PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

# Pr TEVA-TICAGRELOR

Ticagrelor Tablets

Tablets, 60 mg and 90 mg, Oral

Ph. Eur.

Platelet Aggregation Inhibitor

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RECENT MAJOR LABEL CHANGES

| | |
|---|---|
| 7 WARNINGS AND PRECAUTIONS, Cardiovascular | 01/2023 |
| 7 WARNINGS AND PRECAUTIONS, Central Sleep Apnea | 01/2023 |

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**Sections or subsections that are not applicable at the time of authorization are not listed.**

PART I: HEALTH PROFESSIONAL INFORMATION

## 1 INDICATIONS

### Acute Coronary Syndrome

TEVA-TICAGRELOR (ticagrelor), co-administered with low-dose acetylsalicylic acid (ASA: 75-150 mg), is indicated for the secondary prevention of atherothrombotic events in patients with acute coronary syndromes (ACS) (see **14 CLINICAL TRIALS**).

### History of Myocardial Infarction (at least one year ago)

TEVA-TICAGRELOR (ticagrelor), co-administered with low-dose acetylsalicylic acid (ASA: 75-150 mg), is indicated for the secondary prevention of atherothrombotic events in patients with a history of myocardial infarction (MI occurred at least one year ago) and a high risk of developing an atherothrombotic event (see **14 CLINICAL TRIALS**).

### 1.1 Pediatrics

**Pediatrics (< 18 years of age):** The safety and efficacy of ticagrelor in pediatric patients below the age of 18 have not been established. Therefore, Health Canada has not authorized an indication for pediatric use.

### 1.2 Geriatrics

**Geriatrics (≥ 65 years):** No overall differences in safety or efficacy were observed between geriatric patients and younger adult patients with acute coronary syndrome (PLATO), or a history of MI (≥one year) (PEGASUS) (see **8 ADVERSE REACTIONS** and **14 CLINICAL TRIALS**).

## 2 CONTRAINDICATIONS

TEVA-TICAGRELOR (ticagrelor) is contraindicated in:

- Patients who are hypersensitive to this medication or to any ingredient in the formulation. For a complete listing of ingredients, see **6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING**.
- Patients who have active pathological bleeding such as peptic ulcer or intracranial hemorrhage (see **7WARNINGS AND PRECAUTIONS** and **8 ADVERSE REACTIONS**).
- Patients with a history of intracranial hemorrhage (see **7 WARNINGS AND PRECAUTIONS** and **8 ADVERSE REACTIONS**).

- Patients with moderate to severe hepatic impairment (see **4 DOSAGE AND ADMINISTRATION** and **10 CLINICAL PHARMACOLOGY**).

- Patients who are also taking strong CYP3A4 inhibitors (e.g. ketoconazole, clarithromycin, nefazodone, ritonavir, and atazanavir) (see **7 WARNINGS AND PRECAUTIONS** and **9 DRUG INTERACTIONS**).

## 4 DOSAGE AND ADMINISTRATION

### 4.1 Dosing Considerations

Patients taking TEVA-TICAGRELOR should also take a daily low maintenance dose of ASA 75-150 mg, unless specifically contraindicated.

The PLATO trial data suggest the efficacy of ticagrelor 90 mg bid relative to clopidogrel 75 mg od is associated with ASA dose during maintenance therapy. Patients receiving a low maintenance dose of ASA benefit more than those receiving a high maintenance dose of ASA. Because the data from patients receiving high maintenance dose ASA (> 300 mg daily) do not provide conclusive evidence of the efficacy of ticagrelor 90 mg bid compared to clopidogrel 75 mg od, high maintenance dose ASA (> 150 mg daily) is not recommended for maintenance dual antiplatelet therapy with TEVA-TICAGRELOR 90 mg. There is no conclusive evidence regarding the underlying biological mechanism (see **14 CLINICAL TRIALS**).

### 4.2 Recommended Dose and Dosage Adjustment

***Acute Coronary Syndrome***

TEVA-TICAGRELOR 90 mg therapy should be initiated with a single 180 mg oral loading dose (two 90 mg tablets) and then continued at 90 mg twice daily.

**Switching from clopidogrel to TEVA-TICAGRELOR 90 mg**:
Patients can be switched from clopidogrel to TEVA-TICAGRELOR without interruption of antiplatelet effect. This results in an absolute inhibition of platelet aggregation (IPA) increase of 26.4%. Conversely, switching from TEVA-TICAGRELOR 90 mg twice daily to clopidogrel 75 mg results in an absolute IPA decrease of 24.5%. Clinicians who desire to switch patients, with a prior ACS event, from clopidogrel to TEVA-TICAGRELOR should administer the first dose of TEVA-TICAGRELOR 24 hours following the last dose of clopidogrel (see **10.2 Pharmacodynamics**).

**History of Myocardial Infarction (≥One Year)**

TEVA-TICAGRELOR 60 mg twice daily is the recommended dose when an extended treatment is required for patients with a history of spontaneous MI of at least one year and at high risk of developing an atherothrombotic event. No loading dose of TEVA-TICAGRELOR is required. The TEVA-TICAGRELOR 90 mg dose should not be used for this indication (see **14 CLINICAL TRIALS**).

TEVA-TICAGRELOR 60 mg may be started without interruption after the initial one-year treatment with TEVA-TICAGRELOR 90 mg or other adenosine diphosphate (ADP) receptor antagonist therapy in ACS patients at high risk of an atherothrombotic event.

Treatment can also be initiated up to two years from the spontaneous myocardial infarction, or within one year after stopping previous ADP receptor antagonist treatment (see **14 CLINICAL TRIALS**).

Treatment with TEVA-TICAGRELOR should be continued in patients with a history of MI for as long as the patient remains at high risk of an atherothrombotic event for a duration up to three years. Efficacy and safety data are insufficient to establish whether the benefits of TEVA-TICAGRELOR still outweigh the risks after three years of extended treatment.

**Switching from another $P2Y_{12}$ receptor antagonist to TEVA-TICAGRELOR 60 mg in patients with a history of MI:**

Physicians who desire to switch patients with a history of MI to TEVA-TICAGRELOR should administer the first dose of TEVA-TICAGRELOR 24 hours following the last dose of the other $P2Y_{12}$ receptor antagonist.

**Premature Discontinuation**
Premature discontinuation with any antiplatelet therapy, including TEVA-TICAGRELOR, could result in an increased risk of cardiovascular (CV) death or MI due to the patient's underlying disease (see **7 WARNINGS AND PRECAUTIONS**).

**Dosing Considerations in Special Populations**

**Geriatrics (≥ 65 years of age)***:* No dosage adjustment is required in elderly (≥ 65 years) patients (see **Special Populations and Conditions**).

**Patients with Renal Insufficiency:** No dosage adjustment is required in patients with renal impairment. Ticagrelor is not dialyzable. Appropriate caution should be used in patients requiring renal replacement therapy (see **Special Populations and Conditions**).

**Patients with Hepatic Insufficiency***:* No dosage adjustment is required in patients with mild hepatic impairment. No studies have specifically been conducted for ticagrelor in patients with

moderate or severe hepatic impairment. There is only limited information on the treatment of patients with moderate hepatic impairment. Therefore, use in patients with moderate or severe hepatic impairment is contraindicated (see **2 CONTRAINDICATIONS** and **Special Populations and Conditions**).

### 4.4 Administration

**Timing of administration of a dose with respect to food**

TEVA-TICAGRELOR may be taken orally with or without food, may be given without regard to meals. In a study of healthy subjects, 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 changes are considered of minimal clinical significance. Ticagrelor was administered without regard to food in PLATO (90 mg), and PEGASUS (60 mg).

**Alternate Methods of Administration**

For patients who are unable to swallow the tablet(s) whole TEVA-TICAGRELOR tablets (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. The mixture can also be administered via a nasogastric tube (CH8 or greater). It is important to flush the nasogastric tube through with water after administration of the mixture.

### 4.5 Missed Dose

Lapses in therapy should be avoided. A patient who misses a dose of TEVA-TICAGRELOR should take their next dose at its scheduled time (see **10.2 Pharmacodynamics**).

## 5 OVERDOSAGE

**Treatment**

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

**Signs and Symptoms**

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 effects which may occur with overdose include dyspnea and ventricular pauses.

Single oral doses of ticagrelor to mice caused no observable effects at doses up to 2000 mg/kg. Single oral doses of 500 and 2000 mg/kg ticagrelor to rats caused a transient reduction in body weight with no other observable effects.

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

For management of a suspected drug overdose, contact your regional Poison Control Centre.

## 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

**Table 1: Dosage Form, Strengths and Composition**

| Route of Administration | Dosage Form / Strength / Composition | Nonmedicinal Ingredients |
|---|---|---|
| Oral | Tablet 60 mg and 90 mg | Mannitol, anhydrous dibasic calcium phosphate, povidone, sodium starch glycolate, magnesium stearate, hypromellose, titanium dioxide, polyethylene glycol, talc, iron oxide yellow (90 mg), iron oxide red |

TEVA-TICAGRELOR (ticagrelor) is available as 60 mg film-coated tablets which are light pink to pink colored, round shaped, debossed with"137" on one side and "A" on other side.

TEVA-TICAGRELOR (ticagrelor) is available as 90 mg film-coated tablets which are light yellow to yellow colored, round shaped, debossed with"A91" on one side and plain on other side.

**Packaging**
TEVA-TICAGRELOR 90 mg is available in HDPE bottles of 60 tablets for institutional use only and blister packs of 60 tablets (6 x 10 tablets).

TEVA-TICAGRELOR 60 mg is available in HDPE bottles of 60 tablets and blister packs of 60 tablets (6 x 10 tablets).

## 7 WARNINGS AND PRECAUTIONS

### General

**Bleeding Risk:** As with other antiplatelet agents, the use of TEVA-TICAGRELOR in patients at known increased risk for bleeding should be balanced against the benefit in terms of prevention of thrombotic events (see **8 ADVERSE REACTIONS**). The treating physician should regularly reassess whether treatment with TEVA-TICAGRELOR remains appropriate, particularly if there is a change in the factors associated with an increased risk of bleeding.

If clinically indicated, TEVA-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 recent gastrointestinal bleeding). The use of TEVA-TICAGRELOR is contraindicated in patients with active pathological bleeding, in those with a history of intracranial hemorrhage, and moderate to severe hepatic impairment (see **2 CONTRAINDICATIONS**).
- Patients who are at increased risk of trauma. The treating physician should inform patients of this risk and discuss preventive measures of trauma (see **8 ADVERSE REACTIONS**).
- Patients requiring oral anticoagulants (e.g. warfarin, see **9 DRUG INTERACTIONS**) and/or fibrinolytics agents (within 24 hours of TEVA-TICAGRELOR dosing). Such agents confer an independent bleeding risk as they function in a distinct and complementary mechanism of hemostasis compared to ticagrelor. The combination of ticagrelor with either of these classes of drugs has not been studied.
  - **Warfarin Therapy**: Due to an increased propensity to bleed, caution is advised in patients taking warfarin during TEVA-TICAGRELOR therapy. A specific drug-drug interaction study with warfarin has not been performed (see **9 DRUG INTERACTIONS**).
- Patients with concomitant administration of medicinal products that may increase the risk of bleeding, e.g. non-steroidal anti-inflammatory drugs (NSAIDs).

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.

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

**Maintenance Dose Acetylsalicylic Acid (ASA):** Based on a relationship observed in PLATO between maintenance ASA dose and relative efficacy of ticagrelor compared to clopidogrel, co-administration of TEVA-TICAGRELOR and high maintenance dose ASA (> 150 mg daily) is not recommended (see **1 INDICATIONS** and **4 DOSAGE AND ADMINISTRATION**).

**Cytochrome P450 3A4 Strong Inhibitors:** Co-administration of ticagrelor with strong CYP3A4 inhibitors (e.g. ketoconazole, clarithromycin, nefazodone, ritonavir, and atazanavir) is contraindicated as co-administration may lead to a substantial increase in exposure to ticagrelor (see **2 CONTRAINDICATIONS** and **9 DRUG INTERACTIONS**).

**Premature Discontinuations:** Patients who require discontinuation of TEVA-TICAGRELOR are at increased risk for cardiac events. Premature discontinuation of treatment should be avoided. If TEVA-TICAGRELOR must be temporarily stopped due to an adverse event, 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.

**Uric Acid Increase:** In PLATO, patients on ticagrelor had a higher risk of hyperuricemia than those receiving clopidogrel. In PEGASUS, a greater incidence of gout, gouty arthritis and hyperuricemias was reported in patients on ticagrelor compared to aspirin alone. Caution should be exercised when administering TEVA-TICAGRELOR to patients with a history of hyperuricemia or gouty arthritis. As a precautionary measure, the use of TEVA-TICAGRELOR in patients with uric acid nephropathy is discouraged.

**Cardiovascular**

**Patients at Risk for Bradyarrhythmia:** Holter ECG monitoring conducted during clinical trials has shown an increased frequency of mostly asymptomatic ventricular pauses during treatment with ticagrelor compared with clopidogrel. In Phase 3 studies (PLATO and PEGASUS) evaluating the safety and efficacy of ticagrelor, patients with history of sick sinus syndrome, second and third degree atrioventricular (AV) block or bradycardic-related syncope and not protected with a pacemaker were excluded as they may be at increased risk of developing bradyarrhythmias with ticagrelor. The incidence of bradyarrhythmic events in these studies were reported in a similar frequency for ticagrelor and comparators (i.e., clopidogrel or aspirin alone). Bradyarrhythmic events, including second and third degree AV block, have been reported in the post-marketing setting in patients with or without history of bradyarrhythmia, in most cases, shortly after initiation of treatment with ticagrelor. These events occurred primarily in patients with ACS, where cardiac ischemia and concomitant drugs reducing the heart rate or affecting cardiac conduction are potential confounders. In some cases, the bradyarrhythmic events resolved after ticagrelor specifically was discontinued. Some cases of bradyarrhythmia were severe and the patients required pacing (usually temporary). A meta-analysis of randomized control trials suggests that the risk of bradyarrhythmia with ticagrelor may be dose-dependent and that the increased risk with ticagrelor, relative to comparators, is specific to patients with a

history of bradyarrhythmia. Therefore, TEVA-TICAGRELOR should be used with caution in patients deemed at higher risk for bradyarrhythmia and these patients should be closely monitored during the first few weeks on treatment (see **8 ADVERSE REACTIONS** and **14 CLINICAL TRIALS**).

In addition, caution should be exercised when administering TEVA-TICAGRELOR concomitantly with drugs known to induce bradycardia. However, no evidence of clinically significant adverse interactions was observed in the PLATO and the PEGASUS trials during concomitant administration with one or more drugs known to induce bradycardia. In PLATO, 96% of patients took beta blockers, 33% took diltiazem or verapamil (calcium channel blockers), and 4% took digoxin.

**Driving and Operating Machinery**

**Effects on Ability to Drive and Use Machines:** No studies on the effects of ticagrelor on the ability to drive and use machines have been performed. During treatment with ticagrelor, dizziness, confusion, vertigo and syncope have been reported. Therefore, patients who experience these symptoms should be cautious while driving or using machines (see **8 ADVERSE REACTIONS**).

**Hematologic**

**Thrombotic Thrombocytopenic Purpura (TTP):** TTP has been reported very rarely with the use of ticagrelor. TTP is a serious, potentially fatal condition and requires prompt treatment, plasmapheresis should be considered. TTP is characterized by some or all of the following symptoms and findings; thrombocytopenia, microangiopathic hemolytic anemia (schistocytes seen on peripheral blood smear), neurological findings, renal dysfunction, and fever.

**Monitoring and Laboratory Tests**

**Platelet function tests to diagnose Heparin induced thrombocytopenia (HIT):** False negative results in platelet function 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.

Before considering discontinuation of 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.

**Neurologic**

**Central Sleep Apnea:** Central sleep apnea including Cheyne-Stokes respiration has been reported in the post-marketing setting in patients taking ticagrelor. If central sleep apnea is suspected, further clinical assessment may be considered.

**Patients with Prior Ischemic Stroke:** ACS patients with prior ischemic stroke can be treated with ticagrelor 90 mg for up to 12 months (PLATO). In PEGASUS (history of MI ≥ one year), patients with prior ischemic stroke were excluded because previous studies have shown that combination use of antiplatelet agents (not ticagrelor) is associated with increased risks of intracranial hemorrhage. Therefore, in the absence of data, ticagrelor treatment beyond one year in ACS patients with prior ischemic stroke is not recommended.

**Peri-Operative Considerations**

**Surgery:** If a patient requires surgery, clinicians should consider each patient's clinical profile as well as the benefits and risks of continued antiplatelet therapy when determining when discontinuation of TEVA-TICAGRELOR treatment should occur.

In PLATO patients undergoing CABG, ticagrelor had a similar rate of major bleeds compared to clopidogrel at all days after stopping therapy except Day 1 where ticagrelor had a higher rate of major bleeding (see **8 ADVERSE REACTIONS**).

Because of the reversible binding of ticagrelor, restoration of platelet aggregation occurs faster with ticagrelor compared to clopidogrel.

In the OFFSET study, mean Inhibition of Platelet Aggregation (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 antiplatelet therapy must be temporarily discontinued due to surgery or trauma (see **10.2 Pharmacodynamics**).

To minimize the risk of bleeding, if a patient is to undergo elective surgery and antiplatelet effect is not desired, TEVA-TICAGRELOR should be discontinued 5 days prior to surgery.

**Renal**

**Renal Impairment:** No dosage adjustment is required in patients with renal impairment. Ticagrelor is not dialyzable. Appropriate caution should be used in patients requiring renal replacement therapy. Creatinine levels may increase during treatment with TEVA-TICAGRELOR. The mechanism has not been identified. Renal function should be monitored in the course of patient management (see **8 ADVERSE REACTIONS** and **Special Populations and Conditions**).

**Respiratory**

**Dyspnea:** In clinical trials, approximately 14% of patients randomized to ticagrelor 90 mg (PLATO) or 60 mg twice daily (PEGASUS) reported dyspnea, including dyspnea at rest, exertional dyspnea, paroxysmal nocturnal dyspnea, and nocturnal dyspnea (see **8 ADVERSE REACTIONS**). The patients experienced a single episode in 85% of the cases. The dyspnea is usually mild to moderate in intensity and often resolves during continued ticagrelor treatment.

Ticagrelor should be used with caution in older patients and in patients with history of asthma and/or chronic obstructive pulmonary disease. If a patient reports new, prolonged or worsened dyspnea this should be investigated fully and if not tolerated, treatment with TEVA-TICAGRELOR should be stopped (see **8 ADVERSE REACTIONS**). The mechanism has not yet been elucidated.

PLATO data do not suggest that the higher frequency of dyspnea with ticagrelor 90 mg is due to new or worsening heart or lung disease. In patients who underwent pulmonary function testing in the clinical program, there was no indication of an adverse effect of ticagrelor 90 mg on pulmonary function.

## 7.1 Special Populations

### 7.1.1 Pregnant Women

The safety of ticagrelor during pregnancy has not been established, as no clinical study has been conducted in pregnant women and limited clinical data on exposure to ticagrelor during pregnancy are available. Women of child bearing potential should use appropriate contraceptive measures to avoid pregnancy.

### 7.1.2 Breast-feeding

It is not known whether this drug is excreted in human milk, as no clinical study has been conducted in lactating women. Studies in rats have shown that ticagrelor and its active metabolites are excreted in milk (see **Special Populations and Conditions**). Therefore, the use of TEVA-TICAGRELOR during breastfeeding is not recommended.

### 7.1.3 Pediatrics

**Pediatrics (< 18 years of age):** The safety and efficacy of ticagrelor in pediatric patients below the age of 18 have not been established. Therefore, Health Canada has not authorized an indication for pediatric use.

### 7.1.4 Geriatrics

**Geriatrics (≥ 65 years of age):** No overall differences in safety or efficacy were observed in geriatric patients in the PLATO and PEGASUS trials (see **1 INDICATIONS** and **14 CLINICAL TRIALS**), and no dosage adjustment is required in elderly (≥ 65 years) patients (see **4 DOSAGE**

AND ADMINISTRATION).

## 8 ADVERSE REACTIONS

### 8.1 Adverse Reaction Overview

The safety profile of ticagrelor has been evaluated in two large randomized phase 3 outcome trials (PLATO and PEGASUS) including more than 39,000 patients (see **14 CLINICAL TRIALS**).

**Acute Coronary Syndrome**
In PLATO, a total of 6,762 patients with Acute Coronary Syndromes (UA, NSTEMI and STEMI) were exposed to ticagrelor (180 mg loading dose followed by a 90 mg twice daily maintenance dose) for at least 6 months and up to 12 months for 3,138 of them.

The commonly reported adverse events in patients treated with ticagrelor were dyspnea, headache and epistaxis and these events occurred at higher rates than in the clopidogrel treatment group (see Table 4).

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 dyspnea (0.7% vs. 0.4%).

The rate of study drug discontinuation because of adverse events was 7.4% for ticagrelor and 5.4% for clopidogrel. Dyspnea was the most common adverse events leading to study drug discontinuation for ticagrelor (0.9% for ticagrelor and 0.1% for clopidogrel).

**History of Myocardial Infarction (≥One Year)**
The safety of ticagrelor in patients with a history of spontaneous MI (MI occurred at least one year ago) and high risk of developing an atherothrombotic event was evaluated in the PEGASUS study, which compared patients treated with ticagrelor 60 mg twice daily (N=6,958) or 90 mg twice daily combined with low dose ASA (75-150 mg) (N=6,988) to low dose ASA (75-150 mg) therapy alone (N=6,996). The ticagrelor 60 mg dose is the only dose approved for this indication. Median treatment duration for ticagrelor 60 mg was 29.4 months (see **14 CLINICAL TRIALS**).

The commonly reported adverse events in this patient population on ticagrelor were dyspnea, epistaxis, increased tendency to bruise and contusion, and these events occurred at higher rates with ticagrelor than on ASA alone (see Table 7).

The proportion of patients who had serious adverse events was similar across the treatment

groups (21.5% for ticagrelor 60 mg and 21.6% for ASA alone). The most common serious adverse events more frequently reported with ticagrelor were atrial fibrillation, syncope, dyspnea, iron deficiency anemia and epistaxis.

In PEGASUS patients on ticagrelor had a higher incidence of discontinuation due to adverse events compared to ASA alone (16.1% for ticagrelor 60 mg and 8.5% for ASA therapy alone). The most common adverse events leading to study discontinuation reported at higher rates with ticagrelor than on ASA alone were dyspnea, increased tendency to bruise, epistaxis and spontaneous hematoma.

## 8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

### Acute Coronary Syndrome

#### Bleeding Events

The primary safety endpoint in the PLATO study was the composite endpoint of 'Total Major' bleeding, which consisted of the components of 'Major Fatal/Life-threatening' and 'Major Other'. Table 2 shows the 12 month rates of patients experiencing bleeding events in the PLATO study (PLATO defined).

**Table 2: Analysis of overall bleeding events, Kaplan-Meier estimate of bleeding rates by treatment at 12 months - PLATO-defined**

| | Ticagrelor 90 mg twice daily N=9235 (%) | Clopidogrel 75 mg once daily N=9186 (%) | p-value* |
|---|---|---|---|
| **Primary Safety Endpoint** | | | |
| Total Major | 11.6 | 11.2 | 0.4336 |
| **Secondary Safety Endpoints** | | | |
| Major Fatal/Life-Threatening | 5.8 | 5.8 | 0.6988 |
| Combined Total Major + Minor | 16.1 | 14.6 | 0.0084 |
| Non-Procedural Major | 3.1 | 2.3 | 0.0058 |
| Non-Procedural Major + Minor | 5.9 | 4.3 | <0.0001 |
| Non-CABG Total Major | 4.5 | 3.8 | 0.0264 |
| Non-CABG Major Fatal/Life-threatening | 2.1 | 1.9 | 0.2516 |

* Nominal p-value not corrected for multiple testing.

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

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.

**Location of 'Total Major + Minor' Bleeding (ticagrelor versus clopidogrel):** intracranial 0.3% vs. 0.2%, pericardial 0.1% vs. 0.1%, retroperitoneal 0.03% vs. 0.03%, intraocular 0.02% vs. 0.04% and intra-articular 0.02% vs. 0.01%. Other common locations were in rank order of event frequency: gastrointestinal 1.8% vs. 1.5%, epistaxis 1.3% vs. 0.7%, urinary 0.5% vs. 0.4%, subcutaneous/dermal 0.5% vs. 0.4% and hemoptysis 0.1% vs. 0.08%.

**Non-procedural Fatal Bleeding:** There was no difference with ticagrelor compared to clopidogrel for overall non-procedural fatal bleeding. There were numerically more 'Major Fatal/Life-threatening' intracranial non-procedural bleeding events with ticagrelor (n=27 events, 0.3%) than with clopidogrel (n=14 events, 0.2%). Of the intracranial non-procedural bleeding events, 11 bleeding events with ticagrelor and 1 with clopidogrel were fatal. 'Major Fatal/Life-threatening' gastrointestinal bleeding was the same with ticagrelor and clopidogrel, with numerically more fatal events for clopidogrel (5) than for ticagrelor (none).

**Bleeding in Patient Subpopulations:** Baseline characteristics including age, gender, weight, race, geographic region, medical history, concurrent conditions and concomitant therapy were assessed to explore any increase in risk of bleeding with ticagrelor. No particular risk group was identified for any subset of bleeding.

Table 3 shows the overall rates of TIMI-defined bleeding events.

**Table 3: Analysis of overall bleeding events - TIMI-defined**

| | Ticagrelor N=9235 (%) | Clopidogrel N=9186 (%) | p-value |
|---|---|---|---|
| Major | 7.9 | 7.7 | 0.5669 |
| Major + Minor | 11.4 | 10.9 | 0.3272 |
| Non-CABG Major | 2.8 | 2.2 | 0.0246 |
| Non-CABG Major + Minor | 4.5 | 3.6 | 0.0093 |

TIMI Major: Clinically apparent with > 50 g/L decrease in hemoglobin or intracranial hemorrhage.
TIMI Minor: Clinically apparent with 30 to ≤ 50 g/L decrease in hemoglobin.

**Other Adverse Events**

The incidence of adverse events (regardless of causality) reported for ≥ 1% of patients treated with ticagrelor and clopidogrel in the PLATO study are presented in Table 4.

**Table 4: Summary of adverse events (regardless of causality) reported for ≥ 1% of patients in either group (PLATO)**

| Adverse Event (System Organ Class) | Ticagrelor N=9235 (%) | Clopidogrel N=9186 (%) |
|---|---|---|
| **Blood and Lymphatic System Disorders** | | |
| Anemia | 1.9 | 1.7 |
| **Cardiac Disorders** | | |
| Atrial fibrillation | 4.2 | 4.6 |
| Bradycardia[a] | 2.9 | 2.9 |
| Cardiac failure | 2.3 | 2.6 |
| Ventricular tachycardia | 2.0 | 2.1 |
| Palpitations | 1.2 | 1.1 |
| Angina pectoris | 1.2 | 1.1 |
| Sinus bradycardia | 1.1 | 0.8 |
| Ventricular extrasystoles | 1.1 | 1.1 |
| Ventricular fibrillation | 0.8 | 1.0 |
| **Ear and Labyrinth Disorders** | | |
| Vertigo[b] | 1.5 | 1.3 |
| **Gastrointestinal Disorders** | | |
| Nausea[b] | 4.3 | 3.8 |
| Diarrhea[b] | 3.7 | 3.3 |
| Vomiting[b] | 2.5 | 2.3 |
| Constipation[b] | 2.2 | 2.6 |
| Dyspepsia[b] | 2.0 | 1.8 |
| Abdominal pain upper | 1.9 | 2.0 |
| Abdominal pain[b] | 1.5 | 1.2 |
| **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 |
| Edema peripheral | 2.3 | 2.5 |
| Asthenia | 2.0 | 2.1 |
| **Hemorrhages or bleeding** | | |
| Epistaxis[b] | 6.0 | 3.4 |
| Contusion | 3.9 | 2.0 |
| Hematoma | 2.2 | 1.3 |

**Table 4: Summary of adverse events (regardless of causality) reported for ≥ 1% of patients in either group (PLATO)**

| Adverse Event (System Organ Class) | Ticagrelor N=9235 (%) | Clopidogrel N=9186 (%) |
|---|---|---|
| Post-procedural hemorrhage[b] | 2.1 | 2.0 |
| Vessel puncture site hematoma | 1.7 | 1.1 |
| Ecchymosis | 1.5 | 0.6 |
| **Infections and Infestations** | | |
| Urinary tract infection | 2.0 | 1.8 |
| Hematuria | 1.9 | 1.6 |
| Nasopharyngitis | 1.8 | 1.6 |
| Pneumonia | 1.4 | 1.9 |
| Bronchitis | 1.3 | 1.4 |
| **Metabolism and Nutrition Disorders** | | |
| Diabetes mellitus | 1.2 | 1.1 |
| Dyslipidaemia | 1.0 | 1.0 |
| Hypercholesterolaemia | 1.0 | 0.9 |
| Hypokalaemia | 1.6 | 1.5 |
| **Musculoskeletal and Connective Tissue Disorders** | | |
| Back pain | 3.6 | 3.3 |
| Pain in extremity | 2.1 | 2.3 |
| Musculoskeletal chest pain | 1.5 | 1.4 |
| Musculoskeletal pain | 1.5 | 1.5 |
| Arthralgia | 1.5 | 1.4 |
| Myalgia | 1.4 | 1.6 |
| **Nervous System Disorders** | | |
| Headache | 6.5 | 5.8 |
| Dizziness | 4.5 | 3.9 |
| Syncope | 1.1 | 0.8 |
| **Psychiatric Disorders** | | |
| Anxiety | 2.2 | 1.9 |
| Insomnia | 1.7 | 2.0 |
| Depression | 1.1 | 1.1 |
| **Renal and Urinary Disorders** | | |
| Renal failure | 1.0 | 0.7 |
| **Respiratory Disorders** | | |
| Dyspnea[a, b] | 12.0 | 6.5 |
| Cough | 4.9 | 4.6 |
| Dyspnea Exertional | 1.9 | 1.4 |
| **Skin and Subcutaneous Tissue Disorders** | | |
| Rash[b] | 1.8 | 1.7 |
| Pruritus[b] | 1.0 | 1.0 |
| **Vascular Disorders** | | |

**Table 4: Summary of adverse events (regardless of causality) reported for ≥ 1% of patients in either group (PLATO)**

| Adverse Event (System Organ Class) | Ticagrelor N=9235 (%) | Clopidogrel N=9186 (%) |
|---|---|---|
| Hypertension | 3.8 | 4.0 |
| Hypotension | 3.2 | 3.3 |

a. Several MedDRA PT combined.
b. These events have also been reported as Adverse Drug Reactions (possibly or probably related to ticagrelor).

Additional clinical Adverse Drug Reactions that were reported as possibly or probably related to ticagrelor are listed below by body system:

**Common (≥ 1% to < 10%)**

- *Skin and subcutaneous tissue disorders:* subcutaneous or dermal bleeding
- *Gastrointestinal disorders:* gastrointestinal hemorrhages
- *Renal and urinary disorders:* urinary tract bleeding

**History of Myocardial Infarction (≥One Year)**

**Bleeding Events**

The primary safety endpoint in the PEGASUS study was the 'TIMI Major bleeding'. The safety analysis included: time to first TIMI Major bleeding event following the first dose of study drug, time to first TIMI Major or Minor bleeding event and time to first PLATO Major bleeding event.

Table 5 shows the 36-month rates of patients experiencing bleeding events in the 'on treatment' analysis of the PEGASUS study (TIMI defined).

**Table 5: Analysis of overall bleeding events, Kaplan-Meier estimate of bleeding rates by treatment at 36 months (PEGASUS) - TIMI-defined**

| | Ticagrelor 60 mg twice daily with ASA N=6958 (%) | ASA alone N=6996 (%) | p-value |
|---|---|---|---|
| **Primary Safety Endpoint** | | | |
| TIMI Major bleeding* | 2.3 | 1.1 | <0.0001 |
| **Other Safety Endpoints** | | | |
| Fatal | 0.3 | 0.3 | 1.0000 |
| ICH | 0.6 | 0.5 | 0.3130 |
| Other Major | 1.6 | 0.5 | <0.0001 |
| TIMI Major or Minor | 3.4 | 1.4 | <0.0001 |
| TIMI Major or Minor or Requiring medical attention | 16.6 | 7.0 | <0.0001 |

*__TIMI Major__: Fatal bleeding OR any intracranial bleeding OR clinically overt signs of hemorrhage associated with a drop in hemoglobin (Hgb) of ≥50 g/L, or when Hgb is not available, a fall in hematocrit (Hct) ≥15%.
__Fatal__: A bleeding event that directly led to death within 7 days.
__ICH__: Intracranial hemorrhage.
__Other TIMI Major__: Non-fatal non-ICH TIMI Major bleeding.
__TIMI Minor__: Clinically apparent with 30 to <50 g/L decrease in hemaglobin, or when Hgb is not available, a fall in hematocrit (Hct) of 9 to <15%.
__TIMI Requiring medical attention__: Requiring intervention, OR leading to hospitalization, OR prompting evaluation.

In PEGASUS, TIMI Major bleeding for ticagrelor 60 mg twice daily was higher than for ASA alone. No increased bleeding risk was seen for fatal bleeding and a small increase was observed in intracranial haemorrhages, as compared to ASA therapy alone. The number of fatal bleeding events in the study was, 11 (0.3%) for ticagrelor 60 mg and 12 (0.3%) for ASA therapy alone and most of these events involved cases of intracranial and gastrointestinal bleedings. The observed increased risk of TIMI Major bleeding with ticagrelor 60 mg was primarily due to a higher frequency of Other TIMI Major bleeding driven by events in the system organ class (SOC) gastrointestinal disorders; and injury, poisoning and procedural complications. The majority of TIMI major bleeding was reported as spontaneous.

Increased bleeding patterns similar to TIMI Major were seen for TIMI Major or Minor (see Table 5) and PLATO-defined Major and PLATO-defined Major or Minor bleeding categories (see Table 6). Discontinuation of treatment due to bleeding was more common with ticagrelor 60 mg compared to ASA therapy alone (6.2% and 1.5%, respectively). The majority of these bleedings were classified as TIMI Requiring medical attention, e.g. epistaxis, bruising and spontaneous hematomas. The most common causes of discontinuation due to a TIMI major bleeding event were gastrointestinal and traumatic intracranial hemorrhage.

Table 6 shows the overall rates of PLATO-defined bleeding events.

**Table 6: Analysis of overall bleeding events -PLATO-defined**

| | Ticagrelor 60 mg bd N=6958 (%) | ASA alone N=6996 (%) | p-value |
|---|---|---|---|
| PLATO Major bleeding* | 3.5 | 1.4 | <0.0001 |
| Fatal/life-threatening | 2.4 | 1.1 | <0.0001 |
| Other PLATO Major | 1.1 | 0.3 | <0.0001 |
| PLATO Major or Minor | 15.2 | 6.2 | <0.0001 |

*__PLATO Major Fatal/life-threatening__: Fatal bleeding, OR any intracranial bleeding, OR intrapericardial with cardiac tamponade, OR with hypovolemic shock or severe hypotension requiring pressors/inotropes or surgery OR clinically apparent with ≥50 g/L decrease in hemoglobin or when Hgb is not available, a fall in hematocrit (Hct) ≥15%) OR ≥4 red cell units transfused.
__PLATO Major Other__: Significantly disabling, OR clinically apparent with 30 to <50 g/L decrease in hemoglobin (or when Hgb is not available, a fall in hematocrit (Hct) of 9 to <15%), OR 2-3 red cell units transfused.
__PLATO Minor__: Requires medical intervention to stop or treat bleeding.

**Intracranial bleeding:** Spontaneous ICHs were reported in similar rates for ticagrelor 60 mg and ASA therapy alone (0.2% in both treatment groups). Traumatic and procedural ICHs showed an increase with ticagrelor 60 mg treatment, (n=15, 0.2%) compared with ASA therapy alone (n=10, 0.1%). There were 6 fatal ICHs with ticagrelor 60 mg and 5 with ASA therapy alone.

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

**Common Bleeding Adverse Drug Reactions (≥1% to <10%) with ticagrelor by body system:**

*Blood and lymphatic system disorders:* blood disorder bleedings (increased tendency to bruise, spontaneous hematoma, hemorrhagic diathesis)

*Gastrointestinal disorders:* gastrointestinal hemorrhages (gingival, rectal, hemorrhoidal, gastrointestinal ulcer)

*Injury, poisoning and procedural complications:* post procedural hemorrhage, traumatic bleedings

*Respiratory, thoracic and mediastinal disorders:* respiratory system bleedings (epistaxis, hemoptysis)

*Renal and urinary disorders:* urinary tract bleeding (hematuria, cystitis hemorrhage)

*Skin and subcutaneous tissue disorders:* subcutaneous or dermal bleeding (ecchymosis, skin hemorrhage, petechiae)

**Other Adverse Events**
The incidence of adverse events (regardless of causality) reported for ≥ 1% of patients treated with ticagrelor 60 mg combined with ASA or ASA alone in the PEGASUS study are presented in Table 7.

**Table 7: Summary of adverse events (regardless of causality) reported for ≥ 1% of patients in the different treatment groups and at a greater incidence with ticagrelor combined with ASA than ASA alone (PEGASUS)**

| Adverse Event (System Organ Class) | Ticagrelor 60 mg N=6958 (%) | Placebo - ASA alone N=6996 (%) |
|---|---|---|
| **Blood and Lymphatic System Disorders** | | |
| Increased tendency to bruise[b] | 6.0 | 0.9 |

**Table 7: Summary of adverse events (regardless of causality) reported for ≥ 1% of patients in the different treatment groups and at a greater incidence with ticagrelor combined with ASA than ASA alone (PEGASUS)**

| Adverse Event (System Organ Class) | Ticagrelor 60 mg N=6958 (%) | Placebo - ASA alone N=6996 (%) |
|---|---|---|
| Spontaneous hematoma[b] | 3.1 | 0.6 |
| **Cardiac Disorders** | | |
| Atrial fibrillation | 2.8 | 2.5 |
| Palpitations | 1.0 | 0.9 |
| **Ear and Labyrinth Disorders** | | |
| Vertigo[b] | 1.1 | 1.0 |
| **Gastrointestinal Disorders** | | |
| Diarrhea[b] | 3.3 | 2.5 |
| Nausea[b] | 2.1 | 1.9 |
| Dyspepsia | 1.8 | 1.8 |
| Abdominal pain | 1.3 | 1.2 |
| **Infections and Infestations** | | |
| Bronchitis | 2.7 | 2.6 |
| Urinary tract infection | 2.1 | 1.9 |
| Sinusitis | 1.1 | 1.0 |
| **Injury, Poisoning and Procedural Complications** | | |
| Contusion[b] | 5.0 | 1.5 |
| Traumatic hematoma[b] | 2.3 | 0.6 |
| Fall | 1.1 | 1.0 |
| **Investigations** | | |
| Blood pressure increased | 1.0 | 0.8 |
| **Metabolism and Nutrition Disorders** | | |
| Gout/gouty arthritis/gouty tophus[b] | 1.5 | 1.1 |
| **Nervous System Disorders** | | |
| Dizziness[b] | 4.2 | 3.7 |
| Syncope[b] | 1.2 | 0.9 |
| **Psychiatric Disorders** | | |
| Anxiety | 1.4 | 1.2 |
| Insomnia | 1.2 | 1.0 |
| **Renal and Urinary Disorders** | | |
| Hematuria[b] | 2.2 | 1.1 |
| **Reproductive System and Breast Disorders** | | |
| Benign prostatic hyperplasia | 1.4 | 1.3 |
| **Respiratory, Thoracic and Mediastinal Disorders** | | |
| Dyspnea[a,b] | 14.4 | 5.5 |
| Epistaxis[b] | 6.1 | 2.2 |

**Table 7: Summary of adverse events (regardless of causality) reported for ≥ 1% of patients in the different treatment groups and at a greater incidence with ticagrelor combined with ASA than ASA alone (PEGASUS)**

| Adverse Event (System Organ Class) | Ticagrelor 60 mg N=6958 (%) | Placebo - ASA alone N=6996 (%) |
|---|---|---|
| Cough | 2.8 | 2.5 |
| **Skin and Subcutaneous Tissue Disorders** | | |
| Ecchymosis[b] | 1.5 | 0.2 |
| Pruritus[b] | 1.0 | 0.9 |
| **Vascular Disorders** | | |
| Hypotension | 1.4 | 1.0 |

a. includes events of dyspnea, dyspnea exertional and dyspnea at rest.
b. These events have also been reported as Adverse Drug Reactions (possibly or probably related to ticagrelor).

## 8.3 Less Common Clinical Trial Adverse Reactions

***Acute Coronary Syndrome***

**Uncommon (≥ 0.1% to < 1%)**
**Eye disorders:** eye hemorrhage (intraocular, conjunctival, retinal)
**Gastrointestinal disorders:** gastritis, retroperitoneal hemorrhage
**Nervous system disorders:** intracranial hemorrhage (may be fatal or life threatening), confusion, paraesthesia
**Respiratory, thoracic and mediastinal disorders:** hemoptysis

**Rare (≥ 0.01% to < 0.1%)**
**Musculoskeletal connective tissue and bone:** hemarthrosis

***History of Myocardial Infarction (≥ One Year)***

**Blood and lymphatic system disorders:** anemia
**Ear and labyrinth disorders:** ear hemorrhage
**Eye disorders:** eye hemorrhage (intraocular, conjunctival, retinal)
**Gastrointestinal disorders:** gastritis erosive
**Musculoskeletal connective tissue and bone:** muscular bleedings (hemarthrosis, muscle hemorrhage)
**Neoplasms benign, malignant and unspecified (including cysts and polyps):** Tumour bleedings (bleeding from bladder cancer, gastric cancer, colon cancer)
**Nervous system disorders:** intracranial hemorrhage (may be fatal or life threatening), loss of consciousness
**Psychiatric disorders:** confusion
**Renal and urinary disorders:** nephrolithiasis and urinary calculus (bladder, ureteric, urethral)

**Reproductive system and breast disorders:** reproductive system bleedings (vaginal hemorrhage, hematospermia, postmenopausal hemorrhage)
**Respiratory, thoracic and mediastinal disorders:** pulmonary fibrosis, pulmonary hypertension
**Skin and subcutaneous tissue disorders:** purpura

## 8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

### *Acute Coronary Syndrome*

**Table 8: Number (%) of patients with blood creatinine increased and hyperuricemia (PLATO)**

| | Number (%) of patients | |
|---|---|---|
| **Abnormal Clinical Chemistry Findings** | **Ticagrelor 90 mg bd (N=9235)** | **Clopidogrel 75 mg od (N=9186)** |
| Blood creatinine increased[a] | 335 (8.3%) | 271 (6.7%) |
| Hyperuricemia[b] | 889 (22.1%) | 537 (13.3%) |

Derived from lab observations.

a. creatinine increased: >50% from baseline in patients with lab data [ticagrelor 90 mg bd (N=4031); clopidogrel 75 mg od (N=4035)]

b. hyperuricemia: uric acid increase from ≤ ULN at baseline to > ULN in patients with lab data [ticagrelor 90 mg bd (N=4031); clopidogrel 75 mg od (N=4035)]

Upper limit normal (ULN), provided by central lab, is:
8.0 mg/dl for male (age ≤90), 8.3 mg/dl for male (age >90)
6.9 mg/dl for female (age ≤65), 7.3 mg/dl for female (age 66-90), 7.7 mg/dl for female (age >90)

### *History of Myocardial Infarction (≥ One Year)*

**Table 9: Number (%) of patients with blood creatinine increased, hyperuricemia and hemoglobin decreased (PEGASUS)**

| | Number (%) of patients | |
|---|---|---|
| **Abnormal Clinical Chemistry Findings** | **Ticagrelor 60 mg bd (N=6958)** | **ASA alone (N=6996)** |
| Blood creatinine increased[a] | 243 (3.9%) | 234 (3.6%) |
| Hyperuricemia[b] | 444 (9.1%) | 296 (5.7%) |
| Hemoglobin decreased[c] | 637 (11.4%) | 460 (7.7%) |

Derived from lab observations.

a. creatinine increased: >50% from baseline in patients with lab data [ticagrelor 60 mg (N=6240); ASA alone (N=6543)]

b. hyperuricemia: uric acid increase from ≤ ULN at baseline to > ULN in patients with lab data [ticagrelor 60 mg (N=4857); ASA alone (N=5229)]

Upper limit normal (ULN), provided by central lab, is:
8.0 mg/dl for male (age ≤90), 8.3 mg/dl for male (age >90)
6.9 mg/dl for female (age ≤65), 7.3 mg/dl for female (age 66-90), 7.7 mg/dl for female (age >90)

[c.] ≥ LLN at baseline and any on-treatment value < LLN: the denominator is patients with hemoglobin at baseline and at least one on-treatment [ticagrelor 60 mg (N=5595); ASA alone (N=5976)]

Lower limit normal (LLN), provided by central lab is:
130 g/L for male (age ≤65); 126 g/L for male (age >65)
116 g/L for female (age ≤65); 110 g/L for female (age >65)

### 8.5 Post-Market Adverse Reactions

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.

**Blood disorders:** Thrombotic Thrombocytopenic Purpura (see **Hematologic**)
**Cardiac disorders:** Bradyarrhythmia, second degree AV block, third degree AV block (see **Cardiovascular**).
**Immune system disorders:** hypersensitivity reactions, including angioedema (see **2 CONTRAINDICATIONS**)
**Nervous system disorders:** Central sleep apnea including Cheyne-Stokes respiration (see **Neurologic**)
**Skin and subcutaneous tissue disorders:** urticaria, rash

## 9 DRUG INTERACTIONS

### 9.1 Serious Drug Interactions

**Serious Drug Interactions**

- Patients who are also taking strong CYP3A4 inhibitors (e.g. ketoconazole, clarithromycin, nefazodone, ritonavir and atazanavir) (see **2 CONTRAINDICATIONS** and **7 WARNINGS AND PRECAUTIONS**)

### 9.2 Drug Interactions Overview

Cytochrome P450 (CYP) 3A4/5 are the major enzymes responsible for the metabolism of ticagrelor and the formation of the active metabolite. Clinical pharmacology and in vitro data show that there is a complex interaction between ticagrelor and CYP3A4/5. Indeed, depending on the substrate, ticagrelor and its active metabolite are shown to weakly inhibit or weakly activate CYP3A4/5 (see 10.3 **Pharmacokinetics**). CYP enzymes 1A2, 2C19, and 2E1 do not contribute meaningfully *in vitro* to ticagrelor metabolism. Ticagrelor is also a p-glycoprotein (P-gp) substrate and a weak inhibitor of P-gp.

### 9.3 Drug-Behavioural Interactions

Interactions with behaviour have not been studied.

### 9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

**Table 10: Established or Potential Drug-Drug Interactions**

| Proper Name | Source of Evidence | Effect | Clinical Comment |
|---|---|---|---|
| Ketoconazole, a strong CYP3A4 inhibitors | CT | 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 ticagrelor's 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 are contraindicated with TEVA-TICAGRELOR (see **2 CONTRAINDICATIONS** and **General**). |
| Diltiazem, a moderate CYP3A4 inhibitor | CT | Co-administration of diltiazem with ticagrelor increased the ticagrelor $C_{max}$ by 69% and AUC by 174% and decreased its 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 similar effects. These exposure changes are not considered clinically significant, and therefore, can as well be co- administered with TEVA-TICAGRELOR. |
| CYP3A4 inducers, including Rifampin | CT | Co-administration of rifampin 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%. | Other strong CYP3A4 inducers (e.g., phenytoin, carbamazepine and phenobarbital) and potentially also weak to moderate inducers (e.g., dexamethasone) would be expected to decrease the exposure to ticagrelor as well and may result in reduced efficacy of TEVA-TICAGRELOR. Alternative treatments should be considered. |

**Table 10: Established or Potential Drug-Drug Interactions**

| Proper Name | Source of Evidence | Effect | Clinical Comment |
|---|---|---|---|
| Cyclosporine, a P-gp and CYP3A4 inhibitor | CT | 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 of ticagrelor was increased by 32% and $C_{max}$ was decreased by 15%.<br>There was no effect of ticagrelor on cyclosporine blood levels. | If the association cannot be avoided, use concomitantly with caution. |
| Heparin, enoxaparin, acetylsalicylic acid (ASA) | CT | Co-administration of ticagrelor with heparin, enoxaparin and acetylsalicylic acid (ASA) did not have any effect on ticagrelor or its active metabolite plasma levels.<br>Co-administration of ticagrelor and heparin had no effect on heparin based on activated partial thromboplastin time (aPTT) and activated coagulation time (ACT) assays.<br>Co-administration of ticagrelor and enoxaparin had no effect on enoxaparin based on factor Xa assay. | |
| CY P3A4/5 substrates with narrow therapeutic indices | CT | Ticagrelor and its active metabolite have the capacity to weakly inhibit or weakly activate CYP3A4/5. | Co-administration of TEVA-TICAGRELOR with CYP3A4/5 substrates with narrow therapeutic indices is not recommended.<br>TEVA-TICAGRELOR treatment should be interrupted and resumed when therapy with the CYP3A4/5 substrate is no longer required. |

**Table 10: Established or Potential Drug-Drug Interactions**

| Proper Name | Source of Evidence | Effect | Clinical Comment |
|---|---|---|---|
| Simvastatin | CT | 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.<br>There was no effect of simvastatin on ticagrelor plasma levels. | Consideration of the clinical significance should be given to the magnitude and range of changes on the exposure to patients requiring greater than 40 mg of simvastatin.<br>TEVA-TICAGRELOR may have similar effect on lovastatin, but is not expected to have a clinically meaningful effect on other statins. |
| Atorvastatin | CT | 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. |
| Tolbutamide, a CYP2C9 substrate | CT | Co-administration of ticagrelor with tolbutamide resulted in no change in the plasma levels of either drug. | Ticagrelor is not a CYP2C9 inhibitor and unlikely to alter the metabolism of other drugs metabolized via CYP2C9. |
| Warfarin | T | A drug-drug interaction study with warfarin has not been performed.<br>As with other oral antiplatelet therapy, there is a potential for increased risk of bleeding. | Warfarin and TEVA-TICAGRELOR should be co-administered with caution (see **7 WARNINGS AND PRECAUTIONS, General**). |
| Oral Contraceptives | CT | Co-administration of ticagrelor and levonorgestrel and ethinyl estradiol increased the ethinyl estradiol exposure by 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 TEVA-TICAGRELOR. |
| Digoxin (P-gp Substrate) | CT | Concomitant administration of ticagrelor increased the digoxin $C_{max}$ by 75% and AUC by 28%. | Appropriate clinical and/or laboratory monitoring is recommended when giving narrow therapeutic index P-gp-dependent drugs like digoxin concomitantly with TEVA-TICAGRELOR. |

**Table 10: Established or Potential Drug-Drug Interactions**

| Proper Name | Source of Evidence | Effect | Clinical Comment |
|---|---|---|---|
| Morphine | CT | Co-administration of morphine with ticagrelor decreased the ticagrelor AUC by approximately 35%. | Delayed and decreased exposure to oral $P2Y_{12}$ inhibitors. This interaction may be related to reduced gastrointestinal motility and apply to other opioids. The clinical relevance is unknown, but data indicate the potential for reduced ticagrelor efficacy in patients co-administered ticagrelor and morphine. |

Legend: CT = Clinical Trial; T = Theoretical

In clinical studies, ticagrelor was commonly administered with ASA, 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.

### 9.5 Drug-Food Interactions

In a study of healthy subjects, 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 changes are considered of minimal clinical significance. Ticagrelor was administered without regard to food in PLATO and PEGASUS. Therefore, TEVA-TICAGRELOR may be given with or without food.

**Grapefruit Juice Interaction:** Ingestion of 600 mL of grapefruit juice for four days was shown to increase ticagrelor $C_{max}$ by 65% and AUC by 121% and to decrease its active metabolite $C_{max}$ by 45% and AUC by 14%. Elimination half-life of ticagrelor was prolonged from 6.7 to 7.2 h and of its active metabolite from 8.2 to 12 h. These exposure changes, despite slightly delaying the recovery of platelet reactivity, are not expected to substantially increase bleeding risk in most patients. See **7 WARNINGS AND PRECAUTIONS, Peri-Operative Considerations,** Surgery for stopping TEVA-TICAGRELOR and bleeding risk with respect to surgery.

### 9.6 Drug-Herb Interactions

Interactions with herbal products have not been studied.

### 9.7 Drug-Laboratory Test Interactions

False negative results in platelet function test for Heparin induced thrombocytopenia (HIT) have been reported in patients administered ticagrelor.

## 10 CLINICAL PHARMACOLOGY

### 10.1 Mechanism of Action

Ticagrelor, a member of the chemical class cyclopentyl-triazolo-pyrimidines (CPTP), 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. Indeed, ticagrelor and its active metabolite AR-C124910XX were shown to similarly displace a specific $P2Y_{12}$ receptor radioligand from the $P2Y_{12}$ receptors on the surface of human washed platelets *in vitro*, with a Ki of 2.0 nM and 2.5 nM, respectively. Ticagrelor concentration-dependently inhibited ADP-induced platelet aggregation in suspensions of human and rat washed platelets. It also inhibited ADP-induced platelet aggregation in human platelet rich plasma as well as in marmoset and human whole blood. The ADP induced platelet aggregation measured *ex vivo* as well as dynamic arterial thrombosis in the damaged femoral artery were also reduced following i.v. administration of ticagrelor in anaesthetised male Beagle dogs. The major circulating metabolite of ticagrelor, O-deethylated AR-C124910XX, showed pharmacological activity comparable to that of the parent molecule.

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.

**Effects on the adenosine system**
There is also evidence that ticagrelor reduces cellular uptake of adenosine and prolongs this nucleotide half-life, thereby increasing local endogenous adenosine levels, via potent, concentration dependent and reversible inhibition of equilibrative nucleoside transporter type I (ENT-1). The affinity of ticagrelor for ENT-1 has been documented to be 41 nM. The main circulating metabolite of ticagrelor, AR C124910XX, that has been reported to have a similar affinity for $P2Y_{12}$ as ticagrelor, only has weak affinity for ENT-1, 330 nM. Whether the ticagrelor-induced increase in adenosine is clinically relevant to the safety and efficacy of ticagrelor remains to be demonstrated.

**Effects on the uric acid uptake**
Ticagrelor, AR-C124910 (active metabolite) and AR-C133913 (inactive metabolite) were shown to have an inhibitory effect on the OAT-3-dependent uric acid uptake (Ki: AZD6140: 4.9 mcM; AR-C124910: 16.3 mcM; and AR-C133913: 13.4 mcM). They also have a weak inhibitory effect on the URAT1-mediated uric acid uptake. These results suggest that ticagrelor and its

metabolites may interfere with the renal transport of uric acid which is consistent with the observation that patients on ticagrelor had a higher risk of hyperuricemia.

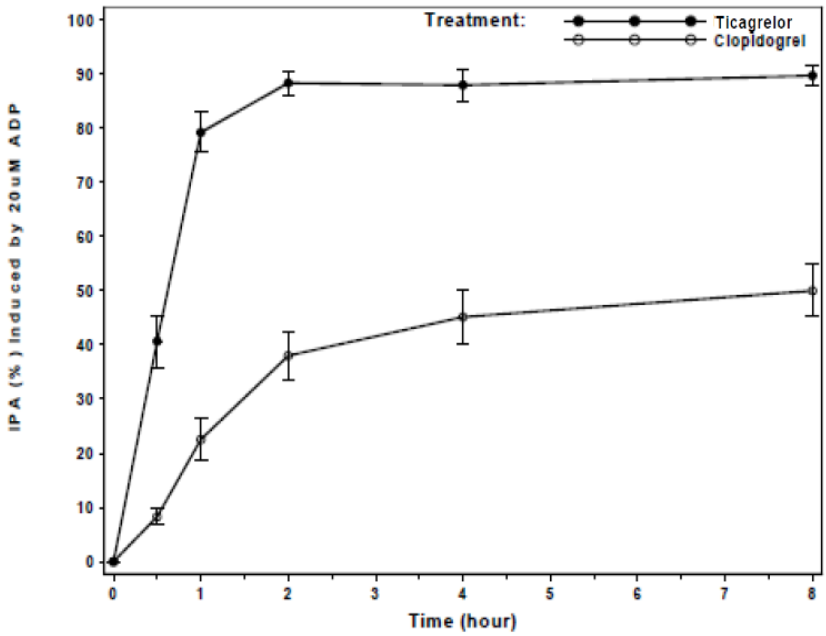
## 10.2 Pharmacodynamics

Inhibition of platelet aggregation mediated by ticagrelor increases with increasing plasma concentrations of ticagrelor and its active metabolite (AR-C124910XX), until almost complete inhibition is attained. The Inhibition of Platelet Aggregation (IPA) gradually decreases with declining plasma ticagrelor and active metabolite concentrations, as the IPA mediated by ticagrelor is reversible. Since ticagrelor reversibly binds to the $P2Y_{12}$ receptor, the recovery of platelet function is expected to be dependent on the plasma concentrations of ticagrelor and the active metabolite and not on the replacement of irreversibly inhibited platelets as with thienopyridine antiplatelet agents.

The IPA of ticagrelor is generally independent of factors such as race, hepatic or renal disease or co-administered ASA, heparin and enoxaparin.

**Onset of Action**
In patients with stable coronary artery disease on ASA, ticagrelor demonstrates a rapid onset of IPA effect (Figure 1). Mean IPA for ticagrelor at 0.5 hours after 180 mg loading dose is about 41%, which is similar to clopidogrel's (600 mg) maximum effect of 50% observed at 8 hours. Ninety percent of patients had final extent IPA > 70% by 2 hours post dose versus 16% for clopidogrel. Ticagrelor's maximum IPA effect of approximately 88% is reached at around 2 hours, and the IPA between 87%-89% was maintained from 2-8 hours.

**Figure 1: Mean final extent IPA (±SD) following single oral doses of 180 mg ticagrelor or 600 mg clopidogrel in patients with stable coronary artery disease**

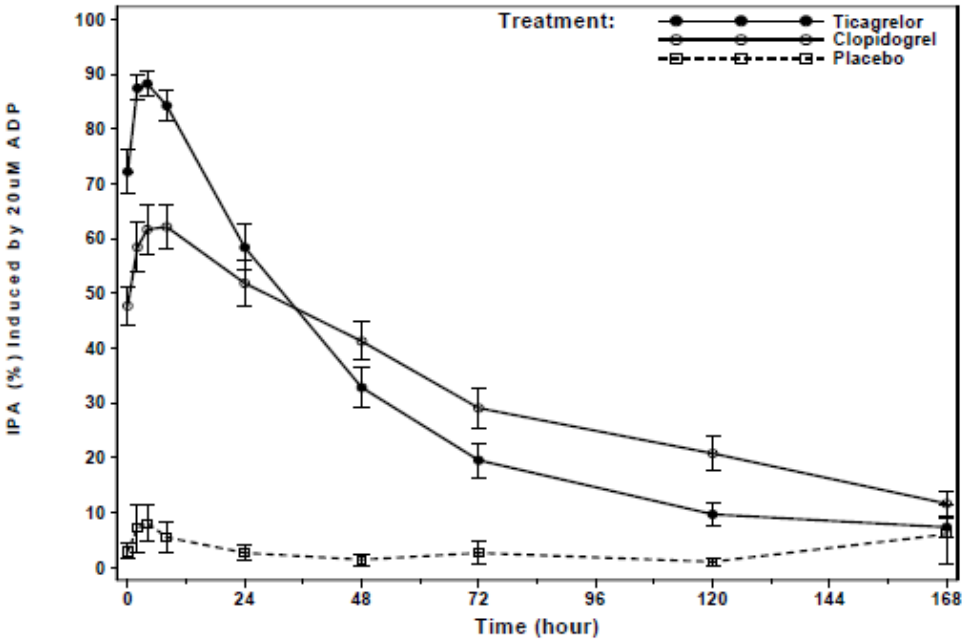



**Offset of Effect**

After ticagrelor and its active metabolite 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 (see **Peri-Operative Considerations**).

Final extent IPA during the 90 mg twice daily-dosing interval is approximately 20%-30% (absolute difference) higher for ticagrelor compared to clopidogrel (75 mg, once daily). However, by 24 hours following the last maintenance dose, the IPA is similar between ticagrelor (58%) and clopidogrel (52%), indicating that patients who miss a dose of ticagrelor would have an IPA level comparable to those treated with once daily clopidogrel (Figure 2).

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




**Responders to Ticagrelor**

The IPA induced by ticagrelor has less variability with the 90 mg twice daily dose compared to clopidogrel 75 mg once daily. Patients with stable coronary artery disease predetermined to have low IPA response to clopidogrel (non-responders), and given a concomitant dose of ASA, exhibited higher mean IPA response after administration of ticagrelor as compared to clopidogrel.

**Switching Data**

Switching from clopidogrel 75 mg 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%. Patients can be switched from clopidogrel to TEVA-TICAGRELOR without interruption of antiplatelet effect (see **4 DOSAGE AND ADMINISTRATION**).

### 10.3 Pharmacokinetics

Ticagrelor demonstrates linear pharmacokinetics. Exposure to ticagrelor and its active metabolite are approximately dose proportional.

The main pharmacokinetic parameters for ticagrelor are presented in the table below.

**Table 11: Summary of Ticagrelor Pharmacokinetic Parameters**

| | $C_{max}$ (ng/mL) | $T_{max}$ (h) | $t_{½}$ (h) | $AUC_{0-\infty}$ (ng.h/mL) | CL (L/h)* | Vss (L)* |
|---|---|---|---|---|---|---|
| **Single oral dose mean (90 mg)** | 500 | 1.5 | 6.9 | 2233 | 14.2 | 87.5 |

* Following a single intravenous dose of 15 mg ticagrelor

**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 (30-1260 mg). The pharmacokinetics of ticagrelor and AR-C124910XX in patients with a history of MI (> one year) were generally similar to that in the ACS population. Based on a population pharmacokinetic analysis of the PEGASUS study the median ticagrelor $C_{max}$ was 391 ng/ml and AUC was 3801 ng*h/ml at steady state for ticagrelor 60 mg. For ticagrelor 90 mg $C_{max}$ was 627 ng/ml and AUC was 6255 ng*h/ml at steady state.

The mean absolute bioavailability of ticagrelor was estimated to be 36%, (range 25.4%-64.0%). In a study of healthy subjects, 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 changes are considered of minimal clinical significance. Ticagrelor was administered without regard to food in PLATO. Therefore, TEVA-TICAGRELOR may be given with or without food.

Ticagrelor as crushed tablets mixed in water, given orally or administered through a nasogastric tube into the stomach to 36 healthy volunteers, is bioequivalent to whole tablets. Ticagrelor and the active metabolite (AUC and $C_{max}$ are well within the 80-125% range required to demonstrate bioequivalence. Initial exposure (0.5 and 1 hour post-dose) from crushed ticagrelor tablets mixed in water was higher compared to whole tablets, with a generally identical concentration profile thereafter (2 to 48 hours).

**Distribution**

The steady state volume of distribution of ticagrelor is 87.5 L. Ticagrelor and the active metabolite are extensively bound to human plasma proteins (> 99%).

Ticagrelor was found to be widely distributed in rat tissues and the major organs identified were those associated with metabolism and excretion (liver, pancreas and kidney) as well as glandular tissues (adrenal and pituitary glands), but no accumulation seemed to occur.

**Metabolism**

The major metabolite of ticagrelor is AR-C124910XX, which is also active as assessed by *in vitro* binding to the platelet P2Y12 ADP-receptor. The systemic exposure to the active metabolite is approximately 30-40% of that obtained for ticagrelor.

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 weak p-glycoprotein inhibitors.

There is a complex interaction between ticagrelor and CYP3A4/5, depending on the substrate used. *In vitro*, ticagrelor weakly inhibits testosterone 6ß-hydroxylation, moderately inhibits midazolam 4-hydroxylation and weakly activates nifedipine oxidation and midazolam 1-hydroxylation.

**Elimination**
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 feces, 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 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.

**Special Populations and Conditions**

- **Pediatrics (< 18 years of age):** Ticagrelor has not been evaluated in a pediatric population. Therefore, Health Canada has not authorized an indication for pediatric use.

- **Geriatrics (≥ 65 years of age):** 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 (18-45 years) subjects. These differences are not considered clinically significant. No dose adjustment is needed for elderly patients (see **7.1 Special Populations** and **Dosing Considerations in Special Populations**).

- **Sex:** 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.

- **Pregnancy and Breast-feeding:** A study performed with pregnant female rats, demonstrated that peak placental concentrations of ticagrelor after i.v. administration were noted at 5 min post-dose, but no significant transfer to the fetus was observed. Moreover, following oral administration of ticagrelor in lactating rats, the maximum

milk concentration of ticagrelor and/or its metabolites were found at 4 h post-dose. The observation that the mean concentration in milk was higher than in maternal plasma at all time-points indicates that ticagrelor and its metabolites are easily transferred into milk. The analysis of suckling young animals suggests that these molecules were well absorbed and widely distributed in the pups. Overall, the safety of ticagrelor during pregnancy has not been established and the use of TEVA-TICAGRELOR during breastfeeding is not recommended (see **7.1 Special Populations**)

- **Body Weight**: Body weight was determined to have less than a 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.

- **Ethnic Origin**: Patients of Asian descent have a 39% higher 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. These differences are not considered clinically relevant. The exposure in patients self-identified as Hispanic or Latino was similar to that in Caucasian.

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

- **Renal Insufficiency:** Exposure to ticagrelor was approximately 20% lower and exposure to the active metabolite was approximately 17% higher in patients with severe renal impairment 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. 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 ticagrelor is not dialysable. Exposure of the active metabolite increased to a lesser extent. The IPA effect of ticagrelor appeared to be unaffected by dialysis in patients with end stage renal disease and was similar to subjects with normal renal function; the clinical impact of these findings is unknown. Appropriate caution should be used in patients requiring renal replacement therapy (see **7.1 Special Populations** and **Dosing Considerations in Special Populations**).

- **Hepatic Insufficiency:** 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. No studies have specifically been conducted with ticagrelor in patients with moderate or severe hepatic impairment. Only limited information is available in patients with moderate hepatic impairment. Therefore it is contraindicated for use in patients with moderate or severe hepatic impairment (see **2 CONTRAINDICATIONS** and **Dosing Considerations in Special Populations**).

## 11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature (15°C - 30°C).

## 12 SPECIAL HANDLING INSTRUCTIONS

No special requirements.

PART II: SCIENTIFIC INFORMATION

## 13 PHARMACEUTICAL INFORMATION

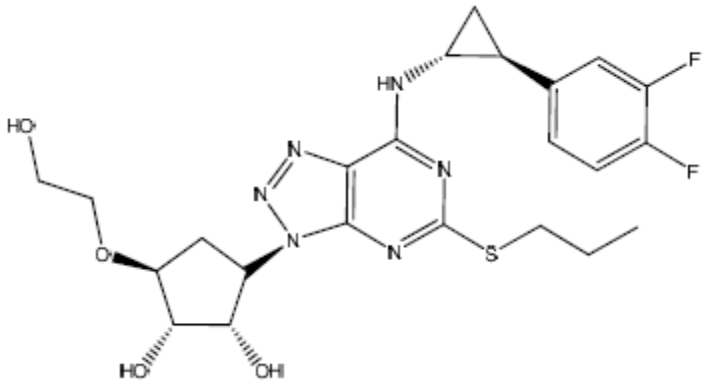
### Drug Substance

Proper name: Ticagrelor

Chemical name: (lS,2S,3R,5S)-3-[7-{[(lR,2S)-2-(3,4- difluorophenyl)cyclo propyl] amino}-5-(propylthio)-3H-[l,2,3]-triazolo[4,5-d]pyrimidin-3-yl]-5-(2-hydroxyethoxy)cyclopentane-l,2-diol.
OR
(lS, 2S, 3R, 5S)-3-[7-{[(lR, 2S)-2-(3,4-difluorophenyl)cyclopropyl] amino}-5-(propylthio)-3H-[l,2,3]triazolo[4,5-d]pyrimidin-3-yl]-5-(2-hydroxyethoxy)cyclopentane-l,2-diol.

Molecular formula and molecular mass: $C_{23}H_{28}F_2N_6O_4S$, 522.56 g/mol

Structural formula:




Physicochemical properties: Ticagrelor is white or off white to pale pink powder. Freely soluble in N,N-dimethyl formamide, slightly soluble in methanol and practically insoluble in Water. The specific optical rotation of ticagrelor is between -50° and -60°

## 14 CLINICAL TRIALS

The safety and efficacy of ticagrelor in preventing atherothrombotic events has been evaluated in two large randomized double-blind trials involving more than 39,000 patients: the PLATO study (Ticagrelor 90 mg b.i.d. vs. Clopidogrel 75 mg o.d. both given in combination with acetylsalicylic acid (ASA) and other standard therapy in patients with acute coronary syndrome) and the PEGASUS TIMI-54 study (Ticagrelor 90 mg b.i.d. and 60 mg b.i.d. both combined with ASA vs. ASA alone in patients with history of spontaneous MI (reported at least 1 year ago) and at risk of an atherothrombotic event).

### 14.1 Clinical Trials by Indication

#### Acute Coronary Syndrome

**Table 12: Summary of patient demographics for clinical trials in acute coronary syndrome**

| Study Name | Study design | Dosage, route of administration and duration | Study subjects (n) | Mean age (Range) | Sex |
|---|---|---|---|---|---|
| PLATO | International, randomized, double-blind, parallel-group study comparing ticagrelor to clopidogrel | Dosage: Ticagrelor (90 mg twice daily) or clopidogrel (75 mg once daily), in combination with ASA;<br>Administration: oral;<br>Duration: up to one year | N=18,624<br><br>Ticagrelor n=9,333;<br>Clopidogrel n=9,291 | Mean = 62 years (19-97 years)<br>< 65=57% ≥ 65 years=43%<br>< 75years=85%<br>≥ 75 years=15% | Male 72%<br>Female 28% |

#### Study Design

The PLATO study was a Phase III efficacy and safety study of ticagrelor compared with clopidogrel for the prevention of vascular events in patients with ACS (unstable angina [UA], non ST elevation Myocardial Infarction [NSTEMI] or ST elevation Myocardial Infarction [STEMI]).

Patients were randomized to receive ticagrelor (a loading dose of 180 mg followed by a maintenance dose of 90 mg twice daily) or clopidogrel (75 mg once daily, with an initial loading dose of 300 mg if previous thienopyridine therapy had not been given. An additional loading dose of 300 mg was allowed at investigator discretion).

The study was comprised of patients who presented within 24 hours of onset of the most recent episode of chest pain or symptoms. The initiation of treatment in PLATO occurs shortly after symptom onset, prior to the assessment of coronary anatomy by angiography. Patients could have been medically managed, treated with percutaneous coronary intervention (PCI) or

coronary artery bypass graft (CABG). Patients were treated for at least 6 months and up to 12 months duration, and patients were followed to study termination, irrespective of whether study drug had been discontinued. The baseline characteristics, medical history, electrocardiographic changes, and drug therapy were similar for both treatment groups.

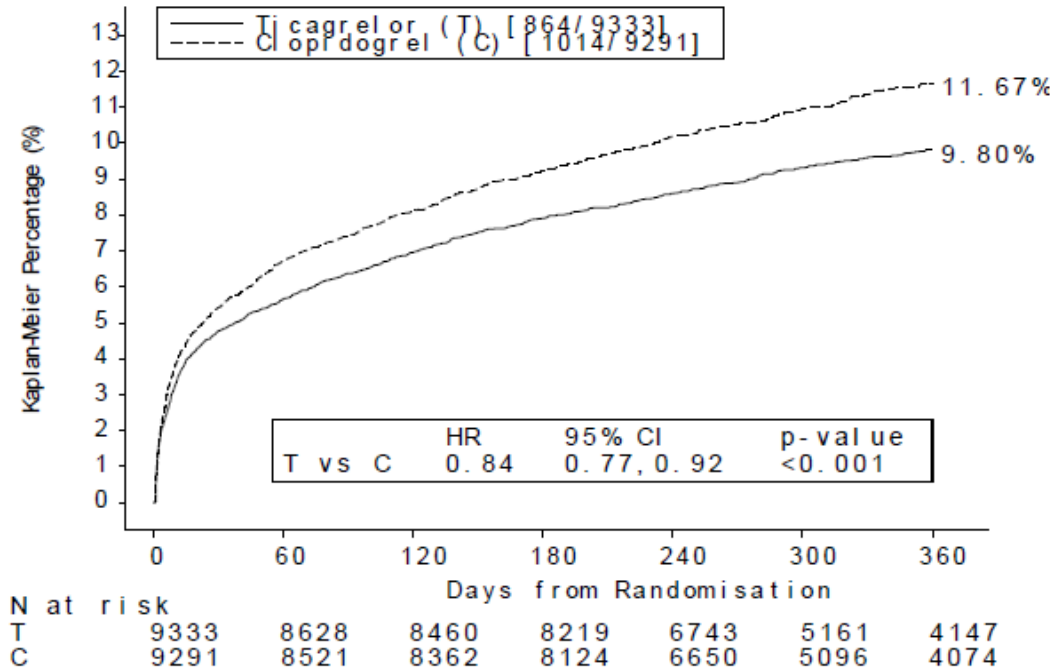
**Study Results**

Ticagrelor was superior to clopidogrel in the prevention of thrombotic events (relative risk reduction [RRR] of 16%, absolute risk reduction [ARR] of 1.9%, number needed to treat [NNT] of 54) in the composite efficacy endpoint (primary endpoint) of CV death, MI, and stroke over 12 months in patients with ACS events (UA, NSTEMI and STEMI population) (hazard ratio [HR] 0.84; p=0.0003) (Table 13). The difference in treatments was driven by CV death and MI with no difference on strokes. Ticagrelor demonstrated a statistically significant RRR of 21% (ARR 1.1%) for CV death and a RRR of 16% (ARR 1.1%) for MI, as compared to clopidogrel (Table 13). Treating 91 patients with ticagrelor instead of clopidogrel will prevent 1 CV death.

Ticagrelor reduced the occurrence of the primary composite endpoint compared to clopidogrel in both the UA/NSTEMI and STEMI population.

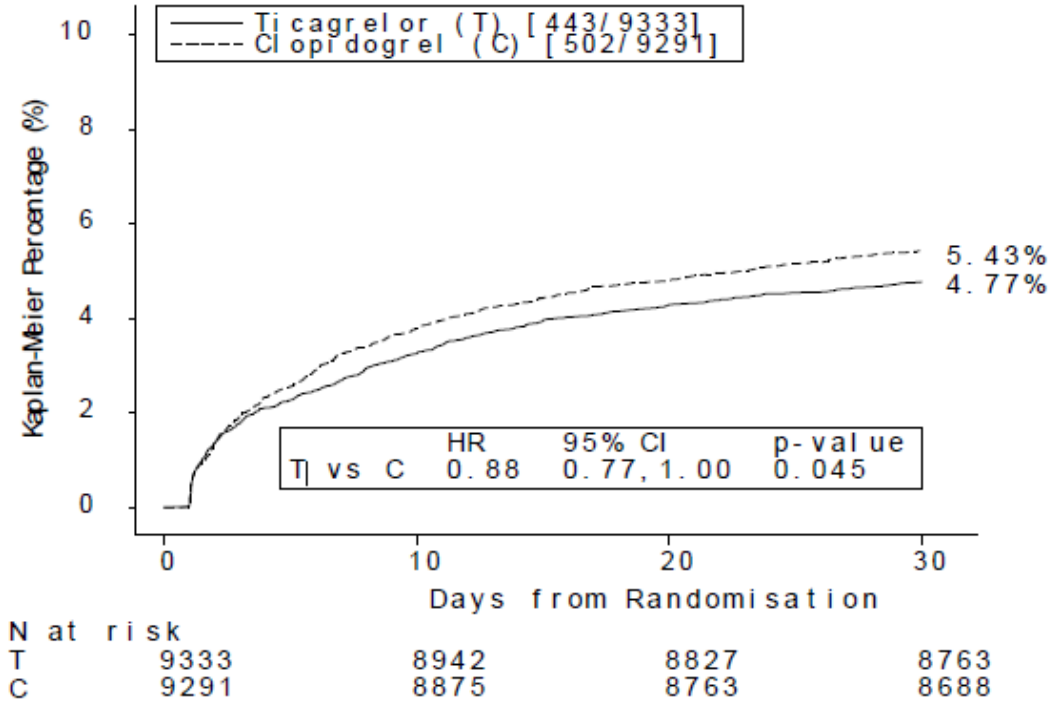
The Kaplan Meier curve (Figure 3) shows the primary composite endpoint of CV death, MI and Stroke in the UA/NSTEMI and STEMI populations. The treatment effect of ticagrelor was apparent in the first 30 days and the degree of benefit continued to increase throughout the 12 month follow-up.

**Figure 3: Time to first occurrence of CV death, MI and stroke (PLATO)**



Within the first 30 days of treatment (Figure 4), ticagrelor shows a statistically significant early benefit (ARR 0.6%, RRR 12%), with a constant treatment effect over the entire 12 month period, yielding ARR 1.9% per year with RRR of 16%. Together, these findings demonstrate that the benefit of ticagrelor treatment continues to accrue over 1 to 12 months, and suggests that it is appropriate to treat ACS patients with ticagrelor for at least 12 months.

**Figure 4: Primary clinical endpoint by consistency of treatment effect over time at 1-30 days**




The final secondary endpoint (all-cause mortality) was evaluated. Ticagrelor demonstrated a RRR of 22% for all-cause mortality compared to clopidogrel at a nominal significance level of p=0.0003 and an ARR of 1.4% (Table 13).

**Table 13: Analysis of primary and secondary efficacy endpoints in PLATO (full analysis set)**

| | Patients with Events | | RRR (%) | HR (95% CI) | p-value |
|---|---|---|---|---|---|
| | Ticagrelor 90 mg twice daily (%) N = 9333 | Clopidogrel 75 mg once daily (%) N = 9291 | | | |
| Primary Endpoint | | | | | |

**Table 13: Analysis of primary and secondary efficacy endpoints in PLATO (full analysis set)**

| | Patients with Events | | RRR (%) | HR (95% CI) | p-value |
|---|---|---|---|---|---|
| | Ticagrelor 90 mg twice daily (%) N = 9333 | Clopidogrel 75 mg once daily (%) N = 9291 | | | |
| Composite of CV Death/MI (excl. silent MI)/Stroke | 9.3 | 10.9 | 16 | 0.84 (0.77,0.92) | 0.0003 |
| Each component of primary efficacy endpoint: | | | | | |
| CV death | 3.8 | 4.8 | 21 | 0.79 (0.69, 0.91) | 0.0013 |
| MI (excl. silent MI) | 5.4 | 6.4 | 16 | 0.84 (0.75, 0.95) | 0.0045 |
| Stroke | 1.3 | 1.1 | -17 | 1.17 (0.91, 1.52) | 0.2249 |
| Secondary Endpoints | | | | | |
| Composite of CV death/MI (excl. silent MI)/stroke intent to invasively manage | 8.5 | 10.0 | 16 | 0.84 (0.75, 0.94) | 0.0025 |
| Composite of all-cause mortality/MI (excl. silent MI)/stroke | 9.7 | 11.5 | 16 | 0.84 (0.77, 0.92) | 0.0001 |
| Composite of CV Death/Total MI/Stroke/SRI/RI/TIA/Other ATE | 13.8 | 15.7 | 12 | 0.88 (0.81, 0.95) | 0.0006 |
| All-cause mortality | 4.3 | 5.4 | 22 | 0.78 (0.69, 0.89) | 0.0003* |

Note: A single event may be counted in more than 1 row.
ATE Arterial thrombotic events; excl. Excluding; HR Hazard ratio; RI Recurrent cardiac ischaemia; SRI Severe recurrent cardiac ischaemia; TIA Transient ischaemic attack.
* Nominal p-value.

**Subgroup Analyses:** 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 versus clopidogrel appears consistent across multiple patient subgroups by demographic characteristics including age, gender, weight, diabetes mellitus, planned treatment approach (medically managed or invasive), prior TIA or stroke, medical history, concomitant therapy, and by final index event diagnosis (UA, NSTEMI and STEMI).

A marginally significant treatment interaction was observed with region whereby the HR for the primary endpoint favours ticagrelor in the rest of world but favours clopidogrel in North America, which represented approximately 10% of the overall population studied (interaction

p-value=0.045). This apparent treatment-by-region interaction observed in PLATO could plausibly be attributed to chance, at least in part. Additional analyses suggest that the efficacy of ticagrelor relative to clopidogrel is associated with ASA dose during maintenance therapy. The data show greater efficacy of ticagrelor compared to clopidogrel when used in conjunction with low maintenance dose ASA (75-150 mg daily). The relative efficacy of ticagrelor versus clopidogrel when used with high doses of ASA (> 300 mg daily) is less certain. Based on this observed relationship between maintenance ASA dose and relative efficacy of ticagrelor compared to clopidogrel, it is recommended that ticagrelor is used with a daily low maintenance dose of ASA 75-150 mg (see **1 INDICATIONS**, **7 WARNINGS AND PRECAUTIONS** and **4 DOSAGE AND ADMINISTRATION**).

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 (PPIs). The use of oral anticoagulants, and non-study antiplatelet drugs was not allowed in PLATO (see **9 DRUG INTERACTIONS**).

**Holter Substudy**

To study the occurrence of ventricular pauses and other arrhythmic episodes during PLATO, investigators performed Holter monitoring in a subset of nearly 3,000 patients, of whom approximately 2,000 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. However, there were no adverse clinical consequences associated with this imbalance (including pacemaker insertions) in this population of patients.

**PLATO *Genetic Substudy***

*CYP2C19* genotyping of 10,285 patients in PLATO provided associations of genotype groups with the efficacy and safety outcomes. The effects of ticagrelor compared to clopidogrel on major CV events and bleeding were not significantly affected by *CYP2C19* genotype. The efficacy and safety results of the substudy were consistent with the main PLATO study.

**Patients with History of Myocardial Infarction (≥One Year)**

**Table 14: Summary of patient demographics for clinical trials in patients with history of myocardial infarction (≥ one year)**

| Study Name | Study design | Dosage, route of administration and duration | Study subjects (n) | Mean age (Range) | Sex |
|---|---|---|---|---|---|
| PEGASUS | Randomized, double-blind, placebo-controlled, parallel-group study | Dosage: 90 mg bid, 60 mg bid, or placebo bid on a background of ASA (75-150 mg od)<br>Administration: Oral<br>Maximum duration: 47 months<br>Event rates calculated at 36 months | N=21,162<br>90 mg: 7,050<br>60 mg: 7,045<br>Placebo: 7,067 | Mean=65 years (50-95 years)<br>< 65 years=46%<br>65-75 years= 42%<br>>75 years=12% | Male 76%<br>Female 24% |

**Study Design**

The PEGASUS study assessed the prevention of atherothrombotic events with ticagrelor given at 2 doses (either 90 mg twice daily or 60 mg twice daily) combined with low dose ASA (75-150 mg) compared to ASA therapy alone, in patients with history of spontaneous MI and additional risk factors for atherothrombosis.

Patients were eligible to participate if they were aged 50 years of over, with a history of spontaneous MI (1 to 3 years prior to randomisation), and had at least one of the following risk factors for atherothrombosis: age ≥65 years, diabetes mellitus requiring medication, a second prior MI, evidence of multivessel CAD, and/or chronic non-end-stage renal dysfunction.

Patients were ineligible if there was planned use of ADP receptor antagonist, dipyridamole, cilostazol, or needed chronic anticoagulant therapy; if they had a bleeding disorder or a history of an ischemic stroke or intracranial bleeding, a central nervous system tumour, or an intracranial vascular abnormality; if they had had intracranial or spinal cord surgery within the previous 5 years; if they had had gastrointestinal bleeding within the previous 6 months or major surgery within the previous 30 days.

The PEGASUS study was conducted for a duration up to 47 months with mean (median) duration of exposure to ticagrelor 60 mg of 25.3 months (29.4 months): 5, 481 patients (79%) were exposed for at least 12 months; 4, 505 patients (65%) for at least 24 months; and 1,620 patients (23%) for at least 36 months of extended treatment. Patients were followed to study termination, irrespective of whether study drug had been discontinued.

**Study Results**

Although the efficacy profile of ticagrelor 90 mg twice daily and 60 mg twice daily were similar,

there is evidence that the lower dose has a better tolerability and safety profile in relation to the risk of bleeding and dyspnea. Therefore, ticagrelor 60 mg twice daily co-administered with ASA is the approved dose for the prevention of atherothrombotic events (CV death, MI and stroke) in patients with a history of spontaneous myocardial infarction (MI occurred at least one year ago) and a high risk of developing an atherothrombotic event.

Ticagrelor 60 mg twice daily, in combination with ASA, was superior to ASA alone in the prevention of atherothrombotic events (composite endpoint: CV death, MI and stroke), with a consistent treatment effect over the entire study period, yielding a 16% relative risk reduction [RRR] and 1.27% absolute risk reduction [ARR] (number needed to treat [NNT] of 79) after 36 months of treatment (Table 13). Each of the components contributed to the reduction in the primary composite endpoint (CV death 17% RRR, MI 16% RRR and stroke 25% RRR). Treating 189 patients for up to 36 months with ticagrelor 60 mg twice daily in combination with ASA instead of ASA therapy alone will prevent one CV death.

The benefit of ticagrelor seen on the primary composite endpoint was also reflected across the two secondary endpoints, with a numerical decrease in both CV death and all-cause mortality for ticagrelor 60 mg combined with ASA compared to ASA therapy alone, but this did not reach statistical significance (see Table 15).

**Table 15: Analysis of primary and secondary efficacy endpoints in PEGASUS (full analysis set)**

| | Patients with Events | | RRR (%) | HR (95% CI) | *p*-value |
|---|---|---|---|---|---|
| | Ticagrelor 60 mg twice daily + ASA N=7045 | ASA alone N=7067 | | | |
| Primary Endpoint | | | | | |
| Composite of CV Death/MI/Stroke | 487 (6.9%) | 578 (8.2%) | 16% | 0.84 (0.74, 0.95) | 0.0043 |
| CV death | 174 (2.5%) | 210 (3.0%) | 17% | 0.83 (0.68, 1.01) | 0.0676 |
| MI | 285 (4.0%) | 338 (4.8%) | 16% | 0.84 (0.72, 0.98) | 0.0314 |
| Stroke | 91 (1.3%) | 122 (1.7%) | 25% | 0.75 (0.57, 0.98) | 0.0337 |
| Secondary Endpoint | | | | | |
| CV death | 174 (2.5%) | 210 (3.0%) | 17% | 0.83 (0.68, 1.01) | - |
| All-cause mortality | 289 (4.1%) | 326 (4.6%) | 11% | 0.89 (0.76, 1.04) | - |

Hazard ratio and p-values are calculated separately for ticagrelor versus ASA alone from Cox proportional hazards model with treatment group as the only explanatory variable.

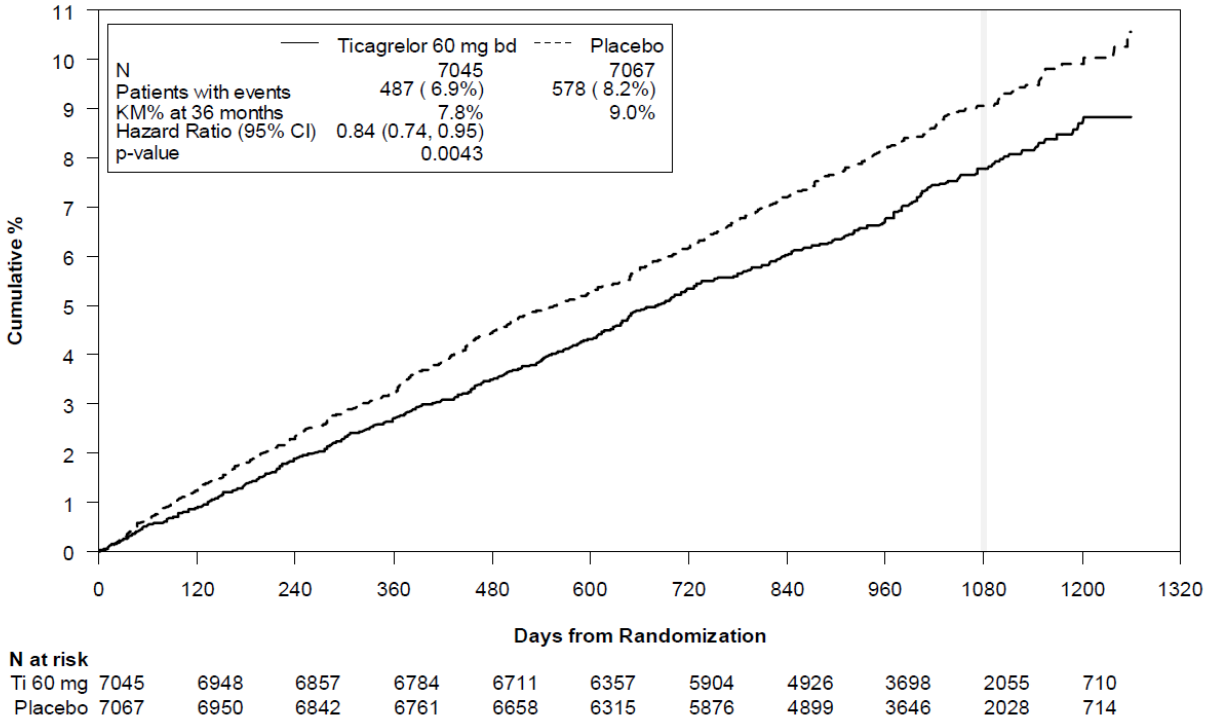
Note: the number of first events for the components CV Death, MI and Stroke are the actual number of first events for each component and do not add up to the number of events in the composite endpoint.

CI = Confidence interval; CV = Cardiovascular; HR = Hazard ratio; MI = Myocardial infarction; N = Number of patients.

The RRR for the composite endpoint from 1 to 360 days (17% RRR) and from 361 days and onwards (16% RRR) was similar. The Kaplan-Meier plot (Figure 5) shows the analysis of the primary clinical composite endpoint of CV death, MI and stroke.

Treatment with ticagrelor should be continued in patients with a history of spontaneous MI for as long as the patient remains at high risk of an atherothrombotic event for a duration up to three years. Efficacy and safety data are insufficient to establish whether the benefits of ticagrelor still outweigh the risks after three years of extended treatment (see **4 DOSAGE AND ADMINISTRATION**).

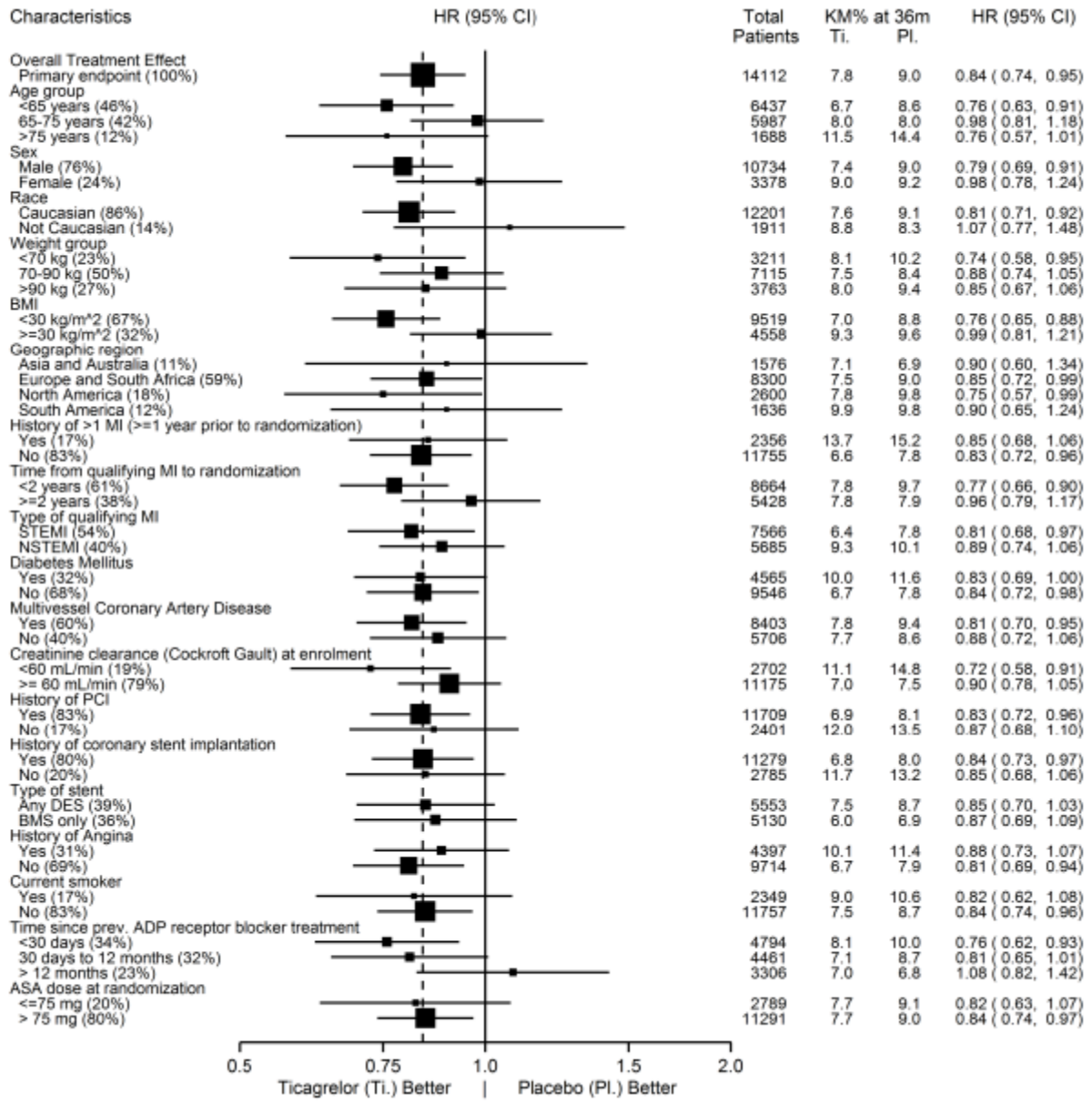
**Figure 5: Primary clinical composite endpoint of CV death, MI and stroke in PEGASUS (full an alysis set)**




**Analysis of patient subgroups**

The treatment effect of ticagrelor 60 mg twice daily versus ASA across major subgroups is presented in Figure 6. There was no evidence of benefit (no reduction in the primary composite endpoint of CV death, MI and stroke), but an increase in major bleedings when ticagrelor 60 mg twice daily was introduced in clinically stable patients more than 2 years after the qualifying MI, or more than one year after stopping previous ADP receptor antagonist treatment. This also resulted in numerical increases in CV death and all-cause mortality (see **4 DOSAGE AND ADMINISTRATION**).

**Figure 6: Hazard ratios and rates of the primary clinical composite endpoint of CV death, MI and stroke by patient subgroup in PEGASUS (full analysis set)**




## 14.2 Comparative Bioavailability Studies

A double blinded, randomized. single dose, two way crossover study of TEVA-TICAGRELOR (ticagrelor) Tablets, 90 mg (Teva Canada Limited) and BRILINTA® (ticagrelor) Tablets, 90 mg (AstraZeneca Canada Inc.), administered as a single 1 x 90 mg dose, was conducted in healthy,

adult, female, Asian Indian subjects under fasting conditions. The results of the measured data from the 26 subjects who completed the study are summarized in the table below.

| Ticagrelor (1 x 90 mg) From measured data Geometric Mean Arithmetic Mean (CV %) | | | | |
|---|---|---|---|---|
| Parameter | Test* | Reference† | % Ratio of Geometric Means | 90% Confidence Interval |
| $AUC_T$ (ng.h/ml) | 6738.2 7170.9 (35.9) | 6441.9 6882.2 (35.3) | 104.6 | 99.5 - 110.0 |
| $AUC_I$ (ng.h/ml) | 6980.4 7418.7 (35.6) | 6688.6 7117.2 (34.4) | 104.4 | 99.5 - 109.5 |
| $C_{max}$ (ng /mL) | 983.7 1028.9 (30.1) | 984.1 1025.3 (26.5) | 100.0 | 91.1 - 109.7 |
| $T_{max}$§ (h) | 2.7 (1.4 - 5.0) | 2.0 (1.3 - 4.0) | | |
| $T_{½}$€ (h) | 9.2 (24.6) | 8.9 (29.2) | | |

* TEVA-TICAGRELOR (ticagrelor) tablets 90 mg (Teva Canada Limited)
† PrBRILINTA® (ticagrelor) tablets, 90 mg (AstraZeneca Canada Inc.) were purchased in Canada
§ Expressed as median (range) only
€ Expressed as arithmetic mean (CV%) only

## 15 MICROBIOLOGY

No microbiological information is required for this drug product.

## 16 NON-CLINICAL TOXICOLOGY

### General Toxicology

**Acute toxicity:** The acute toxicity of ticagrelor is considered low. The results of single dose studies in CD-1 mice and Sprague-Dawley rats showed that ticagrelor was well tolerated when given orally by gavage following doses up to 2000 mg/kg (the highest dose tested). This dose represents approximately 550 times the recommended human daily dose on a mg/kg basis.

**Chronic toxicity:** Repeat-dose studies were conducted in mice, rats and marmosets. Consistent observations across species in repeat dose studies were seen primarily in the gastrointestinal

tract, but were inconsistent with respect to the location, severity, and type of the observations. Indications of subclinical bleeding were also observed across species.

Increased liver weight at high doses occurred in rodents. In rats, this was accompanied by centrilobular hypertrophy and induction of cytochrome P450 liver enzymes, and was reversible upon withdrawal of treatment.

Adrenal weights increased at higher doses in the repeat dose studies in rodents, and were reversible upon withdrawal of treatment.

The metabolic pathways for ticagrelor were found to be qualitatively similar across species and no human specific metabolites were detected.

**Carcinogenicity**
No ticagrelor-related tumours were observed in a 2-year mouse study at oral doses up to 250 mg/kg/day (>18-fold the maximum human therapeutic exposure). There was no increase in tumours in male rats at oral doses up to 120 mg/kg/day (>15-fold the maximum human therapeutic exposure). There was an increase in uterine adenocarcinomas and hepatocellular adenomas plus adenocarcinomas and a decrease in pituitary adenomas and mammary fibroadenomas in female rats only exposed to high doses (>25-fold the maximum human therapeutic exposures). No change in individual tumour incidence was observed at 60 mg/kg/day (8-fold difference to the maximum human therapeutic exposure). When ovarian sex cord/stromal tumors were combined, there was a small, but statistically significant (Peto analysis) increase for the low- and high-dose female rats, but not for the mid-dose females. A treatment-related effect on combined ovarian sex cord/stromal tumors is uncertain due to the low incidence values, but cannot definitively be ruled out. Plasma exposures for the low dose females were 1.5 times greater than therapeutic exposures in humans. The uterine tumours seen only in rats were found to be the result of a non-genotoxic endocrine effect of hormonal imbalance triggered by inhibition of prolactin secretion in rats given high doses of ticagrelor. This mechanism of uterine tumour formation in rats is not relevant to humans. The benign liver tumours are considered likely related to the pleiotropic response that included increased liver weight, hepatocellular hypertrophy, and microsomal enzyme induction.

**Genotoxicity**
Ticagrelor and the active metabolite AR-C124910XX do not demonstrate any genotoxic potential in bacterial, *in vitro* mouse lymphoma L5178Y TK+/- 3.7.2C cell, and *in vivo* rat bone marrow micronucleus assays. The active metabolite AR-C124910XX was not genotoxic in the same *in vitro* assays.

**Reproductive and Developmental Toxicology**
Ticagrelor was found to have no effect on fertility of female rats at oral doses up to 200 mg/kg/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 (15.7 times the maximum human therapeutic exposure).

Ticagrelor given during the period of organogenesis had no effect on fetal development at oral doses up to 100 mg/kg/day in rats (5.1 times the maximum human therapeutic exposure) and up to 42 mg/kg/day in rabbits (equivalent to the maximum human therapeutic exposure). Fetal effects that were considered to be developmental variants or delays were seen in fetuses from female rats given 300 mg/kg (decreased body weight, 27 pre-pelvic vertebral arches, extra 14th ribs, and incomplete ossification of various skeletal structures), that may have resulted from maternal toxicity, and fetal developmental delays were also seen in rabbits given 63 mg/kg (increased incidences of clear gall bladder contents, incompletely ossified hyoid and pubis, one or more incomplete ossification of various skeletal structures), at which there was no overt maternal toxicity.

Ticagrelor had no effects on parturition or postnatal development in rats at doses up to 60 mg/kg/day (4.6 times the maximum human therapeutic exposure), but did cause maternal (reduced body weight gain and food consumption) and developmental toxicity in pups (reduced post-natal viability, lower birth weight, and delayed growth and physical development) at 180 mg/kg.

## 17 SUPPORTING PRODUCT MONOGRAPHS

BRILINTA (ticagrelor tablets, 60 mg and 90 mg) Submission Control Number 255611, Product Monograph, AstraZeneca Canada Inc., January 4, 2022.

**PATIENT MEDICATION INFORMATION**

**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE**

**[Pr] TEVA-TICAGRELOR**
**Ticagrelor Tablets**

Read this carefully before you start taking **TEVA-TICAGRELOR** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **TEVA-TICAGRELOR**.

**What is TEVA-TICAGRELOR used for?**
TEVA-TICAGRELOR is used in combination with low dose acetylsalicylic acid (aspirin) in adults to help prevent blood clots and reduce the risk of having or dying from conditions caused by blood clots. This includes:

- stroke
- heart attack
- heart or blood vessel problems.

TEVA-TICAGRELOR is given to patients who:

- have had a heart attack or angina (chest pain)
- have had a heart attack over a year ago and are at high risk of having a heart attack or stroke

**How does TEVA-TICAGRELOR work?**
TEVA-TICAGRELOR belongs to a group of medicines called antiplatelet agents.
Platelets are very small fragments in the blood that clump together during blood clotting.

TEVA-TICAGRELOR helps prevent this clumping and reduces the risk of blood clots forming.

**What are the ingredients in TEVA-TICAGRELOR?**
Medicinal ingredient: Ticagrelor

Non-medicinal ingredients: Mannitol, anhydrous dibasic calcium phosphate, povidone, sodium starch glycolate, magnesium stearate, hypromellose, titanium dioxide, polyethylene glycol, talc, iron oxide yellow (90 mg), iron oxide red.

**TEVA-TICAGRELOR comes in the following dosage forms:**
Film-coated tablets, 60 mg and 90 mg.

**Do not use TEVA-TICAGRELOR if:**

- you are allergic to ticagrelor or any of the ingredients in TEVA-TICAGRELOR.

- you are actively bleeding due to a medical condition, such as bleeding in your stomach or gut from an ulcer or bleeding in your skull or brain.
- you have a history of bleeding inside your skull or brain
- you have liver problems
- you are taking the following medicines:
    - ketoconazole, a medicine used to treat fungal infections
    - clarithromycin, a medicine used to treat bacterial infections,
    - nefazodone, a medicine used to treat depression
    - ritonavir or atazanavir, medicines used to treat HIV/AIDS.

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TEVA-TICAGRELOR. Talk about any health conditions or problems you may have, including if you:**

- have an increased risk of bleeding because of:
    - a recent serious injury
    - your daily activities put you at high risk of having a serious injury
    - recent surgery (including dental procedures)
    - recent bleeding from your stomach or gut (such as a stomach ulcer or colon 'polyps')
    - a bleeding disorder
- have an increased risk of bleeding because you take any of the following:
    - blood thinners such as warfarin
    - medicines that help dissolve blood clots such as streptokinase and alteplase
    - non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, celecoxib and naproxen
    - high dose acetylsalicylic acid (aspirin)
- are having surgery (including dental procedures) at any time while taking TEVA-TICAGRELOR.
- had a stroke in the past.
- have a history of slow heartbeat, are taking medicines that slow down your heartbeat or have a condition that puts you at risk of having slow heartbeat episodes.
- have a history of asthma or other breathing problems.
- have a history of gout.
- have been told by a healthcare professional that you have high levels of uric acid in your blood.
- have kidney problems.

**Other warnings you should know about:**

**Do not stop taking TEVA-TICAGRELOR without first talking to your healthcare professional. If you stop taking TEVA-TICAGRELOR, blood clots may form and cause a stroke, heart attack, or other serious complications. This can lead to severe disability or even death.**

**TEVA-TICAGRELOR may cause serious side effects, including:**

- **Increased levels of uric acid in the blood:** This can lead to a disease called gout that causes painful joints. Tell your healthcare professional **right away** if you experience red, swollen, hot or painful joints.

- **Bradyarrhythmia** (slower than normal heart rate related to problems with the control of the heart rhythm): This may happen shortly after taking TEVA-TICAGRELOR. Your healthcare professional will closely monitor your heart rate during the first few weeks of treatment. Tell your healthcare professional **right away** if you experience a slow heart rate.

- **Thrombotic Thrombocytopenic Purpura (TTP)** (a rare disorder that causes blood clots to form in small blood vessels throughout the body): Rare cases of TTP were reported in patients taking TEVA-TICAGRELOR. This condition can cause serious complications or even death. Tell your healthcare professional right away if you experience some or all of the following symptoms:
    - fever
    - purplish spots on the skin or in the mouth (purpura)
    - yellowing of the skin or eyes (jaundice)
    - unexplained extreme tiredness or confusion

- **Dyspnea** (shortness of breath): This includes shortness of breath when you are at rest, active and during sleep. It usually stops as you continue taking TEVA-TICAGRELOR. Tell your healthcare professional **right away** if you experience shortness of breath, especially if it gets worse or does not seem to go away.

See the **Serious side effects and what to do about them** table, below, for more information on these and other serious side effects.

**Irregular breathing:** The following side effects were reported in a small number of patients while taking TEVA-TICAGRELOR:

- **Central sleep apnea** (disorder in which your breathing repeatedly stops and starts during sleep)
- **Cheyne-Stokes respiration** (a rare abnormal breathing pattern that involves a period of fast, shallow breathing followed by slow heavier breathing and moments without any breath at all)

Tell your healthcare professional if you develop any of the irregular breathing side effects above. Your healthcare professional will decide if you need further evaluation.

**Surgery:**

- If you should see another healthcare professional or a dentist, you should inform them that you are taking TEVA-TICAGRELOR.
- Tell your healthcare professional if you are going to have any surgeries, including dental procedures, while taking TEVA-TICAGRELOR. There is an increased risk of bleeding if you take TEVA-TICAGRELOR during these procedures. It can be life threatening.
- Your healthcare professional may ask you to stop taking TEVA-TICAGRELOR before the surgery, and to resume taking TEVA-TICAGRELOR after the procedure. It is important that you take

TEVA-TICAGRELOR before and after the procedure exactly at the times the healthcare professional has instructed.

**Driving and using machines:** TEVA-TICAGRELOR can cause dizziness, confusion, vertigo and fainting. You should not drive or use machines until you know how TEVA-TICAGRELOR affects you.

**Pregnancy:**

- It is not known if TEVA-TICAGRELOR can cause harm to your baby during pregnancy. Therefore, TEVA-TICAGRELOR should not be used while you are pregnant.
- Your healthcare professional may recommend that you use a highly effective birth control method while taking TEVA-TICAGRELOR.
- Talk to your healthcare professional **right away** if you discover that you are pregnant while taking TEVA-TICAGRELOR.

**Breastfeeding:** It is not known if TEVA-TICAGRELOR can pass into breast milk. Therefore, TEVA-TICAGRELOR should not be used during breastfeeding. Talk to your healthcare professional about ways to feed your baby if you were planning to breastfeed while taking TEVA-TICAGRELOR.

**Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.**

**Serious Drug Interactions**

**Do not take TEVA-TICAGRELOR with:**

- ketoconazole, a medicine used to treat fungal infections,
- clarithromycin, a medicine used to treat bacterial infections,
- nefazodone, a medicine used to treat depression,
- ritonavir or atazanavir, medicines used to treat HIV/AIDS.

Taking TEVA-TICAGRELOR with these medicines may cause serious drug interactions. Ask your healthcare professional if you are unsure.

**The following may interact with TEVA-TICAGRELOR:**

- blood thinners such as warfarin.
- medicines that help dissolve blood clots such as streptokinase and alteplase
- non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, celecoxib and naproxen.
- high dose (greater than 150 mg daily) acetylsalicylic acid (aspirin).
- rifampin, a medicine used to treat bacterial infections
- medicines used to prevent epilepsy or seizures such as carbamazepine, phenytoin, or phenobarbital
- dexamethasone, a medicine used to relieve inflammation and treat other conditions
- cyclosporine, a medicine used to suppress your immune system.

- simvastatin or lovastatin, medicines used to treat high blood cholesterol
- digoxin, a medicine used to treat various heart conditions
- morphine, a medicine used to relieve pain

Know the medicines you take. Ask your healthcare professional if you are not sure whether your medicine is one of the medicines listed above. Keep a list of them to show your healthcare professional or pharmacist when you get a new medicine.

While you are on TEVA-TICAGRELOR it is important that you do not take any medicine other than that prescribed by your healthcare professional.

**How to take TEVA-TICAGRELOR:**
- Take TEVA-TICAGRELOR with or without food.
- Take TEVA-TICAGRELOR exactly as your healthcare professional tells you.
- Swallow the TEVA-TICAGRELOR tablet whole with some water.
- Take one in the morning and one in the evening at around the same time every day.
- Your healthcare professional will also tell you to take low dose acetylsalicylic acid (aspirin) (between 75 mg and 150 mg) once a day.
- Your healthcare professional will tell you how long you should take TEVA-TICAGRELOR. Do not stop taking TEVA-TICAGRELOR without first talking to your healthcare professional.

**If you have trouble swallowing the tablet(s),** follow the steps below to crush the TEVA-TICAGRELOR tablet(s). This will help make sure that all of the crushed tablet(s) will be transferred to the drinking glass.

- use a mortar and pestle or a similar device to crush the tablet(s)
- add a small amount of water (100 mL) to the mortar and pestle/device and stir for 1 minute
- transfer the water and crushed tablet mixture to a drinking glass
- add more water (100 mL) to the mortar and pestle/device and stir for 30 seconds
- transfer the water and crushed tablet mixture to the same drinking glass
- stir the contents of the drinking glass and drink it right away

**How to use the blister (6x10 tablets) pack:**
TEVA-TICAGRELOR comes in a blister pack with the time of day printed on the back of the blister (to help you keep track of your doses).

There are 10 tablets in each blister: 10 are labelled with the time of day (AM or PM). All 10 tablets are exactly the same. Use the following dosing instructions:

First dose for each blister pack:
- Start with the tablet that is labelled **"AM" or "PM"**,

Second dose (one tablet) from the blister pack:

- Take your second tablet (about 12 hours later) that matches the time of day (AM or PM),

Next doses from the blister pack:

- Continue to take one tablet alternating morning (AM) and evening (PM), until they are all finished.

**Usual dose:**

**Adults - 90 mg**

If you had a recent heart attack or angina (chest pain), a healthcare professional will give you 180 mg (two 90 mg tablets) of TEVA-TICAGRELOR for your first dose. After this first dose, the usual dose is one 90 mg tablet twice a day.

After one year your healthcare professional may continue your treatment with a lower dose of TEVA-TICAGRELOR.

**Adults - 60 mg**

The usual dose is one 60 mg tablet twice a day if you:

- had a heart attack over a year ago.

**Overdose:**

Symptoms of an overdose include:

- Excessive bleeding
- Shortness of breath
- Pauses in heart beat

If you think you, or a person you are caring for, have taken too much TEVA-TICAGRELOR, contact a healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

**Missed Dose:**

If you forget or miss a dose of TEVA-TICAGRELOR, skip the missed dose and take the next dose as scheduled. **Do not double the dose to make up for the missed dose.**

**What are possible side effects from using TEVA-TICAGRELOR?**

These are not all the possible side effects you may have when taking TEVA-TICAGRELOR. If you experience any side effects not listed here, tell your healthcare professional.

The most common side effects of TEVA-TICAGRELOR are:

- Headache
- Feeling dizzy or like the room is spinning
- Abdominal pain, constipation, diarrhea or indigestion (heartburn)
- Nausea or vomiting

- Itching
- A tingling feeling
- Inflamed stomach lining
- Fatigue, muscle weakness
- Anxiety
- Sore throat or runny nose
- Cough
- Feeling dizzy or lightheaded, or having blurred vision (signs of low blood pressure)
- Bleeding gums

TEVA-TICAGRELOR affects blood clotting, so most side effects are related to bleeding. Bleeding may occur in any part of the body. Some bleeding is common (like bruising and nose bleeds). Severe bleeding is uncommon, but can be life threatening (see Serious side effects and what to do about them table below).

Signs of irregular breathing (Central sleep apnea and Cheyne-Stokes respiration) have been reported in a small number of patients taking ticagrelor (frequency cannot be estimated from the available data). Central sleep apnea is associated with irregular breathing and may occur in patients with heart disease, stroke or other causes. Tell your healthcare professional if you develop irregular breathing patterns such as speeding up, slowing down or short pauses in breathing. Your healthcare professional will decide if you need further evaluation.

TEVA-TICAGRELOR can cause abnormal blood test results. Your healthcare professional will decide when to perform blood tests and will interpret the results.

| **Serious side effects and what to do about them** | | | |
|---|---|---|---|
| **Symptom / effect** | **Talk to your healthcare professional** | | **Stop taking drug and get immediate medical help** |
| | **Only if severe** | **In all cases** | |
| **VERY COMMON** | | | |
| Bleeding caused by blood disorder | | **X** | |
| **Dyspnea** (shortness of breath) | | **X** | |
| **Increased levels of uric acid in the blood:** possible red, swollen, hot and painful joint (signs of gout) | | **X** | |
| **COMMON** | | | |
| **Bleeding:** blood in your urine (pink, red or brown urine) or stools (red or black stools – looks like tar), vomiting blood, coughing up blood, nosebleed, bruising or bleeding into the skin, bleeding more than normal after surgery or cuts or wounds, bleeding that is severe or | | **X** | |

| Serious side effects and what to do about them | | | |
|---|---|---|---|
| **Symptom / effect** | **Talk to your healthcare professional** | | **Stop taking drug and get immediate medical help** |
| | **Only if severe** | **In all cases** | |
| that lasts a long time | | | |
| Chest pain | | **X** | |
| **Heart problems:** rapid, slow or irregular heartbeat or increased fatigue, swelling of legs and feet and shortness of breath | | **X** | |
| **Signs of a stroke including:**<br>• sudden numbness or weakness of your arm, leg or face, especially if only on one side of the body.<br>• sudden confusion, difficulty speaking or understanding others.<br>• sudden difficulty in walking or loss of balance or coordination.<br>• suddenly feeling dizzy or sudden severe headache with no known cause. | | | **X** |
| Sleeplessness | | **X** | |
| Swelling of your legs or ankles | | **X** | |
| **Syncope (fainting):** temporary loss of consciousness due to sudden drop in blood flow to the brain | | **X** | |
| **UNCOMMON** | | | |
| **Anemia** (decreased number of red blood cells): shortness of breath, paleness, weakness | | **X** | |
| **Bleeding:** blood in your eye, ear or tumour, heavier vaginal bleeding or bleeding at different times than normal menstrual bleeding, bleeding into joints and muscles causing painful swelling, internal bleeding that may cause dizziness or light-headedness | | **X** | |
| Confusion | | **X** | |
| **Intracranial hemorrhage** (bleeding in the skull or brain): sudden, severe headache; confusion; nausea and vomiting; seizures; loss of consciousness | | | **X** |
| **Kidney stones:** pain when urinating, severe pain in the side and back, below the ribs | | **X** | |
| **Lung fibrosis** (scarring of the lungs)**:** shortness of breath, dry cough, fatigue, aching muscles and joints, unexplained weight loss | | **X** | |

| Serious side effects and what to do about them | | | |
|---|---|---|---|
| **Symptom / effect** | **Talk to your healthcare professional** | | **Stop taking drug and get immediate medical help** |
| | **Only if severe** | **In all cases** | |
| **Pulmonary hypertension** (high blood pressure in the lungs): shortness of breath, dizziness, fatigue, racing pulse | | **X** | |
| **UNKNOWN FREQUENCY** | | | |
| **Allergic Reaction:** rash, hives, itching, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing | | | **X** |
| **Bradyarrhythmia** (slower than normal heart rate related to problems with the control of heart rhythm): fainting or near-fainting, light-headedness, weakness, fatigue, shortness of breath, confusion or memory problems. | | **X** | |
| Rash | | **X** | |
| **Thrombotic Thrombocytopenic Purpura (TTP)** (a rare disorder that causes blood clots to form in small blood vessels throughout the body): as fever and purplish spots (called purpura) on the skin or in the mouth, with or without yellowing of the skin or eyes (jaundice), unexplained extreme tiredness or confusion. | | **X** | |

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

**Reporting Side Effects**

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

*NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

**Storage:**

- Store TEVA-TICAGRELOR tablets at room temperature (15°C - 30°C).
- Keep TEVA-TICAGRELOR and all medicines out of the reach and sight of children.
- The expiry date of this medicine is printed on the package label. Do not use the medicine after this date.

**If you want more information about TEVA-TICAGRELOR:**

- Talk to your healthcare professional
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website http://www.tevacanada.com; or by calling 1-800-268-4127 ext. 3; or email druginfo@tevacanada.com.

This leaflet was prepared by Teva Canada Limited, Toronto, Ontario M1B 2K9

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