AUSTRALIAN PRODUCT INFORMATION
ARX-TICAGRELOR (ticagrelor)

1. NAME OF THE MEDICINE

Ticagrelor.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 90 mg of ticagrelor.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ARX-TICAGRELOR, in combination with aspirin, is indicated for the prevention of atherothrombotic events (cardiovascular death, myocardial infarction and stroke) in adult patients with acute coronary syndromes (unstable angina [UA], non ST elevation Myocardial Infarction [NSTEMI] or ST elevation Myocardial Infarction [STEMI]) including patients managed medically, and those who are managed with percutaneous coronary intervention (PCI) or coronary artery by-pass grafting (CABG).

4.2 DOSE AND METHOD OF ADMINISTRATION

ARX-TICAGRELOR 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 ARX-TICAGRELOR should take aspirin daily unless specifically contraindicated. Following an initial dose of aspirin, ARX-TICAGRELOR should be used with a recommended maintenance dose of aspirin 100 mg daily. If required, the aspirin maintenance dose may vary from 75-150 mg according to clinical need.

Missed dose

Lapses in therapy should be avoided. A patient who misses a dose of ARX-TICAGRELOR should take their next dose at its scheduled time.

Switching

In patients having an ACS event, the loading dose of 180 mg should be given as soon as possible.

Physicians who desire to switch patients with a prior ACS event from existing anti-platelet therapy to ARX-TICAGRELOR should administer the first dose of ARX-TICAGRELOR 24 hours following the last dose of the other anti-platelet medication.

Premature discontinuation

Treatment is recommended for at least 12 months unless discontinuation of ARX-TICAGRELOR is clinically indicated. In patients with ACS, premature discontinuation with any anti-platelet therapy, including ARX-TICAGRELOR, could result in an increased risk of cardiovascular death, or myocardial infarction due to the patient's underlying disease.

Administration

For oral use. ARX-TICAGRELOR can be taken with or without food.

For patients who are unable to swallow the tablet(s) whole, ARX-TICAGRELOR tablets (90 mg and 2 x 90 mg) can be crushed to a fine powder and mixed in half a glass of water and drunk immediately. The glass should be rinsed with a further half glass of water and the contents drunk.

For oral administration or crushed tablets, crush ARX-TICAGRELOR tablets using a mortar and pestle or a similar device. Adding approximately 100 mL of water to the mortar/crushing device and stir for approximately 1 minute before transferring the dispersion to a glass/dosing cup and administer. Add another 100 mL of water to the mortar/crushing device and stir for approximately ½ minute to ensure that all the remaining powder is dispersed before transferring this to the glass/dosing cup. Stir the contents of the glass again for approximately ½ minute and administer the remaining water/dispersed tablet.

For administration via a nasogastric tube (CH8 or greater), crush the tablets as stated above and use approximately 50 mL of water to disperse the crushed powder before withdrawing the dispersion into a suitable syringe. Then administer the full contents of the syringe via the nasogastric tube. Add another 50 mL to the mortar/crushing device and stir for approximately ½ minute to ensure that all the remaining powder is dispersed, before withdrawing the dispersion into the syringe and administering via the nasogastric tube. Refill the syringe with approximately 25 mL of water and shake before flushing any remaining contents from the nasogastric tube into the stomach.

Special populations

<u>Paediatric patients</u>

Safety and efficacy in children below the age of 18 years have not been established. ARX-TICAGRELOR is not indicated in a paediatric population (see Section 5.1 PHARMACODYNAMIC PROPERTIES).

Elderly

No dose adjustment is required.

Patients with renal impairment

No dose adjustment is necessary for patients with renal impairment or for patients on renal dialysis (see Section 5.2 PHARMACOKINETIC PROPERTIES - Special population - Patients with renal impairment).

Patients with hepatic impairment

No dose adjustment is necessary for patients with mild hepatic impairment. ARX-TICAGRELOR has not been studied in patients with severe hepatic impairment and there is limited information on treatment of patients with moderate hepatic impairment (refer to Sections 4.3 CONTRAINDICATIONS, 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, and 5.2 PHARMACOKINETIC PROPERTIES).

4.3 CONTRAINDICATIONS

- Hypersensitivity to ticagrelor or any of the excipients
- Active pathological bleeding
- History of intracranial haemorrhage (refer to Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS)
- Moderate to severe hepatic impairment (refer to Sections 4.2 DOSE AND METHOD OF ADMINISTRATION, 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, and 5.2 PHARMACOKINETIC PROPERTIES)
- 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 (refer to Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Bleeding risk

In the PLATO study, the 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 ACS treated with ticagrelor and aspirin 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 (refer to Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). In the PHILO and PLATO studies, a statistically significant higher incidence of ‘Minor Bleeding’ events was reported for ticagrelor compared to clopidogrel in the Asian/Japanese population. The incidence of ‘Major Bleeding’ events was similar for both treatment groups in the PLATO Asian subpopulation, whereas it was numerically higher for the ticagrelor group compared to clopidogrel

group in the PHILO study (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

As with other anti-platelet agents, ARX-TICAGRELOR prolongs bleeding time and should be used with caution in patients who may be at risk of increased bleeding. Therefore, the use of ARX-TICAGRELOR in patients at known increased risk for bleeding should be balanced against the benefit in terms of prevention of atherothrombotic events. If clinically indicated, ARX-TICAGRELOR should be used with caution in the following patient groups:

- Patients with a propensity to bleed (e.g. due to recent trauma, recent surgery, coagulation disorders, or active or recent gastrointestinal bleeding) or who are at increased risk of trauma. The use of ARX-TICAGRELOR 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 CONTRAINDICATIONS).

- Patients with concomitant administration of drugs that may increase the risk of bleeding (e.g. non-steroidal anti-inflammatory drugs (NSAIDS), oral anticoagulants (e.g. warfarin), and/or fibrinolytics/thrombolytics within 24 hours of ARX-TICAGRELOR dosing).

Platelet transfusion did not reverse the anti-platelet effect of ARX-TICAGRELOR in healthy volunteers and is unlikely to be of clinical benefit in patients with bleeding. Since co-administration of ARX-TICAGRELOR with desmopressin did not decrease template bleeding time, desmopressin is unlikely to be effective in managing clinical bleeding events.

Anti-fibrinolytic therapy (aminocaproic acid or tranexamic acid) and/or recombinant factor VIIa therapy may augment haemostasis. ARX-TICAGRELOR may be resumed after the cause of bleeding has been identified and controlled.

Surgery

Patients should be advised to inform physicians and dentists that they are taking ARX-TICAGRELOR before any surgery is scheduled and before any new medicinal product is taken. If a patient requires surgery, physicians should consider each patient's clinical profile as well as the benefits and risks of continued anti-platelet therapy when determining when discontinuation of ARX-TICAGRELOR treatment should occur.

Because of the reversible binding of ticagrelor, restoration of platelet aggregation occurs faster with ticagrelor compared to clopidogrel. In the OFFSET study (refer to Section 5.1 PHARMACODYNAMIC EFFECTS), mean IPA for ticagrelor at 72 hours post-dose was comparable to mean IPA for clopidogrel at 120 hours post-dose. The more rapid offset of effect may predict a reduced risk of bleeding complications (e.g. in settings where anti-platelet therapy must be temporarily discontinued due to surgery or trauma).

In patients undergoing coronary bypass grafting (CABG) in PLATO, those on ticagrelor had a non-statistically significant higher rate of major bleeding compared with those on clopidogrel when the drug was stopped within 1 day prior to surgery but a similar rate of major bleeds compared with those on clopidogrel after stopping therapy 2 or more days before surgery.

Based on the results in PLATO, if a CABG procedure is planned the bleeding risk with ticagrelor is numerically increased compared to that seen with clopidogrel when therapy is discontinued within 96 hours prior to the procedure.

If a patient is to undergo elective surgery and anti-platelet effect is not desired, ARX-TICAGRELOR should be discontinued 5 days prior to surgery.

Patients with prior ischaemic stroke

The PLATO study included ACS patients with prior ischaemic stroke. In the absence of data, caution is advised for treatment with ticagrelor beyond one year.

Use in hepatic impairment

The 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 limited experience with ticagrelor in patients with moderate hepatic impairment. Therefore, use of ARX-TICAGRELOR is contraindicated in patients with moderate to severe hepatic impairment (refer to Sections 4.2 DOSE AND METHOD OF ADMINISTRATION, 4.3 CONTRAINDICATIONS, and 5.2 PHARMACOKINETIC PROPERTIES).

Bradyarrhythmia

Holter ECG monitoring has shown an increased frequency of mostly asymptomatic ventricular pauses during treatment with ticagrelor compared with clopidogrel. In Phase 3 studies evaluating the safety and efficacy of ticagrelor, bradyarrhythmic events were reported in a similar frequency for ticagrelor and comparators (placebo, clopidogrel, and aspirin). Patients with an increased risk of bradycardic events (e.g. patients without a pacemaker who have sick sinus syndrome, 2nd or 3rd degree atrioventricular (AV) block or bradycardic-related syncope) have been excluded from ticagrelor outcome studies. Therefore, due to the limited clinical experience in these patients, caution is advised (see also Section 5.1 PHARMACODYNAMIC PROPERTIES - Clinical trials).

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

In addition, caution should be exercised when administering ARX-TICAGRELOR concomitantly with drugs 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 drugs known to induce bradycardia (e.g. 96% beta blockers, 33% calcium channel blockers diltiazem and verapamil, and 4% digoxin).

During the Holter substudy in PLATO, more patients had ventricular pauses ≥3 seconds with ticagrelor than with clopidogrel during the acute phase of their ACS. The increase in Holter-detected ventricular pauses with ticagrelor was higher in patients with congestive 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 (refer to Section 5.1 PHARMACODYNAMIC PROPERTIES - Clinical trials - Holter Study).

Dyspnoea

Dyspnoea, usually mild to moderate in intensity and often resolving without need for treatment discontinuation, is reported by 13.8% of patients treated with ticagrelor in PLATO and by 7.8% treated with clopidogrel. Discontinuations due to dyspnoea were reported in 0.9% of patients taking ticagrelor and 0.1% of patients taking clopidogrel (refer to Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) - Discontinuations).

Patients with asthma/chronic obstructive pulmonary disorder (COPD) may have an increased absolute risk of experiencing dyspnoea with ticagrelor. Ticagrelor should be used with caution in patients with a 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 ARX-TICAGRELOR should be stopped.

Creatinine elevations

Creatinine levels may increase during treatment with ticagrelor (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) - Lab abnormalities - Creatinine elevations). 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 ≥75 years and patients with moderate/severe renal impairment and those receiving concomitant treatment with an Angiotensin II Receptor Blocker (ARB).

Uric acid increase and gout

Hyperuricaemia and gout may occur during treatment with ticagrelor (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). Caution is advised in patients with a history of hyperuricaemia or gout.

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 may be considered.

Thrombotic thrombocytopenic purpura

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 and requires prompt treatment, including plasmapheresis.

Others

Based on the relationship observed in the PLATO study between maintenance aspirin dose and relative efficacy of ticagrelor compared to clopidogrel, co-administration of ticagrelor and high dose maintenance dose aspirin (>300 mg) is not recommended (refer to Section 5.1 PHARMACODYNAMIC PROPERTIES - Clinical trials).

In PLATO, patients weighing <60 kg were at greater risk of cardiovascular events and slightly higher risk of major bleeding compared with patients weighing ≥60 kg (refer to Sections 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) and 5.1 PHARMACODYNAMIC PROPERTIES - Clinical trials).

Discontinuations

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

Use in the elderly

Higher exposures to ticagrelor and the active metabolite were observed in elderly (≥65 years) subjects compared to younger subjects. These differences are not considered clinically significant. No dose adjustment is needed for elderly patients.

In PLATO, patients ≥65 years or ≥75 years of age were at greater risk of cardiovascular events and slightly higher risk of major bleeding compared with younger patients (refer to 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) and 5.1 PHARMACODYNAMIC PROPERTIES - Clinical trials).

Paediatric use

The safety and efficacy of ARX-TICAGRELOR has not been established in patients under 18 years of age. ARX-TICAGRELOR is not indicated in a paediatric population (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION and 5.1 PHARMACODYNAMIC PROPERTIES).

Effects on laboratory tests

Platelet function tests to diagnose heparin-induced thrombocytopenia

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

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

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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 drugs on ARX-TICAGRELOR

Drugs metabolised by CYP3A4

Ketoconazole and other 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 atanazavir) would be expected to have similar effects and their concomitant use with ARX-TICAGRELOR is contraindicated.

Diltiazem and other moderate CYP3A4 inhibitors

Co-administration of ticagrelor with diltiazem increased the ticagrelor C_{max} by 69% and AUC by 174%, 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, fluconazole, and verapamil) would be expected to have a similar effect as diltiazem leading to increased exposure to ticagrelor, therefore caution is advised.

Rifampicin and other CYP3A4 inducers

Co-administration of rifampicin with ticagrelor decreased the ticagrelor C_{max} and AUC by 73% and 86%, respectively. The C_{max} of its active metabolite was unchanged and the AUC was decreased by 46%, respectively. Other CYP3A4 inducers (e.g. dexamethasone, phenytoin, carbamazepine and phenobarbital) would be expected to decrease the exposure to ticagrelor as well and may result in reduced efficacy of ARX-TICAGRELOR.

Cyclosporin (PgP and CYP3A inhibitor)

Co-administration of cyclosporin (600 mg dose) with ticagrelor (180 mg) as a single oral dose in healthy male volunteers 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 33% and C_{max} was decreased by 15% in the presence of cyclosporin. Caution is advised when cyclosporin and ticagrelor are coadministered.

Others

Morphine

Delayed and decreased exposure to oral $P2Y_{12}$ inhibitors, including ticagrelor and its active metabolite, has been reported in patients treated with morphine (approximately 35% reduction in ticagrelor). This interaction may be related to reduced gastrointestinal motility, and therefore apply to other opioids (e.g. fentanyl). 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 ARX-TICAGRELOR on other drugs

Drugs metabolised by CYP3A4

Simvastatin

Co-administration of ticagrelor with simvastatin increased the 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. There was no effect of simvastatin on ticagrelor plasma levels. There is the potential for an increase in simvastatin-related adverse reactions such as myopathy and rhabdomyolysis with co-administration; no cases of rhabdomyolysis were reported when ticagrelor was co-administered with simvastatin 40 mg daily or lower. Therefore, concomitant use of ticagrelor with doses of simvastatin greater than 40 mg daily is not recommended.

A similar effect on other statins metabolised by CYP3A4 cannot be excluded.

Atorvastatin

Co-administration of atorvastatin and ticagrelor increased the 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.

Others

Ticagrelor is a mild CYP3A4 inhibitor. Co-administration of ARX-TICAGRELOR and CYP3A4 substrates with narrow therapeutic indices (i.e. ergot alkaloids) is not recommended, as ticagrelor may increase the exposure to these drugs.

Drugs metabolised by CYP2C9 – Tolbutamide

Co-administration of ticagrelor with tolbutamide resulted in no change in the plasma levels of either drug, which suggest that ticagrelor is not a CYP2C9

inhibitor and unlikely to alter the CYP2C9 mediated metabolism of drugs like warfarin and tolbutamide.

Oral contraceptives

Co-administration of ticagrelor and levonorgestrel and ethinyl estradiol increased the ethinyl estradiol exposure approximately 20% but did not alter the PK of levonorgestrel. No clinically relevant effect on oral contraceptive efficacy is expected when levonorgestrel and ethinyl estradiol are co-administered with ARX-TICAGRELOR.

P-glycoprotein (P-gp) substrates (including digoxin and cyclosporin)

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. Concomitant administration of ticagrelor had a minor effect on the AUC (G_{mean} ratio 1.12 [90%CI; 105.75-119.20]) and C_{max} (G_{mean} ratio 1.05 [90%CI; 98.67-111.81] of cyclosporin. Appropriate clinical and/or laboratory monitoring is recommended when giving narrow therapeutic index P-gp dependent drugs like digoxin and cyclosporin concomitantly with ARX-TICAGRELOR.

No data are available on concomitant use of ARX-TICAGRELOR with potent P-gp inhibitors (e.g. verapamil, quinidine) that may increase ticagrelor exposure.

Other concomitant therapy

In clinical studies, ticagrelor was commonly administered with aspirin, heparin, low molecular weight heparin, intravenous GpIIb/IIIa inhibitors, proton pump inhibitors, statins, beta-blockers, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers as needed for concomitant conditions. These studies did not produce any evidence of clinically significant adverse interactions. Due to potential pharmacodynamic interactions, caution should be exercised with the concomitant administration of ARX-TICAGRELOR and medicinal products known to alter haemostasis.

<u>Adenosine</u>

Based on the mechanism of action of ticagrelor, patients may transiently experience increased dyspnoea in association with a bolus dose of adenosine while taking ticagrelor (see Section 5.1 PHARMACODYNAMIC PROPERTIES - Mechanism of action).

<u>Aspirin</u>

Clinical pharmacology interaction studies showed that co-administration of ticagrelor with aspirin did not have any effect on ticagrelor or its active metabolite plasma levels.

<u>Heparin and enoxaparin</u>

Clinical pharmacology interaction studies showed that co-administration of ticagrelor with heparin did not have any effect on ticagrelor or its active metabolite

plasma levels. Co-administration of ticagrelor and heparin had no effect on heparin based on activated partial thromboplastin time (aPTT) and activated coagulation time (ACT) assays. Co-administration of ticagrelor and heparin had no effect on enoxaparin based on factor Xa assay.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Concomitant administration with chronic NSAIDs has not been studied. Because of the potential for increased risk of bleeding, chronic NSAIDs and ticagrelor should be co-administered with caution (refer to Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Bleeding risk).

Clopidogrel and Prasugrel

Ticagrelor and clopidogrel or prasugrel should not be co-administered.

Concomitant administration with clopidogrel has not been studied. 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 ARX-TICAGRELOR without interruption of anti-platelet effect (refer to Section 5.1 PHARMACODYNAMIC PROPERTIES - Pharmacodynamic effects - Switching data).

Drugs known to induce bradycardia

Due to observations of mostly asymptomatic ventricular pauses and bradycardia, caution should be exercised when administering ARX-TICAGRELOR concomitantly with drugs 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 drugs known to induce bradycardia (e.g. 96% beta blockers, 33% calcium channel blockers diltiazem and verapamil, and 4% digoxin).

Selective Serotonin Reuptake Inhibitors (SSRIs)

Due to reports of cutaneous bleeding abnormalities with SSRIs, caution is advised when administering SSRIs with ARX-TICAGRELOR as this may increase the risk of bleeding. In PLATO, there was no increase in major bleeding in patients taking ticagrelor concomitantly with SSRIs.

Rosuvastatin (BCRP substrate)

Ticagrelor has been shown to increase rosuvastatin C_{max} by 2.4 to 2.6 fold and AUC by 2.3 fold, which may result in increased risk of myopathy. Consideration should be given to the benefits of prevention of major adverse cardiovascular events by use of rosuvastatin and the risks with increased rosuvastatin plasma concentrations.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Ticagrelor was found to have no effect on fertility of female rats at oral doses up to 200 mg/kg per day (approximately 20 times the maximum human therapeutic

exposure) and had no effect on fertility of male rats at doses up to 180 mg/kg/day (about 16 times the maximum human therapeutic exposure).

Ticagrelor had no effect on foetal development at oral doses up to 100 mg/kg per day in rats (about 5 times the maximum human therapeutic exposure) and up to 42 mg/kg per day in rabbits (equivalent to the maximum human therapeutic exposure). Ticagrelor had no effects on parturition or postnatal development in rats at doses up to 60 mg/kg/day (just under 5 times the maximum human therapeutic exposure).

Use in pregnancy – Category B1

No clinical data on exposed pregnancies are available for ticagrelor.

Animal studies do not indicate direct harmful effects with respect to pregnancy, embryonal/foetal development, parturition, or postnatal development. Because animal reproduction studies are not always predictive of a human response, ticagrelor is not recommended for use during pregnancy.

Use in lactation

It is not known whether ticagrelor is excreted in human milk. Studies in rats have shown that ticagrelor and active metabolites are excreted in the milk. The use of ARX-TICAGRELOR during breastfeeding is not recommended.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects of ARX-TICAGRELOR on the ability to drive and use machines have been performed. ARX-TICAGRELOR is expected to have no or negligible influence on the ability to drive and use machines. During treatment with ARX-TICAGRELOR dizziness and confusion have been reported. Therefore, patients who experience these symptoms should be cautious while driving or using machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The safety profile of ticagrelor in patients with ACS (UA, NSTEMI and STEMI) was evaluated in the PLATO study, which compared patients treated with ticagrelor 90 mg twice daily to patients treated with clopidogrel 75 mg once daily both given in combination with aspirin and other standard therapies.

Median treatment duration for ticagrelor was 277 days.

The most commonly reported adverse drug reactions in patients treated with ticagrelor were bleeding and dyspnoea (see also Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). In PLATO, serious adverse events were reported in a similar frequency between ticagrelor (20.2%) and clopidogrel (20.3%) treated patients. The most frequent serious adverse events observed were cardiac failure (1.1% vs 1.0%), non-cardiac chest pain (0.9% vs 0.9%) and dyspnoea (0.7% vs 0.4%).

Discontinuation

In PLATO, the ticagrelor group had a higher discontinuation rate due to AEs than clopidogrel (7.4% vs 5.4%). The difference was driven mainly by dyspnoea (0.9% vs 0.1%) and epistaxis (0.4% vs 0.1%). The ticagrelor and clopidogrel groups had a similar discontinuation rate due to other AEs. The discontinuation rate due to serious adverse events was 2.8% for ticagrelor and 2.4% for clopidogrel.

Bleeding Events

PLATO Study

Overall outcome of bleeding events in the PLATO study are shown in Table 1.

Table 1 Analysis of Overall Bleeding Events, Kaplan-Meier estimate of bleeding rates by treatment at 12 months (PLATO)

	Ticagrelor 90 mg twice daily N=9235		Clopidogrel 75 mg once daily N=9186	
Safety endpoints	**KM%**	**Hazard Ratio (95% CI)**	**KM%**	p-value*
PLATO-defined bleeding categories				
Primary safety endpoint Plato-defined Total Major	11.6	1.04 (0.95, 1.13)	11.2	0.4336
Secondary endpoints PLATO Major Fatal/Life-Threatening	5.8	1.03 (0.90, 1.16)	5.8	0.6988
PLATO Total Major or Minor	16.1	1.11 (1.03, 1.20)	14.6	0.0084
PLATO Non-CABG Total Major	4.5	1.19 (1.02, 1.38)	3.8	0.0264
PLATO Non-Procedural Major	3.1	1.31 (1.08, 1.60)	2.3	0.0058
PLATO Non-Procedural Major or Minor	5.9	1.39 (1.21, 1.60)	4.3	<0.0001
TIMI-defined bleeding categories				
TIMI Major	7.9	1.03 (0.93, 1.15)	7.7	0.5669
TIMI Major or Minor	11.4	1.05 (0.96, 1.15)	10.9	0.3272

* Nominal p-value not corrected for multiple testing

Bleeding category definitions:

PLATO Major Fatal/life-threatening: Fatal bleeding, OR any intracranial bleeding, OR intrapericardial with cardiac tamponade, OR with hypovolaemic shock or severe hypotension requiring pressors/inotropes or surgery OR clinically apparent with >50 g/L decrease in haemoglobin, OR ≥4 red cell units transfused.
PLATO Major Other: Significantly disabling, OR clinically apparent with 30-50 g/L decrease in haemoglobin, OR 2-3 red cell units transfused.
PLATO Minor: Requires medical intervention to stop or treat bleeding.
TIMI Major: Fatal bleeding, OR any intracranial bleeding, OR clinically overt signs of haemorrhage associated with a drop in haemoglobin (Hgb) of ≥50 g/L, or when Hgb is not available, a fall in haematocrit (Hct) of ≥15%.
TIMI Minor: Clinically apparent with 30-50 g/L decrease in haemoglobin.

In PLATO, time to first PLATO-defined 'Total Major' bleeding for ticagrelor did not differ significantly from that of clopidogrel. The event rate for bleeding was higher for both treatment arms during the first 30 days compared to the remainder of the study; most events occurred during this period. There were few fatal bleeding events in the study, 20 (0.2%) for ticagrelor 90 mg twice daily and 23 (0.3%) for clopidogrel 75 mg once daily. When minor bleeding was included, combined PLATO-defined Major and Minor bleeding events were significantly higher on ticagrelor than on clopidogrel. Minimal bleeding rates on ticagrelor were higher than on clopidogrel. Overall rates of TIMI-defined bleeding events did not differ significantly between ticagrelor and clopidogrel.

CABG-related bleeding: In PLATO, 42% of the 1,584 patients (12% of cohort) who underwent CABG surgery had a PLATO-defined 'Major Fatal/Life-threatening' bleeding with no difference between the treatment groups. Fatal CABG bleeding occurred in 6 patients in each treatment group (refer to Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Non-CABG related bleeding and non-procedural related bleeding: Ticagrelor and clopidogrel did not differ in non-CABG PLATO-defined Major Fatal/Life-threatening bleeding, but PLATO-defined 'Total Major', TIMI Major, and TIMI Major + Minor bleeding were more common with ticagrelor than with clopidogrel. Similarly, when removing all procedure related bleeding, more bleeding occurred with ticagrelor than with clopidogrel (Table 1). Discontinuation of treatment due to non-procedural bleeding was more common for ticagrelor (2.9%) than for clopidogrel (1.2%; $p<0.001$).

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

Patients ≥65 or ≥75 years of age had a slightly higher rate of major bleeding in both treatment arms. For patients ≥75 years of age, the rate of major bleeding was 12.1% on ticagrelor vs 11.8% on clopidogrel. For patients <75 years of age, the rate of major bleeding was 10.1% on ticagrelor vs 9.8% on clopidogrel. Similar differences were seen in patients ≥65 years compared with those <65 years.

In addition, patients weighing <60kg had a slightly higher rate of major bleeding in both treatment arms. For patients weighing <60kg, the rate of major bleeding was

11.2% on ticagrelor vs 13.3% on clopidogrel. For patients weighing ≥60kg, the rate of major bleeding was 10.3% on ticagrelor vs 9.9% on clopidogrel.

In the Asian subpopulation of PLATO the rate of minor bleeding events reported with ticagrelor treatment was 7.0% compared to 4.1% on clopidogrel [HR 1.74 (95% CI: 1.02, 2.97)]. For major bleeding the incidence for the ticagrelor and clopidogrel groups was 10.1% and 9.3% respectively [HR 1.07 (95%CI: 0.73, 1.59)].

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. The percentage of intracranial bleeding was low in both treatment groups given the significant comorbidity and cardiovascular risk factors of the population under study.

Among ticagrelor-treated patients in PLATO, there were similar rates of haemorrhagic stroke between those with a history of prior TIA or ischaemic stroke and those without prior TIA or ischaemic stroke: 2/564 (0.35%) vs 21/8762 (0.24%).

Gastrointestinal bleeding and fatal gastrointestinal bleeding: Total major GI bleeding was higher on ticagrelor than clopidogrel (1.3% vs 1%) however fatal/life threatening GI bleeding rates were similar and fatal GI bleeding events were less on ticagrelor (0 vs 5 events).

PHILO study

In PHILO, an exploratory study with a design similar to that of the PLATO study, minor bleeding events were reported in a higher proportion of Japanese subjects in the ticagrelor group compared with the clopidogrel group (15.2% (59/387) vs 9.2% (35/380) [HR 1.75 (95%CI: 1.15, 2.67]). For major bleeding the incidence in patients on ticagrelor was 10.3% compared to clopidogrel 6.8% [HR 1.54 (95%CI: 0.94, 2.53)].

Dyspnoea

Dyspnoea is reported by patients treated with ticagrelor. In PLATO, dyspnoea adverse events (AEs) were reported in 13.8% of patients taking ticagrelor 90 mg twice daily and in 7.8% taking clopidogrel 75 mg once daily. Most reported dyspnoea AEs were mild to moderate in intensity and often resolved without the need of treatment discontinuation. Eighty-seven percent of patients taking ticagrelor that reported dyspnoea experienced a single episode. Dyspnoea serious AEs were reported in 0.7% taking ticagrelor and 0.4% taking clopidogrel. Dyspnoea was usually reported in the initial phase of treatment; the time to the first dyspnoea AE was numerically shorter with ticagrelor (median of 20 days) than with clopidogrel (median of 33 days) during treatment with study medication.

Compared with clopidogrel, patients with asthma/COPD treated with ticagrelor may have an increased risk of experiencing non-serious dyspnoea (3.29% ticagrelor vs 0.53% clopidogrel) and serious dyspnoea (0.38% ticagrelor vs 0.00% clopidogrel).

Patients who reported dyspnoea tended to be older and more frequently had dyspnoea, CHF, COPD, or asthma at baseline. PLATO data do not suggest that the higher frequency with ticagrelor is due to new or worsening heart or lung disease. There was no indication of an adverse effect of ticagrelor on pulmonary function (refer to Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

In PLATO, the CV benefit of ticagrelor was maintained in patients who reported dyspnoea.

Lab Abnormalities

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 AEs were assessed as causally related by investigators.

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% vs clopidogrel 8.8%), in patients with severe renal impairment at baseline (ticagrelor 17.8% vs clopidogrel 12.5%) and in patients receiving concomitant treatment with ARBs (ticagrelor 11.2% vs clopidogrel 7.1%). Signs of reversibility on discontinuation were observed even in those with the greatest on treatment increases. Treatment groups in PLATO did not differ for related serious AEs. Within these subgroups renal-related serious AEs and adverse AEs 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.

The following adverse events have been identified following studies with ticagrelor (see Table 2).

Table 2 Treatment Emergent Adverse Events Reported by at Least 2.5% of Patients in Either Group[a]

	% Incidence[b]	% Incidence[b]
SYSTEM ORGAN CLASS EVENT	**Ticagrelor (+ASA)**	**Clopidogrel (+ASA)**

Table 2 Treatment Emergent Adverse Events Reported by at Least 2.5% of Patients in Either Group[a]

	% Incidence[b]	% Incidence[b]
Cardiac Disorders		
Atrial Fibrillation	4.2	4.6
Bradycardia	2.9	2.9
Cardiac Failure	2.3	2.6
Gastrointestinal Disorders		
Nausea[c]	4.3	3.8
Diarrhea[c]	3.7	3.3
Vomiting[c]	2.5	2.3
Constipation[c]	2.2	2.6
General Disorders and Administration Site Conditions		
Non-cardiac chest pain	3.7	3.3
Fatigue	3.2	3.2
Chest pain	3.1	3.5
Pyrexia	2.9	2.8
Oedema peripheral	2.3	2.5
Musculoskeletal and Connective Tissue Disorders		
Back pain	3.6	3.3
Nervous System Disorders		
Headache[c]	6.5	5.8
Dizziness[c]	4.5	3.9
Respiratory, Thoracic and Mediastinal Disorders		
Dyspnoea[c,d]	13.8	7.8
Epistaxis	6.0	3.4
Cough	4.9	4.6
Skin and subcutaneous tissue disorders		
Contusion	3.9	2.0
Vascular Disorders		
Hypertension	3.8	4.0
Hypotension	3.2	3.3

a These adverse events are from the PLATO study
b Very common: ≥1/10 (≥10%); Common: ≥1/100 (≥1%) and <1/10 (<10%)
c These events are considered causally related to ticagrelor.
d Several MedDRA PT combined

Tabulated list of adverse drug reactions

Adverse drug reactions from the clinical studies with ticagrelor are listed by MedDRA System Organ Class (SOC) and frequency category (Table 4). Within each SOC and frequency category, adverse drug reactions are presented in order

of decreasing seriousness. Frequency categories are defined according to the following conventions: Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1000 to <1/100).

Table 3 Tabulated list of adverse drug reactions

System Organ Classification	Very Common	Common	Uncommon
Neoplasms benign, malignant and unspecified (including cysts and polyps)			Tumour bleedings[b]
Blood and lymphatic system disorders	Blood disorder bleedings[c]		
Metabolism and nutrition disorders	Hyperuricaemia[a]	Gout	
Psychiatric disorders			Confusion
Nervous system disorders		Dizziness, Syncope	Intracranial haemorrhage[l]
Eye disorders			Eye haemorrhage[d]
Ear and labyrinth disorders		Vertigo	Ear haemorrhage
Vascular disorders		Hypotension	
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Respiratory system bleedings[e]	
Gastrointestinal Disorders		Gastrointestinal haemorrhage[f], Diarrhoea, Nausea	Retroperitoneal haemorrhage
Skin and subcutaneous tissue disorders		Subcutaneous or dermal bleeding[g], Pruritus	
Musculoskeletal connective tissue and bone			Muscular bleedings[h]
Renal and urinary disorders		Urinary tract bleeding[i]	
Reproductive system and breast disorders			Reproductive system bleedings[j]
Investigations		Blood creatinine increased[a]	

System Organ Classification	Very Common	Common	Uncommon
Injury, poisoning and procedural complications		Post procedural haemorrhage, Traumatic bleedings[k]	

[a] Frequencies derived from lab observations (Uric acid increases to >ULN from baseline below or within reference range. Creatinine increases of >50% from baseline) and not crude adverse event report frequency

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

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

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

[e] e.g. epistaxis, haemoptysis.

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

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

[h] e.g. haemarthrosis, muscle haemorrhage.

[i] e.g. haematuria, cystitis haemorrhagic.

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

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

[l] e.g. spontaneous, procedure related or traumatic intracranial haemorrhage.

Post-marketing experience

The following adverse reactions have been identified during post-approval use of ticagrelor. Because these reactions are reported voluntarily from a population of an unknown size, it is not always possible to reliably estimate their frequency.

Immune system disorders: Hypersensitivity reactions including angioedema (refer to Section 4.3 CONTRAINDICATIONS).

Skin and subcutaneous tissue disorders: Rash

Blood disorders: Thrombotic thrombocytopenic purpura (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Cardiac disorders: Bradyarrhythmia, AV block (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Nervous system disorders: Central sleep apnoea including Cheyne-Stokes respiration (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

ARX-TICAGRELOR is well tolerated in single doses up to 900 mg. GI toxicity was dose-limiting in a single ascending dose study. Other clinically meaningful adverse effects which may occur with overdose include dyspnoea and ventricular pauses.

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

There is currently no known antidote to reverse the effects of ticagrelor, and ARX-TICAGRELOR is not dialysable (see Section 5.2 PHARMACOKINETIC PROPERTIES - Special populations - Patients with renal impairment). Treatment of overdose should follow local standard medical practice. The expected effect of excessive ARX-TICAGRELOR dosing is prolonged duration of bleeding risk associated with platelet inhibition. If bleeding occurs appropriate supportive measures should be taken.

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

ARX-TICAGRELOR contains ticagrelor, a member of the chemical class cyclopentyltriazolopyrimidines (CPTP), which is an oral, direct acting selective and reversibly binding $P2Y_{12}$ receptor antagonist that prevents adenosine diphosphate (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 cardiovascular events such as death, myocardial infarction or stroke.

Ticagrelor has an additional mechanism of action, which involves inhibition of equilibrative nucleoside transporter-1 (ENT-1). Adenosine is formed locally at sites of hypoxia and tissue damage through degradation of released adenosine tri- and di-phosphate (ATP and ADP). As adenosine degradation is essentially restricted to the intracellular space, inhibition of ENT-1 by ticagrelor prolongs the half-life of adenosine and thereby increases its local extracellular concentration providing enhanced local adenosine responses. However, a link between the observed increases in adenosine and clinical outcomes (e.g. morbidity-mortality) has not been clearly elucidated. Ticagrelor has no clinically significant direct effect on adenosine receptors (A_1, A_{2A}, A_{2B}, A_3) and is not metabolised to adenosine.

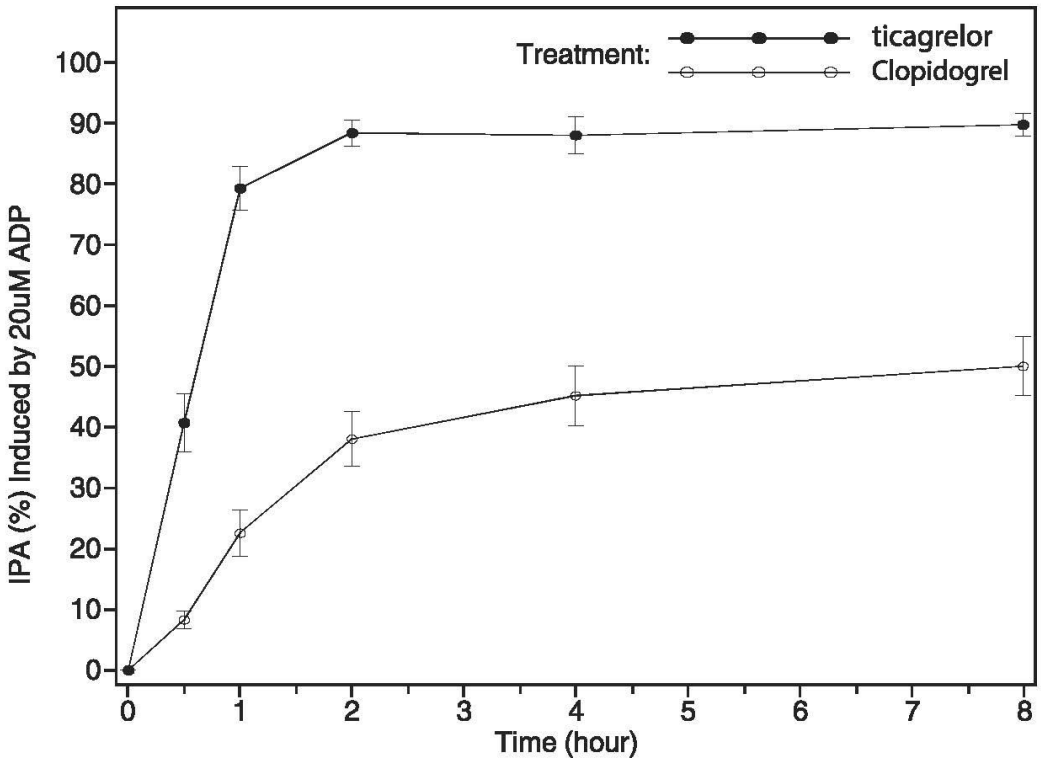
Pharmacodynamic effects

Onset of Action

The inhibition of platelet aggregation (IPA) by ticagrelor and clopidogrel was compared in a 6-week study examining both acute and chronic platelet inhibition effects in response to 20 μM ADP as the platelet aggregation agonist in patients with stable coronary artery disease (CAD) on aspirin. The onset was evaluated following a loading dose of 180 mg ticagrelor or 600 mg clopidogrel.

Ticagrelor demonstrates a rapid onset of pharmacological effect as demonstrated by a mean IPA for ticagrelor at 0.5 hours after 180 mg loading dose of about 41%, with the maximum IPA effect of 87.9% to 89.6% by 2-4 hours post dose (see Figure 1). Ninety percent of patients had final extent IPA >70% by 2 hours post dose. The high IPA effect of ticagrelor between 87-89% was maintained between 2-8 hours.

Figure 1 Mean final extent Inhibition of Platelet Aggregation (IPA) (±SE) following single oral doses of 180 mg ticagrelor or 600 mg clopidogrel in patients with stable Coronary Artery Disease (CAD)



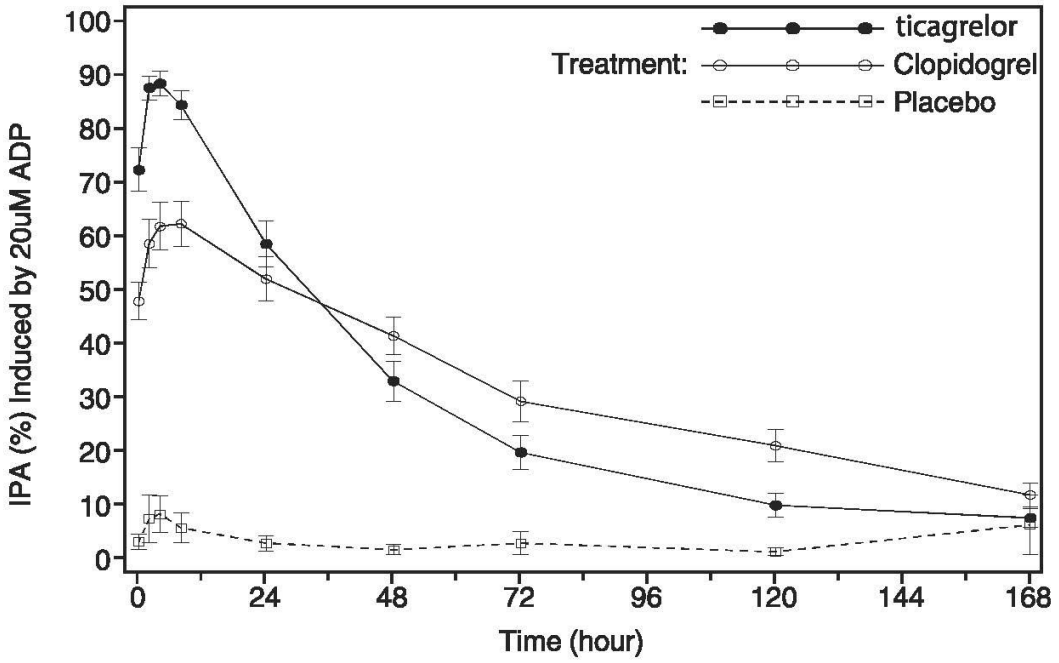
Offset of Effect

The offset was examined after 6 weeks on ticagrelor 90 mg twice daily or clopidogrel 75 mg once daily, again in response to 20 μM ADP. After the ticagrelor concentrations decline to a level less than that required for receptor saturation, IPA gradually decreases with declining plasma concentrations. Since ticagrelor binds reversibly, the recovery of platelet function does not depend on

replacement of platelets. Ticagrelor has a faster rate of offset of IPA as compared to clopidogrel as determined by the slope of offset from 4-72 hours after last dose.

Median final extent IPA measured after the last dose of ticagrelor is approximately 20-30% higher for ticagrelor compared to clopidogrel. However, by 24 hours post-dose, %IPA is similar between ticagrelor and clopidogrel, indicating that patients who miss a dose of ticagrelor would have an IPA level comparable to those treated with once daily clopidogrel. In addition, %IPA is lower for ticagrelor from 72 hours through 7 days compared with clopidogrel. Mean %IPA for ticagrelor at 72 hours (Day 3) post last dose was comparable to clopidogrel at Day 5, and %IPA for ticagrelor at Day 5 was similar to clopidogrel at Day 7, which is not statistically different from placebo (see Figure 2).

Figure 2 Mean final extent Inhibition of Platelet Aggregation (IPA) (±SE) following the last maintenance dose of 90 mg twice daily ticagrelor or 75 mg clopidogrel once daily or placebo



ticagrelor	58.4%	32.8%	19.5%	9.7%	7.3%
Clopidogrel	51.8%	41.3%	29.1%	20.8%	11.6%
Placebo	2.6%	1.4%	2.6%	1.0%	6.0%

Responders to ticagrelor

The IPA induced by ticagrelor has less variability at peak plasma concentrations of ticagrelor observed with the 90 mg twice daily dose compared to clopidogrel 75 mg once daily. Patients with stable CAD predetermined to have low IPA response to clopidogrel (non-responders), and given a concomitant dose of aspirin, exhibited higher mean IPA response after administration of ticagrelor as compared to clopidogrel. In non-responders to clopidogrel, the IPA response to ticagrelor was observed to be higher and more consistent. ticagrelor treatment resulted in

consistently higher IPA compared with clopidogrel, and this was apparent post dose for both responders and non-responders.

Switching data

Patients can be switched from clopidogrel to ticagrelor without interruption of anti-platelet effect. Patients switching from 75 mg clopidogrel once daily 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% (also refer to Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Adenosine mechanism (ENT-1)

Ticagrelor increased plasma adenosine concentrations in ACS patients. Adenosine is a vasodilator; ticagrelor has been shown to augment adenosine-induced coronary blood flow increases in healthy volunteers and ACS patients. Adenosine is an endogenous platelet inhibitor; ticagrelor has been shown to augment adenosine-mediated inhibition of platelet aggregation in addition to platelet inhibition due to its $P2Y_{12}$ antagonism. Adenosine has been linked to the cardio-protective effect of preconditioning. Ticagrelor has been shown to augment adenosine-induced dyspnoea in healthy volunteers (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Clinical trials

PLATO study

The clinical evidence for the efficacy of ticagrelor is derived from the PLATO [PLATelet Inhibition and Patient Outcomes] study, a randomised, double-blind comparison of ticagrelor to clopidogrel, both given in combination with aspirin and other standard therapy.

The PLATO study was a phase 3 randomised, double-blind, parallel group, efficacy and safety study with 18,624 patients comparing ticagrelor with clopidogrel for prevention of atherothrombotic events (cardiovascular [CV] death, myocardial infarction [MI] and stroke) in patients with acute coronary syndromes (unstable angina, non-ST elevation MI [NSTEMI] or ST elevation MI [STEMI]). The study was comprised of patients who presented within 24 hours of onset of the most recent episode of chest pain or symptoms. Patients could have been medically managed, treated with percutaneous coronary intervention (PCI) (with or without stent) or coronary artery bypass graft (CABG).

Patients were excluded from participation in the study for any of the following: 1) Active bleeding, history of previous intracranial bleed, gastrointestinal (GI) bleed within the past 6 months, major surgery within 30 days 2) Moderate or severe liver disease 3) Patient required dialysis 4) Oral anticoagulation therapy that could not be stopped 5) Fibrinolytic therapy in the 24 hours prior to randomisation, or planned fibrinolytic treatment following randomisation 6) Known clinically important anaemia or thrombocytopenia 7) Increased risk of bradycardic events unless treated with a pacemaker 8) A need for chronic concomitant oral strong CYP3A inhibitors, CYP3A substrates with narrow therapeutic indices, or strong CYP3A inducers.

Patients were randomised to receive a loading dose of 180 mg of ticagrelor followed by a maintenance dose of 90 mg of ticagrelor twice daily or clopidogrel 75 mg once daily, with an initial loading dose of 300 mg. Patients were to receive concomitant aspirin 75-100 mg daily. For patients not previously on aspirin a loading dose of 160 mg to 500 mg was allowed.

The patient population was 92% Caucasian, 28% female, 42% greater than 65 years of age with 15% greater than 75 years of age. Concomitant medications taken post-randomisation included beta-blockers (86%), lipid-lowering agents (93%) and ACE inhibitors (79%).

Planned treatment duration was a minimum of 6 months to a maximum of 12 months. Mean exposure to study drug in PLATO was 246 days for ticagrelor; median exposure was 276 days (interquartile range 177-365 days). Patients who prematurely discontinued study drug, but did not withdraw from the study, continued to be followed for study endpoint events. Study visits were scheduled 1, 3, 6, 9 and 12 months following randomisation. Enrolment was stopped based on primary endpoint projections. To ensure 6 months minimum treatment, patients continued on-trial until their next scheduled visit at 6, 9 or 12 months, which became their final visit. Of the randomised patients, 18,062 (98%) completed the study. Patients were considered to have completed the study if they had a final visit (81.9% for ticagrelor, 81.2% for clopidogrel) died (4.4% for ticagrelor, 5.6% for clopidogrel), or were followed up/alive (vital status collected when contacted, but patient did not want to continue participation in the study (10.4% for ticagrelor, 10.5% for clopidogrel). The most common reason for premature termination of study participation was withdrawal of informed consent (2.9%). There were 2 patients on the ticagrelor arm (none on clopidogrel) for whom vital status was unknown at the end of the study period.

The primary endpoint was time to first occurrence of any event from the composite of death from vascular causes, MI and stroke. Planned accrual of 1,780 primary endpoint events in PLATO provided 90% power to detect a relative risk reduction of 13.5% with ticagrelor compared with clopidogrel over a 12-month period given an event rate of 11% in the clopidogrel group at 12 months.

Ticagrelor reduced the occurrence of the primary composite endpoint compared to clopidogrel in both the UA/NSTEMI and STEMI population (Figure 3 and Table 4). Primary and Secondary efficacy endpoints were hierarchically tested in the sequence shown in Table 4.

Figure 3 Kaplan-Meier plot and analysis of the primary clinical composite endpoint of CV Death, MI and Stroke in PLATO (full analysis set)

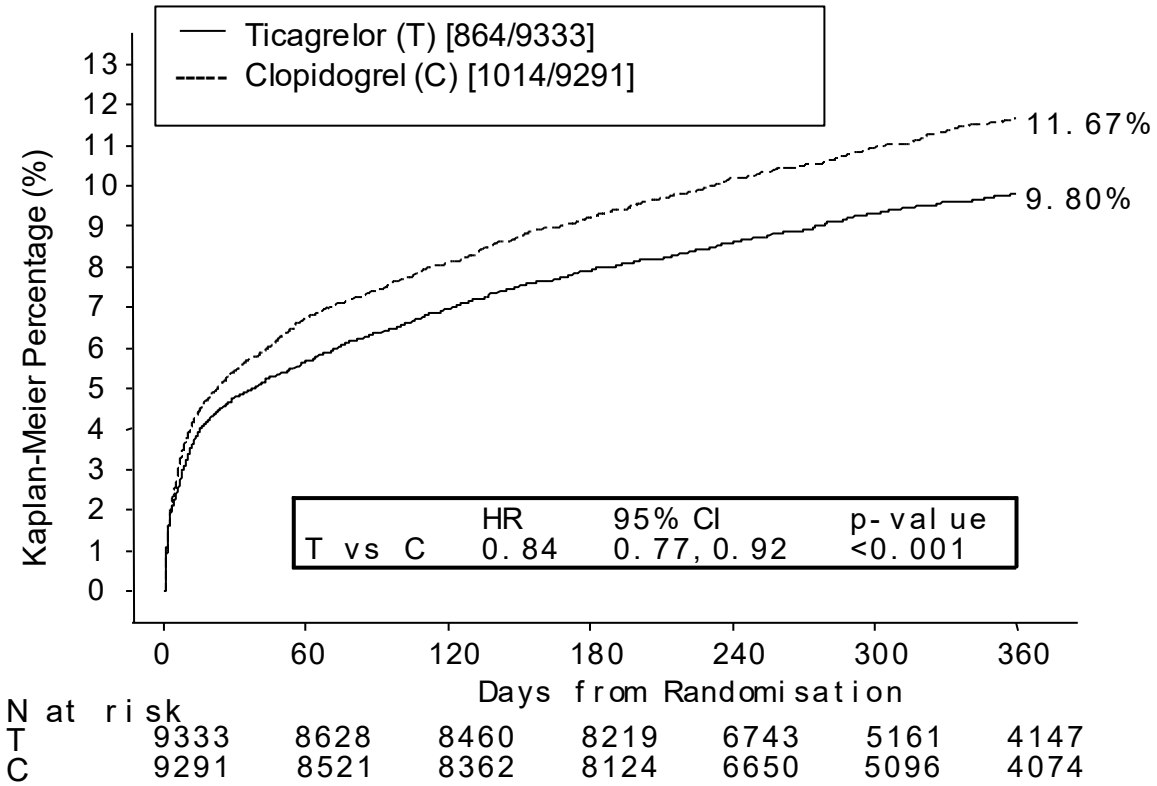


Table 4 Analysis of Primary and Secondary Efficacy endpoints in PLATO (full analysis set)

Primary Endpoints	% Patients with events		Absolute Risk Reduction %	Relative Risk Reduction[a] %	Hazard Ratio (95% CI)	p-value
	Ticagrelor 90 mg twice daily N=9333 (KM%/Year[b])	Clopidogrel 75 mg once daily N=9291 (KM%/Year[b])				
Composite of CV Death/MI (excl. silent MI)/Stroke	9.3 (9.8)	10.9 (11.7)	1.9	16	0.84 (0.77, 0.92)	p=0.0003
Each component of primary efficacy endpoints						
MI (excl. silent MI)	5.4 (5.8)	6.4 (6.9)	1.1	16	0.84 (0.75, 0.95)	p=0.0045
CV death	3.8 (4.0)	4.8 (5.1)	1.1	21	0.79 (0.69, 0.91)	p=0.0013

Table 4 Analysis of Primary and Secondary Efficacy endpoints in PLATO (full analysis set)

Primary Endpoints	% Patients with events		Absolute Risk Reduction %	Relative Risk Reduction[a] %	Hazard Ratio (95% CI)	p-value
	Ticagrelor 90 mg twice daily N=9333 (KM%/Year[b])	Clopidogrel 75 mg once daily N=9291 (KM%/Year[b])				
Stroke	1.3 (1.5)	1.1 (1.3)	-0.2	-17	1.17 (0.91, 1.52)	p=0.2249
All-cause mortality	4.3 (4.5)	5.4 (5.9)	1.4	22	0.78 (0.69, 0.89)	**
Secondary endpoints						
Composite of CV Death/MI (excl. silent MI)/Stroke – intent to invasively manage	8.5 (8.9)	10.0 (10.6)	1.7	16	0.84 (0.75, 0.94)	p=0.0025
Composite of all-cause mortality/MI (excl. silent MI)/Stroke	9.7 (10.2)	11.5 (12.3)	2.1	16	0.84 (0.77, 0.92)	p=0.0001
Composite of CV Death/Total MI/Stroke/SRI[c]/RI[d]/TIA[e]/ Other ATE[f]	13.8 (14.6)	15.7 (16.7)	2.1	12	0.88 (0.81, 0.95)	p=0.0006

a RRR = (1-Hazard Ratio) x 100%. Values with a negative relative risk reduction indicate a relative risk increase
b Kaplan-Meier percentages calculated at 12 months
c SRI – Severe Recurrent Cardiac Ischaemia
d RI – Recurrent Ischaemia
e TIA – Transient Ischaemic Attack
f ATE – Arterial Thrombotic Events
** Formal hierarchical statistical testing of secondary endpoints concluded after stroke; all-cause mortality was evaluated for completeness resulting in a nominal p-value of p=0.0003

Ticagrelor is superior to clopidogrel in the prevention of thrombotic events (relative risk reduction [RRR] 16%, absolute risk reduction [ARR] 1.9%, NNT=54) of the composite efficacy endpoint (CV death, MI, or stroke) over 12 months. The difference in treatments was driven by cardiovascular death and myocardial infarction with no significant difference in the rate of strokes (1.5% on ticagrelor vs 1.3% on clopidogrel) ticagrelor demonstrated a statistically significant relative RRR

of 16% (ARR 1.1%) for MI and a 21% RRR (ARR 1.1%) for CV death. Treating 91 patients with ticagrelor instead of clopidogrel will prevent 1 CV death.

The superiority of ticagrelor over clopidogrel appeared early (ARR 0.6% and 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 for at least 12 months. Figure 3 reveals that the estimate of the risk to the first occurrence of any event in the composite efficacy endpoint for ticagrelor and clopidogrel continues to diverge at 12 months.

In PLATO, a large number of subgroup comparisons were conducted for the primary efficacy endpoint to assess the robustness and consistency of the overall benefit. The treatment effect of ticagrelor over clopidogrel appears consistent across multiple patient subgroups by demographic characteristics including weight, gender, medical history, concomitant therapy, and by final index event diagnosis (STEMI, NSTEMI, and UA). The benefits associated with ticagrelor were also independent of the use of other acute and long-term cardiovascular therapies, including heparin, low molecular weight heparin (LMWH), intravenous GpIIb/IIIa inhibitors, lipid-lowering drugs, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists, and proton pump inhibitors.

Patients ≥65 years or ≥75 years of age had a higher rate of major CV events in both treatment arms. For patients ≥75 years of age, the rate of major CV events was 15.9% on ticagrelor vs 16.9% on clopidogrel. For patients <75 years of age, the rate of major CV events was 8.1% on ticagrelor vs 9.8% on clopidogrel. Similar differences were seen in patients ≥ 65 years compared with those <65 years.

In addition, patients weighing <60kg had a higher rate of major CV events in both treatment arms. For patients weighing <60kg, the rate of major CV events was 12.4% on ticagrelor vs 16.4% on clopidogrel. For patients weighing ≥60kg, the rate of major CV events was 9.0% on ticagrelor vs 10.4% on clopidogrel.

In the PLATO Asian subpopulation, the efficacy result for the primary endpoint (ticagrelor 13.0% vs clopidogrel 16.2%; HR 0.82 [95% CI: 0.59, 1.14]) was consistent with the overall efficacy results in the PLATO population, as were the secondary composite endpoints.

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). The explanation for this apparent treatment-by-region interaction observed in PLATO is uncertain. It could be due to chance, however additional analyses suggest that the efficacy of ticagrelor relative to clopidogrel is associated with aspirin dose during maintenance therapy. The data show greater efficacy of ticagrelor compared to clopidogrel when used in conjunction with low maintenance dose aspirin (75-150 mg). The relative efficacy of ticagrelor versus clopidogrel when used with high doses of aspirin (>300 mg) is less certain.

Based on this observed relationship between maintenance aspirin dose and relative efficacy of ticagrelor compared to clopidogrel, it is recommended that ticagrelor is used with a low maintenance dose of aspirin 75-150 mg (refer to Sections 4.2 DOSE AND METHOD OF ADMINISTRATION and 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Ticagrelor demonstrated a statistically significant RRR in the primary composite endpoint (CV death, MI, or stroke) in acute coronary syndromes (ACS) patients planned for invasive management (RRR 16%, ARR 1.7%, p=0.0025). In a pre-specified, exploratory analysis, ticagrelor demonstrated a RRR of the primary composite endpoint in ACS patients intended for medical management (RRR 15%, ARR 2.3%, nominal p=0.0444). Consistent with the primary endpoint of the study, the effect in these two groups was driven by CV death and MI with no effect on stroke. In patients receiving stents, there were fewer definite stent thromboses among patients treated with ticagrelor compared to clopidogrel (73 vs 107, RRR 32%, ARR 0.6%; nominal p=0.0123).

Ticagrelor demonstrated a statistically significant RRR of 16% (p=0.0001, ARR 2.1%) for the composite of all-cause mortality, MI, and stroke compared to clopidogrel.

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.

The increase in ventricular pauses in the acute phase of ACS was more pronounced in ticagrelor patients with history of congestive heart failure (CHF) (9.2% vs 5.4% in patients without CHF history; for clopidogrel patients, 4.0% in those with vs 3.6% in those without CHF history). This imbalance did not occur at one month: 2.0% vs 2.1% for ticagrelor patients with and without CHF history respectively; and 3.8% vs 1.4% with clopidogrel. There were no adverse clinical consequences associated with this imbalance (including pacemaker insertions) in this population of patients.

Genetic substudy

In the PLATO genotyping substudy of 10,285 patients ticagrelor findings were consistent with overall PLATO findings. Ticagrelor was more efficacious than clopidogrel in reducing major CV events irrespective of CYP2C19 and ABCB1 polymorphisms. 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 to clopidogrel in patients with one or more CYP2C19 loss of function alleles, but was similar clopidogrel in patients with no loss of function allele.

Renal

The PLATO study included 15,202 ACS patients who had serum creatinine levels available at baseline. Of these patients, 3237 (21.2%) had chronic kidney disease (CKD) (defined as Creatinine Clearance <60mL/min by the Cockroft-Gault equation). In patients with CKD, treatment with ticagrelor resulted in a statistically significant reduction in major CV events compared with clopidogrel and absolute risk reduction with ticagrelor increased as renal function declined. No significant difference in major bleeding was observed between ticagrelor and clopidogrel irrespective of renal function, while numerically more non-procedure related bleeding was observed with ticagrelor.

Combined efficacy and safety composite

A combined efficacy and safety composite (CV death, MI, stroke, or PLATO-defined 'Total Major' bleeding) supports the clinical benefit of ticagrelor compared to clopidogrel (RRR 8%, ARR 1.4%, HR 0.92; p=0.0257) over 12 months after ACS events.

PHILO study

This was an exploratory randomised, double-blind, parallel group, multicentre trial to assess the efficacy and safety of ticagrelor compared to clopidogrel in Asian/Japanese patients with non-ST or ST-elevation Acute Coronary Syndrome (ACS) for whom PCI is planned, unlike PLATO where patients intended for medical management were also included.

A total of 800 patients, from 3 countries [Japan, South Korea and Taiwan; most were Japanese (723/800; 90%)], were randomised to one of two treatment groups: ticagrelor 90 mg tablet twice daily orally, with an initial loading dose of 180 mg or clopidogrel 75 mg once daily orally, with an initial loading dose of 300 mg in clopidogrel-naïve patients. All patients also received aspirin 75-100 mg daily during the treatment period in the study.

The duration of study treatment was 6-12 months. At the end of follow up, the incidence of the primary efficacy endpoint, a composite of CV Death/MI [excluding silent MI]/stroke, was 36/401 (10.2% per year) in the ticagrelor group compared to 25/400 (8.1% per year) in the clopidogrel group. The hazard ratio (ticagrelor/clopidogrel) was 1.47 (95%CI 0.88, 2.44).

Paediatric population

In a randomised, double-blind, placebo-controlled, phase 3 trial, the primary objective of reducing the rate of vaso-occlusive crises in paediatric patients aged 2 to less than 18 years with sickle cell disease, was not met.

5.2 PHARMACOKINETIC PROPERTIES

Ticagrelor demonstrates linear pharmacokinetics. Exposure to ticagrelor and active metabolite AR-C124910XX are approximately dose proportional.

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. The C_{max} and AUC of ticagrelor and the active metabolite increased in an approximately proportional manner with dose over the dose range studied (30-1,260 mg).

The mean absolute bioavailability of ticagrelor was estimated to be 36% (range 25.4% to 64.0%). Ingestion of a high-fat meal had no effect on ticagrelor C_{max} or the AUC of the active metabolite, but resulted in a 21% increase in ticagrelor AUC and 22% decrease in the active metabolite C_{max}. These small changes are considered of minimal clinical significance; therefore, ticagrelor can be given with or without food.

Ticagrelor as crushed tablets mixed in water, given orally or administered through a nasogastric tube into the stomach, is bioequivalent to whole tablets (AUC and C_{max} within 80-125% for ticagrelor and the active metabolite). Compared to whole tablets, the geometric least-squares (LS) mean concentrations of ticagrelor were higher at 0.5 hour and 1 hour following administration of crushed tablets suspended in water and dispersed tablets suspended in water administered via NGT, respectively. At two hours post-dose the geometric LS mean concentrations following administration of the crushed tablet suspended in water and the dispersed tablet suspended in water administered via NGT were similar to the geometric LS mean concentration following administration of the whole tablet. The geometric LS mean concentrations of the major metabolite of ticagrelor, AR-C124910XX, were higher, compared with whole tablets, following administration of crushed tablets suspended in water at 0.5 hour and 1 hour post-dose, respectively, and higher at 0.5 hour, 1 hour and 2 hours post-dose respectively following administration of dispersed tablets suspended in water administered via a NGT.

Distribution

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

Metabolism

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

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

Excretion

The primary route of ticagrelor elimination is via hepatic metabolism. When 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 mostly via biliary secretion. The mean $t_{1/2}$ was approximately 6.9 hours (range 4.5-12.8 hours) for ticagrelor and 8.6 hours (range 6.5-12.8 hours) for the active metabolite.

Clearance of ticagrelor

The systemic clearance of ticagrelor is 14.2 L/h.

Special populations

Elderly

Higher exposures to ticagrelor (approximately 60% for both C_{max} and AUC) and the active metabolite (approximately 50% for both C_{max} and AUC) were observed in elderly (≥65 years) subjects compared to younger subjects. These differences are not considered clinically significant. No dose adjustment is needed for elderly patients.

Paediatric

ARX-TICAGRELOR is not indicated in a paediatric population (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION and 5.1 PHARMACODYNAMIC PROPERTIES).

Gender

Higher exposures to ticagrelor (approximately 52% and 37% for C_{max} and AUC, respectively) and the active metabolite (approximately 50% for both C_{max} and AUC) were observed in women compared to men. These differences are not considered clinically significant.

Body weight

Body weight was determined to have less than 20% change in the population mean clearance for both ticagrelor and the active metabolite at the 10^{th} or 90^{th} percentile of the body weight distribution compared to the population mean clearance at the median. This small effect on the clearance is not considered clinically relevant. Accordingly, no dose adjustment is necessary for ticagrelor based on weight.

Smoking

Habitual smoking increased population mean clearance of ticagrelor by approximately 22%. This effect on the clearance is not considered clinically relevant.

Patients with renal impairment

Exposure to ticagrelor was approximately 20% lower and exposure to the active metabolite was approximately 17% higher as measured by AUC in patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2) compared to subjects with normal renal function. The IPA effect of ticagrelor was similar between the two groups, however, there was more variability observed in individual response in

patients with severe renal impairment. These differences are not considered clinically significant.

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, respectively, compared to subjects with normal renal function. A similar increase in exposure was observed when ticagrelor was administered immediately prior to dialysis showing that ARX-TICAGRELOR is not dialysable. Exposure of the active metabolite increased to a lesser extent.

No dosing adjustment is needed in patients with renal impairment.

Patients with hepatic impairment

The 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. These differences are not considered clinically significant. No dose adjustment is needed for patients with mild hepatic impairment.

No studies have specifically been conducted with ticagrelor in patients with moderate or severe hepatic impairment. No pharmacokinetic information is available in patients with moderate hepatic impairment. Therefore, ARX-TICAGRELOR is contraindicated for use in patients with moderate or severe hepatic impairment (refer to Sections 4.2 DOSE AND METHOD OF ADMINISTRATION, 4.3 CONTRAINDICATIONS, and 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Ethnicity

Patients of Asian descent have a 39% higher mean bioavailability of ticagrelor compared to Caucasian patients. Patients self-identified as Black had an 18% lower bioavailability of ticagrelor compared to Caucasian patients. The exposure in patients self-identified as Hispanic or Latino was similar to that in Caucasians. 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 (see Sections 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) and 5.1 PHARMACODYNAMIC PROPERTIES - Clinical trials).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Ticagrelor showed no genotoxic potential in assays for gene mutations (bacterial reverse mutation, mouse lymphoma TK) and chromosomal damage (rat micronucleus *in vivo*).

Carcinogenicity

No compound-related tumours were observed in a 2-year mouse study at oral doses up to 250 mg/kg/day (*ca*.18-fold the maximum human therapeutic exposure to ticagrelor). There was no increase in tumours in male rats at oral doses up to

120 mg/kg/day (*ca*. 15-fold the maximum human therapeutic exposure). Increases in uterine adenocarcinomas and hepatocellular adenomas/adenocarcinomas and decreases in pituitary adenomas and mammary fibroadenomas were observed in female rats at more than 25 times the maximum human therapeutic exposure to ticagrelor, with no change in tumour incidence seen at around 8 times the maximum human therapeutic exposure. The uterine tumours seen only in rats were hypothesised to result from a hormonal imbalance present in rats given high doses of ticagrelor. The benign liver tumours are considered secondary to the response by the liver to the metabolic load placed on the liver from the high doses of ticagrelor.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Mannitol, calcium hydrogen phosphate dihydrate, sodium starch glycollate, hyprolose, magnesium stearate, hypromellose, titanium dioxide, purified talc, macrogol 400, iron oxide yellow. ARX-TICAGRELOR does not contain gluten.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Calendar blister (PVC/PVDC) in cartons of 56 (4 x 14 tablets).

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

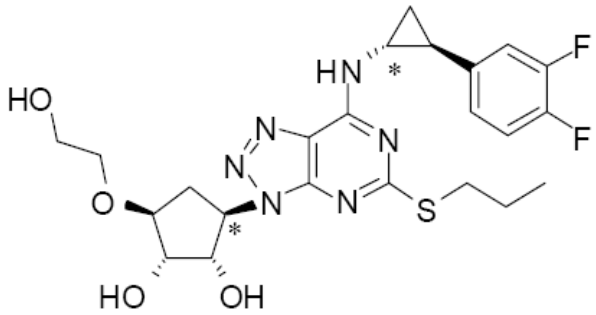
6.7 PHYSICOCHEMICAL PROPERTIES

Ticagrelor is a white or off-white to pale pink crystalline powder. The log P (octanol/water) has been measured to >4.0 at pH 7.4. The molecule has no pKa values within physiological range and does not demonstrate pH dependent solubility. It is non-hygroscopic, exhibiting no significant increase in water content after exposure at 40°C/75% RH.

Chemical structure

Chemical Name (IUPAC): (1*S*,2*S*,3*R*,5*S*)-3-[7-{[(1*R*,2*S*)-2-(3,4-Difluorophenyl)cyclopropyl]amino}-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl]-5-(2-hydroxyethoxy)cyclopentane-1,2-diol

The chemical structure of ticagrelor is:



Molecular weight: 522.57

CAS number

The CAS number for ticagrelor is 274693-27-5.

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8. SPONSOR

AstraZeneca Pty Ltd
ABN 54 009 682 311
66 Talavera Road
MACQUARIE PARK NSW 2113

Telephone: 1800 805 342

9. DATE OF FIRST APPROVAL

07 August 2024

10. DATE OF REVISION

10 October 2025

Summary table of changes

Section changed	Summary of new information
4.5	Include magnitude of interaction between ticagrelor and rosuvastatin.

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