Rx

BRILINTA®

ticagrelor
film-coated tablets

USE UPON PRESCRIPTION ONLY
KEEP OUT OF REACH OF CHILDREN.
READ THE PACKAGE INSERT CAREFULLY BEFORE USING.

COMPOSITION AND STRENGTH

Each film-coated tablet contains:
Active ingredient: ticagrelor 90 mg.
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.
Brilinta contains less than 1 mmol sodium (23 mg) per dose, i.e. is essentially 'sodium-free'.

PHARMACEUTICAL DOSAGE FORM

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

THERAPEUTIC INDICATIONS

Acute Coronary Syndrome

BRILINTA, co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of atherothrombotic events in adult patients with acute coronary syndrome (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 bypass grafting (CABG).
For the demonstration of efficacy in this indication see *Pharmacodynamic Properties*.

Acute Stroke or Transient Ischaemic Attack (TIA)

BRILINTA is indicated to reduce the risk of stroke in patients with acute ischemic stroke (NIH Stroke Scale score ≤5) or high-risk transient ischemic attack (TIA) (see Pharmacodynamic Properties)

POSOLOGY AND METHOD OF ADMINISTRATION

Posology

Acute Coronary Syndrome

BRILINTA treatment can 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 ASA daily, unless specifically contraindicated. Following an initial dose of ASA, BRILINTA should be used with a maintenance dose of ASA of 75-100 mg (see section *Pharmacodynamic Properties*).
Treatment is recommended for up to 12 months unless discontinuation of BRILINTA is clinically indicated (see section *Pharmacodynamic Properties*). Discontinuation of BRILINTA prior to 12 months in patients with acute coronary syndromes (ACS), 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. 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 (not more) at the scheduled time of dosing.
Patients treated with clopidogrel can be directly switched to BRILINTA if needed (see section *Pharmacodynamic Properties*). Switching from prasugrel to BRILINTA has not been investigated.

Acute Ischemic Stroke or Transient Ischemic Attack (TIA)

Initiate treatment with a 180 mg loading dose of BRILINTA and then continue with 90 mg twice daily for up to 30 days.
The treatment effect accrued early in the course or therapy (see Pharmacodynamic Properties). Data from PLATO with a loading dose of aspirin (300 mg) suggest a daily maintenance dose of aspirin of 75 to 100 mg *(see Special Warnings and Precautions for use and Pharmacodynamic Properties).*
Antiplatelet therapy
About half of the patients in PLATO and THALES were ≥ 65 years of age and at least 15% were ≥ 75 years of age. No overall differences in safety or effectiveness were observed between elderly and younger patients. No dose adjustment is required in elderly (see section Pharmacodynamic Properties).
Renal impairment
Patients with End-Stage Renal Disease on dialysis
Clinical efficacy and safety data with BRILINTA did not enroll patients with end-stage renal disease (ESRD) on dialysis. In patients with ESRD maintained on intermittent hemodialysis, no clinically significant pharmacokinetic or pharmacodynamic changes in ticagrelor and active metabolite are expected compared to those observed in patients with normal renal function (see section Pharmacodynamic Properties). Insufficient data are available on whether these concentrations are similar efficacy and safety in patients with ESRD on dialysis as were seen in PLATO, PEGASUS and THALES. No dose adjustment is necessary for patients with renal impairment (see section Pharmacokinetic Properties).
Hepatic impairment
Ticagrelor has not been studied in patients with severe hepatic impairment and its use in these patients is therefore not established. Ticagrelor should be administered to patients with moderate hepatic impairment in patients with moderate hepatic impairment. Dose adjustment is not recommended, but ticagrelor should be used with caution (see *Special warnings and precautions for use* and *Pharmacokinetic properties*). No dose adjustment is necessary for patients with mild hepatic impairment (see section *Pharmacokinetic properties*).
Paediatric population
The safety and efficacy of ticagrelor in children below the age of 18 in the approved adult indication has not been established. No data are available.
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, the tablets can be crushed to a fine powder and mixed with 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 suitable for the nasogastric tube through with water after administration of the mixture.

CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients listed in the list of excipients (see section *Undesirable effects*).
- Active pathological bleeding.
- History of intracranial haemorrhage (see section *Undesirable Effects*).
- Severe hepatic impairment (see section *Posology and method of administration*, *Special Warnings and Precautions for Use* and *Pharmacokinetic Properties*).
- Co-administration of ticagrelor with strong CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin, nefazodone, ritonavir, and atazanavir), as co-administration may lead to a substantial increase in exposure to ticagrelor (see section *Interaction with other Medicinal Products and other Forms of Interaction*).

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Bleeding risk
The use of ticagrelor in patients at known increased risk for bleeding should be balanced against the benefit in terms of prevention of atherothrombotic events (see section *Undesirable effects* and *Pharmacodynamic Properties*). If clinically indicated, ticagrelor 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 who are at increased risk of trauma. The use of ticagrelor is contraindicated in patients with active pathological bleeding or in those with a history of intracranial haemorrhage, and in patients with severe hepatic impairment (see section *Contraindications*).
- Patients with concomitant administration of medicinal products that may increase the risk of bleeding (e.g. non-steroidal anti-inflammatory drugs (NSAIDs), oral anticoagulants and/or fibrinolytics) within 24 hours of bleeding onset.
Platelet transfusion did not reverse the antiplatelet effect of ticagrelor in healthy volunteers and is unlikely to be of clinical benefit in patients with life-threatening bleeding. Since dose-dependent reversal of ticagrelor with desmopressin did not decrease template-bleeding time, desmopressin is unlikely to be effective in managing clinical bleeding events (see section *Interaction with other medicinal products and other forms of interactions*).
Antifibrinolytic therapy (aminocaproic acid or tranexamic acid) and/or recombinant factor VIIa therapy may increase haemostasis. Ticagrelor may be resumed after the cause of bleeding has been identified and controlled.
Patients treated for acute ischemic stroke or TIA
Patients with NIHSS >5 and patients receiving thrombolysis were excluded from THALES and use of BRILINTA in such patients is not recommended.
Surgery
Patients should be advised to inform physicians and dentists that they are taking ticagrelor before any surgery is scheduled and before any new medicinal product is taken.
In PLATO patients undergoing coronary artery bypass grafting (CABG), ticagrelor had more bleeding than clopidogrel when stopped within 1 day prior to surgery but a similar rate of major bleeds compared to clopidogrel when stopping therapy 5 days prior to surgery (see section *Undesirable Effects*). If a patient is to undergo elective surgery and antiplatelet effect is not desired, ticagrelor should be used with caution in these patients (see section *Pharmacodynamic Properties*).
Patients with prior ischaemic stroke
ACS patients with prior ischaemic stroke can be treated with ticagrelor for up to 12 months (PLATO study). In PEGASUS, patients with history of MI with prior ischaemic stroke were not included. Therefore, in the absence of data, treatment beyond one year is not recommended in these patients.
Hepatic impairment
Use of ticagrelor is contraindicated in patients with severe hepatic impairment (see section *Posology and administration and Contraindications*). There is limited experience with ticagrelor in patients with moderate hepatic impairment. Therefore, caution is advised in these patients (see sections *Posology and administration and Pharmacokinetic properties*).
Patients at risk for bradycardia
Holter ECG monitoring has shown an increased frequency of mostly asymptomatic ventricular pauses during treatment with ticagrelor compared with clopidogrel. 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 bradycardia-related syncope) have been excluded from the main PLATO study evaluating the safety and efficacy of ticagrelor. Therefore, due to the limited clinical experience, ticagrelor should be used with caution in these patients (see section *Pharmacodynamic Properties*). In addition, caution should be exercised when administering ticagrelor 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, 30% calcium channel blockers diltiazem and verapamil, and 4% digoxin) (see section *Interaction with other Medicinal Products and other Forms of Interaction*).
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 ventricular pauses with ticagrelor was observed in patients with sinus rhythm and normal AV function, but also in patients in the overall study population during the acute phase of ACS, but not at one month following initiation of ticagrelor treatment. There were no adverse clinical consequences associated with this increase in pauses (including syncope or pacemaker insertion) in this patient population (see section *Pharmacodynamic Properties*).
Dyspnoea
In clinical trials, about 14% (PLATO and PEGASUS) of patients treated with BRILINTA developed dyspnea. Dyspnea was usually mild in character or intensity and often resolved during continued treatment but led to study drug discontinuation in 0.9% (PLATO), 1.0% (THALES), and 4.3% (PEGASUS) of patients.
Dyspnoea was reported in patients treated with ticagrelor. Patients with asthma/ chronic obstructive pulmonary disease (COPD) may have a greater frequency or more severe response. Patients with ticagrelor. 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 persistent or worsened dyspnoea this should be investigated fully and if not tolerated, treatment with ticagrelor should be stopped. For further details see *Pharmacodynamic Properties*.
Central sleep apnoea
Central sleep apnoea including Cheyne-Stokes respiration has been reported in the post-marketing setting in patients taking ticagrelor. If central sleep apnoea is suspected, further clinical assessment should be considered.
Creatinine elevations
Creatinine levels may increase during treatment with ticagrelor. The mechanism has not been elucidated. Renal function should be checked according to routine medical practice. In patients with ACS, it is recommended that renal function is also checked one month after initiating the treatment with ticagrelor 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 angiotensin receptor blocker (ARB).
Uric acid levels
Hyperuricaemia may occur during treatment with ticagrelor (see section *Undesirable Effects*). Caution is advised in patients with history of hyperuricaemia or gouty arthritis. As a precautionary measure, the use of ticagrelor in patients with uric acid nephropathy is discouraged.
Thrombotic Thrombocytopenic Purpura
Thrombotic Thrombocytopenic Purpura (TTP) has been reported very rarely with the use of ticagrelor. It is characterized by thrombocytopenia and microangiopathic haemolytic anaemia associated with other neurological findings, renal dysfunction or fever. TTP is a potentially fatal condition requiring prompt treatment including plasmapheresis.
Interference with platelet function tests in patients treated with ticagrelor
In the heparin induced platelet activation (HIPA) test used to diagnose HIT, anti-platelet factor 4/heparin antibodies in patient serum activate platelets of healthy donors in the presence of heparin. False negative results in a patient treated with ticagrelor cannot be ruled out. The platelet function tests for 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 serum/plasma. Information on concomitant treatment with ticagrelor is required for interpretation of HIT platelet function tests.
In patients who have developed HIT, the benefit-risk of continued treatment with ticagrelor should be assessed, taking both the prothrombotic state of HIT and the increased risk of bleeding with concomitant administration of non-heparin alternative anticoagulants.
Interference with laboratory tests
Ticagrelor has no effect on male or female fertility in animals.
EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Ticagrelor has no or negligible influence on the ability to drive and use machines. During treatment with ticagrelor, dizziness and confusion have been reported. Therefore, patients who experience should be cautious while driving or using machines.
INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION
Ticagrelor is primarily a CYP3A4 substrate and a mild inhibitor of CYP3A4. Ticagrelor is also a *P-glycoprotein (P-gp) substrate and a weak P-gp inhibitor and may increase the exposure of P-gp substrates.*
Effects of medicinal and other products on ticagrelor
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 therefore concomitant use of strong CYP3A4 inhibitors with ticagrelor is contraindicated (see section *Contraindications*).
- 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 ticagrelor.
- A 2-fold increase of ticagrelor exposure was observed after daily consumption of large quantities of grapefruit juice (3x200 ml). This magnitude of increased exposure is not expected to be clinically relevant to most patients.

CYP3A4 substrates
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 have a similar effect and can as well be co-administered with ticagrelor.
CYP3A4 inhibitors, inducers and substrates
Co-administration of simvastatin with ticagrelor increased simvastatin 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 ticagrelor.
No data are available on concomitant use of ticagrelor with other active substances 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.
Others
Other pharmacology interaction studies showed that co-administration of ticagrelor with heparin, enoxaparin and ASA or desmopressin did not have any effect on the pharmacokinetics of ticagrelor or the active metabolite. Non-ASA induced platelet aggregation was reduced with ticagrelor alone. If clinically indicated, medical treatment with desmopressin could still be considered in combination with ticagrelor.
A delayed and decreased exposure to oral $P2Y_{12}$ inhibitors, which also inhibit platelet aggregation, has been observed in patients with ACS treated with morphine (30% reduction in ticagrelor exposure). This interaction may be related to reduced gastrointestinal motility and apply to other opioids. The clinical relevance is unknown, but one can postulate the potential for reduced effect of ticagrelor in patients co-administered ticagrelor and morphine. In patients with ACS, in whom morphine cannot be withheld and but $P2Y_{12}$ inhibition is deemed crucial, the use of a parenteral $P2Y_{12}$ inhibitor may be considered.
Effects of ticagrelor on other medicinal products
Medicinal products metabolized by CYP3A4
- *Simvastatin* – Co-administration of ticagrelor with simvastatin increased simvastatin C_{max} by 81% and AUC by 56% and increased simvastin acid C_{max} by 64% and AUC by 52% with some individual increases equal to 3 to 3 fold. Co-administration of ticagrelor with doses of simvastatin exceeding 40 mg for subjects at high risk could cause adverse effects of statins based on clinical experience with potential benefits. There was no effect of simvastatin on ticagrelor plasma levels. Ticagrelor may have similar effect on lovastatin. 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 considered clinically significant.
- A similar effect on other statins metabolized by CYP3A4 cannot be excluded. Patients in PLATO receiving ticagrelor took a variety of statins. There was no observed an association with statin safety among the 93% of the PLATO cohort taking these medicinal products.

Ticagrelor is a direct CYP3A 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 (e.g. cisapride).*
P-glycoprotein (P-gp) substrates (including digoxin, cyclosporine)
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 increases to 2 fold. In the presence of ticagrelor, 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.
Ciclosporin was given with ticagrelor on cyclosporine blood levels. Effect of ticagrelor on other P-gp substrates has not been studied.
Medicinal products metabolized by CYP2C9
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.
Medicinal products excreted
Co-administration of ticagrelor and bromocriptine and ethinyl estradiol increased ethinyl estradiol exposure approximately 20% but did not alter the pharmacokinetics of levonorgestrel. No clinically significant pharmacodynamic efficacy is expected when bromocriptine and ethinyl estradiol are co-administered with ticagrelor.
Medicinal products known to induce bradycardia
Due to observations of mostly asymptomatic ventricular pauses and bradycardia, caution should be exercised when administering ticagrelor concomitantly with medicinal products known to induce bradycardia (see section *Special Warnings and Precautions for Use*). 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 and 4% digoxin).
Other concomitant therapy
In clinical studies, ticagrelor was commonly administered with ASA, proton pump inhibitors, statins, beta-blockers, angiotensin converting enzyme inhibitors and angiotensin receptor blockers as needed for medical management of patients with ACS. Ticagrelor did not increase the bleeding time with ASA and intravenous Gp IIb/IIIa inhibitors for short durations (see section *Pharmacodynamic Properties*). No clinically significant adverse interactions with these medicinal products were observed. Co-administration of ticagrelor with heparin, enoxaparin or desmopressin had no effect on activated partial thromboplastin time (aPTT), standard coagulation time (SCT) or heparin anti-Xa activity. However, due to potential pharmacodynamic interactions, caution should be exercised when the concomitant administration of ticagrelor with medicinal products known to alter hemostasis (see section *Special Warnings and Precautions for Use*).
Due to reports of serotonin syndrome developing 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.

UNDESIRABLE EFFECTS

Summary of the safety profile
The safety profile of ticagrelor has been evaluated in more than 58000 patients (see section Pharmacodynamic properties).
In PLATO, patients on ticagrelor had a higher incidence of discontinuation due to adverse events than clopidogrel (7.4% vs. 5.4%). In PEGASUS, patients on ticagrelor had a higher incidence of discontinuation due to adverse events compared to placebo (10.2% versus 4.6% for ASA alone (16.1% for ticagrelor plus ASA vs. 8.5% for ASA therapy alone). The most commonly reported adverse reactions in patients treated with ticagrelor were bleeding and dyspnea (see section Special warnings and precautions for use).
Tabulated list of adverse reactions
The following adverse reactions have been identified following studies or have been reported in post-marketing experience with ticagrelor (Table 1).
Adverse reactions are listed by MedDRA System Organ Class (SOC). With in each SOC the adverse reactions are ranked by frequency category. Frequency categories are defined according to the following convention: 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 reactions by frequency and system organ class (SOC)

System Organ Classification	Very Common	Common	Uncommon	Not known
Blood and lymphatic system disorders (including bone marrow failure, haemolytic anaemia and haemolysis)			Tumour bleedings*	
Blood and lymphatic system disorders	Blood disorder bleedings*			Thrombotic Thrombocytopenic Purpura**
Immune system disorders			Hypersensitivity reactions, including angioedema*	
Metabolism and nutrition disorders	Hyperuricaemia*	Gout/Gouty Arthritis		
Nervous system disorders		Dizziness, Syncope, Headache	Confusion Intracranial haemorrhage*	
Eye disorders			Eye haemorrhage*	
Ear and labyrinth disorders		Vertigo	Ear haemorrhage	
Vascular disorders		Hypotension		
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Respiration system bleedings*		
Gastrointestinal disorders		Gastrointestinal haemorrhage*, Diarrhea, Nausea, Dyspepsia, Constipation	Retroperitoneal haemorrhage	
Skin and subcutaneous tissue disorders		Subcutaneous or dermal bleedings*, Rash, Pruritus		
Musculoskeletal disorders, tissue and bone			Muscular bleedings*	
Renal and urinary disorders		Urinary tract bleeding*		
Reproductive system and breast disorders			Reproductive system bleedings*	
Investigations			Blood creatinine increased*	
Injury, poisoning and procedural complications			Post procedural haemorrhage, Post procedural bleedings*	

*e.g. bleeding from bladder cancer, gastric cancer, colon cancer
*e.g. increased tendency to bruise, spontaneous haematoma, haemorrhagic diathesis
*identified in post-marketing experience
*Frequencies derived from lab observations (Uric acid increases to supper limit of normal from baseline (normal within reference range. Creatinine increases of >50% from baseline.) and not crude adverse event report frequency.
*e.g. conjunctival, retinal, subcapsular bleeding
*e.g. epistaxis, haemoptysis
*e.g. gingival bleeding, rectal haemorrhage, gastric ulcer haemorrhage
*e.g. ecchymosis, skin haemorrhage, petechiae
*e.g. hematuria, genitourinary haemorrhage
*e.g. hematoma, joint haemorrhage
*e.g. vaginal haemorrhage, haematoperitonia, postmenopausal haemorrhage
*e.g. circumcision, traumatic haemorrhage, haematoma
*i.e. spontaneous, procedure related or traumatic intracranial haemorrhage
Description of selected adverse reactions
Bleeding
Bleeding frequencies in PLATO
Overall outcome of bleeding rates in the PLATO study are shown in Table 2.
Table 2 – Analysis of overall bleeding events, Kaplan-Meier estimates at 12 months (PLATO)

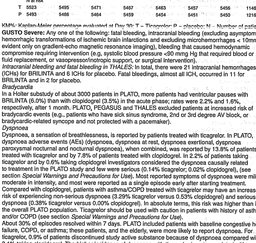
	BRILINTA (%/year) N=9235	Clopidogrel (%/year) N=9186	*P-value**
PLATO Total Major	11.6	11.2	0.4336
PLATO Major Fatal/Life-Threatening	5.8	5.8	0.9588
Non-CABG PLATO Major	4.5	3.8	0.0264
Non-Procedural PLATO Major	3.1	2.3	0.0058
PLATO Total Major + Minor	16.1	14.6	0.0084
Non-Procedural PLATO Major + Minor	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 support 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: 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.
*p-value calculated from Cox proportional hazards model with treatment group as the only explanatory variable.
Ticagrelor and clopidogrel did not differ in rates of PLATO Major Fatal/Life-threatening bleeding, PLATO total Major Bleed and Major Minor Bleeding, or TIMI Major bleeding (Table 2). However, more PLATO combined Major + Minor bleeding occurred with ticagrelor compared with clopidogrel. Few patients in PLATO had bleeds (n=30 (0.2%) for ticagrelor and 23 (0.3%) for clopidogrel (see section *Special Warnings and Precautions for Use*).
Age, sex, weight, geographic region, concurrent conditions, concomitant therapy, and medical history, including a previous stroke or transient ischaemic attack, all did not predict either overall or intracranial PLATO Major bleeding. There no particular group was identified at risk for any subset of major 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 bleedings occurred in 9 patients in each treatment group (see section *Special Warnings and Precautions for Use*).
Non-CABG related bleeding and non procedural related bleeding: BRILINTA and clopidogrel did not differ in non-CABG PLATO-defined Major Fatal/Life-threatening Bleeding, but PLATO-defined Total Major, TIMI Major, and TIMI Major + Minor bleeding were more common with ticagrelor. Similarly, when removing all procedural 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 1 with clopidogrel were fatal. There was no difference in overall fatal bleeds.
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 estimates at 36 months (PEGASUS)

Safety Endpoints	Ticagrelor 60 mg twice daily + ASA N=6958 KM%	Hazard Ratio (95% CI)	ASA alone N=6959 KM%	*p-value*
TIMI-defined bleeding categories				
TIMI Major	2.3	2.32 (1.68, 3.21)	1.1	<0.0001
Fatal	0.3	1.00 (0.44, 2.27)	0.3	1.0000
ICH	0.6	1.33 (0.77, 2.31)	0.5	0.3130
Other TIMI Major	1.6	3.61 (2.31, 5.65)	0.5	<0.0001
TIMI Major or Minor	3.4	2.54 (1.93, 3.35)	1.4	<0.0001
TIMI Major or Minor or Requiring medical attention	16.6	2.64 (2.35, 2.97)	7.0	<0.0001
PLATO-defined bleeding categories				
PLATO Major	3.5	2.57 (1.95, 3.37)	1.4	<0.0001
Fatal/Life-threatening	2.4	2.39 (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	2.77 (2.40, 3.08)	6.2	<0.0001

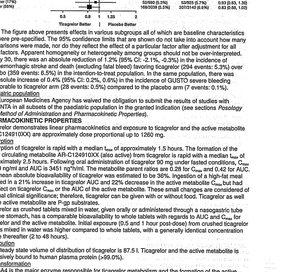
Bleeding category definitions:
TIMI Major: Fatal bleeding, OR any intracranial bleeding, OR clinically overt signs of haemorrhage associated with a drop in haemoglobin (Hgb) of ≥50 g/L, or when Hgb is not available, a fall in haematocrit (Hct) of 15%.
Fatal: A bleeding event that directly led to death 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 or surgery OR clinically apparent with >50 g/L decrease in haemoglobin or >4 red cell units transfused.
PLATO Major Other: Significant bleeding, OR clinically apparent with 30-50 g/L decrease in haemoglobin, OR 2-3 red cell units transfused.
PLATO Minor: Requiring medical intervention to stop or treat bleeding.
In PEGASUS, TIMI Major bleeding for ticagrelor 60 mg twice daily was higher than for ASA alone. Most of the major bleedings were seen for fatal bleeding and only a minor increase was observed in intracranial haemorrhages, as compared to ASA therapy alone. There were few fatal bleeding events in the study, 11 (0.3%) for ticagrelor 60 mg and 12 (0.3%) for ASA therapy alone. The observed increased risk of TIMI Major bleeding with ticagrelor 60 mg was primarily due to a higher frequency of *Other TIMI Major bleeds* driven by events in the gastrointestinal tract.
Increased bleeding patterns similar to TIMI Major were seen for TIMI Major or Minor and PLATO Major and PLATO Major or Minor bleeding categories (see Table 3). Discontinuation of treatment due to bleeding was more common with ticagrelor 60 mg compared to ASA therapy alone (6.2% and 1.5%, respectively). The majority of these bleedings were less severe (classified as TIMI Required Medical Intervention or Worsening Renal Function).
The bleeding profile of ticagrelor 60 mg was consistent across multiple pre-defined subgroups (e.g. by age, gender, weight, geographic region, concomitant conditions, concomitant therapy, and medical history) for TIMI Major, TIMI Major or Minor, and PLATO Major bleeding events.
Intracranial bleeding: Intracranial bleeds were observed in similar rates for ticagrelor 60 mg and ASA therapy alone (n=13, 0.2% in both treatment groups). Traumatic and procedural ICHs showed a minor imbalance with ticagrelor 60 mg treatment, (n=5, 0.2%) compared with ASA therapy alone (n=1), 0.1%). There were 6 fatal ICHs with ticagrelor 60 mg and 5 fatal ICHs with ASA therapy alone. The incidence of non-traumatic bleeding was low in both treatment groups given the significantly reduced stability and CV risk factors of the population under study.
Bleeding in THALES (Reduction in risk of stroke in patients with acute ischemic stroke or TIA)
The Kaplan-Meier curve of time course of GUSTO severe bleeding events is presented in Figure 1

Figure 1 - Time course of GUSTO severe bleeding events



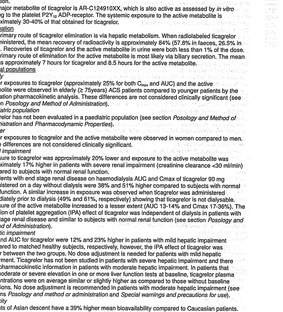
KM%: Kaplan-Meier percentage evaluated at Day 30; T=Ticagrelor; P=placebo; N=Number of patients randomized; PR=Patient-event Rate; n=Number of patients with event; KM%=Kaplan-Meier percentage evaluated at Day 30; CI=Confidence Interval; HR = Hazard ratio; KM = Kaplan-Meier percentage calculated at 30 days; N = Number of patients
The number of patients with the event of interest. In the time to first stroke, patients who died are censored at the time of death.
The Kaplan-Meier curve (Figure 3) shows the time to first occurrence of the primary composite endpoint of stroke or death.

Figure 3 – Time to First Occurrence of Stroke or Death (THALES)



KM%: Kaplan-Meier percentage evaluated at Day 30; T=Ticagrelor; P=placebo; N=Number of patients randomized; PR=Patient-event Rate; n=Number of patients with event
BRILINTA's treatment effect on stroke and on death accrued over the first 10 days and was sustained at 30 days.
Although not studied, this suggests that shorter treatment could result in similar benefit and reduced bleeding risk.
The treatment effect of BRILINTA was generally consistent across pre-defined subgroups (Figure 4).

Figure 4 – Subgroup analyses of ticagrelor 90 mg (THALES)


Characteristic
Ticagrelor n/N (%)
Placebo n/N (%)
HR (95% CI)
All patients in full analysis set (100%) 35/5503 (0.6%) 38/5493 (0.7%) 0.92 (0.71, 0.98)
Age (years)
<65 (65%) 13/3576 (0.4%) 16/3552 (0.5%) 0.79 (0.55, 0.98)
65-75 (25%) 12/1378 (0.9%) 12/1392 (0.9%) 0.85 (0.55, 1.17)
>75 (10%) 7/1105 (0.6%) 7/1102 (0.6%) 0.88 (0.44, 1.20)
Sex (n/N)
Male (67%) 19/3674 (0.5%) 25/3702 (0.7%) 0.82 (0.58, 0.93)
Female (33%) 16/1829 (0.9%) 12/1171 (1.0%) 0.85 (0.45, 1.10)
Weight (kg)
Black or African American (≥1%) 1/60 (0.2%) 0/52 (0.0%) 0.98 (0.71, 1.00)
Other (2%) 1/116 (0.9%) 1/117 (0.9%) 0.98 (0.71, 1.00)
Weight (kg)
≤60 (25%) 12/1330 (0.9%) 18/1338 (0.9%) 0.68 (0.53, 1.01)
>60 (75%) 23/4173 (0.6%) 20/4155 (0.5%) 0.98 (0.71, 1.00)
BMI (kg/m²)
≤25 (40%) 20/1974 (1.0%) 20/1974 (1.0%) 0.98 (0.71, 1.00)
>25 (60%) 15/3529 (0.4%) 18/3519 (0.5%) 0.83 (0.57, 1.05)
Geographic region
Japan (10%) 1/543 (0.2%) 2/532 (0.4%) 0.49 (0.04, 4.64)
Europe (51%) 19/2563 (0.7%) 19/2563 (0.7%) 1.00 (0.54, 1.91)
North America (≤1%) 0/32 (0.0%) 1/31 (3.2%) 0.31 (0.01, 8.14)
Central and S America (8%) 3/402 (0.7%) 1/404 (0.2%) 3.00 (0.31, 28.78)
Stroke NIHSS score (≤ 20 N%) 15/3303 (0.5%) 19/3312 (0.6%) 0.80 (0.39, 1.65)
Stroke NIHSS score (> 5 N%) 19/1401 (1.3%) 23/1421 (1.6%) 0.83 (0.45, 1.52)
Stroke NIHSS score (missing N%) 1/799 (0.1%) 0/760 (0.0%) 2.85 (0.11, 71.19)

110034866

Rx

BRILINTA®

ticagrelor

Viên nén bao phim

THUỐC NÀY CHỈ DÙNG THEO ĐƠN THUỐC.
ĐỂ XA TẦM TAY TRẺ EM.
ĐỌC KỸ HƯỚNG DẪN SỬ DỤNG TRƯỚC KHI DÙNG.

THÀNH PHẦN CÔNG THỨC THUỐC
Mỗi viên nén bao phim chứa:
Thành phần hoạt chất: Ticagrelor 90 mg
Thành phần tá dược:
Viên nhân: Manitol, dibasic calci phosphat, magnesi stearat, natri stearyl fumarat, hydroxypropylcellulose
Lớp bao phim: Talc, titan dioxyd, sắt oxyd vàng, polyethylen glycol 400, hypromellose.
BRILINTA chứa 6 hoặc 1 mmol Natri (23 mg) trên liều, nghĩa là xem như "không Có Natri".

DÙNG BAO CHẾ
Viên nén bao phim.
Viên nén màu vàng, hai mặt lồi, hình tròn, một mặt có khắc "90" trên "T" và một mặt trơn.

CÔNG DỤNG
Hội chứng mạch vành cấp
BRILINTA, dùng đồng thời với acetylsalicylic (ASA), được chỉ định để phòng ngừa các biến cố huyết khối do xơ vữa động mạch ở bệnh nhân người trưởng thành bị Hội chứng mạch vành cấp (đau thắt ngực không đến gây nhồi máu cơ tim hoặc nhồi máu cơ tim có sóng ST chênh lên [non ST elevation Myocardial Infarction – NSTEMI], chẩn đoán nhồi máu cơ tim có sóng ST chênh lên ST elevation Myocardial Infarction – STEMI), gồm bệnh nhân được điều trị bằng can thiệp mạch vành qua da (Percutaneous coronary intervention – PCI) hoặc phẫu thuật bắc cầu mạch vành (Coronary artery bypass grafting – CABG).
Các thông tin khác, xin tham khảo phần *Đặc tính dược lực học của dược tố thông qua (TTA)*.
Độ an toàn và hiệu quả của BRILINTA được thiết lập trong các nghiên cứu lâm sàng bệnh nhân được điều trị kết hợp với aspirin (ASA) dùng liều thấp (≤ 100 mg/ngày). Vì vậy, nghĩa là xem như "không Có Natri".
Các thông tin khác, xin tham khảo phần *Đặc tính dược lực học của dược tố thông qua (TTA)*.

CÁCH DÙNG, LIỀU DÙNG
Liều dùng
Hội chứng mạch vành cấp
Nên khởi đầu điều trị với chế phẩm liều nạp 180 mg BRILINTA (hai viên 90 mg) và sau đó dùng tiếp liều 90 mg hai lần mỗi ngày.
Bệnh nhân dùng BRILINTA cùng với uống ASA hằng ngày, trừ khi có chống chỉ định cụ thể. Sau khi điều trị khởi đầu với ASA, nên dùng BRILINTA với liều duy trì 75-100 mg ASA, dùng mỗi ngày một lần.
Khuyến cáo dùng kéo dài liều 12 tháng tới khi có chỉ định lâm sàng ngưng dùng BRILINTA (xem phần *Đặc tính dược lực học*). Nên thu thập thêm số liệu 12 tháng cho giai đoạn sau.
Ở bệnh nhân bị Hội Chứng Mạch Vành Cấp, việc ngừng sớm bất kỳ liệu pháp chống kết tập tiểu cầu nào, kể cả BRILINTA, có thể gây tăng nguy cơ tim mạch do bệnh nhân chưa đáp ứng đầy đủ với liệu pháp kết hợp.
Do đó, nên hạnh ngưng điều trị sớm.
Nên tránh quên uống thuốc liều kế tiếp. Bệnh nhân quên 1 liều BRILINTA nên dùng chỉ 1 viên 90 mg liều kế tiếp vào đúng giờ thông lệ.
Bệnh nhân đã được điều trị với clopidogrel có thể chuyển thẳng sang dùng BRILINTA nếu cần thiết (xem phần *Đặc tính Dược lực học*). Chuyển từ pravasugrel sang dùng BRILINTA chưa được nghiên cứu.
Cần nhấn sau quy trình (xem phần *Đặc tính dược lực học*).
Khởi đầu điều trị với liều nạp 180 BRILINTA và sau đó tiếp tục với liều 90 mg x 2 lần mỗi ngày trong 8 ngày.
Hiệu quả điều trị tiếp tục sẽ bị giảm trong quá trình điều trị bằng phẩm (xem phần *Đặc tính Dược lực học*).
Sử dụng BRILINTA cùng với Thuốc ức chế CYP3A mạnh và trung bình (xem phần *Tương tác thuốc*).
Nên tránh dùng BRILINTA cùng với Thuốc ức chế CYP3A mạnh và trung bình.
Nếu phải dùng BRILINTA cùng với Thuốc ức chế CYP3A mạnh và trung bình, nghĩa là xem như "không Có Natri".
Nên cẩn thận khi