



TICAGRELOR

TIGLOR

90 mg Film-Coated Tablet

Antithrombotic Agent (Platelet Aggregation Inhibitor)

PRODUCT NAME:
TICAGRELOR

DOSAGE FORM AND STRENGTH:
Ticagrelor Tablets 90 mg

PHARMACOLOGIC CATEGORY:
Antithrombotic Agent (Platelet Aggregation Inhibitor)

PRODUCT DESCRIPTION:
Yellow, round, biconvex film coated tablets debossed with 'T' above '90' on one face and plain on other surface

FORMULATION/COMPOSITION:
Each film-coated tablet contains:
Ticagrelor 90 mg

PHARMACODYNAMICS/PHARMACOKINETICS:

Mechanism of Action

Ticagrelor and its major metabolite reversibly interact with the platelet P2Y12 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 μ M 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 μ M ADP.

Pharmacokinetics

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

Absorption

Ticagrelor Tablets 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 Tablets 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 $t_{1/2}$ is approximately 7 hours for ticagrelor and 9 hours for the active metabolite.

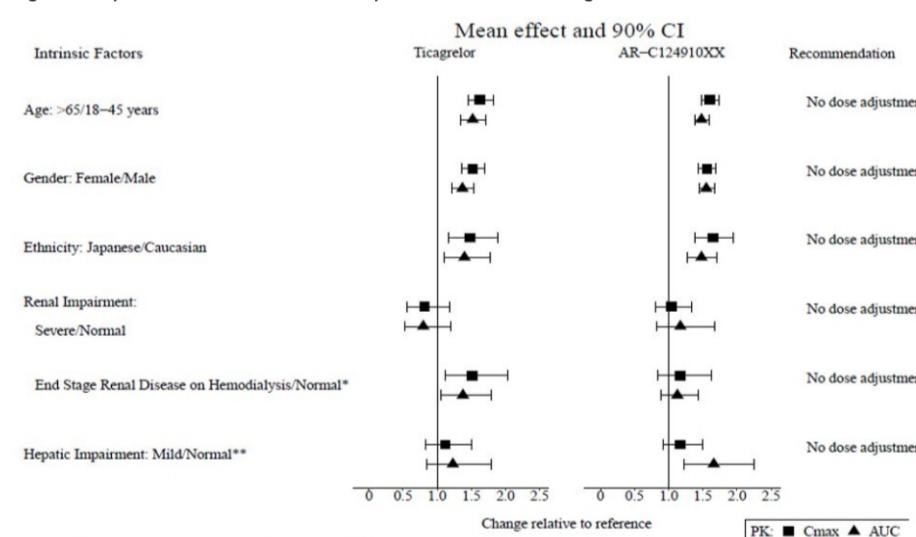
Specific Populations

The effects of age, gender, ethnicity, renal impairment and mild hepatic impairment on the pharmacokinetics of ticagrelor are presented in Figure 1. 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 Tablets 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 Tablets was administered immediately prior to dialysis showing that Ticagrelor Tablets is not dialyzable. Exposure of the active metabolite increased to a lesser extent. The IPA effect of Ticagrelor Tablets was independent of dialysis in patients with end stage renal disease and similar to healthy adults with normal renal function.

Figure 1 - Impact of intrinsic factors on the pharmacokinetics of ticagrelor



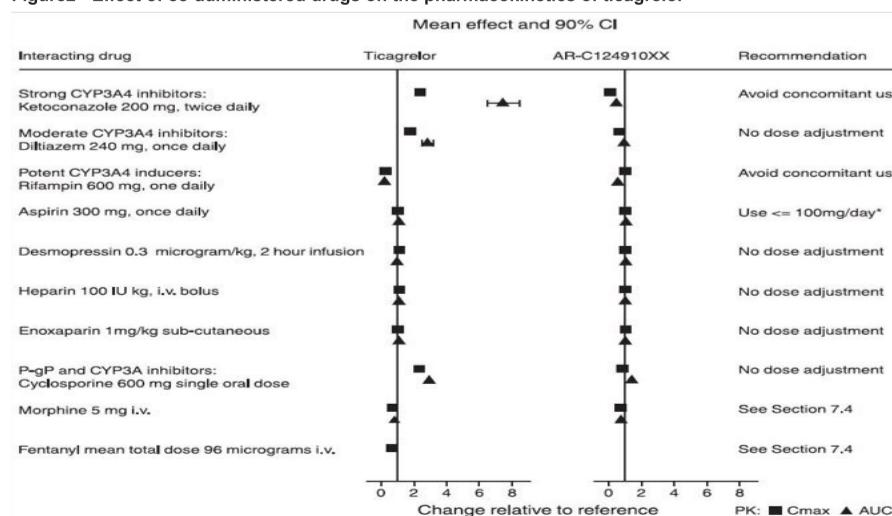
* Single dose of BRILINTA administered on a day without dialysis.

** BRILINTA has not been studied in patients with moderate or severe hepatic impairment.

Effects of Other Drugs on Ticagrelor Tablets

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 2 as change relative to ticagrelor given alone (test/reference). Strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, and clarithromycin) substantially increase ticagrelor exposure. Moderate CYP3A4 inhibitors have lesser effects (e.g., diltiazem). CYP3A4 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's 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 2 - Effect of co-administered drugs on the pharmacokinetics of ticagrelor

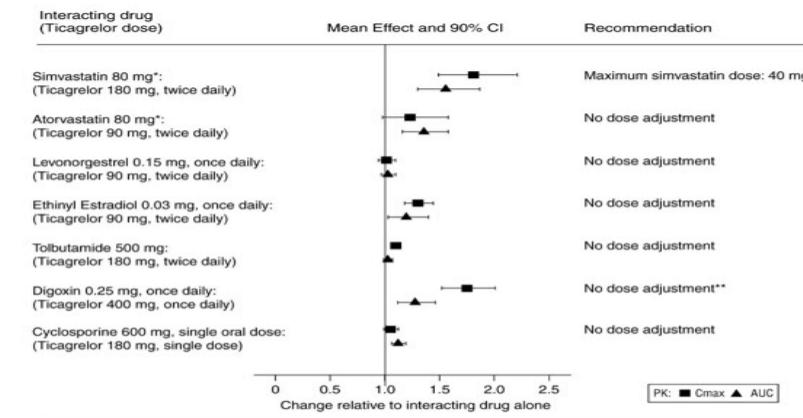


Effects of Ticagrelor Tablets on Other Drugs

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 3.

Figure 3 - Impact of Ticagrelor Tablets 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

Pharmacogenetics

In a genetic substudy cohort of PLATO, the rate of thrombotic CV events in the Ticagrelor Tablets arm did not depend on CYP2C19 loss of function status.

INDICATIONS:

Acute Coronary Syndrome or a History of Myocardial Infarction

Ticagrelor Tablets 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 Tablets 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 Tablets 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 Tablets was established in a population with type 2 diabetes mellitus (T2DM).

Acute Ischemic Stroke or Transient Ischemic Attack (TIA)

Ticagrelor Tablets 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).

DOSAGE AND MODEL ROUTE OF ADMINISTRATION:

Acute Coronary Syndrome or a History of Myocardial Infarction

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

Use Ticagrelor Tablets with a daily maintenance dose of aspirin of 75 to 100 mg [see WARNINGS AND PRECAUTIONS and CLINICAL STUDIES].

Coronary Artery Disease but No Prior Stroke or Myocardial Infarction

Administer 60 mg of Ticagrelor Tablets twice daily. For all patients with ACS see DOSAGE AND ADMINISTRATION

Use Ticagrelor Tablets with a daily maintenance dose of aspirin of 75 to 100 mg [see WARNINGS AND PRECAUTIONS and CLINICAL STUDIES].

Acute Ischemic Stroke or Transient Ischemic Attack (TIA)

Initiate treatment with a 180 mg loading dose of Ticagrelor Tablets and then continue with 90 mg twice daily for up to 30 days.

The treatment effect accrues early in the course of therapy.

Use Ticagrelor Tablets with a loading dose of aspirin (300 to 325 mg) and a daily maintenance dose of aspirin of 75 to 100 mg [see WARNINGS AND PRECAUTIONS and CLINICAL STUDIES].

Pediatric Use

The safety and effectiveness of Ticagrelor Tablets 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 Tablets in patients with severe hepatic impairment. There is limited experience with Ticagrelor Tablets 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 Hemodialysis

Clinical efficacy and safety studies with Ticagrelor Tablets 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.

Administration

A patient who misses a dose of Ticagrelor Tablets 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 Tablets with another oral P2Y₁₂ platelet inhibitor.

CONTRAINDICATIONS & PRECAUTION(S), WARNING(S):

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.

PRECAUTIONS & WARNINGS:

General 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 Tablets in such patients is not recommended.

Concomitant Aspirin Maintenance Dose for Patients Being Treated for ACS

In the management of patients with ACS, the use of Ticagrelor Tablets with maintenance doses of aspirin above 100 mg decreased the effectiveness of Ticagrelor Tablets. In such patients, use a maintenance dose of aspirin of 75–100 mg.

Dyspnea

In clinical trials, about 14% (PLATO and PEGASUS) to 21% (THEMIS) of patients treated with Ticagrelor Tablets 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% (PLATO), 1.0% (THEMIS), 4.3% (PEGASUS), and 6.9% (THEMIS) of patients.

In a substudy 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 Tablets, no specific treatment is required; continue Ticagrelor Tablets without interruption if possible. In

Size: 280 (L) x 420 (H) mm

Folding size: 35 x 65 mm

Carton size: 38 x 27 x 87 mm

Bible Paper 40 gsm

Back

INTERACTIONS:**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 P2Y12 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.

ADVERSE EFFECTS:**Summary of the safety profile**

The safety profile of Ticagrelor has been evaluated in two large phase 3 outcome trials (PLATO and PEGASUS) including more than 39,000 patients.

In PLATO, patients on Ticagrelor had a higher incidence of discontinuation due to adverse events than clopidogrel (7.4% vs. 5.4%). In PEGASUS, patients on Ticagrelor had a higher incidence of discontinuation due to adverse events compared to ASA therapy alone (16.1% for Ticagrelor 60 mg with ASA vs. 8.5% for ASA therapy alone). The most commonly reported adverse reactions in patients treated with Ticagrelor were bleeding and dyspnoea.

Tabulated list of adverse reactions: The following adverse reactions have been identified following studies or have been reported in post-marketing experience with Ticagrelor (Table 1).

Adverse reactions are listed by MedDRA and System Organ Class (SOC). Within each SOC the adverse reactions are ranked by frequency category. Frequency categories are defined according to the following conventions: Very common ($\geq 1/10$), common ($>1/100$ to $<1/10$), uncommon ($\geq 1/1,000$ to $<1/100$), rare ($\geq 1/10,000$ to $<1/1,000$), very rare ($<1/10,000$), not known (cannot be estimated from the available data).

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

System Organ Classification	Very Common	Common	Uncommon
Neoplasms benign, malignant and unspecified (including cysts and polyps)			Tumour bleedings ^a
Blood and lymphatic system disorders	Blood disorder bleedings ^b		
Immune system disorders			Hypersensitivity including angioedema ^c
Metabolism and nutrition disorders	Hyperuricaemia ^d	Gout/Gouty Arthritis	
Psychiatric disorders			Confusion
Nervous system disorders		Dizziness, Syncope, Headache	Intracranial haemorrhage
Eye disorders			Eye haemorrhage ^e
Ear and labyrinth disorders		Vertigo	Ear haemorrhage
Vascular disorders		Hypotension	
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Respiratory system bleedings ^f	
Gastrointestinal disorders		Gastrointestinal haemorrhage ^g , Diarrhoea, Nausea, Dyspepsia, Constipation	Retroperitoneal haemorrhage
Skin and subcutaneous tissue disorders		Subcutaneous or dermal bleeding ^h , Rash, Pruritus	
Musculoskeletal connective tissue and bone			Muscular bleedings ⁱ
Renal and urinary disorders		Urinary tract bleeding ^j	
Reproductive system and breast disorders			Reproductive system bleedings ^k
Investigations		Blood creatinine increased ^l	
Injury, poisoning and procedural complications		Post procedural haemorrhage, Traumatic bleedings ^m	

^ae.g. bleeding from bladder cancer, gastric cancer, colon cancer

^be.g. increased tendency to bruise, spontaneous haematoma, haemorrhagic diathesis

^cIdentified in post-marketing experience

^dFrequencies derived from lab observations (Uric acid increases to $>$ upper limit of normal from baseline below or within reference range. Creatinine increases of $>50\%$ from baseline.) and not crude adverse event report frequency.

^ee.g. conjunctival, retinal, intraocular bleeding

^fe.g. epistaxis, haemoptysis

^ge.g. gingival bleeding, rectal haemorrhage, gastric ulcer haemorrhage

^he.g. ecchymosis, skin haemorrhage, petechial

ⁱe.g. haemarthrosis, muscle haemorrhage

^je.g. haematuria, cystitis haemorrhagic

^ke.g. vaginal haemorrhage, haematospermia, postmenopausal haemorrhage

^le.g. contusion, traumatic haematoma, traumatic haemorrhage

Description of selected adverse reactions**Bleeding****Bleeding findings in PLATO**

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

Table 2 –Analysis of overall bleeding events, Kaplan-Meier estimates at 12 months (PLATO)

	Ticagrelor 90 mg twice daily N=9235	Clopidogrel N=9186	p-value*
PLATO Total Major	11.6	11.2	0.4336
PLATO Major Fatal/Life-Threatening	5.8	5.8	0.6988
Non-CABG PLATO Major	4.5	3.8	0.0264
Non-Procedural PLATO Major	3.1	2.3	0.0058
PLATO Total Major + Minor	16.1	14.6	0.0084
Non-Procedural PLATO Major + Minor	5.9	4.3	<0.0001
Timi-defined Major	7.9	7.7	0.5669
Timi-defined Major + Minor	11.4	10.9	0.3272

Bleeding category definitions:

Major Fatal/Life-threatening Bleed: Clinically apparent with >50 g/l decrease in haemoglobin or ≥ 4 red cell units transfused; or fatal; or intracranial; or intrapericardial with cardiac tamponade; or with hypovolaemic shock or severe hypotension requiring pressors or surgery.

Major Other: Clinically apparent with 30–50 g/L decrease in haemoglobin or 2–3 red cell units transfused; or significantly disabling.

Minor Bleed: Requires medical intervention to stop or treat bleeding.

Timi Major Bleed: Clinically apparent with >50 g/l decrease in haemoglobin or intracranial haemorrhage.

Timi Minor Bleed: Clinically apparent with 30–50 g/l decrease in haemoglobin.

*p-value calculated from Cox proportional hazards model with treatment group as the only explanatory variable.

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

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

CABG-related bleeding: In PLATO, 42% of the 1584 patients (12% of cohort) who underwent coronary artery bypass graft (CABG) surgery had a PLATO Major Fatal/Life-threatening bleeding with no difference between treatment groups. Fatal CABG bleeding occurred in 6 patients in each treatment group.

Non-CABG related bleeding and non-procedural related bleeding: Ticagrelor and clopidogrel did not differ in non-CABG PLATO-defined Major Fatal/Life-threatening bleeding, but PLATO-defined Total Major, Timi Major, and Timi Major + minor bleeding were more common with Ticagrelor. Similarly, when removing all procedure related bleeds, more bleeding occurred with Ticagrelor than with clopidogrel (Table 2). Discontinuation of treatment due to non-procedural bleeding was more common for Ticagrelor (2.9%) than for clopidogrel (1.2%; p<0.001).

Intracranial bleeding: There were more intracranial non-procedural bleeds with ticagrelor (n=27 bleeds in 26 patients, 0.3%) than with clopidogrel (n=14 bleeds, 0.2%), of which 11 bleeds with ticagrelor and 1 with clopidogrel were fatal. There was no difference in overall fatal bleeds.

Bleeding findings in PEGASUS

Overall outcome of bleeding events in the PEGASUS study are shown in Table 3.

Table 3 –Analysis of overall bleeding events, Kaplan-Meier estimates at 36 months (PEGASUS)

	Ticagrelor 60 mg twice daily + ASA N=6958	ASA alone N=6996		
Safety Endpoints	KM%	Hazard Ratio (95% CI)	KM%	p-value

TIMI-defined bleeding categories				
Timi Major	2.3	2.32 (1.68, 3.21)	1.1	<0.0001
Fatal	0.3	1.00 (0.44, 2.27)	0.3	1.0000
ICH	0.6	1.33 (0.77, 2.31)	0.5	0.3130
Other Timi Major	1.6	3.61 (2.31, 5.65)	0.5	<0.0001
Timi Major or Minor	3.4	2.54 (1.93, 3.35)	1.4	<0.0001
Timi Major or Minor or Requiring medical attention	16.6	2.64 (2.35, 2.97)	7.0	<0.0001

PLATO-defined bleeding categories				
PLATO Major	3.5	2.57 (1.95, 3.37)	1.4	<0.0001
Fatal/Life-threatening	2.4	2.38 (1.73, 3.26)	1.1	<0.0001
Other PLATO Major	1.1	3.37 (1.95, 5.83)	0.3	<0.0001
PLATO Major or Minor	15.2	2.71 (2.40, 3.08)	6.2	<0.0001

Bleeding category definitions:

Timi Major: Fatal bleeding, OR any intracranial bleeding, OR clinically overt signs of haemorrhage associated with a drop in haemoglobin (Hgb) of ≥ 50 g/L, or when Hgb is not available, a fall in haematocrit (Hct) of 15%.

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

ICH: Intracranial haemorrhage.

Other Timi Major: Non-fatal non-ICH Timi major bleeding.

Timi Minor: Clinically apparent with 30–50 g/L decrease in haemoglobin.

Timi Requiring medical attention: Requiring intervention, OR leading to hospitalisation, OR prompting evaluation.

PLATO Major Fatal/Life-threatening: Fatal bleeding, OR any intracranial bleeding, OR intrapericardial with cardiac tamponade, OR with hypovolaemic shock or severe hypotension requiring pressors/inotropes or surgery OR clinically apparent with >50 g/L decrease in haemoglobin or ≥ 4 red cell units transfused.

PLATO Major Other: Significantly disabling, OR clinically apparent with 30–50 g/L decrease in haemoglobin, OR 2–3 red cell units transfused.

PLATO Minor: Requires medical intervention to stop or treat bleeding.

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 only a minor increase was observed in intracranial haemorrhages, as compared to ASA therapy alone. There were few fatal bleeding events in the study, 11 (0.3%) for ticagrelor 60 mg and 12 (0.3%) for ASA therapy alone. The observed increased risk of Timi Major bleeding with ticagrelor 60 mg was primarily due to a higher frequency of Other Timi Major bleedings driven by events in the gastrointestinal SOC.

Increased bleeding patterns similar to Timi Major were seen for Timi

MICRO LABS LIMITED, BANGALORE, INDIA

1	Product Name	Tiglor	<u>Colours Used</u>						
2	Strength	90 mg	 BLACK						
3	Component	Leaflet							
4	Category	Export - Philippines							
5	Dimension	280 (L) x 420 (H) mm							
6	Artwork Code	EXG-ML01I-1749							
7	Pharma Code	N/A							
8	Reason for Change	New Artwork	<u>Colours not for Printing</u>  Keylines						
Prepared by (DTP)		Approved by							
Sign	Kantharaju L.	Head CQA		Head Production/ Packing (Site)		Head QC (Site)		Head QA (Site)	
Date	27-01-2022								