ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Brilique 90 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 90 mg ticagrelor.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Brilique, 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 section 5.1.

4.2 Posology and method of administration

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

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

In patients with Acute Coronary Syndromes (ACS), premature discontinuation with any antiplatelet therapy, including Brilique, could result in an increased risk of cardiovascular death, or myocardial infarction due to the patient's underlying disease (see section 4.4). Therefore, premature discontinuation of treatment should be avoided.

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

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

Special populations

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

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

Hepatic impairment
No dose adjustment is necessary for patients with mild hepatic impairment. Brilique has not been studied in patients with moderate or severe hepatic impairment. Its use in patients with moderate to severe hepatic impairment is therefore contraindicated (see section 4.3, 4.4 and 5.2).

Paediatric population
The safety and efficacy of Brilique in children below the age of 18 in the approved adult indication has not been established. No data are available (see section 5.1 and 5.2).

Method of administration
For oral use. Brilique can be administered with or without food.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Active pathological bleeding
- History of intracranial haemorrhage (see section 4.8)
- Moderate to severe hepatic impairment (see section 4.3, 4.4 and 5.2)
- Co-administration of ticagrelor with strong CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin, nefazodone, ritonavir, and atazanavir) is contraindicated, as co-administration may lead to a substantial increase in exposure to ticagrelor (see section 4.4 and 4.5).

4.4 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 Brilique 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 section 4.8).

Therefore, the use of Brilique in patients at known increased risk for bleeding should be balanced against the benefit in terms of prevention of atherothrombotic events. If clinically indicated, Brilique should be used with caution in the following patient groups:

- Patients with a propensity to bleed (e.g. due to recent trauma, recent surgery, coagulation disorders, active or recent gastrointestinal bleeding). The use of Brilique is contraindicated in patients with active pathological bleeding, in those with a history of intracranial haemorrhage, and in patients with moderate to severe hepatic impairment (see section 4.3).
- Patients with concomitant administration of medicinal products that may increase the risk of bleeding (e.g. non-steroidal anti-inflammatory drugs (NSAIDs), oral anticoagulants and/or fibrinolytics) within 24 hours of Brilique dosing.

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

Antifibrinolytic therapy (aminocaproic acid or tranexamic acid) and/or recombinant factor VIIa may increase haemostasis. Brilique 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 Brilique before any surgery is scheduled and before any new medicinal product is taken.

In PLATO patients undergoing coronary artery bypass grafting (CABG), Brilique had more bleeding than clopidogrel when stopped within 1 day prior to surgery but a similar rate of major bleeds compared to clopidogrel after stopping therapy 2 or more days before surgery (see section 4.8). If a patient is to undergo elective surgery and antiplatelet effect is not desired, Brilique should be discontinued 7 days prior to surgery (see section 5.1).

Patients at risk for bradycardic events
Due to observations of mostly asymptomatic ventricular pauses in an earlier clinical study, patients with an increased risk of bradycardic events (e.g. patients without a pacemaker who have sick sinus syndrome, 2nd or 3rd degree AV block or bradycardic-related syncope) were excluded from the main PLATO study evaluating the safety and efficacy of Brilique. Therefore, due to the limited clinical experience, Brilique should be used with caution in these patients (see section 5.1).

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

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

Dyspnoea
Dyspnoea was reported by 13.8% of patients treated with Brilique and by 7.8% of patients treated with clopidogrel. In 2.2% of patients, investigators considered the dyspnoea causally related to treatment with Brilique. It is usually mild to moderate in intensity and often resolves without need for treatment discontinuation. Patients with asthma/COPD may have an increased absolute risk of experiencing dyspnoea with Brilique (see section 4.8). Ticagrelor should be used with caution in patients with history of asthma and/or COPD. The mechanism has not been elucidated. If a patient reports new, prolonged or worsened dyspnoea this should be investigated fully and if not tolerated, treatment with Brilique should be stopped.

Creatinine elevations
Creatinine levels may increase during treatment with Brilique (see section 4.8). The mechanism has not been elucidated. Renal function should be checked after one month and thereafter according to routine medical practice, paying special attention to patients $\geq$ 75 years, patients with moderate/severe renal impairment and those receiving concomitant treatment with an ARB.

Uric acid increase
In PLATO study, patients on ticagrelor had a higher risk of hyperuricaemia than those patients receiving clopidogrel (see section 4.8). Caution should be exercised when administering ticagrelor to patients with history of hyperuricaemia or gouty arthritis. As a precautionary measure, the use of ticagrelor in patients with uric acid nephropathy is discouraged.

Other
Based on a relationship observed in PLATO between maintenance ASA dose and relative efficacy of ticagrelor compared to clopidogrel, co-administration of Brilique and high maintenance dose ASA (>300 mg) is not recommended (see section 5.1).

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

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

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

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

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

4.5 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-gp substrate and a weak P-gp inhibitor and may increase the exposure of P-gp substrates.

Effects of other medicinal products on Brilique

Medicinal products metabolised by CYP3A4
CYP3A4 inhibitors

- Strong CYP3A4 inhibitors – Co-administration of ketoconazole with ticagrelor increased the ticagrelor C_{max} and AUC equal to 2.4-fold and 7.3-fold, respectively. The C_{max} and AUC of the active metabolite were reduced by 89% and 56%, respectively. Other strong inhibitors of CYP3A4 (clarithromycin, nefazodone, ritonavir, and atazanavir) would be expected to have similar effects and their concomitant use with Brilique is contraindicated (see section 4.3 and 4.4).

- Moderate CYP3A4 inhibitors – Co-administration of diltiazem with ticagrelor increased the ticagrelor C_{max} by 69% and AUC to 2.7 fold and decreased the active metabolite C_{max} by 38% and AUC was unchanged. There was no effect of ticagrelor on diltiazem plasma levels. Other moderate CYP3A4 inhibitors (e.g. amprenavir, aprepitant, erythromycin and fluconazole) would be expected to have a similar effect and can as well be co-administered with Brilique.

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. dexamethasone, phenytoin, carbamazepine and phenobarbital) would be expected to decrease the exposure to Brilique as well. Co-administration of ticagrelor with potent CYP3A inducers may decrease exposure and efficacy of ticagrelor (see section 4.4).

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 Brilique (see section 4.4).

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

Effects of Brilique 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. Brilique may have similar effect on lovastatin. The concomitant use of Brilique with doses of simvastatin or lovastatin greater than 40 mg is not recommended (see section 4.4).
- *Atorvastatin* - Co-administration of atorvastatin and ticagrelor increased atorvastatin acid C_{max} by 23% and AUC by 36%. Similar increases in AUC and C_{max} were observed for all atorvastatin acid metabolites. These increases are not considered clinically significant.
- A similar effect on other statins metabolised by CYP3A4 cannot be excluded. Patients in PLATO receiving ticagrelor took a variety of statins, with no concern of an association with statin safety among the 93% of the PLATO cohort taking these medicinal products.

Ticagrelor is a mild CYP3A4 inhibitor. Co-administration of Brilique and CYP3A4 substrates with narrow therapeutic indices (i.e., cisapride or ergot alkaloids) is not recommended, as ticagrelor may increase the exposure to these medicinal products (see section 4.4).

Medicinal products metabolised by CYP2C9
Co-administration of Brilique 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 Brilique 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 Brilique.

P-glycoprotein (P-gp) substrates (including digoxin, cyclosporin)
Concomitant administration of Brilique increased the digoxin C_{max} by 75% and AUC by 28%. The mean trough digoxin levels were increased about 30% with ticagrelor co-administration with some individual maximum increases to 2 fold. In the presence of digoxin, the C_{max} and AUC of ticagrelor and its active metabolite were not affected. Therefore, appropriate clinical and/or laboratory monitoring is recommended when giving narrow therapeutic index P-gp dependent medicinal products like digoxin or cyclosporin concomitantly with Brilique (see section 4.4).

Other concomitant therapy

Medicinal products known to induce bradycardia
Due to observations of mostly asymptomatic ventricular pauses and bradycardia, caution should be exercised when administering Brilique concomitantly with medicinal products known to induce

bradycardia (see section 4.4). However no evidence of clinically significant adverse reactions was observed in the PLATO trial after concomitant administration with one or more medicinal products known to induce bradycardia (e.g., 96% beta blockers, 33% calcium channel blockers diltiazem and verapamil, and 4% digoxin).

In the PLATO study, Brilique 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 section 5.1). No evidence of clinically significant adverse interactions with these medicinal products was observed.

Co-administration of Brilique 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 Brilique with medicinal products known to alter haemostasis (see section 4.4).

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

4.6 Fertility, pregnancy and lactation

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

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

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

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

4.7 Effects on ability to drive and use machines

No studies on the effects of Brilique on the ability to drive and use machines have been performed. Brilique has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

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

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

Tabulated summary of adverse reactions
The following adverse reactions have been identified following studies with Brilique (Table 1).

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

Table 1 Adverse reactions by frequency and System Organ Class (SOC)

System Organ Class	Common	Uncommon	Rare
Metabolism and nutrition disorders			Hyperuricaemia[a]
Psychiatric disorders			Confusion
Nervous system disorders		Intracranial haemorrhage[b], Dizziness, Headache	Paraesthesia
Eye disorders		Eye haemorrhage (intraocular, conjunctival, retinal)	
Ear and labyrinth disorders			Ear haemorrhage, Vertigo
Respiratory, thoracic and mediastinal disorders	Dyspnoea[c], Epistaxis	Haemoptysis	
Gastrointestinal disorders	Gastrointestinal haemorrhage[d]	Haematemesis, Gastroinstestinal ulcer haemorrhage[e], Haemorrhoidal haemorrhage, Gastritis, Oral haemorrhage (including gingival bleeding), Vomiting, Diarrhoea, Abdominal pain, Nausea, Dyspepsia	Retroperitoneal haemorrhage, Constipation
Skin and subcutaneous tissue disorders	Subcutaneous or dermal bleeding[f], Bruising[g]	Rash, Pruritus	
Musculoskeletal and connective tissue disorders			Haemarthrosis[#]
Renal and urinary disorders		Haemorrhage urinary tract[h]	
Reproductive system and breast disorders		Vaginal bleeding (including metrorrhagia)	
Investigations			Blood creatinine increased
Injury, poisoning and procedural complications	Procedural site haemorrhage[i]	Post procedural haemorrhage, Haemorrhage	Wound haemorrhage, Traumatic haemorrhage

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

[a] Hyperuricaemia, Blood uric acid increased

[b] Cerebral haemorrhage, Haemorrhage intracranial, Haemorrhagic stroke,

[c] Dyspnoea, Dyspnoea exertional, Dyspnoea at rest, Nocturnal dyspnoea

[d] Gastrointestinal haemorrhage, Rectal haemorrhage, Intestinal haemorrhage, Melaena, Occult blood

[e] Gastrointestinal ulcer haemorrhage, Gastric ulcer haemorrhage, Duodenal ulcer haemorrhage, Peptic ulcer haemorrhage

[f] Subcutaneous haematoma, Skin haemorrhage, Haemorrhage subcutaneous, Petechiae

[g] Contusion, Haematoma, Ecchymosis, Increased tendency to bruise, Traumatic haematoma

[h] Haematuria, Blood urine present, Haemorrhage urinary tract

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

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

Description of selected adverse reactions

Bleeding

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

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

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

Bleeding category definitions:

Major Fatal/Life-threatening Bleed: Clinically apparent with >50 g/l decrease in haemoglobin or ≥4 red cell units transfused; or fatal; or intracranial; or intrapericardial with cardiac tamponade; or with hypovolaemic shock or severe hypotension requiring pressors or surgery.
Major Other: Clinically apparent with 30-50 g/l decrease in haemoglobin or 2-3 red cell units transfused; or significantly disabling.
Minor Bleed: Requires medical intervention to stop or treat bleeding.
TIMI Major Bleed: Clinically apparent with >50 g/l decrease in haemoglobin or intracranial haemorrhage.
TIMI Minor Bleed: Clinically apparent with 30-50 g/l decrease in haemoglobin.

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

Age, sex, weight, race, geographic region, concurrent conditions, concomitant therapy, and medical history, including a previous stroke or transient ischaemic attack, all did not predict either overall or non-procedural PLATO Major bleeding. Thus no particular group was identified at risk for any subset of bleeding.

CABG-related bleeding: In PLATO, 42% of the 1584 patients (12% of cohort) who underwent coronary artery bypass graft (CABG) surgery had a PLATO Major Fatal/Life-threatening bleeding

with no difference between treatment groups. Fatal CABG bleeding occurred in 6 patients in each treatment group (see section 4.4).

Non-CABG related bleeding and non-procedural related bleeding: Brilique 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.

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

Compared with clopidogrel, patients with asthma/COPD treated with ticagrelor may have an increased risk of experiencing non-serious dyspnoea (3.29% ticagrelor versus 0.53% clopidogrel) and serious dyspnoea (0.38% ticagrelor versus 0.00% clopidogrel). In absolute terms, this risk was higher than in the overall PLATO population. Ticagrelor should be used with caution in patients with history of asthma and/or COPD (see section 4.4).

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

Investigations
Creatinine elevations: In PLATO, serum creatinine concentration significantly increased by >30% in 25.5% of patients receiving ticagrelor compared to 21.3% of patients receiving clopidogrel and by >50% in 8.3% of patients receiving ticagrelor compared to 6.7% of patients receiving clopidogrel. Creatinine elevations by >50% were more pronounced in patients > 75 years (ticagrelor 13.6% versus clopidogrel 8.8%), in patients with severe renal impairment at baseline (ticagrelor 17.8% versus clopidogrel 12.5%) and in patients receiving concomitant treatment with ARBs (ticagrelor 11.2% versus clopidogrel 7.1%). Within these subgroups renal-related serious adverse events and adverse events leading to discontinuation of study drug were similar between treatment groups. The totality of renal AEs reported were 4.9% for ticagrelor vs. 3.8% for clopidogrel, however a similar percent of patients reported events considered by the investigators as causally related to treatment; 54 (0.6%) for ticagrelor and 43 (0.5%) for clopidogrel.

Uric acid elevations: In PLATO, serum uric acid concentration increased to more than upper limit of normal in 22% of patients receiving ticagrelor compared to 13% of patients receiving clopidogrel. Mean serum uric acid concentration increased approximately 15% with ticagrelor compared to approximately 7.5% with clopidogrel and after treatment was stopped, decreased to approximately 7% on ticagrelor but with no decrease observed for clopidogrel. The hyperuricaemia AEs reported were 0.5% for ticagrelor vs. 0.2% for clopidogrel. Of these AEs 0.05% for ticagrelor vs. 0.02% for

clopidogrel were considered causally related by investigators. For gouty arthritis, the AEs reported were 0.2% for ticagrelor vs 0.1% for clopidogrel; none of these adverse events were assessed as causally related by investigators.

4.9 Overdose

Ticagrelor is well tolerated in single doses up to 900 mg. Gastrointestinal toxicity was dose-limiting in a single ascending dose study. Other clinically meaningful adverse reactions which may occur with overdose include dyspnoea and ventricular pauses (see section 4.8).

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

There is currently no known antidote to reverse the effects of Brilique, and Brilique is not expected to be dialysable (see section 4.4). Treatment of overdose should follow local standard medical practice. The expected effect of excessive Brilique dosing is prolonged duration of bleeding risk associated with platelet inhibition. If bleeding occurs appropriate supportive measures should be taken.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Brilique contains ticagrelor a member of the chemical class cyclopentyltriazolopyrimidines (CPTP), which is a selective adenosine diphosphate (ADP) receptor antagonist acting on the $P2Y_{12}$ ADP-receptor that can prevent ADP-mediated platelet activation and aggregation. Ticagrelor is orally active, and reversibly interacts with the platelet $P2Y_{12}$ ADP-receptor. Ticagrelor does not interact with the ADP binding site itself, but interacts with platelet $P2Y_{12}$ ADP-receptor to prevent signal transduction.

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 to ticagrelor results in an absolute IPA increase of 26.4% and switching from ticagrelor to clopidogrel results in an absolute IPA decrease of 24.5%. Patients can be switched from clopidogrel to ticagrelor without any interruption of antiplatelet effect (see section 4.2).

Clinical efficacy and safety

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

On a background of daily 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] 1.0% and Relative Risk Reduction [RRR] of 12% at 30 days), with a constant treatment effect over the entire 12 month period, yielding ARR 1.9% per year with RRR of 16%. This suggests it is appropriate to treat patients with ticagrelor for up to 12 months (see section 4.2). Treating 54 ACS patients with ticagrelor instead of clopidogrel will prevent 1 atherothrombotic event; treating 91 will prevent 1 CV death (see Figure 1 and Table 3).

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

A weakly significant treatment interaction was observed with region whereby the HR for the primary endpoint favours ticagrelor in the rest of world but favours clopidogrel in North America, which represented approximately 10% of the overall population studied (interaction p-value=0.045). Exploratory analyses suggest a possible association with ASA dose such that reduced efficacy was observed with ticagrelor with increasing ASA doses. Chronic daily ASA doses to accompany Brilique should be 75-150 mg (see section 4.2 and 4.4).

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

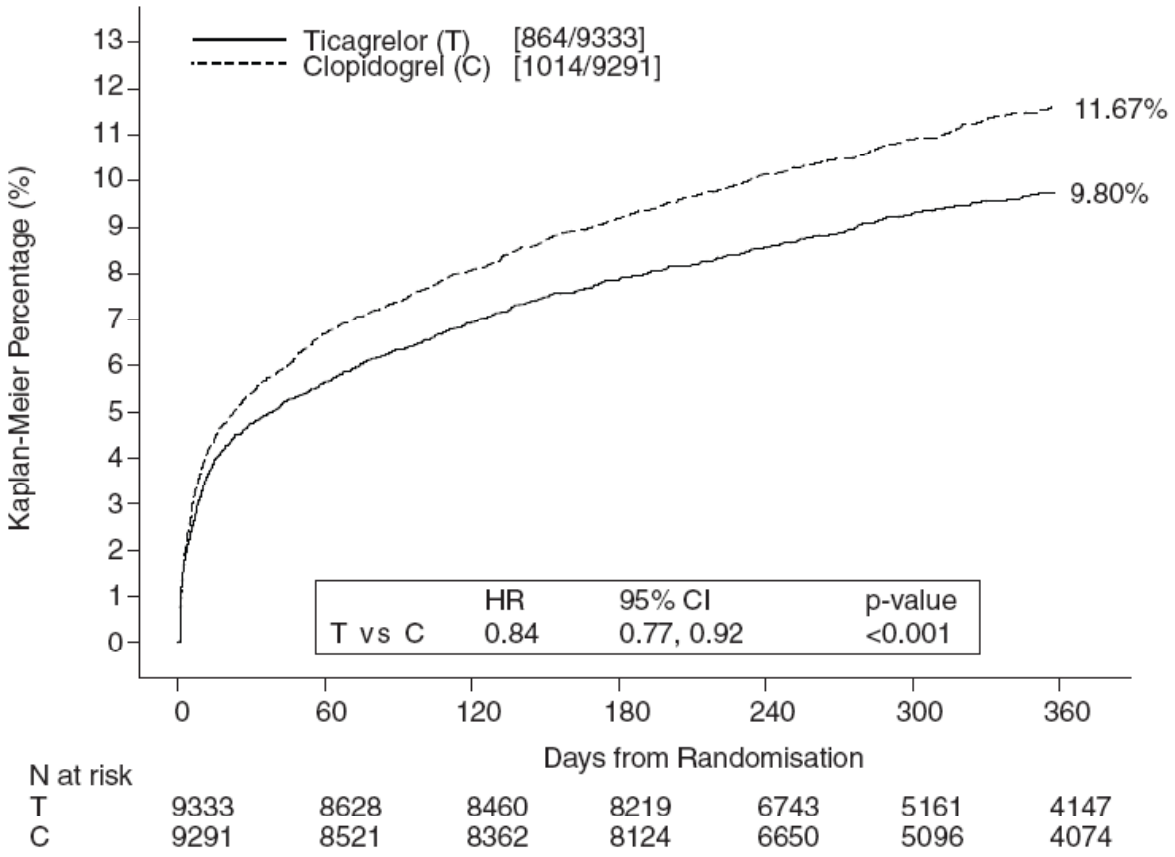

Figure 1 – Time to first occurrence of CV death, MI and Stroke (PLATO)

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

Table 3 -Outcome Events in PLATO

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

[a]ARR = absolute risk reduction; RRR = relative risk reduction = (1-Hazard ratio) x 100%. A negative RRR indicates a relative risk increase.
[b]excluding silent myocardial infarction.
[c]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.
[d]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 ≥3 seconds. More patients had ventricular pauses with ticagrelor (6.0%) than with clopidogrel (3.5%) in the acute phase; and 2.2% and 1.6% respectively after 1 month (see section 4.4). The increase in ventricular pauses in the acute phase of ACS was more pronounced in ticagrelor patients with history of CHF (9.2% versus 5.4% in patients without CHF history; for clopidogrel patients, 4.0% in those with versus 3.6% in those without CHF history) This imbalance did not occur at one month: 2.0% versus 2.1% for ticagrelor patients with and without CHF history respectively; and 3.8% versus 1.4% with clopidogrel. There were no adverse clinical consequences associated with this imbalance (including pacemaker insertions) in this population of patients.

PLATO genetic substudy

CYP2C19 and ABCB1 genotyping of 10,285 patients in PLATO provided associations of genotype groups with PLATO outcomes. The superiority of ticagrelor over clopidogrel in reducing major CV events was not significantly affected by patient CYP2C19 or ABCB1 genotype. Similar to the overall PLATO study, total PLATO Major bleeding did not differ between ticagrelor and clopidogrel, regardless of CYP2C19 or ABCB1 genotype. Non-CABG PLATO Major bleeding was increased with ticagrelor compared clopidogrel in patients with one or more CYP2C19 loss of function alleles, but similar to clopidogrel in patients with no loss of function allele.

Combined efficacy and safety composite

A combined efficacy and safety composite (CV death, MI, stroke, or PLATO-defined 'Total Major' bleeding) indicates that the benefit in efficacy of Brilique compared to clopidogrel is not offset by the major bleeding events (ARR 1.4%, RRR 8%, HR 0.92; p=0.0257) over 12 months after ACS.

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

5.2 Pharmacokinetic properties

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

Absorption
Absorption of ticagrelor is rapid with a median t_{max} of approximately 1.5 hours. The formation of the major circulating metabolite AR-C124910XX (also active) from ticagrelor is rapid with a median t_{max} of approximately 2.5 hours. Following oral administration of ticagrelor 90 mg under fasted conditions, C_{max} is 529 ng/ml and AUC is 3451 ng*h/ml. The metabolite parent ratios are 0.28 for C_{max} and 0.42 for AUC.

The mean absolute bioavailability of ticagrelor was estimated to be 36%. Ingestion of a high-fat meal resulted in a 21% increase in ticagrelor AUC and 22% decrease in the active metabolite C_{max} but had no effect on ticagrelor C_{max} or the AUC of the active metabolite. These small changes are considered of minimal clinical significance; therefore, ticagrelor can be given with or without food. Ticagrelor as well as the active metabolite are P-gp substrates.

Distribution
The steady state volume of distribution of ticagrelor is 87.5 l. Ticagrelor and the active metabolite is extensively bound to human plasma protein (>99.7%).

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 $P2Y_{12}$ 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 (≥ 75years) ACS patients compared to younger patients by the population pharmacokinetic analysis. These differences are not considered clinically significant (see section 4.2).

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

Gender
Higher exposures to ticagrelor and the active metabolite were observed in women compared to men. These differences are not considered clinically significant.

Renal impairment
Exposure to ticagrelor and the active metabolite were approximately 20% lower in patients with severe renal impairment (creatinine clearance <30 ml/min) compared to subjects with normal renal function (see section 4.2).

Hepatic impairment
C_{max} and AUC for ticagrelor were 12% and 23% higher in patients with mild hepatic impairment compared to matched healthy subjects, respectively (see section 4.2). Ticagrelor has not been studied in patients with moderate or severe hepatic impairment and its use in these patients is contraindicated (see section 4.3 and 4.4).

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

5.3 Preclinical safety data

Preclinical data for ticagrelor and its major metabolite have not demonstrated unacceptable risk for adverse effects for humans based on conventional studies of safety pharmacology, single and repeated dose toxicity and genotoxic potential.

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

In female rats, ticagrelor at high dose showed an increased incidence of uterine tumors (adenocarcinomas) and an increased incidence of hepatic adenomas. The mechanism for uterine tumors 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 foetuses from dams at high dose without showing maternal toxicity (safety margin of 4.5).

Studies in rats and rabbits have shown reproductive toxicity, with slightly reduced maternal body weight gain and reduced neonatal viability and birth weight, with delayed growth. Ticagrelor produced irregular cycles (mostly extended cycles) in female rats, but did not affect overall fertility in male and female rats. Pharmacokinetic studies performed with radio-labeled ticagrelor have shown that the parent compound and its metabolites are excreted in the milk of rats (see section 4.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

- PVC-PVDC/Al transparent blister (with sun/moon symbols) of 10 tablets; cartons of 60 tablets (6 blisters) and 180 tablets (18 blisters).
- PVC-PVDC/Al transparent calendar blister (with sun/moon symbols) of 14 tablets; cartons of 14 tablets (1 blister), 56 tablets (4 blisters), and 168 tablets (12 blisters).
- PVC-PVDC/Al perforated unit dose transparent blister of 10 tablets; cartons of 100x1 tablets (10 blisters).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

AstraZeneca AB
S-151 85
Södertälje
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

AstraZeneca AB
Gärtunavägen
SE-151 85 Södertälje
Sweden

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **Conditions or restrictions regarding supply and use imposed on the marketing authorisation holder**

Medicinal product subject to medical prescription.

- **Conditions or restrictions with regard to the safe and effective use of the medicinal product**

Not applicable

- **Other conditions**

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance, as described in version 11 (21 June 2010) presented in Module 1.8.1. of the Marketing Authorisation Application, is in place and functioning before and whilst the product is on the market.

Risk Management Plan

The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 4 (21 September 2010) of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the EMA.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF 90 mg FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Brilique 90 mg film-coated tablets
ticagrelor

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 90 mg ticagrelor

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
56 film-coated tablets
60 film-coated tablets
100x1 film-coated tablets
168 film-coated tablets
180 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca AB
S-151 85
Södertälje
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Brilique 90 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

PERFORATED UNIT DOSE BLISTER (100X1 TABLETS)

1. NAME OF THE MEDICINAL PRODUCT

Brilique 90 mg tablets
ticagrelor

2. NAME OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca AB

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER (10 TABLETS)

1. NAME OF THE MEDICINAL PRODUCT

Brilique 90 mg tablets
ticagrelor

2. NAME OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca AB

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Sun/Moon symbol

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

CALENDAR BLISTER (14 TABLETS)

1. NAME OF THE MEDICINAL PRODUCT

Brilique 90 mg tablets
ticagrelor

2. NAME OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca AB

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Mon Tue Wed Thu Fri Sat Sun
Sun/Moon symbol

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Brilique 90 mg film-coated tablets
ticagrelor

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT BRILIQUE IS AND WHAT IT IS USED FOR

What Brilique is
Brilique contains the active substance called ticagrelor. This belongs to a group of medicines called anti-platelet medicines.

How Brilique works
Brilique affects cells called 'platelets' (also called thrombocytes). These very small blood cells help stop bleeding by clumping together to plug tiny holes in blood vessels that are cut or damaged.

However, platelets can also form clots inside diseased blood vessels in the heart and brain. This can be very dangerous because:
- the clot can cut off the blood supply completely - this can cause a heart attack (myocardial infarction) or stroke, or
- the clot can partly block the blood vessels to the heart - this reduces the blood flow to the heart and can cause chest pain which comes and goes (called 'unstable angina').

Brilique helps stop the clumping of platelets. This reduces the chance of a blood clot forming that can reduce blood flow.

What Brilique is used for
Brilique is to be used in adults only. You have been given Brilique because you have had:
- a heart attack, or
- unstable angina (angina or chest pain that is not well controlled).

Brilique reduces the chances of you having another heart attack or a stroke or of dying from a disease related to your heart or blood vessels.

2. BEFORE YOU TAKE BRILIQUE

Do not take Brilique if:
- You are allergic (hypersensitive) to ticagrelor or any of the other ingredients of Brilique (listed in Section 6: Further information).

- You are bleeding now or have bled recently inside your body, such as bleeding in your stomach or gut from an ulcer.
- You have moderate to severe liver disease
- You are taking any of the following medicines: ketoconazole (used to treat fungal infections), clarithromycin (used to treat bacterial infections), nefazodone (an antidepressant), ritonavir and atazanavir (used to treat HIV infection and AIDS).
- You have had a stroke caused by bleeding in the brain.

Do not take Brilique if any of the above applies to you. If you are not sure, talk to your doctor or pharmacist before taking Brilique.

Take special care with Brilique
Check with your doctor, pharmacist or dentist before taking Brilique if:
- You have an increased risk of bleeding because of:
  - a recent serious injury
  - recent surgery (including dental work)
  - you have a condition that affects blood clotting
  - recent bleeding from your stomach or gut (such as a stomach ulcer or colon 'polyps')
- You are due to have surgery (including dental work) at any time while taking Brilique. This is because of the increased risk of bleeding. Your doctor may want you to stop taking Brilique 7 days prior to surgery.
- Your heart rate is abnormally low (usually lower than 60 beats per minute) and you do not already have in place a device that paces your heart (pacemaker).
- You have asthma or other lung problem or breathing difficulties.
- You have had a blood test that showed more than the usual amount of uric acid

If any of the above apply to you (or you are not sure), talk to your doctor, pharmacist or dentist before taking Brilique.

Children
Brilique is not recommended for children and adolescents under 18 years.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines that you buy without a prescription, dietary supplements and herbal remedies. This is because Brilique can affect the way some medicines work and some medicines can have an effect on Brilique.

Tell your doctor or pharmacist if you are taking any of the following medicines:
- more than 40 mg daily of either simvastatin or lovastatin (medicines used to treat high cholesterol)
- rifampicin (an antibiotic), phenytoin, carbamazepine and phenobarbital (used to control seizures), dexamethasone (used to treat inflammatory and auto immune conditions), digoxin (used to treat heart failure), cyclosporin (used to lessen your body's defenses), quinidine and diltiazem (used to treat abnormal heart rhythms), beta blockers and verapamil (used to treat high blood pressure).

In particular, tell your doctor or pharmacist if you are taking any of the following medicines that increase your risk of bleeding:
- 'oral anticoagulants' often referred to as 'blood thinners' which include warfarin.
- non-steroidal anti-inflammatory drugs (abbreviated as NSAIDs) often taken as pain killers such as ibuprofen and naproxen.
- selective serotonin reuptake inhibitors (abbreviated as SSRIs) taken as antidepressants such as paroxetine, sertraline and citalopram
- other medicines such as ketoconazole (used to treat fungal infections), clarithromycin (used to treat bacterial infections), nefazodone, (an antidepressant), ritonavir and atazanavir (used to treat HIV infection and AIDS), cisapride (used to treat heartburn), ergot alkaloids (used to treat migraines and headaches).

Also tell your doctor that because you are taking Brilique, you may have an increased risk of bleeding if your doctor gives you fibrinolytics, often called 'clot dissolvers', such as streptokinase or alteplase.

Taking Brilique with food and drink
You can take Brilique with or without food.

Pregnancy and breast-feeding
It is not recommended to use Brilique if you are pregnant or may become pregnant. Women should use appropriate contraceptive measures to avoid pregnancy while taking this medicine.
Talk to your doctor before taking Brilique if you are breast-feeding. Your doctor will discuss with you the benefits and risks of taking Brilique during this time.

Ask your doctor or pharmacist for advice before taking any medicine, if you are pregnant or breast-feeding.

Driving and using machines
Brilique is not likely to affect your ability to drive or use machines.

3. HOW TO TAKE BRILIQUE

Always take Brilique exactly as your doctor has told you. You should talk with your doctor or pharmacist if you are not sure.

How much to take
- The starting dose is two tablets at the same time (loading dose of 180 mg). This dose will usually be given to you in the hospital.
- After this starting dose, the usual dose is one tablet of 90 mg twice a day for up to 12 months unless your doctor tells you differently. Take Brilique around the same time everyday (for example, one tablet in the morning and one in the evening).

Your doctor will usually also tell you to take acetylsalicylic acid. This is a substance present in many medicines used to prevent blood clotting. Your doctor will tell you how much to take (usually between 75-150 mg daily).

How to take Brilique
- You can take the tablet with or without food.
- You can check when you last took a tablet of Brilique by looking on the blister. There is a sun (for the morning) and a moon (for the evening). This will tell you whether you have taken the dose.

If you take more Brilique than you should
If you take more Brilique than you should, talk to a doctor or go to hospital straight away. Take the medicine pack with you. You may be at increased risk of bleeding.

If you forget to take Brilique
- If you forget to take a dose, just take your next dose as normal.
- Do not take a double dose (two doses at the same time) to make up for the forgotten dose.

If you stop taking Brilique
Do not stop taking Brilique without talking to your doctor. Take Brilique on a regular basis and for as long as your doctor keeps prescribing it. If you stop taking Brilique, it may increase your chances of having another heart attack or stroke or dying from a disease related to your heart or blood vessels.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Brilique can cause side effects, although not everybody gets them. The following side effects may happen with this medicine:

The frequency of possible side effects listed below is defined using the following convention: common (affects 1 to 10 users in 100); uncommon (affects 1 to 10 users in 1,000); rare (affects 1 to 10 users in 10,000)

See a doctor straight away if you notice any of the following – you may need urgent medical treatment:

- **Signs of a stroke such as:**
  - sudden numbness or weakness of your arm, leg or face, especially if only on one side of the body
  - sudden confusion, difficulty speaking or understanding others
  - sudden difficulty in walking or loss of balance or co-ordination
  - suddenly feeling dizzy or sudden severe headache with no known cause

  These are signs of a kind of stroke caused by bleeding into the brain. This is uncommon.

- **Bleeding** – some bleeding is common. However, severe bleeding is uncommon, but can be life threatening. Bleeding of many different kinds can be increased, for example:
  - nosebleed (common)
  - blood in your urine (uncommon)
  - black stools or blood in your stools (common)
  - blood in your eye (uncommon)
  - coughing up or bringing up blood (uncommon)
  - vaginal bleeding that is heavier, or happens at different times, to your normal period (menstrual) bleeding (uncommon)
  - bleeding after surgery or from cuts and wounds that is more than normal (common)
  - bleeding from your stomach lining (ulcer) (uncommon).
  - bleeding gums (uncommon)
  - blood in your ear (rare)
  - internal bleeding (rare)
  - bleeding into joints causing painful swelling (rare)

Discuss with your doctor if you notice any of the following:

- **Feeling short of breath** - this is common. It might be due to your heart disease or another cause, or it might be a side effect of Brilique. If your feeling of shortness of breath gets worse or lasts a long time, tell your doctor. Your doctor will decide if it needs treatment or further investigations.

Other possible side effects

Common (affects 1 to 10 users in 100)

- Bruising

Uncommon (affects 1 to 10 users in 1,000)

- Headache
- Feeling dizzy or like the room is spinning
- Abdominal pain
- Diarrhoea or indigestion
- Feeling or being sick
- Rash
- Itching
- Inflamed stomach (gastritis)

Rare (affects 1 to 10 users in 10,000)
- Constipation
- A tingling feeling
- Confusion

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist, but do not stop taking Brilique until you have spoken to them.

5. HOW TO STORE BRILIQUE

Keep out of the reach and sight of children.
Do not use Brilique after the expiry date, which is stated on the blister and carton after EXP. The expiry date refers to the last day of that month.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Brilique contains
- The active substance is ticagrelor. Each film-coated tablet contains 90 mg of ticagrelor.

- The other ingredients are:
  Tablet core: mannitol (E421), dibasic calcium phosphate, sodium starch glycolate, hydroxypropyl-cellulose (E463), magnesium stearate (E470b)

  Tablet film coating: hypromellose (E464), titanium dioxide (E171), talc, polyethylene--glycol 400, and ferric oxide yellow (E172).

What Brilique looks like and contents of the pack
Film-coated tablet (tablet): The tablets are round, biconvex, yellow, film-coated marked with a “90” above “T” on one side.

Brilique is available in:
- standard blisters (with sun/moon symbols) in cartons of 60 and 180 tablets
- calendar blisters (with sun/moon symbols) in cartons of 14, 56 and 168 tablets
- perforated blisters in a carton of 100x1 tablets

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
AstraZeneca AB
S-151 85
Södertälje
Sweden

Manufacturer:
AstraZeneca AB
Gärtunavägen
SE-151 85
Södertälje
Sweden

Manufacturer:
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