

## **Brilinta 90 mg Film-coated tablets**

### **NAME OF THE MEDICINAL PRODUCT**

Brilinta 90 mg film-coated tablets.

### **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each film-coated tablet contains 90 mg ticagrelor.

Brilinta contains less than 1 mmol sodium (23 mg) per dose, i.e. is essentially 'sodium-free'.

For the full list of excipients, see List of excipients.

### **PHARMACEUTICAL FORM**

Film-coated tablet (tablet).

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

### **CLINICAL PARTICULARS**

#### **Therapeutic indications**

Brilinta, co-administered with acetylsalicylic acid (ASA), 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 Pharmacodynamic properties.

#### **Posology and method of administration**

##### Posology

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 ASA daily, unless specifically contraindicated. Following an initial dose of ASA, Brilinta should be used with a maintenance dose of ASA of 75-150 mg (see Pharmacodynamic properties).

Treatment is recommended for up to 12 months unless discontinuation of Brilinta is clinically indicated (see Pharmacodynamic properties). 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, myocardial infarction 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 (their next dose) at its scheduled time.

Patients treated with clopidogrel can be directly switched to Brilinta if needed (see Pharmacodynamic properties). Switching from prasugrel to Brilinta has not been investigated.

### Special populations

#### *Elderly*

No dose adjustment is required in elderly (see Pharmacokinetic properties).

#### *Patients with renal impairment*

No dose adjustment is necessary for patients with renal impairment (see Pharmacokinetic properties).

#### *Patients with hepatic impairment*

Ticagrelor has not been studied in patients with severe hepatic impairment and its use in these patients is therefore contraindicated (see Contraindications). Only limited information is available 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 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. There is no relevant use of ticagrelor in children with sickle cell disease (see Pharmacodynamic properties and Pharmacokinetic properties).

### Method of administration

For oral use. Brilinta can be administered with or without food. For patients who are unable to swallow the tablet(s) whole, Brilinta tablets can be crushed to a fine powder and mixed in half a glass of water and drunk immediately. The glass should be rinsed with a further half glass of water and the contents drunk. The mixture can also be administered via a nasogastric tube (CH8 or greater). It is important to flush the nasogastric tube through with water after administration of the mixture.

### **Contraindications**

- Hypersensitivity to the active substance or to any of the excipients listed in the list of excipients section (see Undesirable effects).
- Active pathological bleeding.
- History of intracranial haemorrhage (see Undesirable effects).
- Severe hepatic impairment (see 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 Interaction with other medicinal products and other forms of interaction).

### **Special warnings and precautions for use**

#### **Bleeding risk**

In the phase 3 pivotal trial (PLATO [PLATelet Inhibition and Patient Outcomes], 18,624 patients) key exclusion criteria included an increased risk for bleeding, clinically important thrombocytopenia or anaemia, previous intracranial bleed, gastrointestinal bleed within the past 6 months or major surgery within the past 30 days. Patients with acute coronary syndromes treated with Brilinta and ASA showed an increased risk of non-CABG major bleeding and also more generally in bleeds requiring medical attention i.e. Major + Minor PLATO bleeds, but not Fatal or Life-threatening bleeds (see Undesirable effects).

Therefore, 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. 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, in those with a history of intracranial haemorrhage, and in patients with severe hepatic impairment (see 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 ticagrelor dosing.

Platelet transfusion did not reverse the antiplatelet effect of ticagrelor in healthy volunteers and is unlikely to be of clinical benefit in patients with bleeding. Since co-administration of ticagrelor with desmopressin did not decrease template-bleeding time, desmopressin is unlikely to be effective in managing clinical bleeding events (see Interaction with other medicinal products and other forms of interaction).

Antifibrinolytic therapy (aminocaproic acid or tranexamic acid) and/or recombinant factor VIIa may increase haemostasis. Ticagrelor 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 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 after stopping therapy 2 or more days before surgery (see Undesirable effects). If a patient is to undergo elective surgery and antiplatelet effect is not desired, ticagrelor should be discontinued 5 days prior to surgery (see Pharmacodynamic properties).

### Hepatic Impairment

Use of ticagrelor is contraindicated in patients with severe hepatic impairment (see 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 Posology and administration and pharmacokinetic properties).

### Patients at risk for bradycardic events

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 bradycardic-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 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, 33% calcium channel blockers diltiazem and verapamil, and 4% digoxin) (see Interaction with other medicinal products and other forms of interaction).

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

Bradyarrhythmic events and AV blocks have been reported in the post-marketing setting in patients taking ticagrelor (see Undesirable effects), 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.

### Dyspnoea

Dyspnoea was reported in patients treated with ticagrelor. Dyspnoea is usually mild to moderate in intensity and often resolves without need for treatment discontinuation. Patients with asthma/chronic obstructive pulmonary disease (COPD) may have an increased absolute risk of experiencing dyspnoea 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 new, prolonged or worsened dyspnoea this should be investigated fully and if not tolerated, treatment with ticagrelor should be stopped. For further details see undesirable effects.

### 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  $\geq 75$  years, patients with moderate/severe renal impairment and those receiving concomitant treatment with an angiotensin receptor blocker (ARB).

#### Uric acid increase

Hyperuricaemia may occur during treatment with ticagrelor (see 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 (TTP)

Thrombotic Thrombocytopenic Purpura (TTP) has been reported very rarely with the use of ticagrelor. It is characterised by thrombocytopenia and microangiopathic haemolytic anaemia associated with either neurological findings, renal dysfunction or fever. TTP is a potentially fatal condition requiring prompt treatment including plasmapheresis.

#### Interference with platelet function tests to diagnose heparin induced thrombocytopenia (HIT)

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 platelet function test (to include, but may not be limited to the HIPA test) for HIT have been reported in patients administered ticagrelor. This is related to inhibition of the P2Y<sub>12</sub>-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.

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 anticoagulant and ticagrelor treatment into consideration.

#### Other

Based on a relationship observed in PLATO between maintenance ASA dose and relative efficacy of ticagrelor compared to clopidogrel, co-administration of ticagrelor and high maintenance dose ASA (>300 mg) is not recommended (see Pharmacodynamic properties).

### **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<sub>max</sub> and AUC equal to 2.4-fold and 7.3-fold, respectively. The C<sub>max</sub> 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 Contraindications and Special warnings).

- 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.

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

#### *Cyclosporine (P-gp 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.

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 (see Special warnings and precautions for use).

#### *Others*

Clinical 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 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 ticagrelor.

A delayed and decreased exposure to oral P2Y<sub>12</sub> inhibitors, including ticagrelor and its active metabolite, has been observed in patients with ACS treated with morphine (35% reduction in ticagrelor exposure). This interaction may be related to reduced gastrointestinal motility and apply to other opioids. The clinical relevance is unknown, but data indicate the potential for reduced ticagrelor efficacy in patients co-administered ticagrelor and morphine. In patients with ACS, in whom morphine cannot be withheld and fast P2Y<sub>12</sub> inhibition is deemed crucial, the use of a parenteral P2Y<sub>12</sub> inhibitor may be considered.

#### Effects of ticagrelor 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. 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 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 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.

*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 maximum increases to 2-fold. In the presence of digoxin, the  $C_{max}$  and AUC of ticagrelor and its active metabolite were not affected. Therefore, appropriate clinical and/or laboratory monitoring is recommended when giving narrow therapeutic index P-gp dependent medicinal products like digoxin concomitantly with ticagrelor.

There was no effect of ticagrelor on cyclosporine blood levels. Effect of ticagrelor on other P-gp substrates has not been studied.

*Medicinal products metabolised 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.

*Oral contraceptives*

Co-administration of ticagrelor and levonorgestrel and ethinyl estradiol increased ethinyl estradiol 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 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 Brilinta concomitantly with medicinal products known to induce bradycardia (see 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 diltiazem and verapamil, and 4% digoxin).

#### Other concomitant therapy

In the PLATO study, ticagrelor was commonly administered with ASA, 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 Pharmacodynamic properties). No evidence of clinically significant adverse interactions with these medicinal products was observed.

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

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

### **Fertility, pregnancy and lactation**

#### Women of childbearing potential

Women of childbearing potential should use appropriate contraceptive measures to avoid pregnancy during ticagrelor 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 Preclinical safety data). Ticagrelor is not recommended during pregnancy.

#### Breast-feeding

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

#### Fertility

Ticagrelor had no effect on male or female fertility in animals (see Preclinical safety data).

### **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 these symptoms should be cautious while driving or using machines.

### **Undesirable effects**

#### Summary of the safety profile



The safety profile of ticagrelor has been evaluated in two large phase 3 outcome trials (PLATO and PEGASUS) including more than 39,000 patients (see 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 ASA therapy alone (16.1% for ticagrelor 60 mg with ASA vs. 8.5% for ASA therapy alone). The most commonly reported adverse reactions in patients treated with ticagrelor were bleeding and dyspnea (see 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). Within each SOC the adverse reactions are ranked by frequency category. 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)**

<b>System Organ Classification</b>	<b>Very Common</b>	<b>Common</b>	<b>Uncommon</b>	<b>Not known</b>
<i>Neoplasms benign, malignant and unspecified (including cysts and polyps)</i>			Tumour bleedings <sup>a</sup>	
<i>Blood and lymphatic system disorders</i>	Blood disorder bleedings <sup>b</sup>			Thrombotic Thrombocytopenic Purpura <sup>c</sup>
<i>Immune system disorders</i>			Hypersensitivity including angioedema	
<i>Metabolism and nutrition disorders</i>	Hyperuricaemia <sup>d</sup>	Gout/Gouty Arthritis		
<i>Psychiatric disorders</i>			Confusion	
<i>Nervous system disorders</i>		Dizziness, Syncope, Headache	Intracranial haemorrhage <sup>m</sup>	
<i>Eye disorders</i>			Eye haemorrhage <sup>e</sup>	
<i>Ear and labyrinth disorders</i>		Vertigo	Ear haemorrhage	
<i>Cardiac disorders</i>				Bradyarrhythmia, AV block <sup>c</sup>
<i>Vascular disorders</i>		Hypotension		

System Organ Classification	Very Common	Common	Uncommon	Not known
<i>Respiratory, thoracic and mediastinal disorders</i>	Dyspnoea	Respiratory system bleedings <sup>f</sup>		
<i>Gastrointestinal disorders</i>		Gastrointestinal haemorrhage <sup>g</sup> , Diarrhoea, Nausea, Dyspepsia, Constipation	Retroperitoneal haemorrhage	
<i>Skin and subcutaneous tissue disorders</i>		Subcutaneous or dermal bleeding <sup>h</sup> , Rash, Pruritus		
<i>Musculoskeletal connective tissue and bone</i>			Muscular bleedings <sup>i</sup>	
<i>Renal and urinary disorders</i>		Urinary tract bleeding <sup>j</sup>		
<i>Reproductive system and breast disorders</i>			Reproductive system bleedings <sup>k</sup>	
<i>Investigations</i>		Blood creatinine increased <sup>d</sup>		
<i>Injury, poisoning and procedural complications</i>		Post procedural haemorrhage, Traumatic bleedings <sup>l</sup>		

<sup>a</sup> e.g. bleeding from bladder cancer, gastric cancer, colon cancer

<sup>b</sup> e.g. increased tendency to bruise, spontaneous haematoma, haemorrhagic diathesis

<sup>c</sup> Identified in post-marketing experience

<sup>d</sup> Frequencies derived from lab observations (Uric acid increases to >upper limit of normal from baseline below or within reference range Creatinine increases of >50% from baseline.) and not crude adverse event report frequency.

<sup>e</sup> e.g. conjunctival, retinal, intraocular bleeding

<sup>f</sup> e.g. epistaxis, haemoptysis

<sup>g</sup> e.g. gingival bleeding, rectal haemorrhage, gastric ulcer haemorrhage

<sup>h</sup> e.g. ecchymosis, skin haemorrhage, petechiae

<sup>i</sup> e.g. haemarthrosis, muscle haemorrhage

<sup>j</sup> e.g. haematuria, cystitis haemorrhagic

<sup>k</sup> e.g. vaginal haemorrhage, haemospermia, postmenopausal haemorrhage

<sup>l</sup> e.g. contusion, traumatic haematoma, traumatic haemorrhage

<sup>m</sup> i.e. spontaneous, procedure related or traumatic intracranial haemorrhage

### Description of selected adverse reactions

#### Bleeding

#### Bleeding findings 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	Clopidogrel	p-value
--	----------	-------------	---------

	(%/year) N=9235	(%/year) N=9186	
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.

\*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 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 Special warnings and precautions for use).

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 Special warnings and precautions for use).

**Non-CABG related bleeding and non-procedural related bleeding:** Ticagrelor 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 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)**

	<b>Ticagrelor 60 mg twice daily + ASA N=6958</b>		<b>ASA alone N=6996</b>	
<b>Safety Endpoints</b>	<b>KM%</b>	<b>Hazard Ratio (95% CI)</b>	<b>KM%</b>	<b>p-value</b>
<b>TIMI-defined bleeding categories</b>				
<b>TIMI Major</b>	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
<b>PLATO-defined bleeding categories</b>				
<b>PLATO Major</b>	3.5	2.57 (1.95, 3.37)	1.4	<0.0001
Fatal/Life-threatening	2.4	2.38 (1.73, 3.26)	1.1	<0.0001
Other PLATO Major	1.1	3.37 (1.95, 5.83)	0.3	<0.0001
PLATO Major or Minor	15.2	2.71 (2.40, 3.08)	6.2	<0.0001

**Bleeding category definitions:**

**TIMI Major:** Fatal bleeding, OR any intracranial bleeding, OR clinically overt signs of haemorrhage associated with a drop in haemoglobin (Hgb) of  $\geq 50$  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 hospitalization, OR prompting evaluation.

**PLATO Major Fatal/life-threatening:** Fatal bleeding, OR any intracranial bleeding, OR intrapericardial with cardiac tamponade, OR with hypovolaemic shock or severe hypotension requiring pressors/inotropes or surgery OR clinically apparent with  $>50$  g/L decrease in haemoglobin or  $\geq 4$  red cell units transfused.

**PLATO Major Other:** Significantly disabling, OR clinically apparent with 30-50 g/L decrease in haemoglobin, OR 2-3 red cell units transfused.

**PLATO Minor:** Requires medical intervention to stop or treat bleeding.

In PEGASUS, TIMI Major bleeding for ticagrelor 60 mg twice daily was higher than for ASA alone. No increased bleeding risk was 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 bleedings driven by events in the gastrointestinal SOC.

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 of less severity (classified as TIMI Requiring medical attention), e.g. epistaxis, bruising and haematomas.

The bleeding profile of ticagrelor 60 mg was consistent across multiple pre-defined subgroups (e.g. by age, gender, weight, race, geographic region, concurrent conditions, concomitant therapy, and medical history) for TIMI Major, TIMI Major or Minor and PLATO Major bleeding events.

*Intracranial bleeding:* Spontaneous ICHs were reported 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 increase with ticagrelor 60 mg treatment, (n=15, 0.2%) compared with ASA therapy alone (n=10, 0.1%). There were 6 fatal ICHs with ticagrelor 60 mg and 5 fatal ICHs with ASA therapy alone. The incidence of intracranial bleeding was low in both treatment groups given the significant comorbidity and CV risk factors of the population under study

#### *Dyspnoea*

Dyspnoea, a sensation of breathlessness, is reported by patients treated with ticagrelor. In PLATO dyspnoea adverse events (AEs) (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 Special warnings and precautions for use). 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 Special warnings and precautions for use).

About 30% of episodes resolved within 7 days. PLATO included patients with baseline congestive heart failure, COPD, or asthma; these patients, and the elderly, were more likely to report dyspnoea. For ticagrelor, 0.9% of patients discontinued study active substance because of dyspnoea compared with 0.1% taking clopidogrel. The higher incidence of dyspnoea with ticagrelor is not associated with new or worsening heart or lung disease (see Special warnings and precautions for use). Ticagrelor does not affect tests of pulmonary function.

In PEGASUS, dyspnoea was reported in 14.2% of patients taking ticagrelor 60 mg twice daily and in 5.5% of patients taking ASA alone. As in PLATO, most reported dyspnoea was mild to moderate in intensity (see Special warnings and precautions for use). Patients who reported dyspnoea tended to be older and more frequently had dyspnoea, COPD or asthma at baseline.

#### *Investigations*

Uric acid elevations: In PLATO, serum uric acid increased to more than upper limit of normal in 22% of patients receiving ticagrelor compared to 13% of patients receiving clopidogrel. The corresponding numbers in PEGASUS were 9.1%, 8.8% and 5.5% for ticagrelor 90 mg, 60 mg and placebo, respectively. Mean serum uric acid 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.

In PEGASUS, a reversible increase in mean serum uric acid levels of 6.3% and 5.6% was found for ticagrelor 90 mg and 60 mg, respectively, compared to a 1.5% decrease in the placebo group. In PLATO, the frequency of gouty arthritis, was 0.2% for ticagrelor vs 0.1% for clopidogrel. The corresponding numbers for gout/gouty arthritis in PEGASUS were 1.6%, 1.5% and 1.1% for ticagrelor 90 mg, 60 mg and placebo, respectively.

#### **Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

#### **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 Undesirable effects).

In the event of an overdose, the above potential adverse reactions could occur and ECG monitoring should be considered.

There is currently no known antidote to reverse the effects of ticagrelor, and ticagrelor is not dialysable (see Special warnings and precautions for use). Treatment of overdose should follow local standard medical practice. The expected effect of excessive ticagrelor dosing is prolonged duration of bleeding risk associated with platelet inhibition. Platelet transfusion is unlikely to be of clinical benefit in patients with bleeding (see Special warnings and precautions for use). If bleeding occurs other appropriate supportive measures should be taken.

### **PHARMACOLOGICAL PROPERTIES**

#### **Pharmacodynamic properties**

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

#### **Mechanism of action**

Brilinta contains ticagrelor, a member of the chemical class cyclopentyltriazolopyrimidines (CPTP), which is an oral, direct acting, selective and reversibly binding P2Y<sub>12</sub> receptor antagonist that prevents adenosine diphosphate (ADP)- mediated P2Y<sub>12</sub> dependent platelet activation and aggregation. Ticagrelor does not prevent ADP binding but when bound to the P2Y<sub>12</sub> 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, also increases local endogenous adenosine levels by inhibiting the equilibrative nucleoside transporter -1 (ENT-1).

Ticagrelor has been documented to augment the following adenosine-induced effects in healthy subjects and in patients with ACS: vasodilation (measured by coronary blood flow increases in healthy volunteers and ACS patients; headache), inhibition of platelet function (in human whole blood *in vitro*) and dyspnoea. However, a link between the observed increases in adenosine and clinical outcomes (e.g. morbidity-mortality) has not been clearly elucidated.

#### Pharmacodynamic effects

##### *Onset of Action*

In patients with stable coronary artery disease on 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 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 75 mg to ticagrelor 90 mg 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 Posology and method of administration).

#### 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 Therapeutic indications).

On a background of daily ASA, 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.

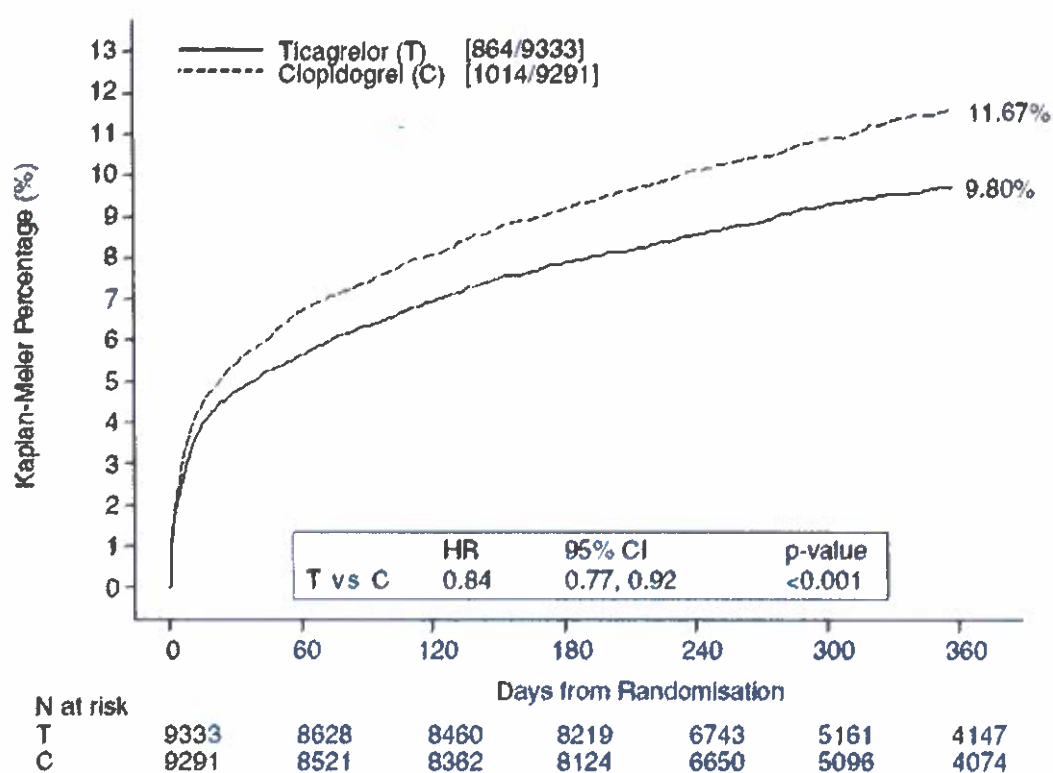
The result appeared early (absolute risk reduction [ARR] 0.6% and relative risk Reduction [RRR] of 12% at 30 days), with a constant treatment effect over the entire 12 month period, yielding ARR 1.9% per year with RRR of 16%. This suggests it is appropriate to treat patients with ticagrelor for up to 12 months (see Posology and method of administration). 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 Interaction with other medicinal products and other forms of interaction); 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 ASA dose such that reduced efficacy was observed with ticagrelor with increasing ASA doses. Chronic daily ASA doses to accompany ticagrelor should be 75-150 mg (see Posology and method of administration and Special warnings and precautions for use).

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 4).



**Table 4 -Outcome Events in PLATO**

	<b>Ticagrelor (% patients with event) N=9333</b>	<b>Clopidogrel (% patients with event) N=9291</b>	<b>ARR * (%/y r)</b>	<b>RRR<sup>a</sup> (%) (95% CI)</b>	<b>p-value</b>
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 <sup>d</sup>
CV death	3.8	4.8	1.1	21 (9, 31)	0.0013
MI (excl. silent MI) <sup>b</sup>	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 <sup>c</sup>	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 <sup>d</sup>
Definite stent thrombosis	1.2	1.7	0.6	32 (8, 49)	0.0123 <sup>d</sup>

<sup>a</sup>ARR = absolute risk reduction; RRR = relative risk reduction = (1-Hazard ratio) x 100%. A negative RRR indicates a relative risk increase.

<sup>b</sup>excluding silent myocardial infarction.

<sup>c</sup>SRI = 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.

<sup>d</sup>nominal 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  $\geq 3$  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 Special warnings and precautions for use). 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 ticagrelor 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

In a randomised, double-blind, parallel-group Phase III study (HESTIA 3), 193 paediatric patients (ages 2 to less than 18 years) with sickle cell disease were randomised to receive either placebo or ticagrelor at doses of 15 mg to 45 mg twice daily depending on body weight. Ticagrelor resulted in a median platelet inhibition of 35% at pre-dose and 56% at 2 hours post-dose at steady state.

Compared to placebo, there was no treatment benefit of ticagrelor on the rate of vaso-occlusive crises.

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 Posology and method of administration and Pharmacokinetic properties).

#### **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 well as the active metabolite are P-gp substrates.

Ticagrelor as crushed tablets mixed in water, given orally or administered through a nasogastric tube into the stomach, has a comparable bioavailability to whole tablets with regards to AUC and  $C_{max}$  for ticagrelor and the active metabolite. Initial exposure (0.5 and 1-hour post-dose) from crushed ticagrelor tablets mixed in water was higher compared to whole tablets, with a generally identical concentration profile thereafter (2 to 48 hours).

#### Distribution

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

#### 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 P2Y<sub>12</sub> 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 ( $\geq 75$  years) ACS patients compared to younger patients by the population pharmacokinetic analysis. These differences are not considered clinically significant (see Posology and method of administration).

##### *Paediatric population*

Limited data are available in children with sickle cell disease (see Posology and method of administration and Pharmacodynamic properties).

In the HESTIA 3 study, patients aged 2 to less than 18 years weighing  $\geq 12$  to  $\leq 24$  kg,  $> 24$  to  $\leq 48$  kg and  $> 48$  kg, were administered ticagrelor as paediatric dispersible 15 mg tablets at doses of respectively 15, 30 and 45 mg twice daily. Based on population pharmacokinetic analysis, the mean AUC ranged from 1095 ng\*h/mL to 1458 ng\*h/mL and the mean  $C_{max}$  ranged from 143 ng/mL to 206 ng/mL at steady state.

##### *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.

In patients with end stage renal disease on haemodialysis AUC and  $C_{max}$  of ticagrelor 90 mg administered on a day without dialysis were 38% and 51% higher compared to subjects with normal renal function. A similar increase in exposure was observed when ticagrelor was administered immediately prior to dialysis (49% and 61%, respectively) showing that ticagrelor is not dialysable. Exposure of the active metabolite increased to a lesser extent

(AUC 13-14% and  $C_{max}$  17-36%). The inhibition of platelet aggregation (IPA) effect of ticagrelor was independent of dialysis in patients with end stage renal disease and similar to subjects with normal renal function (see Posology and method of administration).

#### *Hepatic impairment*

$C_{max}$  and AUC for ticagrelor were 12% and 23% higher in patients with mild hepatic impairment compared to matched healthy subjects, respectively. However, the IPA effect of ticagrelor was similar between the two groups. No dose adjustment is needed for patients with mild hepatic impairment. Ticagrelor has not been studied in patients with severe hepatic impairment and there is no pharmacokinetic information in patients with moderate hepatic impairment. In patients that had moderate or severe elevation in one or more liver function tests at baseline, ticagrelor plasma concentrations were on average similar or slightly higher as compared to those without baseline elevations. No dose adjustment is recommended in patients with moderate hepatic impairment (see Posology and method of administration and Special warnings and precautions for use).

#### *Ethnicity*

Patients of Asian descent have a 39% higher mean bioavailability compared to Caucasian patients. Patients self-identified as black had an 18% lower bioavailability of ticagrelor compared to Caucasian patients. In clinical pharmacology studies, the exposure ( $C_{max}$  and AUC) to ticagrelor in Japanese subjects was approximately 40% (20% after adjusting for body weight) higher compared to that in Caucasians. The exposure in patients self-identified as Hispanic or Latino was similar to that in Caucasians.

#### **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 Undesirable effects).

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 tumors 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 fetuses 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 Fertility, pregnancy and lactation).

#### **PHARMACEUTICAL PARTICULARS**

### **List of excipients**

#### *Tablet core*

Mannitol (E421).  
Calcium hydrogen phosphate dihydrate.  
Magnesium stearate (E470b).  
Sodium starch glycolate type A  
Hydroxypropyl-cellulose (E463).

#### *Tablet coating*

Talc.  
Titanium dioxide (E171).  
Iron oxide yellow (E172).  
Macrogol 400.  
Hypromellose (E464).

### **Incompatibilities**

Not applicable.

### **Shelf life**

Please refer to expiry date on outer carton

### **Special precautions for storage**

Do not store above 30°C

### **Pack size**

Please refer to the outer carton for pack size.

### **Special precautions for disposal**

No special requirements.

### **Date of revision of text**

March 2022

Doc ID-001607915 V.13.0

Brilinta is a trademark of the AstraZeneca group of companies.

© AstraZeneca 2011-2022

### **Name and address of manufacturer**

AstraZeneca AB  
SE-151 85  
Södertälje  
Sweden