SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Pocira 90 mg/50 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 90 mg of ticagrelor and 50 mg of acetylsalicylic acid.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule (capsule).

A white opaque hard gelatin capsule of size '00' (23.1-23.9 mm) printed with black ink '90-50 mg' on the capsule's body.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

<Product name> is indicated for the prevention of atherothrombotic events in adult patients with acute coronary syndromes (ACS).

4.2 Posology and method of administration

Posology

Treatment should be initiated with a single ticagrelor/acetylsalicylic acid 180 mg/100 mg loading dose (two capsules of <Product name>) and then continued at one capsule of <Product name> twice daily. Treatment with <Product name> twice daily is recommended for 12 months in ACS patients unless discontinuation is clinically indicated (see section 5.1).

In patients with ACS who have undergone a percutaneous coronary intervention (PCI) procedure and have an increased risk of bleeding, discontinuation of treatment with <Product name> may be considered after 3 months. In that case, treatment with ticagrelor as a single antiplatelet therapy should be continued for 9 months (see section 4.4).

Missed dose
Lapses in therapy should be avoided. A patient who misses a dose of <Product name> should take only one capsule (their next dose) at its scheduled time.

Special populations

Elderly
No dose adjustment is required in elderly (see section 5.2). In general, <Product name> should be used with caution in the elderly, as they are more prone to adverse reactions. The usual adult

dosage is recommended in the absence of severe renal or hepatic impairment (see sections 4.3 and 4.4). Treatment should be reviewed at regular intervals.

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

Hepatic impairment
<Product name> has not been studied in patients with severe hepatic impairment and its use in these patients is therefore contraindicated (see section 4.3). Only limited information is available in patients with moderate hepatic impairment. Dose adjustment is not recommended, but <Product name> should be used with caution (see sections 4.4 and 5.2). No dose adjustment is necessary for patients with mild hepatic impairment (see section 5.2).

Paediatric population
The safety and efficacy of <Product name> in children below the age of 18 years have not been established.

Method of administration
For oral use.
<Product name> can be administered with or without food.

For patients who are unable to swallow whole capsules, the capsules may be opened, and the content of the capsule may be crushed and mixed with half a glass of water immediately prior to use and administered orally. The glass should be rinsed with a further half glass of water and the contents drunk.

4.3 Contraindications

- Hypersensitivity to any of the active substances, to salicylic compounds or prostaglandin synthetase inhibitors (e.g. certain asthma patients who may suffer an attack or faint), or to any of the excipients listed in section 6.1 (see section 4.8).
- Active pathological bleeding.
- Active, or history of recurrent peptic ulcer and/or gastric/intestinal haemorrhage, or other kinds
  of bleeding such as cerebrovascular haemorrhages (see section 4.8).
- Haemorrhagic diathesis; coagulation disorders such as haemophilia and thrombocytopenia;
- Severe hepatic impairment (see sections 4.2, 4.4 and 5.2).
- Severe renal impairment (see sections 4.2, 4.4 and 5.2).
- Gout.
- Co-administration of <Product name> with strong CYP3A4 inhibitors (e.g. ketoconazole, clarithromycin, nefazodone, ritonavir and atazanavir), as co-administration may lead to a substantial increase in exposure to ticagrelor (see section 4.5).
- Methotrexate used at doses >15mg/week (see section 4.5)

4.4 Special warnings and precautions for use

Bleeding risk
The use of <Product name> in patients at known increased risk for bleeding should be balanced against the benefit in terms of prevention of atherothrombotic events (see sections 4.8 and 5.1). If clinically indicated, <Product name> 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 <Product name> is contraindicated in patients with active pathological bleeding, in those with a history of intracranial haemorrhage, and in

patients with severe hepatic impairment (see section 4.3).

- Patients during or after operative procedures (even in cases of minor procedures, e.g. tooth extraction) as there is an increased risk of haemorrhage. Use with caution before surgery, including tooth extraction. Temporary discontinuation of treatment may be necessary.
- Patients during menorrhagia where it may increase menstrual bleeding.
- 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 <Product name> dosing.
- Patients with concomitant treatment with <Product name> and other medicinal products that alter haemostasis (i.e. anticoagulants such as warfarin, thrombolytic and antiplatelet agents, anti-inflammatory drugs and selective serotonin reuptake inhibitors) is not recommended, unless strictly indicated, because they may enhance the risk of haemorrhage (see section 4.5). If the combination cannot be avoided, close observation for signs of bleeding is recommended.

In two randomised controlled studies of ticagrelor (TICO and TWILIGHT) in patients with ACS who have undergone a PCI procedure with a drug-eluting stent, discontinuing ASA after 3 months dual antiplatelet therapy with ticagrelor and ASA (DAPT), and continuing with ticagrelor as single antiplatelet therapy (SAPT) for 9 and 12 months, respectively, has been shown to decrease the risk of bleeding with no observed increase in risk of major adverse cardiovascular events (MACE) compared with continued DAPT. The decision to discontinue <Product name> after 3 months and continue with ticagrelor as single antiplatelet therapy for 9 months in patients with an increased risk of bleeding should be based on clinical judgment considering the risk of bleeding versus the risk of thrombotic events (see section 4.2).

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 section 4.5).

Antifibrinolytic therapy (aminocaproic acid or tranexamic acid) and/or recombinant factor VIIa therapy may increase haemostasis. <Product name> may be resumed after the cause of bleeding has been identified and controlled.

Patients should report any unusual bleeding symptoms to their physician. If gastrointestinal bleeding or ulceration occurs the treatment should be withdrawn.

Surgery

Patients should be advised to inform physicians and dentists that they are taking <product name> before any surgery is scheduled and before any new medicinal product is taken.

In PLATO study of ticagrelor, 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 section 4.8). If a patient is to undergo elective surgery and antiplatelet effect is not desired, <Product name> should be discontinued 5 days prior to surgery (see section 5.1).

Patients with prior ischaemic stroke

ACS patients with prior ischaemic stroke can be treated with ticagrelor for up to 12 months (according to PLATO study).

Hepatic impairment

Use of <Product name> is contraindicated in patients with severe hepatic impairment (see

sections 4.2 and 4.3).

There is limited experience with ticagrelor in patients with moderate hepatic impairment (see sections 4.2 and 5.2), therefore <Product name> should be used with caution in these patients. Liver function tests should be performed regularly in patients presenting slight or moderate hepatic insufficiency.

Renal impairment
Use of <Product name> is contraindicated in patients with severe renal impairment (see sections 4.2 and 4.3).

<Product name> should be used with caution in patients with moderately impaired renal function, or in patients who are dehydrated since the use of NSAIDs may result in deterioration of renal function.

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 studies evaluating the safety and efficacy of ticagrelor. Therefore, due to the limited clinical experience, <Product name> should be used with caution in these patients (see section 5.1).

In addition, caution should be exercised when administering <Product name> 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).

Bradyarrhythmic events and AV blocks have been reported in the post-marketing setting in patients taking ticagrelor (see section 4.8), primarily in patients with ACS, where cardiac ischemia and concomitant drugs reducing the heart rate or affecting cardiac conduction are potential confounders. The patient's clinical condition and concomitant medication should be assessed as potential causes prior to adjusting treatment.

Patients with hypertension or past history of gastric, duodenal ulcer or haemorrhagic episodes or undergoing therapy with anticoagulants
<Product name> is to be used with caution in cases of hypertension and when patients have a past history of gastric or duodenal ulcer or haemorrhagic episodes or are undergoing therapy with anticoagulants.

Hypersensitivity
Acetylsalicylic acid may promote bronchospasm and asthma attacks or other hypersensitivity reactions. Risk factors are existing asthma, hay fever, nasal polyps or chronic respiratory diseases. The same applies for patients who also show allergic reaction to other substances (e.g. with skin reactions, itching or urticaria).

Skin reactions
Serious skin reactions, including Steven-Johnsons syndrome, have rarely been reported in association with the use of acetylsalicylic acid (see section 4.8). <Product name> should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

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 <Product name>. <Product name> 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 <Product name> should be stopped. For further details see section 4.8.

Central sleep apnoea
Central sleep apnoea including Cheyne-Stokes respiration has been reported in the post-marketing setting in patients taking 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 <Product name>, paying special attention to patients ≥75 years, patients with moderate/severe renal impairment and those receiving concomitant treatment with an angiotensin receptor blocker (ARB).

Uric acid increase
Hyperuricaemia may occur during treatment with ticagrelor and acetylsalicylic acid (see section 4.8). Caution is advised in patients with history of hyperuricaemia or gouty arthritis. As a precautionary measure, the use of <Product name> 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 $P2Y_{12}$-receptor on the healthy donor platelets in the test by ticagrelor in the patient's sera/plasma. Information on concomitant treatment with ticagrelor is required for interpretation of HIT platelet function tests.
In patients who have developed HIT, the benefit-risk of continued treatment with <product name>should be assessed, taking both the prothrombotic state of HIT and the increased risk of bleeding with concomitant anticoagulant and <Product name> treatment into consideration.

Elderly patients
Elderly patients are particularly susceptible to the adverse effects of NSAIDs, including

acetylsalicylic acid especially gastrointestinal bleeding and perforation which may be fatal (see section 4.2). Where prolonged therapy is required, patients should be reviewed regularly.

Premature discontinuation
Premature discontinuation with any antiplatelet therapy, including <Product name>, could result in an increased risk of cardiovascular (CV) death, MI or stroke due to the patient's underlying disease. Therefore, premature discontinuation of treatment should be avoided.

Sodium
<Product name> contains less than 1 mmol sodium (23 mg) per dose, i.e. is essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed using <Product name>. As <Product name> contains ticagrelor and acetylsalicylic acid, any interactions that have been identified with these agents individually may occur with <Product name>.

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. Ticagrelor is a breast cancer resistance protein (BCRP) inhibitor.

Effects of medicinal and other products on ticagrelor

CYP3A4 inhibitors

- Strong CYP3A4 inhibitors – Co-administration of ketoconazole with ticagrelor increased the ticagrelor C_{max} and AUC equal to 2.4-fold and 7.3-fold, respectively. The C_{max} and AUC of the active metabolite were reduced by 89% and 56%, respectively. Other strong inhibitors of CYP3A4 (clarithromycin, nefazodone, ritonavir and atazanavir) would be expected to have similar effects and therefore concomitant use of strong CYP3A4 inhibitors with ticagrelor is contraindicated (see section 4.3).
- 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-gp inhibitors and moderate CYP3A4 inhibitors (e.g. verapamil, quinidine) that also may increase ticagrelor exposure. If the association cannot be avoided, their concomitant use should be made with caution.

Others
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 <Product name>.

A delayed and decreased exposure to oral $P2Y_{12}$ 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 applies 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 $P2Y_{12}$ inhibition is deemed crucial, the use of a parenteral $P2Y_{12}$ inhibitor may be considered.

Effects of ticagrelor on other medicinal products

Medicinal products 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 reactions 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 <Product name> 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 <Product name> 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-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 suggests that ticagrelor is not a CYP2C9 inhibitor and unlikely to alter the CYP2C9 mediated metabolism of medicinal products like warfarin and tolbutamide.

Rosuvastatin (BCRP substrate)
Ticagrelor has been shown to increase rosuvastatin concentrations, which may result in increased risk of myopathy, including rhabdomyolysis. Consideration should be given to the benefits of prevention of major adverse cardiovascular events by use of rosuvastatin versus the risks with increased rosuvastatin plasma concentrations.

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 <Product name> 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).

Other concomitant therapy
In clinical studies, ticagrelor was commonly administered with proton pump inhibitors, statins, beta-blockers, angiotensin converting enzyme (ACE) 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 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 <product name> 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.

Effects of medicinal products on acetylsalicylic acid

Ibuprofen
Experimental data suggest that ibuprofen may inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly. However, the limitations of these data and the uncertainties regarding extrapolation of *ex vivo* data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 5.1).

Metamizole
Metamizole may reduce the effect of acetylsalicylic acid on platelet aggregation, when taken concomitantly. Therefore, this combination should be used with caution in patients taking low dose acetylsalicylic acid for cardio protection.

Antacids
The excretion of acetylsalicylic acid is increased by alkaline urine, which can occur with some antacids.

Effects of acetylsalicylic acid on other medicinal products

Methotrexate
(used at doses >15 mg/week):
The combined drugs, methotrexate and acetylsalicylic acid, enhance haematological toxicity of methotrexate due to the decreased renal clearance of methotrexate by acetylsalicylic acid. Therefore, the concomitant use of methotrexate (at doses >15 mg/week) with acetylsalicylic acid is contraindicated (see section 4.3).
(used at doses <15 mg/week):
The combined drugs, methotrexate and acetylsalicylic acid, may increase haematological toxicity of methotrexate due to decreased renal clearance of methotrexate by acetylsalicylic acid. Weekly blood count checks should be done during the first weeks of the combination. Enhanced monitoring should take place in the presence of even mildly impaired renal function, as well, as in elderly.

Uricosuric agents, e.g. probenecid
Salicylates reverse the effect of probenecid. The combination should be avoided.

Anticoagulants e.g. coumarin, heparin, warfarin
Increased risk of bleeding due to inhibited thrombocyte function, injury of the duodenal mucosa and displacement of oral anticoagulants from their plasma protein binding sites. The bleeding time should be monitored (see section 4.4).

Anti-platelet agents (e.g clopidogrel and dipyridamole) and selective serotonin reuptake inhibitors
(SSRIs; such as sertraline or paroxetine)
Increased risk of gastrointestinal bleeding (see section 4.4).

Antidiabetics, e.g. sulphonylureas
Salicylics may increase the hypoglycaemic effect of sulphonylureas.

Digoxin and lithium
Acetylsalicylic acid impairs the renal excretion of digoxin and lithium, resulting in increased plasma concentrations. Monitoring of plasma concentrations of digoxin and lithium is recommended when initiating and terminating treatment with acetylsalicylic acid. Dose adjustment may be necessary.

Diuretics and antihypertensives
NSAIDs may decrease the antihypertensive effects of diuretics and other antihypertensive agents. As for other NSAIDs concomitant administration with ACE-inhibitors increases the risk of acute renal insufficiency.
Diuretics: Risk of acute renal failure due to the decreased glomerual filtration via decreased renal prostaglandin synthesis. Hydrating the patient and monitoring renal function at the start of the treatment is recommended.

Carbonic anhydrase inhibitors (acetazolamide)
May result in severe acidosis and increased central nervous system toxicity.

Systemic corticosteroids
The risk of gastrointestinal ulceration and bleeding may be increased when acetylsalicylic acid and corticosteroids are co-administered (see section 4.4).

Other NSAIDs
Increased risk of ulcerations and gastrointestinal bleeding due to synergistic effects.

Cyclosporin, tacrolimus
Concomitant use of NSAIDs and cyclospoin or tacrolimus may increase the nephrotoxic effect of ciclosporin and tacrolimus. The renal function should be monitored in case of concomitant use of these agents and acetylsalicylic acid.

Alcohol
Concomitant administration of alcohol and acetylsalicylic acid increases the risk of gastrointestinal bleeding.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
Women of childbearing potential should use appropriate contraceptive measures to avoid pregnancy during therapy with <Product name>.

Pregnancy
Safety and efficacy of <Product name> have not been established in pregnant women.

Clinical studies indicate that doses of acetylsalicylic acid up to 100 mg/day for restricted obstetrical use, which require specialised monitoring, appear safe. There are no or limited amount of data from the use of ticagrelor in pregnant women. Studies in animals have shown reproductive toxicity after administration of ticagrelor (see section 5.3).

Therefore, <Product name> is not recommended during pregnancy.

Breast-feeding
Safety and efficacy of <Product name> have not been established in breast-feeding women.

Available pharmacodynamic/toxicological data in animals have shown excretion of ticagrelor and acetylsalicylic acid and their active metabolites in milk (see section 5.3). A risk to newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from <Product name> therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility
No specific studies with <Product name> in humans have been conducted to evaluate effects on 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

<Product name> 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 not drive or use machines.

4.8 Undesirable effects

No therapeutic clinical trials have been conducted with <Product name>, however bioequivalence of <Product name> with co-administered ticagrelor and acetylsalicylic acid has been demonstrated through a PK/PD clinical trial (clinical trial PAO-P8-766) (see section 5.1 and 5.2).

Summary of the safety profile

The adverse reactions reported for <Product name> during clinical trial PAO-P8-766, were consistent with the known safety profiles of ticagrelor and acetylsalicylic acid when given as separate medicinal products.

In this trial, 74 healthy subjects received <Product name>, and the most commonly reported adverse reactions were constipation (16.7%), headache (9.5%) and epistaxis (9.5%).

Ticagrelor

The safety profile of ticagrelor has been evaluated in a large phase 3 outcome trial (PLATO) including more than 18,000 patients (see section 5.1).

In PLATO, patients on ticagrelor had a higher incidence of discontinuation due to adverse events than clopidogrel (7.4% vs. 5.4%). The most commonly reported adverse reactions in patients treated with ticagrelor were bleeding and dyspnoea (see section 4.4).

Tabulated list of adverse reactions

The following adverse reactions have been identified following studies or have been reported in post-marketing experience with ticagrelor and acetylsalicylic acid, either as monotherapy or in combination (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 (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Table 1 – Adverse reactions by frequency and system organ class (SOC)

SOC	Very common	Common	Uncommon	Rare	Not known
Neoplasms benign, malignant and unspecified (including cysts and polyps)			Tumour bleedings[a]		
Blood and lymphatic system disorders	Blood disorder bleedings[b]	Increased bleeding tendencies[n]		Thrombocytopenia[n], Granulocytosis[n], Aplastic	Thrombotic Thrombocytopenic Purpura[c], Bleeding time

				anaemia[n]	prolonged[n], Iron deficiency anaemia[n]
Immune system disorders			Hypersensitivity including angioedema[c]	Allergic oedema[n], Anaphylactic reactions including shock[n]	
Metabolism and nutrition disorders	Hyperuricaemia[d]	Gout/Gouty Arthritis			
Psychiatric disorders			Confusion		
Nervous system disorders		Dizziness, Syncope, Headache	Intracranial haemorrhage[m]		
Eye disorders			Eye haemorrhage[e]		
Ear and labyrinth disorders		Vertigo	Ear haemorrhage		Reduced hearing ability[n], Tinnitus[n]
Cardiac disorders					Bradyarrhythmia, AV block[c]
Vascular disorders		Hypotension		Hemorrhagic vasculitis[n]	
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Respiratory system bleedings[f]	Rhinitis[n]	Bronchospasm[n] Asthma attacks[n]	
Gastrointestinal disorders		Gastrointestinal haemorrhage[g], Diarrhoea, Nausea, Dyspepsia, Constipation	Retroperitoneal haemorrhage	Severe gastrointestinal haemorrhage[n], Vomiting[n]	Gastric or duodenal ulcers and perforation[n]
Hepatobilary disorders					Hepatic insufficiency[n]
Skin and subcutaneous tissue disorders		Subcutaneous or dermal bleeding[h], Rash, Pruritus	Urticaria[n]	Steven-Johnsons syndrome[n], Lyells syndrome[n], purpura[n], erythema nodosum[n], erythema multiforme[n]	
Musculoskeletal connective tissue and bone			Muscular bleedings[i]		

Renal and urinary disorders		Urinary tract bleeding[j]			Impaired renal function[n], salt and water retention[n]
Reproductive system and breast disorders			Reproductive system bleedings[k]	Menorrhagia[n]	
Investigations		Blood creatinine increased[d]			
Injury, poisoning and procedural complications		Post procedural haemorrhage, Traumatic bleedings[l]			

[a] e.g. bleeding from bladder cancer, gastric cancer, colon cancer

[b] e.g. increased tendency to bruise, spontaneous haematoma, haemorrhagic diathesis

[c] Identified in post-marketing experience of ticagrelor co-administrated with acetylsalicylic acid

[d] 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.

[e] e.g. conjunctival, retinal, intraocular bleeding

[f] e.g. epistaxis, haemoptysis

[g] e.g. gingival bleeding, rectal haemorrhage, gastric ulcer haemorrhage

[h] e.g. ecchymosis, skin haemorrhage, petechiae

[i] e.g. haemarthrosis, muscle haemorrhage

[j] e.g. haematuria, cystitis haemorrhagic

[k] e.g. vaginal haemorrhage, haematospermia, postmenopausal haemorrhage

[l] e.g. contusion, traumatic haematoma, traumatic haemorrhage

[m] i.e. spontaneous, procedure related or traumatic intracranial haemorrhage

n: observed with acetylsalicylic acid as monotherapy

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)

	Ticagrelor 90 mg twice daily N=9235	**Clopidogrel N=9186**	***p*-value***
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 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:
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.

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 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, COPD or asthma; these patients, and the elderly, were more likely to report dyspnoea. For ticagrelor, 0.9% of patients discontinued study drug 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 section 4.4). Ticagrelor does not affect tests of pulmonary function.

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. In PLATO, the frequency of gouty arthritis was 0.2% for ticagrelor vs. 0.1% for clopidogrel. In PLATO, the frequency of gouty arthritis was 0.2% for ticagrelor vs. 0.1% for clopidogrel.

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 via the national reporting system listed in Appendix V.

4.9 Overdose

Ticagrelor

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 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 section 5.2). 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 section 4.4). If bleeding occurs other appropriate supportive measures should be taken.

Acetylsalicylic acid

Although considerable inter-individual variations are involved, it can be considered that the toxic dose is about 200 mg/kg in adults and 100 mg/kg in children. The lethal dose of acetylsalicylic acid is 25-30 grams. Plasma salicylate concentrations above 300 mg/l indicate intoxication. Plasma concentrations above 500 mg/l in adults and 300 mg/l in children generally cause severe toxicity. Overdose may be harmful for elderly patients and particularly

for small children (therapeutic overdose or frequent accidental intoxications may be fatal).
Symptoms of moderate intoxications
Tinnitus, hearing disorders, headache, vertigo, confusion and gastrointestinal symptoms (nausea, vomiting and abdominal pain).

Symptoms of severe intoxications
Symptoms are related to severe disruption of the acid-base balance. In the first instance hyperventilation occurs, which results in respiratory alkalosis. Respiratory acidosis ensues due to suppression of the respiratory centre. In addition, metabolic acidosis occurs as a result of the presence of salicylate.
Since younger children are often not seen until they have reached a late stage of intoxication, they are usually in the stage of acidosis.
Furthermore, the following symptoms may occur: hyperthermia and perspiration, resulting in dehydration: feelings of restlessness, convulsions, hallucinations and hypoglycaemia. Depression of the nervous system may lead to coma, cardiovascular collapse or respiratory arrest.

Treatment of overdose
If a toxic dose has been ingested, hospital admission is required. In the event of moderate intoxication, inducing the patient to vomit should be attempted.
If this fails, gastric lavage may be attempted during the first hour after ingestion of a substantial amount of the medicine. Afterwards, administer activated carbon (adsorbent) and sodium sulphate (laxative).
Activated charcoal may be given as a single dose (50 g for an adult, 1 g/kg body weight for a child up to 12 years).
Alkalisation of the urine (250 mmol $NaHCO_3$, for three hours) whilst checking urine pH levels.
In the event of severe intoxication, haemodialysis is to be preferred. Other symptoms to be treated symptomatically.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Platelet aggregation inhibitors excluding heparin, ATC code: B01AC30

<Product name> combines two antithrombotic agents to prevent atherothrombotic events.

Mechanism of action

Ticagrelor

Ticagrelor is a member of the chemical class cyclopentyltriazolopyrimidines (CPTP), which is an oral, direct acting, selective and reversibly binding $P2Y_{12}$ receptor antagonist that prevents ADP-mediated $P2Y_{12}$ dependent platelet activation and aggregation. Ticagrelor does not prevent ADP binding but when bound to the $P2Y_{12}$ 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 CV events such as death, MI 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.

Acetylsalicylic acid

Acetylsalicylic acid inhibits the platelet activation: blocking the platelet cyclooxygenase by acetylation, it inhibits thromboxane A2 synthesis, a physiological activating substance released by the platelets and which would play a role in the complications of the atheromatosic lesions. Inhibition of TXA2-synthesis is irreversible, because thrombocytes, which have no nucleus, are not capable (due to lack of protein synthesis capability) to synthesise new cyclooxygenase, which had been acetylated by acetylsalicylic acid.

The repeated doses from 20 to 325 mg involve an inhibition of the enzymatic activity from 30 to 95%. Due to the irreversible nature of the binding, the effect persists for the lifespan of a thrombocyte (7-10 days). The inhibiting effect does not exhaust during prolonged treatments and the enzymatic activity gradually begins again upon renewal of the platelets 24 to 48 hours after treatment interruption.
Acetylsalicylic acid extends bleeding time on average by approximately 50 to 100%, but individual variations can be observed.

Pharmacodynamic effects

Onset of action
In patients with stable coronary artery disease (CAD) 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 twice daily 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

No therapeutic clinical trials were conducted with <Product name>, however, bioequivalence of <Product name> with co-administered ticagrelor and acetylsalicylic acid has been demonstrated (clinical trial PAO-P8-766) (for PK parameters see section 5.2). The demonstration of the pharmacodynamic effect of <Product name> was based on a surrogate marker, namely inhibition of thromboxane B_2 (TxB_2) synthesis, which is considered as a widely accepted surrogate for platelet aggregation and also for efficacy in secondary prevention of cardiovascular events.

PD equivalence of <Product name> with co-administered ticagrelor and acetylsalicylic acid tablets (clinical trial PAO-P8-766)

The primary pharmacodynamic (PD) objective of this study was to demonstrate equivalence following multiple oral dose administrations between <Product name> and the individual tablet of Acetylsalicylic acid concomitantly administered with ticagrelor, based on the surrogate marker thromboxane B_2 (TxB_2) levels. In this trial, 42 healthy subjects were treated with the test product (1 x <Product name> administered twice daily (approximately 12 hours apart) for 8 consecutive days (for a total of 16 administrations). 42 healthy subjects (including 10 obese) were treated with the Reference-1 product (1 × 90 mg Ticagrelor (Brilique®) film-coated tablet) administered BID for 8 consecutive days, in the mornings and evenings (approximately 12 hours apart), for a total of 16 administrations and Reference-2 (1 × 100 mg Acetylsalicylic acid (Aspirin®) tablet) administered once a day (QD) in the morning for 8 consecutive days, for a total of 8 administrations. For the morning drug administrations, Reference-1 and Reference-2 were administered concomitantly.

The following PD parameters were estimated following 8 consecutive administration days, to demonstrate therapeutic equivalence:

- TxB_2 concentration after 24 hours (C_{24}) (Table 3)
- TxB_2 area under the concentration-time curve from time zero to 24 hours (AUC_{0-24}) (Table 3)
- Subjects' responsiveness to treatment (Test or Reference) (Table 4)

Table 3 – Comparison of statistical results for TxB_2 following 8 consecutive administration days (PAO P8-766)

Parameter	Geometric LSmeans[a]		95% Confidence Intervals (%)		
	Treatment-3 (Test) **N=41**	**Treatment-4** (Reference) **N=41**	**Ratio (%)**	**Lower**	**Upper**
C_{24}	1.88	3.30	57.10	50.99	63.94
AUC_{0-24}	26.20	34.48	75.99	69.98	82.52

[a] units are ng/mL for C_{24} and ng·h/mL for AUC_{24}

The equivalence limit estimation was based on the target therapeutic range of surrogate marker TxB_2 (1 ng/mL to 10 ng/mL), which corresponds to inhibition of TxB_2 > 97%. Following 8 consecutive administration days, the upper bound limit of the 95% confidence interval (CI) calculated from the exponential of the ln-transformed parameters C_{24} in the Test group and in the Reference group, were within the therapeutic target (<10 ng/mL) with values of 2.04 ng/mL and 3.58 ng/mL respectively.

Following 8 consecutive administration days, the Test/Reference ratios (95% CI) are 57.10% (50.99-63.94%) for C_{24} and 75.99% (69.98-82.52%) for AUC_{24}. The statistical results indicate that the Test /Reference ratios of geometric LSmeans, and the 95% CI of C_{24} and AUC_{0-24} were within the equivalence margins (see Table 3). Based on comparable results of the surrogate marker TxB_2 levels, test product is judged to be therapeutically equivalent to reference product administered under fasting conditions to healthy adult subjects and in subjects with obesity.

Subjects' responsiveness to treatment (test or reference) was also evaluated and categorized. Subjects were categorized as responder (inhibition as successful treatment: I_{24} >97%, responder with incomplete inhibition: I_{24} ≥95% and ≤97%), or non-responder (inhibition as treatment failure: I_{24} <95%) (Table 4).

Table 4 presents the summary of subject's responsiveness to ASA after 8-day oral dose administration of the FDC product (Test – administered BID) and the co-administration of Brilique® (BID) and Aspirin® (100 mg QD) based inhibition categories of the surrogate marker TxB_2.

Table 4 – Summary of Subjects Responsiveness on Day 8 Following Multiple Dose Administration – Pharmacodynamic Population (PAO P8-766)

	Treatment			
	Treatment-3 (Test) (N=40)		**Treatment-4 (Reference) (N=42)**	
Responsiveness	**n**	**(%)**	**n**	**(%)**
Responder ($I_{24} > 97\%$)	39	97.50	41*	100.00
Incomplete Responder ($I_{24} \geq 95\%$ and $\leq 97\%$)	0	0.00	0	0.00
Non-Responder ($I_{24} < 95\%$)	1	2.50	0	0.00

After 8 days of treatment administration, all subjects (100%) responded to the Reference product (I_{24}>97%) and 39 out of 40 subjects (97.50%) responded to the Test product(I_{24}>97%), suggesting equivalent degree of inhibition between Test and Reference formulations (see Table 4).

<Product Name> was shown to provide similar therapeutic effect with regards to prevention of atherothombotic events (via the surrogate marker TxB_2), when compared with the standard treatment, i.e. co-administration of ticagrelor and ASA, despite the difference on the dosing of the ASA component (BID vs QD).

Ticagrelor

The clinical evidence for the efficacy and safety of ticagrelor is derived from a phase 3 trial:

- The PLATO [PLATelet Inhibition and Patient Outcomes] study, a comparison of ticagrelor to clopidogrel, both given in combination with ASA and other standard therapy.

PLATO study (Acute Coronary Syndromes)

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 CABG.

Clinical efficacy
On a background of daily ASA, ticagrelor 90 mg twice daily showed superiority to 75 mg daily clopidogrel in preventing the composite endpoint of CV death, 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 90 mg twice daily for 12 months (see section 4.2). Treating 54 ACS patients with ticagrelor instead of clopidogrel will prevent 1 atherothrombotic event; treating 91 will

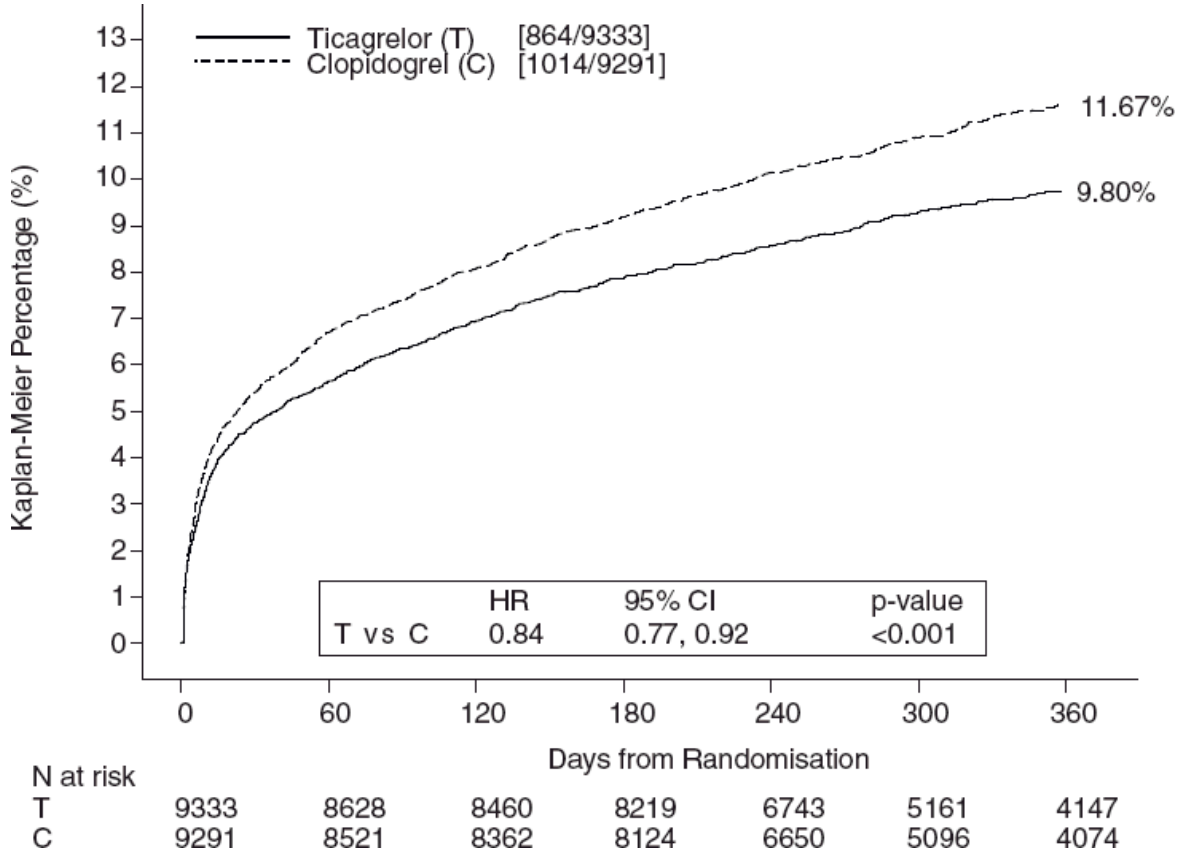
prevent 1 CV death (see Figure 1 and Table 3).

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 hazard ratio (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 sections 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 – Analysis of primary clinical composite endpoint of CV death, MI and stroke (PLATO)



Ticagrelor reduced the occurrence of the primary composite endpoint compared to clopidogrel in both the UA/NSTEMI and STEMI population (Table 5). Thus, Ticagrelor 90 mg twice daily together with low-dose ASA can be used in patients with ACS (unstable angina, non-ST

elevation Myocardial Infarction [NSTEMI] or ST elevation Myocardial Infarction [STEMI]); including patients managed medically, and those who are managed with percutaneous coronary intervention (PCI) or coronary artery by-pass grafting (CABG).

Table 5 - Analysis of primary and secondary efficacy endpoints (PLATO)

	Ticagrelor 90 mg twice daily (% patients with event) N=9333	**Clopidogrel 75 mg once daily (% patients with event) N=9291**	**ARR[a] (%/yr)**	**RRR[a] (%) (95% CI)**	***p*-value**
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 MI.

[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.

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.

Clinical safety

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.

The European Medicines Agency has waived the obligation to submit the results of studies with <Product name> in all subsets of the paediatric population in acute coronary syndromes (ACS) (see section 4.2 for information on paediatric use).

Acetylsalicylic acid

Experimental data suggest that ibuprofen may inhibit the effect of low dose acetylsalicylic acid on platelet aggregation when they are dosed concomitantly.
In one study, when a single dose of ibuprofen 400 mg was taken within 8 h before or within 30 min after immediate release acetylsalicylic acid dosing (81 mg), a decreased effect of acetylsalicylic acid on the formation of thromboxane or platelet aggregation occurred. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use.

5.2 Pharmacokinetic properties

A single and multiple dose crossover study evaluated the pharmacokinetics and pharmacodynamics of <Product name> taken twice daily, versus individual tablets of 90 mg ticagrelor taken twice daily and 100 mg acetylsalicylic acid taken once daily in healthy subjects and in subjects with obesity (see section 5.1).

The study demonstrated that the single dose pharmacokinetics of the ticagrelor component of the <Product name> 90 mg/50 mg hard capsules are bioequivalent to ticagrelor concomitantly administered with acetylsalicylic acid (ASA) as individual medicinal products. PD equivalence between <Product name> and the individual tablet of Acetylsalicylic acid concomitantly administered with Ticagrelor is presented in Section 5.1.

The following information reflects the pharmacokinetic properties of the individual active substances of <Product name>.

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

Absorption

Ticagrelor
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 an oral ticagrelor 90 mg single dose under fasted conditions in healthy subjects, 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 pharmacokinetics of ticagrelor and AR-C124910XX in patients with a history of MI were generally similar to that in the ACS population.

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).

Acetylsalicylic acid
After oral administration, acetylsalicylic acid is rapidly absorbed from the gastrointestinal tract. However, a significant portion of the dosage is already hydrolysed to salicylic acid in the intestinal wall during the absorption process.

Distribution

Ticagrelor
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%).
Acetylsalicylic acid
Acetylsalicylic acid as well as the main metabolite salicylic acid, are extensively bound to plasma proteins, primarily albumin, and distributed rapidly into all parts of the body. Maximum plasma concentration is reached after 0.3 - 2 hours (total salicylate). The volume of distribution of acetylsalicylic acid is ca. 0.16 l/kg of body weight.

Biotransformation

Ticagrelor
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.

Acetylsalicylic acid
Acetylsalicylic acid is rapidly metabolised to salicylic acid, with a half-life of 15-30 minutes. Salicylic acid is subsequently predominantly converted into glycine and glucuronic acid conjugates.
Elimination kinetics of salicylic acid is dose-dependent, because the metabolism is limited by liver enzyme capacity. Thus, elimination half-time varies and is 2-3 hours after low doses (75 mg – 160 mg).

Elimination

Ticagrelor
The primary route of ticagrelor elimination is via hepatic metabolism. When radiolabelled 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.

Acetylsalicylic acid
Salicylic acid and its metabolites are predominantly excreted via the kidneys.

Special populations

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

Paediatric population
There are no data in children with ACS or history of MI taking <Product name> or ticagrelor.

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 (IPA) effect of ticagrelor was independent of dialysis in patients with end stage renal disease and similar 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, 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 sections 4.2 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. The exposure in patients self-identified as Hispanic or Latino was similar to that in Caucasians.

5.3 Preclinical safety data

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

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

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

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

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

Acetylsalicylic acid
The nonclinical safety profile of acetylsalicylic acid is well documented.
In experimental animal studies, salicylates have shown no other organ injury than renal damage. In rat studies, fetotoxicity and teratogenic effects were observed with acetylsalicylic acid at maternotoxic doses. Clinical relevance is unknown as the doses used in non-clinical studies are much higher (7 times at least) than the maximal recommended doses in targeted cardiovascular indications.
Acetylsalicylic acid was extensively investigated with regard to mutagenic and carcinogenic effects. The results as a whole show no relevant signs for any mutagenic or carcinogenic effects in mice and rat studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content
Mannitol (E421)
Calcium Hydrogen Phosphate Dihydrate
Maize Starch
Starch, Pregelatinised (Maize)

Talc (E553b)
Sodium Stearyl Fumarate

Capsule shell
Titanium dioxide (E171)
Water, purified
Gelatin

Printing ink black
Shellac (E904)
Iron Oxide Black (E172)
Potassium Hydroxide (E525)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Aluminium-OPA/Alu/PVC blisters:
21 months

HDPE bottles:
21 months

Shelf life after first opening

This medicinal product should be used within 6 months of first opening the bottle.

6.4 Special precautions for storage

Aluminium-OPA/Alu/PVC blisters:
Do not store above 30°C.

HDPE bottles:
Do not store above 30°C.

6.5 Nature and contents of container

Cartons containing 56, 60 or multipack of 200 (4 packs of 50) hard capsules in Aluminium-OPA/Alu/PVC blisters.
Cartons containing 28 × 1 hard capsules, 56 × 1 hard capsules or multipack of 168 × 1 (3 packs of 56 × 1) hard capsules in Aluminium-OPA/Alu/PVC perforated unit dose blisters.

HDPE bottles with moisture absorbing canisters containing silica gel and with a PP child resistant closure containing 180 hard capsules.

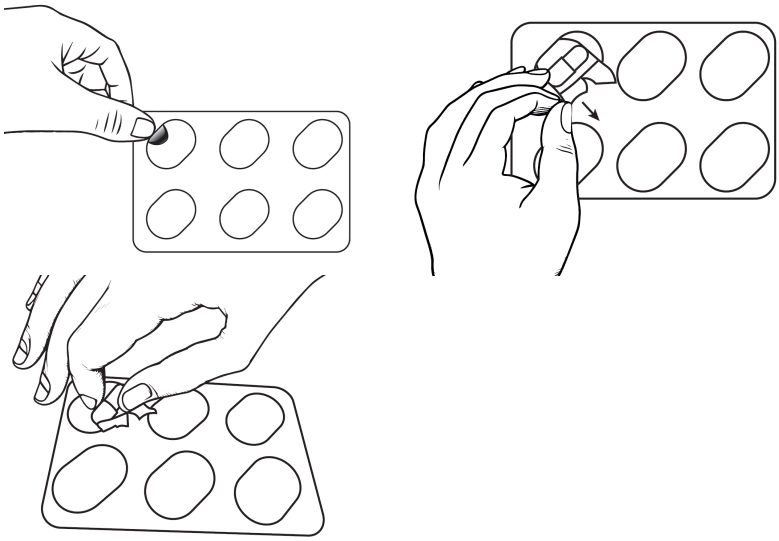
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

The capsule should be removed from the blister pocket with caution after tearing the

aluminum foil near the edge of the pocket on the bottom side of the blister as depicted on the images below.



7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

2025-10-01