Skin and subcutaneous tissue disorders		Subcutaneous or dermal bleeding [g], pruritus	
Musculoskeletal and connective tissue disorders			Muscular bleeding[h]
Renal and urinary disorders		Urinary tract bleeding [i]	
Reproductive system and breast disorders			Reproductive system bleeding[j]
Investigations		Increased blood creatinine[a]	
Injury, poisoning and procedural		Post procedural	

complications		haemorrhage, Traumatic bleeding[k]	

[a] Frequencies derived from laboratory 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.

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.

Blood disorders: Thrombotic Thrombocytopenic Purpura (see section 4.4).

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

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

Skin and subcutaneous tissue disorders: Rash.

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

c. Description of selected adverse reactions

Bleeding:

The following bleeding definitions were used in the PLATO Study:

'Major Fatal/Life-threatening': fatal, or intracranial, or intrapericardial bleed with cardiac tamponade, or hypovolaemic shock or severe hypotension due to bleeding and requiring pressors or surgery, or clinically overt or apparent bleeding associated with a decrease in haemoglobin of more than 5 g/dL, or transfusion of 4 or more units (whole blood or packed red blood cells [PRBCs]) for bleeding.

'Major Other': Significantly disabling (e.g., intraocular with permanent vision loss) or clinically overt or apparent bleeding associated with a decrease in haemoglobin of 3-5 g/dL or transfusion of 2-3 units (whole blood or PRBCs) for bleeding.

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

Minimal bleeds included all other bleeds; these were collected but not adjudicated.

Bleeding events in PLATO were also mapped to the TIMI (Thrombolysis in Myocardial Infarction) scale. **TIMI Major** is defined as clinically overt bleeding associated with a fall in haemoglobin > 5 g/dL, or intracranial haemorrhage and **TIMI Minor** is defined as overt bleeding associated with a fall in haemoglobin of 2 g/dL but ≤ 5 g/dL.

Table 2 – Analysis of overall bleeding events

	BRILINTA **90 mg twice daily** **(%)** **N = 9 235**
Primary Safety Endpoint	

Total Major	11,6
Secondary Endpoints Fatal/Life-Threatening	5,8
Combined Total Major + Minor bleeding	16,1
Non-CABG Major	4,5
Non-Procedural Major	3,1
Non-Procedural Major + Minor	5,9
TIMI-defined bleeding categories	
TIMI-defined Major	7,9
TIMI-defined Major + Minor	11,4

There were few fatal bleeding events in the PLATO Study, 20 (0,2 %) for BRILINTA 90 mg twice daily.

CABG-related bleeding: In the PLATO study, 12 % underwent coronary artery bypass graft (CABG) surgery. 'Major Fatal/Life-threatening' bleeding occurred in approximately 42 % of patients and fatal CABG bleeding occurred in 6 patients.

Non-CABG related bleeding: When CABG bleeding is removed from the analysis (see Table 3 below), the absolute bleeding rates for all categories are lower.

Table 3 – Non-CABG Related PLATO-defined Major Bleeding Events and TIMI-defined Bleeding Events

	BRILINTA **(%)** **N = 9 235**
PLATO-defined bleeding categories	
Total Major Bleeding	4,5
Major Fatal/Life-Threatening	2,1
TIMI-defined bleeding categories	
TIMI-defined Major	2,8

TIMI-defined Major + Minor	4,5

Bleeding unrelated to any procedure: As shown in Table 2 study-defined 'Major' and 'Major + Minor' non-procedural bleeding was common with BRILINTA. Discontinuation of treatment due to non-procedural bleeding was 2,9 %.

'Major Fatal/Life-threatening' intracranial non-procedural bleeding events with BRILINTA occurred in 26 patients, of which 11 bleeding events were fatal.

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

Dyspnoea:

Dyspnoea commonly occurs during treatment with BRILINTA although its mechanism has not been elucidated. In PLATO dyspnoea adverse events were in 13,8 % of the patients taking BRILINTA 90 mg twice daily. Most reported dyspnoea adverse events were mild to moderate in intensity. Dyspnoea usually occurred in the initial phase of treatment and 87 % of patients who reported dyspnoea experienced a single episode without the need to discontinue treatment. Dyspnoea serious adverse events occurred in 0,7 % taking BRILINTA. Patients who had dyspnoea tended to be older and more frequently had dyspnoea, CHF, COPD or asthma at baseline. Clinical data do not suggest that the occurrence of dyspnoea with BRILINTA is due to new or worsening heart or lung disease (see section 4.4).

There was no indication of an adverse effect of BRILINTA on pulmonary function.

Laboratory abnormalities:

In the PLATO study, serum uric acid concentration increased to more than upper limit of normal in 22 % of patients receiving BRILINTA.

Mean serum uric acid concentration increased approximately 15 % with BRILINTA and reduced after treatment was stopped.

In the PLATO study, serum creatinine concentration increased by > 50 % in 8 % of patients receiving BRILINTA. The increases typically did not progress with ongoing treatment and often decreased with continued therapy. Signs of reversibility on discontinuation were observed even in those with the greatest on treatment increases.

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

There is no known antidote to reverse the effects of BRILINTA and BRILINTA is not dialysable (see section 5.2). Treatment of overdose should follow local standard medical practice. The expected effect of excessive BRILINTA dosing is increased bleeding risk associated with platelet inhibition. If bleeding occurs, appropriate supportive measures should be taken.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Ticagrelor is a member of the chemical class cyclopentyltriazolopyrimidines (CPTP), with selective and reversible binding to the $P2Y_{12}$ receptor antagonist that prevents adenosine disphosphate (ADP)-mediated $P2Y_{12}$ dependant platelet activation and aggregation. Ticagrelor does not prevent ADP binding but when bound to the $P2Y_{12}$ receptor prevents ADP-induced signal transduction.

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.

Onset of action:

In patients with stable coronary artery disease on aspirin (acetylsalicylic acid (ASA)), ticagrelor demonstrates a rapid onset of pharmacological effect as demonstrated by a mean Inhibition of Platelet Aggregation (IPA) for ticagrelor at 0,5 hours after 180 mg loading dose of about 41 %, with the maximum IPA effect of 87,9 %-89,6 % by 2-4 hours post dose. Ninety percent 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.

Offset of effect:

After the ticagrelor and the active metabolite concentrations decline to a level less than that required for receptor saturation, IPA gradually decreases with declining plasma concentrations. Since ticagrelor binds reversibly, the recovery of platelet function does not depend on replacement of platelets.

Adenosine mechanism (ENT-1):

Ticagrelor increased plasma adenosine concentrations in Acute Coronary Syndrome (ACS) patients and has been shown to augment several physiological responses to adenosine. Ticagrelor has been shown to augment adenosine-induced coronary blood flow increases in healthy volunteers and ACS patients. Ticagrelor has been shown to augment adenosine-mediated inhibition of platelet aggregation in addition to platelet inhibition due to its $P2Y_{12}$ antagonism. Ticagrelor has been shown to reduce infarct size via an adenosine-mediated mechanism in a rat model of reperfusion injury. 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 or completely be mediated by adenosine.

Summary of clinical studies:

Analyses suggested a possible association between aspirin dose and the primary efficacy results, such that reduced efficacy was observed with ticagrelor and increasing doses of aspirin. Interaction studies have been conducted with ticagrelor and aspirin and no effects were observed on ticagrelor pharmacokinetics or pharmacodynamics, measured as inhibition of platelet aggregation. Nonetheless, based on the possible association between aspirin dose and clinical efficacy, the range of recommended dose of chronic aspirin to be used concomitantly with ticagrelor is 75-150 mg (see section 4.2 and 4.4).

The benefits associated with ticagrelor were also independent of the use of other acute and long-term cardiovascular therapies, including heparin, low molecular weight heparin (LMWH), intravenous glycoprotein GpIIb/IIIa (GpIIb/IIIa) inhibitors, lipid-lowering medicines, betablockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists and proton pump inhibitors.

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.

Absorption:

Ticagrelor has a median t_{max} of approximately 1,5 hours. The formation of the major circulating metabolite AR-C124910XX (also active) from ticagrelor is rapid with a median t_{max} of approximately 2,5 hours. The C_{max} and AUC of ticagrelor and the active metabolite increased in an approximately proportional manner with dose over the dose range studied (30-1 260 mg).

The mean absolute bioavailability of ticagrelor was estimated to be 36 %, (range 25,4-64,0 %). Ingestion of a high-fat meal had no effect on ticagrelor C_{max} or the AUC of the active metabolite, but resulted in a 21 % increase in ticagrelor AUC and 22 % decrease in the active metabolite C_{max}. These 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.

Distribution:

The steady state volume of distribution of ticagrelor is 87,5 litres. Ticagrelor and the active metabolite are extensively bound to human plasma protein (> 99,0 %).

Metabolism:

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

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

Excretion:

The primary route of ticagrelor elimination is via hepatic metabolism. When radio-labelled ticagrelor was administered, the mean recovery of radioactivity was 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 half-life 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:

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

Gender:

Higher exposures to ticagrelor (approximately 52 % and 23 % 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. However, there were no differences in the phase 3 clinical studies for efficacy and safety data between men and women.

Renal impairment:

Exposure to ticagrelor was approximately 20 % lower and the exposure to the active metabolite was approximately 17 % higher in patients with severe renal impairment (Cl_{CR} < 30 ml/min) compared to subjects with normal renal function.

The IPA effect of ticagrelor was similar between the 2 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 35 % higher in patients with mild hepatic impairment (Child Pugh A) compared to matching healthy subjects respectively; however, the IPA effect of ticagrelor was similar between the 2 groups. No dose adjustment is needed for patients with mild hepatic impairment.

Ticagrelor has not been studied in patients with moderate or severe hepatic impairment (see section 4.2, 4.3 and 4.4)

Race:

Patients of Asian descent (573 patients) have a 39 % higher mean bioavailability compared to Caucasian patients (6 198 patients). Patients self-identified as Black (76 patients) 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 (29 patients) was approximately 40 % (20 % after adjusting for body weight) higher compared to that in Caucasians (28 patients). These differences do not require dose adjustment.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core:

Mannitol

Dibasic calcium phosphate

Magnesium stearate

Sodium starch glycolate

Hydroxypropyl cellulose

Tablet Coating:

Talc

Titanium dioxide

Ferric oxide yellow

Polyethylene glycol 400

Hypromellose

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 30 °C.

Do not remove the blisters from the outer carton until required for use.

6.5 Nature and contents of container

BRILINTA is packed in clear PVC/PVDC aluminium foil blister packs in cartons of 14, 56, 60, 168 or 180 tablets.

Packs of 14, 56 and 168 tablets contain 14 tablets per blister.

Packs of 60 and 180 tablets contain 20 tablets per blister.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7 HOLDER OF CERTIFICATE OF REGISTRATION

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8 REGISTRATION NUMBER

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9 DATE OF FIRST AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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