SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

Ticagrelor Tablets

1.1 Strength

90 mg

1.2 Pharmaceutical form

Film coated tablets

2. QUALITATIVA AND QUANTITATIVE COMPOSITION

Each film coated tablet contains

Ticagrelor ..... 90 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablets

Yellow, round, biconvex film coated tablets debossed with 'T' above '90' on one face and plain on other face.

Prescription only medicine

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Acute Coronary Syndrome or a History of Myocardial Infarction

Ticagrelor is indicated to reduce the risk of cardiovascular (CV) death, myocardial infarction (MI), and stroke in patients with acute coronary syndrome (ACS) or a history of MI. For at least the first 12 months following ACS, it is superior to clopidogrel.

Ticagrelor also reduces the risk of stent thrombosis in patients who have been stented for treatment of ACS.

Coronary Artery Disease but No Prior Stroke or Myocardial Infarction

Ticagrelor is indicated to reduce the risk of a first MI or stroke in patients with coronary artery disease (CAD) at high risk for such events. While use is not limited to this setting, the efficacy of Ticagrelor was established in a population with type 2 diabetes mellitus (T2DM).

Acute Ischemic Stroke or Transient Ischemic Attack (TIA)

Ticagrelor is indicated to reduce the risk of stroke in patients with acute ischemic stroke (NIH Stroke Scale score ≤5) or high-risk transient ischemic attack (TIA).

4.2 Posology and method of administration

Acute Coronary Syndrome or a History of Myocardial Infarction

Initiate treatment with a 180 mg loading dose of Ticagrelor. Administer 90 mg of Ticagrelor twice daily during the first year after an ACS event. After one year, administer 60 mg of Ticagrelor twice daily.

Use Ticagrelor with a daily maintenance dose of aspirin of 75 to 100 mg.

Coronary Artery Disease but No Prior Stroke or Myocardial Infarction

Administer 60 mg of Ticagrelor twice daily. For all patients with ACS.

Use Ticagrelor with a daily maintenance dose of aspirin of 75 to 100 mg.

Acute Ischemic Stroke or Transient Ischemic Attack (TIA)

Initiate treatment with a 180 mg loading dose of TICAGRELOR and then continue with 90 mg twice daily for up to 30 days. The treatment effect accrued early in the course of therapy.

Use Ticagrelor with a loading dose of aspirin (300 to 325 mg) and a daily maintenance dose of aspirin of 75 to 100 mg.

4.3 Method of Administration

A patient who misses a dose of Ticagrelor should take one tablet (their next dose) at its scheduled time.

For patients who are unable to swallow tablets whole, TICAGRELOR tablets can be crushed, mixed with water and drunk. The mixture can also be administered via a nasogastric tube (CH8 or greater).

Do not administer Ticagrelor with another oral $P2Y_{12}$ platelet inhibitor.

4.4 Contraindications

History of Intracranial Hemorrhage

Ticagrelor is contraindicated in patients with a history of intracranial hemorrhage (ICH) because of a high risk of recurrent ICH in this population.

Active Bleeding

Ticagrelor is contraindicated in patients with active pathological bleeding such as peptic ulcer or intracranial hemorrhage.

Hypersensitivity

Ticagrelor is contraindicated in patients with hypersensitivity (e.g., angioedema) to Ticagrelor or any component of the product.

4.5 Special warning and precautions

Risk of Bleeding

Drugs that inhibit platelet function including Ticagrelor increase the risk of bleeding.

Patients treated for acute ischemic stroke or TIA

Patients at NIHSS >5 and patients receiving thrombolysis were excluded from THALES and use of Ticagrelor in such patients is not recommended.

Concomitant Aspirin Maintenance Dose

In PLATO the use of Ticagrelor with maintenance doses of aspirin above 100 mg decreased the effectiveness of Ticagrelor. Therefore, after the initial loading dose of aspirin, use Ticagrelor A with a maintenance dose of aspirin of 75-100 mg.

Dyspnea

In clinical trials, about 14% of patients treated with Ticagrelor developed dyspnea. Dyspnea was usually mild to moderate in intensity and often resolved during continued treatment, but led to study drug discontinuation in 0.9% of Ticagrelor and 0.1% of clopidogrel patients in PLATO and 4.3% of Ticagrelor 60 mg and 0.7% on aspirin alone patients in PEGASUS.

In a sub study of PLATO, 199 subjects underwent pulmonary function testing irrespective of whether they reported dyspnea. There was no indication of an adverse effect on pulmonary function assessed after one month or after at least 6 months of chronic treatment.

If a patient develops new, prolonged, or worsened dyspnea that is determined to be related to Ticagrelor, no specific treatment is required; continue Ticagrelor without interruption if possible. In the case of intolerable dyspnea requiring discontinuation of Ticagrelor, consider prescribing another antiplatelet agent.

Discontinuation of Ticagrelor in Patients Treated for Coronary Artery Disease

Discontinuation of Ticagrelor will increase the risk of myocardial infarction, stroke, and death. If Ticagrelor must be temporarily discontinued (e.g., to treat bleeding or for significant surgery), restart it as soon as possible. When possible, interrupt therapy with Ticagrelor for five days prior to surgery that has a major risk of bleeding. Resume Ticagrelor as soon as hemostasis is achieved.

Bradyarrhythmia

Ticagrelor can cause ventricular pauses. Bradyarrhythmia including AV block have been reported in the postmarketing setting. Patients with a history of sick sinus syndrome, 2nd or 3rd degree AV block or bradycardia-related syncope not protected by a pacemaker were excluded from clinical studies and may be at increased risk of developing bradyarrhythmia with ticagrelor.

Severe Hepatic Impairment

Avoid use of Ticagrelor in patients with severe hepatic impairment. Severe hepatic impairment is likely to increase serum concentration of Ticagrelor. There are no studies of Ticagrelor patients with severe hepatic impairment

Central Sleep Apnea

Central sleep apnea (CSA) including Cheyne-Stokes respiration (CSR) has been reported in the post-marketing setting in patients taking ticagrelor, including recurrence or worsening of CSA/CSR following rechallenge. If central sleep apnea is suspected, consider further clinical assessment.

Laboratory Test Interferences

False negative functional tests for Heparin Induced Thrombocytopenia (HIT)

Ticagrelor has been reported to cause false negative results in platelet functional tests (to include, but may not be limited to, the heparin-induced platelet aggregation (HIPA) assay) for patients with Heparin Induced Thrombocytopenia (HIT). This is related to inhibition of the $P2Y_{12}$ - receptor on the healthy donor platelets in the test by ticagrelor in the affected patient's serum/plasma. Information on concomitant treatment with Ticagrelor is required for interpretation of HIT functional tests. Based on the mechanism of Ticagrelor interference, Ticagrelor is not expected to impact PF4 antibody testing for HIT.

4.6 Paediatric population

None stated

4.7 Interactions with Other Medicaments

Strong CYP3A Inhibitors

Strong CYP3A inhibitors substantially increase Ticagrelor exposure and so increase the risk of dyspnea, bleeding, and other adverse events. Avoid use of strong inhibitors of CYP3A (e.g., ketoconazole, itraconazole, voriconazole, clarithromycin, nefazodone, ritonavir, Saquinavir, nelfinavir, indinavir, Atazanavir and telithromycin)

Strong CYP3A Inducers

Strong CYP3A inducers substantially reduce Ticagrelor exposure and so decrease the efficacy of Ticagrelor. Avoid use with strong inducers of CYP3A (e.g., rifampin, phenytoin, carbamazepine and phenobarbital).

Aspirin

Use of Ticagrelor with aspirin maintenance doses above 100 mg reduced the effectiveness of Ticagrelor.

Opioids

As with other oral $P2Y_{12}$ inhibitors, co-administration of opioid agonists delay and reduce the absorption of ticagrelor and its active metabolite presumably because of slowed gastric emptying. Consider the use of a parenteral anti-platelet agent in acute coronary syndrome patients requiring co-administration of morphine or other opioid agonists.

Simvastatin, Lovastatin

Ticagrelor increases serum concentrations of simvastatin and lovastatin because these drugs are metabolized by CYP3A4. Avoid simvastatin and lovastatin doses greater than 40 mg.

Digoxin

Ticagrelor inhibits the P-glycoprotein transporter; monitor digoxin levels with initiation of or change in Ticagrelor therapy

4.8 Additional information on special populations

None stated

4.9 Paediatric population

None stated

4.10 Fertility, pregnancy and lactation

4.10.1 Women of childbearing potential / Contraception in males and females

None stated

4.10.2 Pregnancy

Risk Summary

Available data from case reports with Ticagrelor use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Ticagrelor given to pregnant rats and pregnant rabbits during organogenesis caused structural abnormalities in the offspring at maternal doses about 5 to 7 times the maximum recommended human dose (MRHD) based on body surface area. When ticagrelor was given to rats during late gestation and lactation, pup death and effects on pup growth were seen at approximately 10 times the MRHD.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes.

4.10.3 Lactation

Risk Summary

There are no data on the presence of ticagrelor or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. Ticagrelor and its metabolites were present in rat milk at higher concentrations than in maternal plasma. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Breastfeeding is not recommended during treatment with Ticagrelor.

Pediatric Use

The safety and effectiveness of Ticagrelor in pediatric patients have not been established.

Geriatric Use

About half of the patients in PLATO, PEGASUS, THEMIS, and THALES were ≥65 years of age and at least 15% were ≥75 years of age. No overall differences in safety or effectiveness were observed between elderly and younger patients.

Hepatic Impairment

Ticagrelor is metabolized by the liver and impaired hepatic function can increase risks for bleeding and other adverse events. Avoid use of Ticagrelor in patients with severe hepatic impairment. There is limited experience with Ticagrelor in patients with moderate hepatic impairment; consider the risks and benefits of treatment, noting the probable increase in exposure to ticagrelor. No dosage adjustment is needed in patients with mild hepatic impairment.

Renal Impairment

No dosage adjustment is needed in patients with renal impairment.

Patients with End-Stage Renal Disease on dialysis

Clinical efficacy and safety studies with TICAGRELOR did not enroll patients with end-stage renal disease (ESRD) on dialysis. In patients with ESRD maintained on intermittent hemodialysis, no clinically significant difference in concentrations of ticagrelor and its metabolite and platelet inhibition are expected compared to those observed in patients with normal renal function. It is not known whether these concentrations will lead to similar efficacy and safety in patients with ESRD on dialysis as were seen in PLATO, PEGASUS, THEMIS and THALES.

4.11 Effects on ability to drive and use machine

Ticagrelor has no or negligible influence on the ability to drive and use machines. During treatment with ticagrelor, dizziness and confusion have been reported. Therefore, patients who experience these symptoms should be cautious while driving or using machines.

4.12 Undesirable effects

The following adverse reactions are also discussed elsewhere in the labeling:

Bleeding

Dyspnea

Clinical Trials Experience

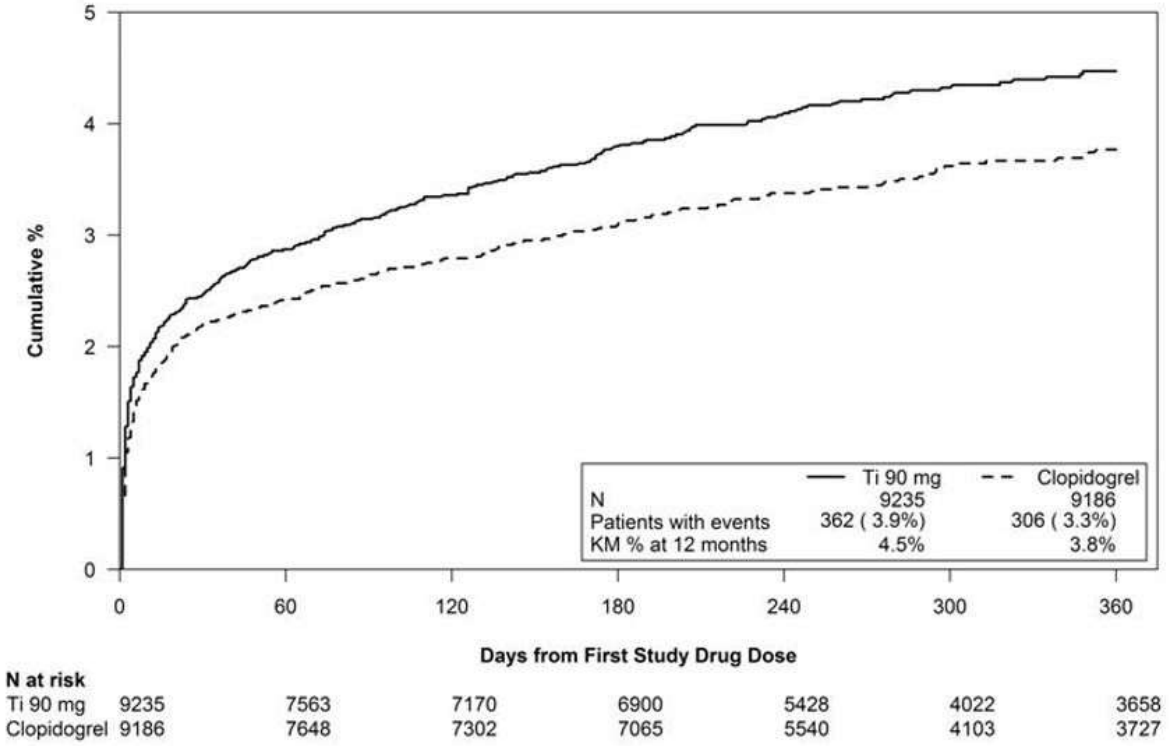
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

TICAGRELOR has been evaluated for safety in more than 58,000 patients.

Bleeding in PLATO (Reduction in risk of thrombotic events in ACS)

Figure 1 is a plot of time to the first non-CABG major bleeding event.

Figure 1 - Kaplan-Meier estimate of time to first non-CABG PLATO-defined major bleeding event (PLATO)



Frequency of bleeding in PLATO is summarized in Tables 1 and 2. About half of the non-CABG major bleeding events were in the first 30 days.

Table 1 - Non-CABG related bleeds (PLATO)

	Ticagrelor* **N=9235**	**Clopidogrel N=9186**
	n (%) patients with event	**n (%) patients with event**
PLATO Major + Minor	713 (7.7)	567 (6.2)

Major	362 (3.9)	306 (3.3)
Fatal/Life-threatening	171 (1.9)	151 (1.6)
Fatal	15 (0.2)	16 (0.2)
Intracranial hemorrhage (Fatal/Life-threatening)	26 (0.3)	15 (0.2)

PLATO Minor bleed: requires medical intervention to stop or treat bleeding.

PLATO Major bleed: any one of the following: fatal; intracranial; intrapericardial with cardiac tamponade; hypovolemic shock or severe hypotension requiring intervention; significantly disabling (e.g., intraocular with permanent vision loss); associated with a decrease in Hb of at least 3 g/dL (or a fall in hematocrit (Hct) of at least 9%); transfusion of 2 or more units.

PLATO Major bleed, fatal/life-threatening: any major bleed as described above and associated with a decrease in Hb of more than 5 g/dL (or a fall in hematocrit (Hct) of at least 15%); transfusion of 4 or more units.

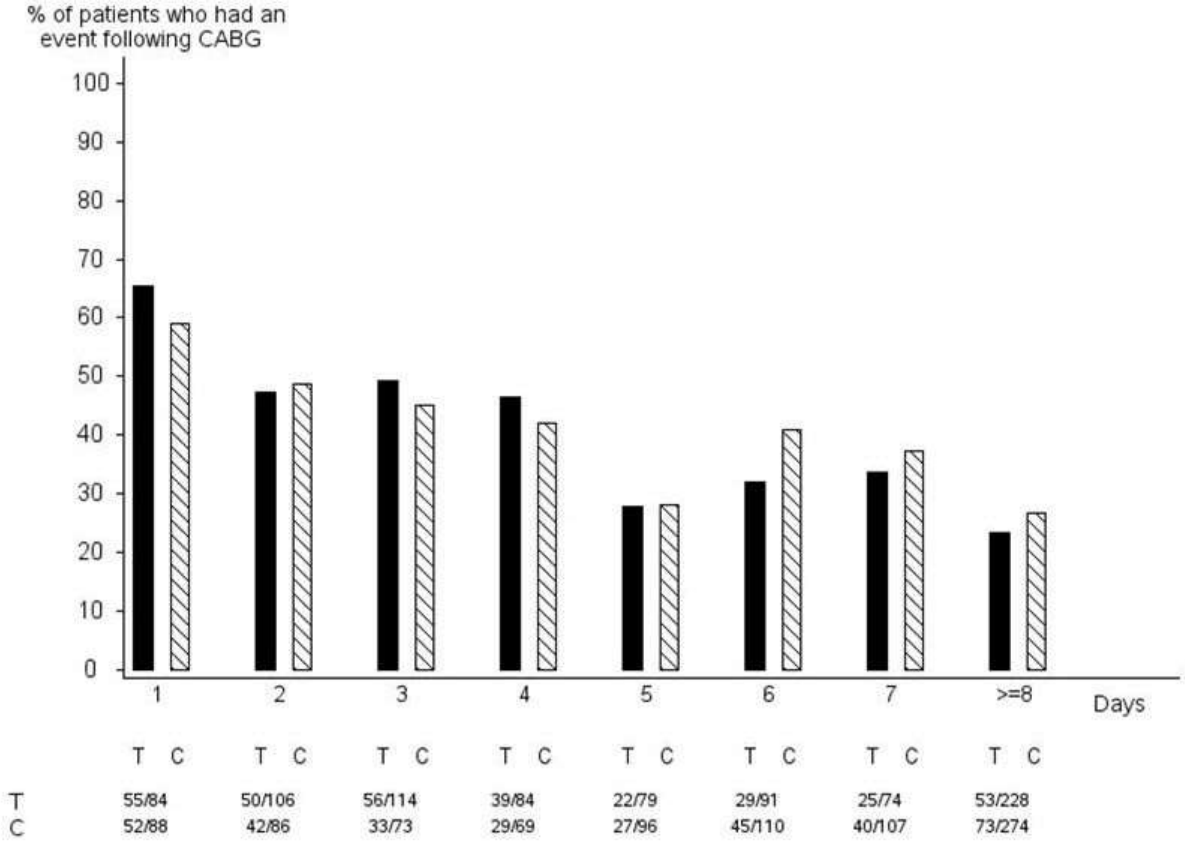
Fatal: A bleeding event that directly led to death within 7 days.

* 90 mg BID

No baseline demographic factor altered the relative risk of bleeding with TICAGRELOR compared to clopidogrel.

In PLATO, 1584 patients underwent CABG surgery. The percentages of those patients who bled are shown in Figure 2 and Table 2.

Figure 2 - 'Major fatal/life-threatening' CABG-related bleeding by days from last dose of study drug to CABG procedure (PLATO)



X-axis is days from last dose of study drug prior to CABG.

The PLATO protocol recommended a procedure for withholding study drug prior to CABG or other major surgery without unbinding. If surgery was elective or non-urgent, study drug was interrupted temporarily, as follows: If local practice was to allow antiplatelet effects to dissipate before surgery, capsules (blinded clopidogrel) were withheld 5 days before surgery and tablets (blinded ticagrelor) were withheld for a minimum of 24 hours and a maximum of 72 hours before surgery. If local practice was to perform surgery without waiting for dissipation of antiplatelet effects capsules and tablets were withheld 24 hours prior to surgery and use of aprotinin or other hemostatic agents was allowed. If local practice was to use IPA monitoring to determine when surgery could be performed both the capsules and tablets were withheld at the same time and the usual monitoring procedures followed.

T Ticagrelor; C Clopidogrel.

Table 2 - CABG-related bleeding (PLATO)

	Ticagrelor [*] **N=770**	**Clopidogrel N=814**
	n (%) patients with event	**n (%) patients with event**
PLATO Total Major	626 (81.3)	666 (81.8)
Fatal/Life-threatening	337 (43.8)	350 (43.0)
Fatal	6 (0.8)	7 (0.9)
PLATO Major bleed: any one of the following: fatal; intracranial; intrapericardial with cardiac tamponade; hypovolemic shock or severe hypotension requiring intervention; significantly disabling (e.g., intraocular with permanent vision loss); associated with a decrease in Hb of at least 3 g/dL (or a fall in hematocrit (Hct) of at least 9%); transfusion of 2 or more units. **PLATO Major bleed, fatal/life-threatening**: any major bleed as described above and associated with a decrease in Hb of more than 5 g/dL (or a fall in hematocrit (Hct) of at least 15%); transfusion of 4 or more units.		

[*] 90 mg BID

When antiplatelet therapy was stopped 5 days before CABG, major bleeding occurred in 75% of TICAGRELOR treated patients and 79% on clopidogrel.

Other Adverse Reactions in PLATO

Adverse reactions that occurred at a rate of 4% or more in PLATO are shown in Table 3.

Table 3 - Percentage of patients reporting non-hemorrhagic adverse reactions at least 4% or more in either group and more frequently on TICAGRELOR (PLATO)

	TICAGRELOR[*] N=9235	Clopidogrel N=9186
Dyspnea	13.8	7.8

	TICAGRELOR* N=9235	Clopidogrel N=9186
Dizziness	4.5	3.9
Nausea	4.3	3.8

* 90 mg BID

Bleeding in PEGASUS (Secondary Prevention in Patients with a History of Myocardial Infarction)

Overall outcome of bleeding events in the PEGASUS study are shown in Table 4.

Table 4 - Bleeding events (PEGASUS)

	TICAGRELOR* N=6958	**Placebo N=6996**
	Events / 1000 patient years	**Events / 1000 patient years**
TIMI Major	8	3
Fatal	1	1
Intracranial hemorrhage	2	1
TIMI Major or Minor	11	5

TIMI Major: Fatal bleeding, OR any intracranial bleeding, OR clinically overt signs of hemorrhage associated with a drop in hemoglobin (Hgb) of ≥5 g/dL, or a fall in hematocrit (Hct) of ≥15%.

Fatal: A bleeding event that directly led to death within 7 days.

TIMI Minor: Clinically apparent with 3-5 g/dL decrease in hemoglobin.

* 60 mg BID

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

Other Adverse Reactions in PEGASUS

Adverse reactions that occurred in PEGASUS at rates of 3% or more are shown in Table 5.

Table 5 - Non-hemorrhagic adverse reactions reported in >3.0% of patients in the ticagrelor 60 mg treatment group (PEGASUS)

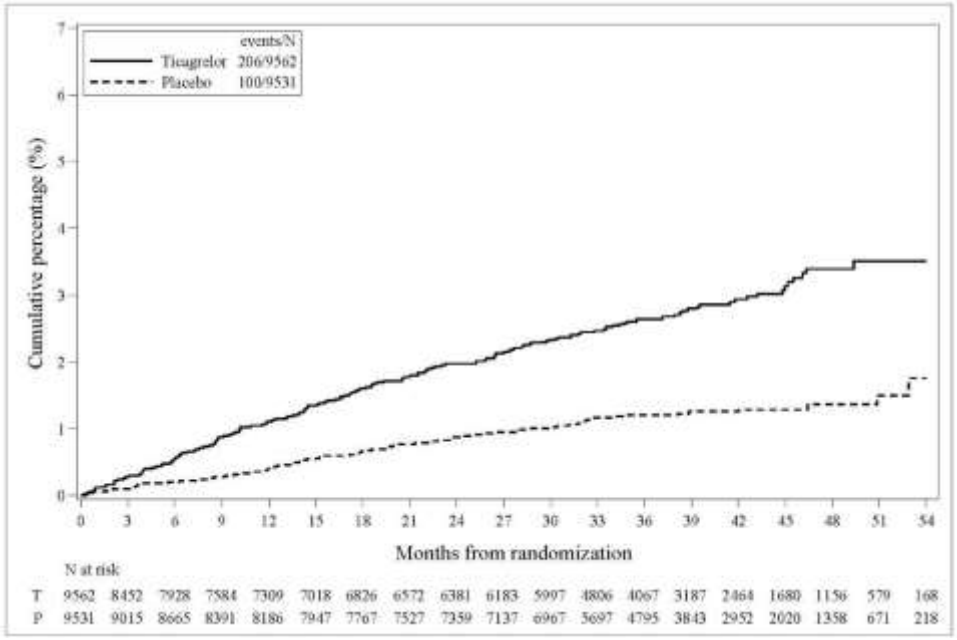
	TICAGRELOR* **N=6958**	**Placebo N=6996**
Dyspnea	14.2%	5.5%
Dizziness	4.5%	4.1%
Diarrhea	3.3%	2.5%

* 60 mg BID

Bleeding in THEMIS (Prevention of major CV events in patients with CAD and Type 2 Diabetes Mellitus)

The Kaplan-Meier curve of time to first TIMI Major bleeding event is presented in Figure 3.

Figure 3 – Time to first TIMI Major bleeding event (THEMIS)



T = Ticagrelor; P = Placebo; N = Number of patients

The bleeding events in THEMIS are shown below in Table 6.

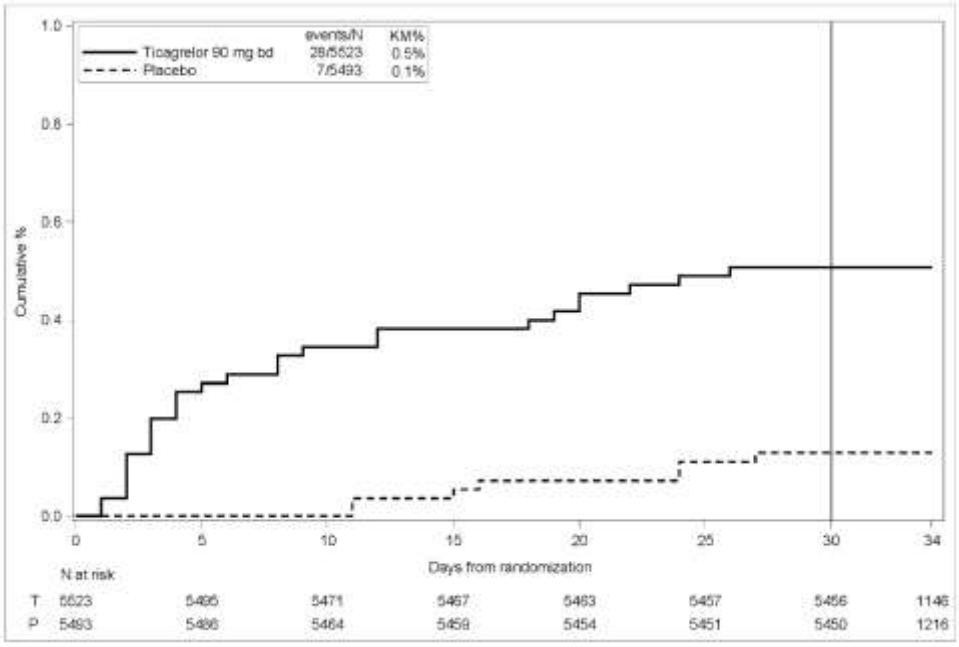
Table 6 – Bleeding events (THEMIS)

	TICAGRELOR N=9562	**Placebo N=9531**
	Events / 1000 patient years	**Events / 1000 patient years**
TIMI Major	9	4
TIMI Major or Minor	12	5
TIMI Major or Minor or Requiring medical attention	46	18
Fatal bleeding	1	0
Intracranial hemorrhage	3	2

Bleeding in THALES (Reduction in risk of stroke in patients with acute ischemic stroke or TIA)

The Kaplan-Meier curve of time course of GUSTO severe bleeding events is presented in Figure 4.

Figure 4 – Time course of GUSTO severe bleeding events



KM%: Kaplan-Meier percentage evaluated at Day 30; T = Ticagrelor; P = placebo; N = Number of patients

GUSTO Severe: Any one of the following: fatal bleeding, intracranial bleeding (excluding asymptomatic hemorrhagic transformations of ischemic brain infarctions and excluding micro hemorrhages < 10 mm evident only on gradient-echo magnetic resonance imaging), bleeding that caused hemodynamic compromise requiring intervention (e.g., systolic blood pressure <90 mmg Hg that required blood or fluid replacement, or vasopressor/inotropic support, or surgical intervention).

Intracranial bleeding and fatal bleeding in THALES: In total, there were 21 intracranial hemorrhages (ICHs) for Ticagrelor and 6 ICHs for placebo. Fatal bleedings, almost all ICH, occurred in 11 for Ticagrelor and in 2 for placebo.

Bradycardia

In a Holter sub study of about 3000 patients in PLATO, more patients had ventricular pauses with Ticagrelor (6.0%) than with clopidogrel (3.5%) in the acute phase; rates were 2.2% and 1.6%, respectively, after 1 month. PLATO, PEGASUS, THEMIS and THALES excluded patients at increased risk of bradycardia events (e.g., patients who have sick sinus syndrome, 2nd or 3rd degree AV block, or bradycardia-related syncope and not protected with a pacemaker).

Lab abnormalities

Serum Uric Acid:

In PLATO, serum uric acid levels increased approximately 0.6 mg/dL from baseline on TICAGRELOR 90 mg and approximately 0.2 mg/dL on clopidogrel. The difference disappeared within 30 days of discontinuing treatment. Reports of gout did not differ between treatment groups in PLATO (0.6% in each group).

In PEGASUS, serum uric acid levels increased approximately 0.2 mg/dL from baseline on Ticagrelor 60 mg and no elevation was observed on aspirin alone. Gout occurred more commonly in patients on Ticagrelor than in patients on aspirin alone (1.5%, 1.1%). Mean serum uric acid concentrations decreased after treatment was stopped.

Serum Creatinine

In PLATO, a >50% increase in serum creatinine levels was observed in 7.4% of patients receiving Ticagrelor 90 mg compared to 5.9% of patients receiving clopidogrel. The increases typically did not progress with ongoing treatment and often decreased with continued therapy. Evidence of reversibility upon discontinuation was observed even in those with the greatest on treatment increases. Treatment groups in PLATO did not differ for renal-related serious adverse events such as acute renal failure, chronic renal failure, toxic nephropathy, or oliguria.

In PEGASUS, serum creatinine concentration increased by >50% in approximately 4% of patients receiving TICAGRELOR 60 mg, similar to aspirin alone. The frequency of renal related

adverse events was similar for ticagrelor and aspirin alone regardless of age and baseline renal function.

Postmarketing Experience

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

Blood and lymphatic system disorders: Thrombotic Thrombocytopenic Purpura (TTP) has been rarely reported with the use of Ticagrelor. TTP is a serious condition which can occur after a brief exposure (<2 weeks) and requires prompt treatment.

Immune system disorders: Hypersensitivity reactions including angioedema.

Respiratory Disorders: Central sleep apnea, Cheyne-Stokes respiration

Skin and subcutaneous tissue disorders: Rash

4.13 Overdose

There is currently no known treatment to reverse the effects of Ticagrelor, and ticagrelor is not expected to be dialyzable. Treatment of overdose should follow local standard medical practice. Bleeding is the expected pharmacologic effect of overdosing. If bleeding occurs, appropriate supportive measures should be taken.

Other effects of overdose may include gastrointestinal effects (nausea, vomiting, and diarrhea) or ventricular pauses. Monitor the ECG.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

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

Mechanism of Action

Ticagrelor and its major metabolite reversibly interact with the platelet $P2Y_{12}$ ADP-receptor to prevent signal transduction and platelet activation. Ticagrelor and its active metabolite are approximately equipotent.

Pharmacodynamics

The inhibition of platelet aggregation (IPA) by ticagrelor and clopidogrel was compared in a 6-week study examining both acute and chronic platelet inhibition effects in response to 20 μM ADP as the platelet aggregation agonist.

The onset of IPA was evaluated on Day 1 of the study following loading doses of 180 mg ticagrelor or 600 mg clopidogrel. As shown in Figure 5, IPA was higher in the ticagrelor group at all time points. The maximum IPA effect of ticagrelor was reached at around 2 hours, and was maintained for at least 8 hours.

The offset of IPA was examined after 6 weeks on ticagrelor 90 mg twice daily or clopidogrel 75 mg daily, again in response to 20 μM ADP.

As shown in Figure 6, mean maximum IPA following the last dose of ticagrelor was 88% and 62% for clopidogrel. The insert in Figure 6 shows that after 24 hours, IPA in the ticagrelor group (58%) was similar to IPA in clopidogrel group (52%), indicating that patients who miss a dose of ticagrelor would still maintain IPA similar to the trough IPA of patients treated with clopidogrel. After 5 days, IPA in the ticagrelor group was similar to IPA in the placebo group. It is not known how either bleeding risk or thrombotic risk track with IPA, for either ticagrelor or clopidogrel.

Figure 5 - Mean inhibition of platelet aggregation (±SE) following single oral doses of placebo, 180 mg ticagrelor or 600 mg clopidogrel.

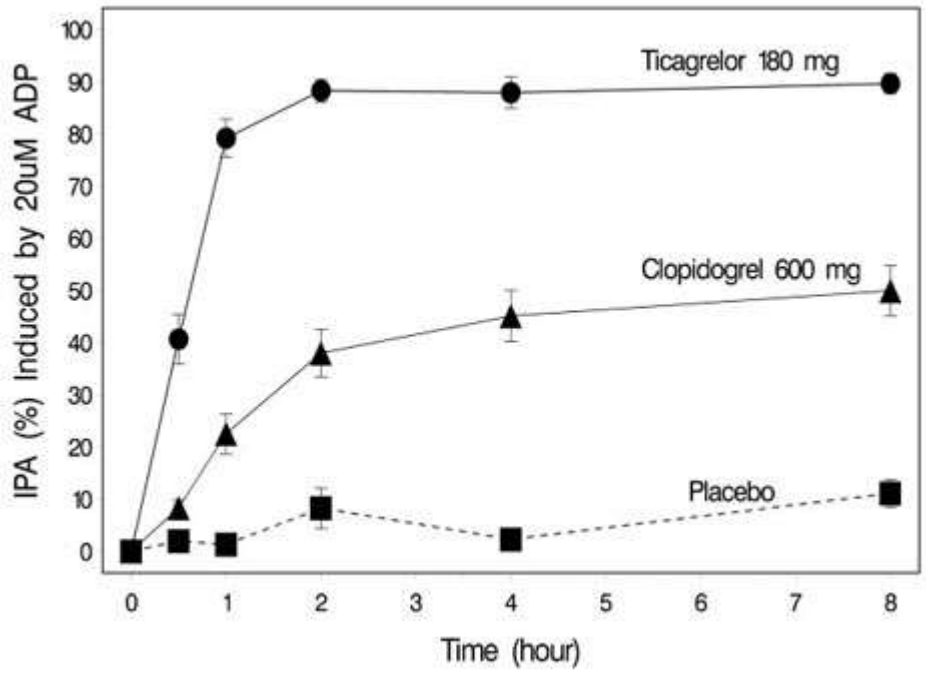
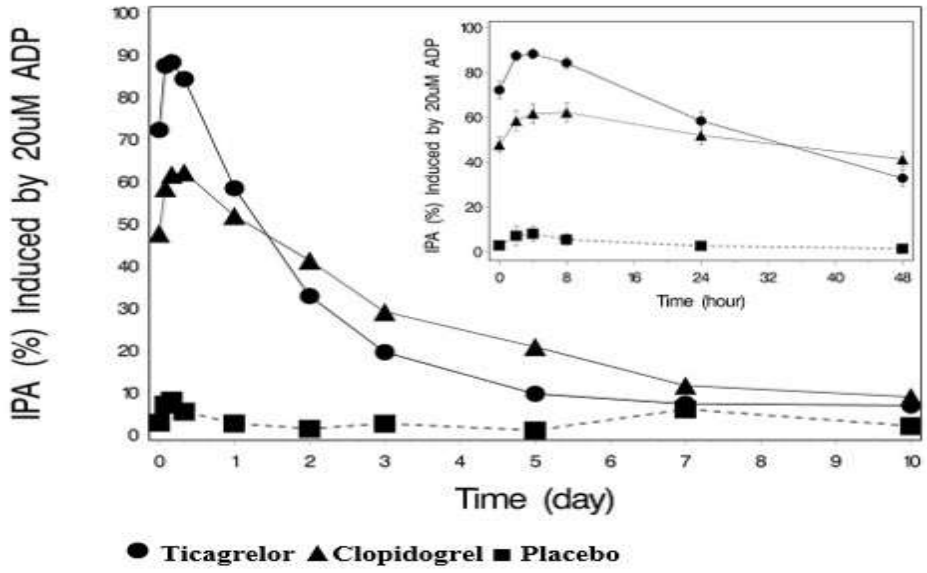


Figure 6 - Mean inhibition of platelet aggregation (IPA) following 6 weeks on placebo, ticagrelor 90 mg twice daily, or clopidogrel 75 mg daily



Transitioning from clopidogrel to Ticagrelor resulted in an absolute IPA increase of 26.4% and from Ticagrelor to clopidogrel resulted in an absolute IPA decrease of 24.5%. Patients can be transitioned from clopidogrel to Ticagrelor without interruption of antiplatelet effect.

5.2 Pharmacokinetic Properties

Ticagrelor demonstrates dose proportional pharmacokinetics, which are similar in patients and healthy volunteers.

Absorption

Ticagrelor can be taken with or without food. Absorption of ticagrelor occurs with a median t_{max} of 1.5 h (range 1.0–4.0). The formation of the major circulating metabolite AR-C124910XX (active) from ticagrelor occurs with a median t_{max} of 2.5 h (range 1.5-5.0).

The mean absolute bioavailability of ticagrelor is about 36% (range 30%-42%). Ingestion of a high-fat meal had no effect on ticagrelor C_{max}, but resulted in a 21% increase in AUC. The C_{max} of its major metabolite was decreased by 22% with no change in AUC.

Ticagrelor as crushed tablets mixed in water, given orally or administered through a nasogastric tube into the stomach, is bioequivalent to whole tablets (AUC and C_{max} within 80-125% for ticagrelor and AR-C124910XX) with a median t_{max} of 1.0 hour (range 1.0 – 4.0) for ticagrelor and 2.0 hours (range 1.0 –8.0) for AR-C124910XX.

Distribution

The steady state volume of distribution of ticagrelor is 88 L. Ticagrelor and the active metabolite are extensively bound to human plasma proteins (>99%).

Metabolism

CYP3A4 is the major enzyme responsible for ticagrelor metabolism and the formation of its major active metabolite. Ticagrelor and its major active metabolite are weak P-glycoprotein substrates and inhibitors. The systemic exposure to the active metabolite is approximately 30-40% of the exposure of ticagrelor.

Excretion

The primary route of ticagrelor elimination is hepatic metabolism. When radiolabeled ticagrelor is administered, the mean recovery of radioactivity is approximately 84% (58% in feces, 26% 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 major metabolite of ticagrelor is most likely to be biliary secretion. The mean t1/2 is approximately 7 hours for ticagrelor and 9 hours for the active metabolite.

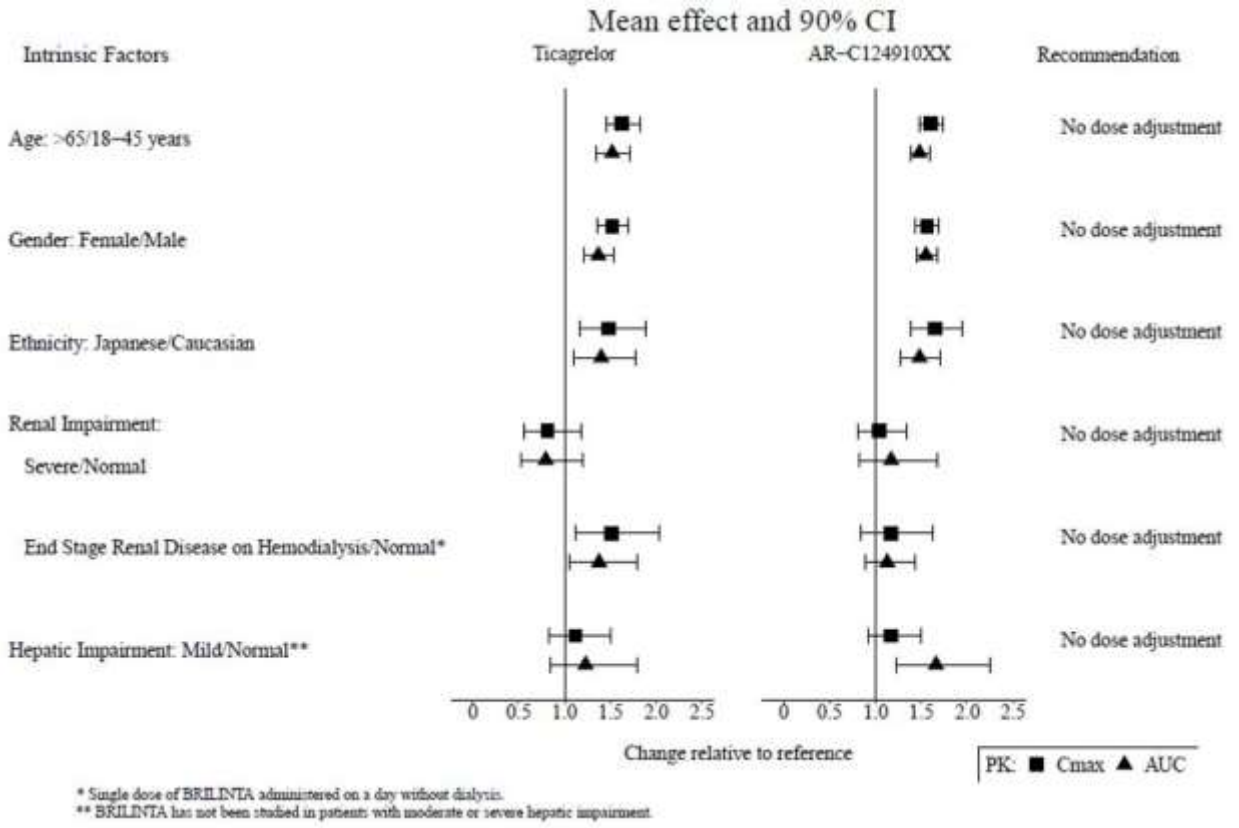
Specific Populations

The effects of age, gender, ethnicity, renal impairment and mild hepatic impairment on the pharmacokinetics of ticagrelor are presented in Figure 7. Effects are modest and do not require dose adjustment.

Patients with End-Stage Renal Disease on Hemodialysis

In patients with end stage renal disease on hemodialysis 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 dialyzable. Exposure of the active metabolite increased to a lesser extent. The IPA effect of Ticagrelor was independent of dialysis in patients with end stage renal disease and similar to healthy adults with normal renal function.

Figure 7 - Impact of intrinsic factors on the pharmacokinetics of ticagrelor



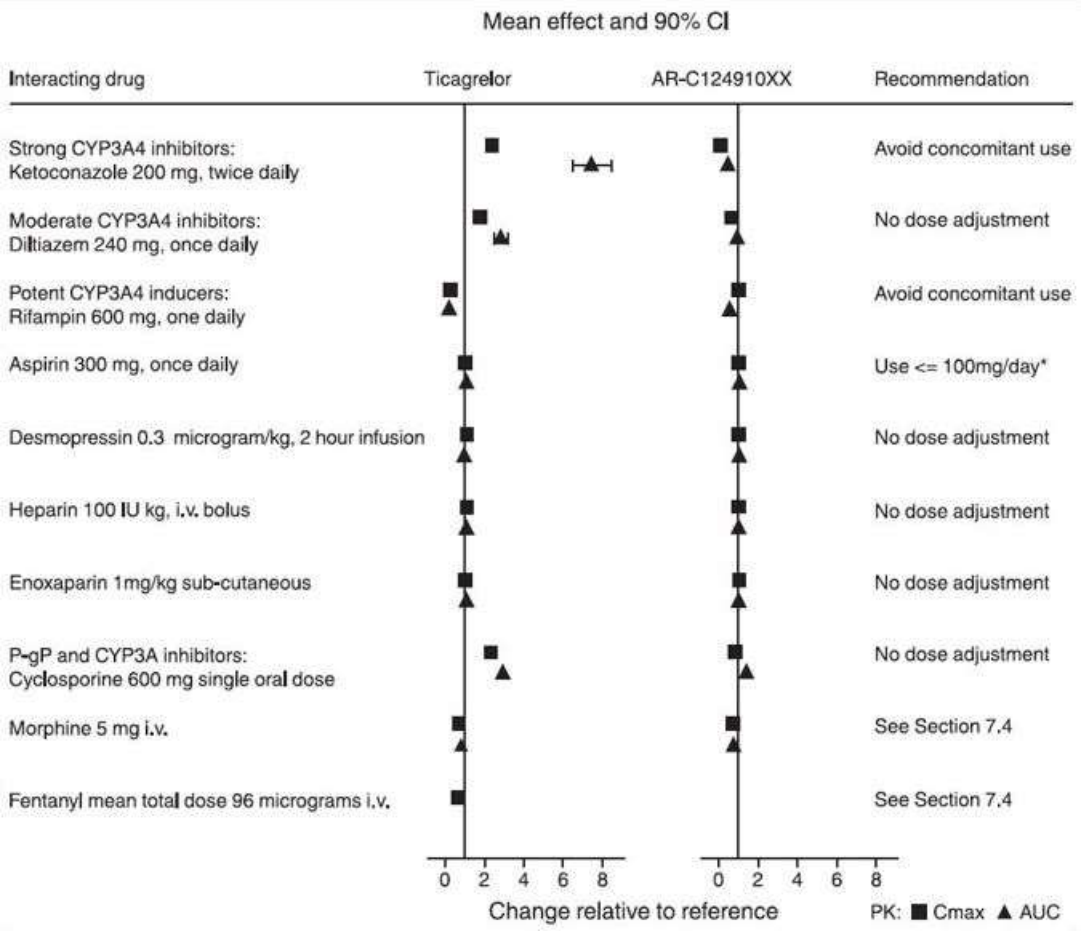
Effects of Other Drugs on Ticagrelor

CYP3A4 is the major enzyme responsible for ticagrelor metabolism and the formation of its major active metabolite. The effects of other drugs on the pharmacokinetics of ticagrelor are presented in Figure 8 as change relative to ticagrelor given alone (test/reference). Strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, and clarithromycin) substantially increase ticagrelor exposure. Moderate CYP3A inhibitors have lesser effects (e.g., diltiazem). CYP3A inducers (e.g., rifampin) substantially reduce ticagrelor blood levels. P-gp inhibitors (e.g., cyclosporine) increase ticagrelor exposure.

Co-administration of 5 mg intravenous morphine with 180 mg loading dose of ticagrelor decreased observed mean ticagrelor exposure by up to 25% in healthy adults and up to 36% in ACS patients undergoing PCI. t_{max} was delayed by 1-2 hours. Exposure of the active metabolite decreased to a similar extent. Morphine co-administration did not delay or decrease platelet inhibition in healthy adults. Mean platelet aggregation was higher up to 3 hours post loading dose in ACS patients co-administered with morphine.

Co-administration of intravenous fentanyl with 180 mg loading dose of ticagrelor in ACS patients undergoing PCI resulted in similar effects on ticagrelor exposure and platelet inhibition.

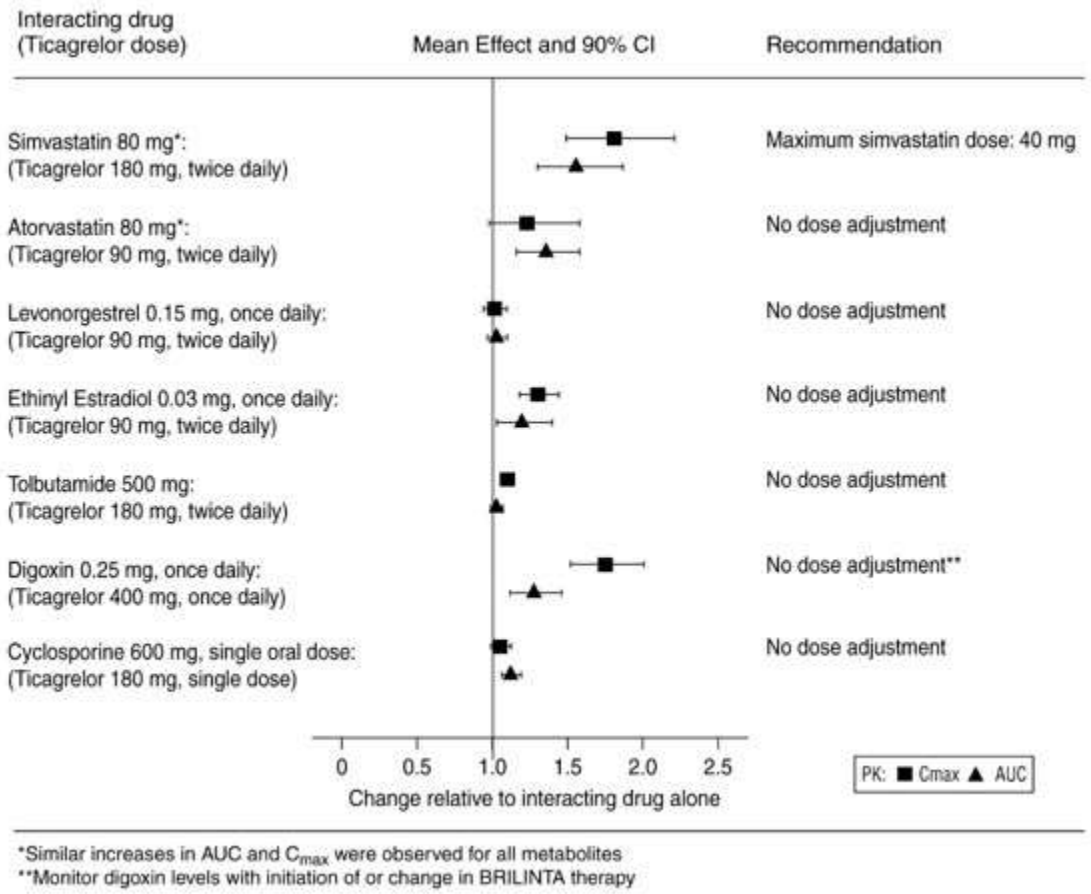
Figure 8 - Effect of co-administered drugs on the pharmacokinetics of ticagrelor



Effects of Ticagrelor on Other Drugs

In vitro metabolism studies demonstrate that ticagrelor and its major active metabolite are weak inhibitors of CYP3A4, potential activators of CYP3A5 and inhibitors of the P-gp transporter. Ticagrelor and AR-C124910XX were shown to have no inhibitory effect on human CYP1A2, CYP2C19, and CYP2E1 activity. For specific in vivo effects on the pharmacokinetics of simvastatin, atorvastatin, ethinyl estradiol, levonorgestrel, tolbutamide, digoxin and cyclosporine, see Figure 9.

Figure 9 - Impact of Ticagrelor on the pharmacokinetics of co-administered drugs



*Similar increases in AUC and C_{max} were observed for all metabolites
**Monitor digoxin levels with initiation of or change in BRILINTA therapy

5.3 Preclinical safety Data

Carcinogenesis

Ticagrelor was not carcinogenic in the mouse at doses up to 250 mg/kg/day or in the male rat at doses up to 120 mg/kg/day (19 and 15 times the MRHD of 90 mg twice daily on the basis of AUC, respectively). Uterine carcinomas, uterine adenocarcinomas and hepatocellular adenomas were seen in female rats at doses of 180 mg/kg/day (29-fold the maximally recommended dose of 90 mg twice daily on the basis of AUC), whereas 60 mg/kg/day (8-fold the MRHD based on AUC) was not carcinogenic in female rats.

Mutagenesis

Ticagrelor did not demonstrate genotoxicity when tested in the Ames bacterial mutagenicity test, mouse lymphoma assay and the rat micronucleus test. The active O-demethylated metabolite did not demonstrate genotoxicity in the Ames assay and mouse lymphoma assay.

Impairment of Fertility

Ticagrelor had no effect on male fertility at doses up to 180 mg/kg/day or on female fertility at doses up to 200 mg/kg/day (>15-fold the MRHD on the basis of AUC). Doses of ≥10 mg/kg/day given to female rats caused an increased incidence of irregular duration estrus cycles (1.5-fold the MRHD based on AUC).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol {Mannogem)

Dicalcium Phosphate Dihydrate (Calipharm D)

Croscarmellose Sodium

Hydroxy propyl cellulose

Magnesium Stearate

Opadry Yellow-036520034

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months from the date of manufacture

6.4 Special precautions for storage

Store below 30°C. Keep out of reach of children.

6.5 Nature and contents of container

Alu-Alu blister pack of 10 Tablets. Such 3 blisters are packed in carton along with pack insert

6.6 Special precautions for disposal and other handling

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

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE ADDRESSES

MICRO LABS LIMITED

31, Race course road

Bangalore-560001

INDIA

8. MARKETING AUTHORISATION NUMBER

--

9. DATE OF FIRST REGISTRATION/RENEWAL OF THE REGISTRATION

--

10. DATE OF REVISION OF THE TEXT

Feb 2023

11. DOSIMETRY (IF APPLICABLE)

Not applicable

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)

Not applicable

13. DOCUMENT REVISION HISTORY

--