

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF MEDICINAL PRODUCT

TALDEROL® 90 mg film coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Ingredient:

Ticagrelor 90 mg

Excipients:

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Film coated tablet

Yellow, round, biconvex film-coated tablet

4. CLINICAL CHARACTERISTICS

4.1 Therapeutic indications

TALDEROL®, administered in combination with acetylsalicylic acid (ASA) or as monotherapy after the first 3 months of use in combination with ASA, is recommended for acute use, including patients under medical supervision and patients treated with percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG). It is indicated for the prevention of thrombotic events (cardiovascular death, myocardial infarction and stroke) in patients with coronary syndromes (with unstable angina, non-ST elevation myocardial infarction [NSTEMI], or ST elevation myocardial infarction [STEMI]). See section 5.1 for more information.

4.2 Posology and method of administration

Posology/frequency and duration of administration:

TALDEROL® treatment is initiated with a single 180 mg loading dose (two 90 mg tablets) and continued with 90 mg twice daily.

Patients taking TALDEROL® should also use one dose of ASA per day unless specifically contraindicated. Following the initial dose of ASA, TALDEROL® should be used together with a maintenance dose of 75-150 mg of ASA (See Section 5.1).

Interruptions in treatment should be avoided. Patients who forget to take a dose of TALDEROL® should take only one 90 mg tablet (next dose) at the scheduled time.

In patients diagnosed with acute coronary syndrome (ACS), direct transition from clopidogrel to TALDEROL® can be made if necessary (See Section 5.1). Switching from prasugrel to TALDEROL® has not been studied.

Unless clinically necessary to discontinue treatment, treatment with TALDEROL® for at least 12 months is recommended (see section 5.1).

In patients with ACS, premature discontinuation of treatment with any antiplatelet, including TALDEROL®, may result in an increased risk of cardiovascular death or myocardial infarction due to the patient's underlying disease (see section 4.4). Therefore, early discontinuation of treatment should be avoided.

Method of administration:

For oral use.

TALDEROL® can be taken with or without food.

For patients who cannot swallow the tablet whole, TALDEROL® tablets can be crushed into a fine powder, mixed with half a glass of water and drunk immediately. To make sure that there is no medicine left at the bottom, you should rinse the empty glass with half a glass of water and drink it. The mixture can also be administered via nasogastric tube (CH8 or larger). After applying the mixture, it is important to rinse the nasogastric tube with water to ensure that there is no medication left in it.

Additional information for special populations:

Kidney Failure

Dosage adjustment is not required in patients with renal impairment (See section 5.2).

Liver Failure

Ticagrelor has not been studied in patients with severe hepatic impairment and its use is contraindicated in these patients (see section 4.3). Limited information is available on the treatment of patients with moderate hepatic impairment. No dose adjustment is necessary, but ticagrelor should be used with caution (see sections 4.4 and 5.2). No dose adjustment is necessary in patients with mild hepatic impairment (see sections 4.4 and 5.2).

Pediatric population

The efficacy and safety of ticagrelor in children under 18 years of age have not been established. There is no relevant use of ticagrelor in children with sickle cell disease (see sections 5.1 and 5.2).

Geriatric Population

There is no need for dose adjustment in the elderly (See section 5.2).

4.3 Contraindications

- Hypersensitivity to the active substance or other excipients (See Section 4.8)
- Active pathological bleeding
- History of intracranial hemorrhage (See Section 4.8)
- Severe liver failure (See Sections 4.2, 4.4 and 5.2)
- Concomitant use of ticagrelor with strong CYP3A4 inhibitors (e.g. ketoconazole, clarithromycin, nefazodone, ritonavir and atazanavir) as concomitant administration may

result in a significant increase in ticagrelor exposure (See Section 4.5)

- **Special usage warnings and precautions**

Bleeding risk

The use of ticagrelor in patients with a known increased risk of bleeding should be balanced against the benefit of preventing atherothrombotic events (see sections 4.8 and 5.1). If clinically indicated, ticagrelor should be used with caution in the following patient groups:

- Patients with bleeding tendencies (e.g., recent trauma, recent surgery, coagulation diseases, active or recent gastrointestinal bleeding) or patients at high risk of trauma. The use of ticagrelor is contraindicated in patients with active pathological bleeding and in those with a history of intracranial haemorrhage and severe hepatic impairment (see section 4.3).
- Patients using concomitant medications that increase the risk of bleeding (e.g., nonsteroidal anti-inflammatory drugs (NSAIDs), oral anticoagulants and/or fibrinolytics) within 24 hours after the ticagrelor dose.

Platelet transfusion does not reverse the antiplatelet effect of ticagrelor in healthy volunteers and is unlikely to provide clinical benefit in bleeding patients. Since co-administration of ticagrelor with desmopressin does not shorten baseline bleeding time, desmopressin is not expected to be effective in treating clinical bleeding events (see section 4.5).

Antifibrinolytic therapy (aminocaproic acid or tranexamic acid) and/or recombinant factor VIIa therapy may improve hemostasis. Once the cause of bleeding is identified and controlled, ticagrelor treatment can be restarted.

Surgical

Patients should be educated to inform their physicians and dentists that they are taking ticagrelor before any surgical procedure and before using any new medicinal product.

Patients in the PLATO study undergoing coronary artery bypass graft (CABG) surgery experienced more bleeding when ticagrelor was discontinued 1 day before surgery compared to clopidogrel, but rates of major bleeding were similar to clopidogrel when treatment was discontinued 2 days or more before surgery (See Section 4.8). . If the patient is to undergo elective surgery and an antiplatelet effect is not desired, ticagrelor should be discontinued 5 days before surgery (See Section 5.1).

Patients who have had a previous ischemic stroke

ACS patients with a previous ischemic stroke can be treated with ticagrelor for up to 12 months (PLATO study).

Patients with a history of MI who had a previous ischemic stroke were not included in the PEGASUS study. Therefore, treatment beyond one year is not recommended in these patients due to lack of data.

Liver failure

The use of ticagrelor is contraindicated in patients with severe hepatic impairment (see

sections 4.2 and 4.3). Experience with ticagrelor in patients with moderate hepatic impairment is limited, so caution is advised in these patients (see section 4.2 and Section 5.2).

Patients at risk for bradycardic events

Holter ECG monitoring has shown an increased frequency of ventricular pauses, which are often asymptomatic, during treatment with ticagrelor compared to clopidogrel. Patients at increased risk of bradycardic events (e.g., patients without a pacemaker with sick sinus syndrome, 2nd or 3rd degree AV block, or bradycardia-induced syncope) were excluded from main studies evaluating the efficacy and safety of ticagrelor. Therefore, due to limited clinical experience in these patients, caution should be exercised (see section 5.1).

Additionally, caution should be exercised when ticagrelor is administered concomitantly with medicinal products known to induce bradycardia. However, in the PLATO study, no evidence of clinically significant adverse reactions was observed following concomitant administration of one or more medicinal products known to induce bradycardia (e.g. beta-blockers in 96%, calcium channel blockers diltiazem and verapamil in 33% and digoxin in 4%) (see section 4.4). Section 4.5).

During the Holter substudy in PLATO, ventricular pauses of ≥ 3 seconds occurred in more patients with ticagrelor than with clopidogrel during the acute phase of ACS. During the acute phase of ACS, the increase in Holter-detected ventricular pauses with ticagrelor was greater in patients with chronic heart failure (CHF) than in the general population, but was not observed with ticagrelor at one month or compared with clopidogrel. No adverse clinical outcomes (including syncope or pacemaker application) associated with this imbalance have been identified in this patient population (See Section 5.1).

Bradyarrhythmic events and AV blocks have been reported postmarketing in patients with ACS receiving ticagrelor, particularly those with potential confounders of cardiac ischemia and drugs that reduce heart rate or affect cardiac conduction (see section 4.8). The patient's clinical condition and concomitant medications should be evaluated as potential confounding factors before adjusting the treatment.

Dyspnea

Dyspnea has been reported in patients treated with ticagrelor. Its severity generally ranged from mild to moderate and often resolved without requiring discontinuation of treatment. The absolute risk of experiencing dyspnea may be increased with ticagrelor in patients with Asthma/Chronic Obstructive Pulmonary Disease (COPD) (see section 4.8). Ticagrelor should be used with caution in patients with a history of asthma and/or COPD. The mechanism has not yet been elucidated. If a patient reports new, prolonged or worsening dyspnoea, this should be evaluated in detail and, if not tolerated, ticagrelor treatment should be discontinued. See Section 4.8 for more information.

Central sleep apnea

Central sleep apnea, including Cheyne-Stokes respiration, has been reported in the post-marketing setting in patients receiving ticagrelor. If central sleep apnea is suspected, further clinical evaluation should be considered.

Creatinine elevations

Creatinine levels may increase during treatment with ticagrelor. The mechanism has not yet

been elucidated. Renal functions should be checked according to routine medical practice. In patients with ACS, it is recommended to check renal function one month after starting treatment with ticagrelor, with particular caution being exercised in patients aged ≥ 75 years, in patients with moderate or severe renal impairment, and in patients receiving concomitant therapy with an angiotensin receptor blocker (ARB).

Increased uric acid

Hyperuricemia may occur during treatment with ticagrelor (see section 4.8). Caution is advised in patients with a history of hyperuricemia or gouty arthritis. As a precautionary measure, the use of ticagrelor is not recommended in patients with uric acid nephropathy.

Thrombotic Thrombocytopenic Purpura (TTP)

Thrombotic Thrombocytopenic Purpura (TTP) has been reported very rarely with the use of ticagrelor. It is characterized by thrombocytopenia and microangiopathic hemolytic anemia, which may be associated with neurological findings, renal dysfunction, or fever. TTP is a potentially fatal condition that requires emergency treatment, including plasmapheresis.

Interference with platelet function tests used to diagnose heparin-induced thrombocytopenia (HIT)

In the heparin-induced platelet activation (HIPA) test used to diagnose HIT, anti-platelet factor 4/heparin antibodies present in the patient's serum activate the platelets of healthy donors in the presence of heparin.

False-negative results on platelet function tests used for HIT (including, but not limited to, HIPA testing) have been reported in patients administered ticagrelor. This is related to the inhibition of the P2Y₁₂ receptor on platelets from healthy donors included in the test by ticagrelor in the patient's serum/plasma. For interpretation of HIT platelet function tests, it is necessary to provide information about concurrent treatment with ticagrelor.

In patients who develop HIT, the benefit-risk assessment of continuing treatment with ticagrelor should be made taking into account both the prothrombotic state of HIT and the increased risk of bleeding during concurrent anticoagulant and ticagrelor therapy.

Other

Based on an association observed in the PLATO study, which investigated the relative efficacy of ticagrelor compared to maintenance ASA dose and clopidogrel, concurrent administration of ticagrelor and a high maintenance dose of ASA above 300 mg is not recommended (see section 5.1).

Early discontinuation of treatment

Early discontinuation of any antiplatelet therapy, including TALDEROL®, may result in an increased risk of cardiovascular (CV) death, MI, or stroke depending on the patient's underlying disease. Therefore, early discontinuation of treatment should be avoided.

• Interactions with other medicinal products and other forms of interaction

Ticagrelor is primarily a CYP3A4 substrate and a weak CYP3A4 inhibitor. Ticagrelor is also a P-glycoprotein (P-gp) substrate and a weak P-gp inhibitor and therefore may increase exposure to P-gp substrates.

Effect of medicinal and other products on ticagrelor

CYP3A4 inhibitors

- Strong CYP3A4 inhibitors - Co-administration of ketoconazole with ticagrelor increased the C_{max} and AUC of ticagrelor by 2.4-fold and 7.3-fold, respectively, and the C_{max} and AUC of the active metabolite decreased by 89% and 56%, respectively. Other strong CYP3A4 inhibitors (clarithromycin, nefazadone, ritonavir and atazanavir) are expected to have similar effects and therefore concomitant use of strong CYP3A4 inhibitors with ticagrelor is contraindicated (See Section 4.3).
- Moderate CYP3A4 inhibitors - Co-administration of diltiazem with ticagrelor increased the C_{max} of ticagrelor by 69% and the AUC by 2.7-fold, and decreased the C_{max} of the active metabolite by 38%, leaving the AUC value unchanged. Ticagrelor has no effect on diltiazem plasma levels. Other moderate CYP3A4 inhibitors (e.g., amprenavir, aprepitant, erythromycin, and fluconazole) are expected to have a similar effect and may be administered concurrently with ticagrelor.
- A 2-fold increase in ticagrelor exposure was observed after consuming high amounts of grapefruit juice (3x200 ml) per day. An increase in exposure of this magnitude is not expected to be clinically significant in most patients.

CYP3A4 inducers

Coadministration of rifampicin with ticagrelor decreased the C_{max} and AUC of ticagrelor by 73% and 86%, respectively. The C_{max} value of the active metabolite remained unchanged and the AUC value

It decreased by 46%. Other CYP3A4 inducers (e.g., phenytoin, carbamazepine, and phenobarbital) are expected to reduce exposure to ticagrelor. Coadministration of ticagrelor with strong CYP3A inducers may decrease ticagrelor exposure and efficacy; Therefore, concurrent administration with ticagrelor is not preferred.

Cyclosporine (P-gp and CYP3A inhibitor)

Concomitant administration of cyclosporine (600 mg) with ticagrelor increased the C_{max} and AUC of ticagrelor by 2.3- and 2.8-fold, respectively. In the presence of cyclosporine, the AUC of the active metabolite increased by 32%, while C_{max} decreased by 15%.

No data are available regarding the concurrent use of ticagrelor with other active substances that are strong P-glycoprotein (P-gp) inhibitors and moderate CYP3A4 inhibitors (e.g. verapamil, quinidine), which may also increase ticagrelor exposure. If this relationship cannot be avoided, caution should be exercised during simultaneous use.

Others

Clinical pharmacology interaction studies have shown that coadministration of ticagrelor with heparin, enoxaparin, and ASA or desmopressin had no effect on the pharmacokinetics of ticagrelor or its active metabolite or ADP-induced platelet aggregation compared to administration of ticagrelor alone. If clinically indicated, hemostasis altering medicinal products should be used with caution when administered in combination with ticagrelor.

Delayed and reduced exposure to oral P2Y₁₂ inhibitors, including ticagrelor and its active metabolite, was observed in patients with ACS treated with morphine (35% reduction in ticagrelor exposure). This interaction may be associated with reduced gastrointestinal motility and may also apply to other opioids. The clinical significance of this condition is unknown, but data indicate the potential for decreased efficacy of ticagrelor in patients receiving concomitant administration of ticagrelor and morphine. The use of a parenteral

P2Y12 inhibitor may be considered in patients with ACS where morphine cannot be stopped and rapid P2Y12 inhibition is deemed necessary.

Effect of ticagrelor on other medicinal products

Medicinal products metabolized by CYP3A4

- Simvastatin - Coadministration of ticagrelor and simvastatin increased simvastatin C_{max} by 81%, AUC by 56%, and increased simvastatin acid C_{max} by 64% and AUC by 52%, with some individual 2- to 3-fold increases. Co-administration of ticagrelor with doses of simvastatin exceeding 40 mg per day may result in adverse effects of simvastatin and such administration should be weighed against the potential benefits. Simvastatin has no effect on ticagrelor plasma levels. Ticagrelor may have a similar effect on lovastatin. Concomitant administration of ticagrelor with simvastatin or lovastatin doses above 40 mg is not recommended.
- Atorvastatin - Co-administration of atorvastatin and ticagrelor increased atorvastatin acid C_{max} by 23% and AUC by 36%. Similar increases in AUC and C_{max} were observed for all atorvastatin acid metabolites. These increases are not thought to be clinically significant.
- A similar effect on other statins metabolized by CYP3A4 cannot be excluded. Patients in the PLATO study receiving ticagrelor used a variety of statins, with 93% of the PLATO cohort receiving these medicinal products experiencing no concerns regarding statin safety.

Ticagrelor is a mild CYP3A4 inhibitor. Concomitant administration of ticagrelor and CYP3A4 substrates with a narrow therapeutic index (e.g., cisapride or ergot alkaloids) is not recommended; because ticagrelor may increase exposure to these medicinal products.

P-glycoprotein (P-gp) substrates (including digoxin, cyclosporine)

Concomitant administration of ticagrelor increased digoxin C_{max} by 75% and AUC by 28%. With concurrent administration of ticagrelor, mean trough digoxin levels are approximately

It increased by 30%, and in some people the increase reached a maximum of 2 times. The C_{max} and AUC values of ticagrelor and its active metabolite were not affected in the presence of digoxin. Therefore, appropriate clinical and/or laboratory monitoring is recommended when narrow therapeutic index and P-gp dependent drugs such as digoxin are given concomitantly with ticagrelor.

Ticagrelor had no effect on cyclosporine blood levels. The effects of ticagrelor on other P-gp substrates have not been studied.

Medicinal products metabolized by CYP2C9

Co-administration of ticagrelor with tolbutamide did not alter the plasma levels of either medicinal product, suggesting that ticagrelor is not a CYP2C9 inhibitor and will not alter the metabolism of medicinal products with CYP2C9-dependent metabolism, such as warfarin and tolbutamide.

Rosuvastatin

Ticagrelor may affect the renal excretion of rosuvastatin, increasing the risk of rosuvastatin accumulation. Although the exact mechanism is unknown, in some cases the

simultaneous use of ticagrelor and rosuvastatin leads to decreased renal function, increased CPK levels and rhabdomyolysis.

Oral contraceptives

Coadministration of ticagrelor with levonorgestrel and ethinyl estradiol increased ethinyl estradiol exposure by approximately 20%; but did not alter the pharmacokinetics of levonorgestrel. No clinically relevant effect on the effectiveness of the oral contraceptive is expected when levonorgestrel and ethinyl estradiol are co-administered with ticagrelor

Medicinal products known to cause bradycardia

Because of observations of ventricular pauses and bradycardia, which are often asymptomatic, caution should be exercised when administering ticagrelor concomitantly with drugs known to induce bradycardia (see section 4.4). However, in the PLATO study, no evidence of clinically significant adverse reactions was observed following concomitant administration of one or more medicinal products known to induce bradycardia (e.g. beta blockers 96%, calcium channel blockers diltiazem and verapamil 33% and digoxin 4%).

Other accompanying treatment

In clinical studies, when necessary for co-administration conditions, ticagrelor was commonly administered long-term with ASA, proton pump inhibitors, statins, beta blockers, angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers, as well as heparin, low molecular weight heparin and intravenous GpIIb. It has been administered for short periods in combination with /IIIa inhibitors (see section 5.1). No evidence of clinically significant adverse interactions has been observed with these medicinal products.

Concomitant administration of ticagrelor with heparin, enoxaparin, or desmopressin had no effect on activated partial thromboplastin time (aPTz), activated clotting time (aPZ), or factor Xa quantification tests. However, due to potential pharmacodynamic interactions, caution should be exercised when administering ticagrelor concurrently with medicinal products known to alter hemostasis.

Due to reports of cutaneous bleeding abnormalities with selective serotonin reuptake inhibitors (SSRIs) (e.g., paroxetine, sertraline, and citalopram), caution is advised when administering ticagrelor with SSRIs as they may increase the risk of bleeding.

• **Pregnancy and lactation**

General Advice

Gebelik kategori: C

Women with childbearing potential/Birth control (Contraception)

Women of childbearing potential who are being treated with ticagrelor should use appropriate contraception to avoid becoming pregnant..

Pregnancy Period

There are no or limited data on the use of ticagrelor in pregnant women. Studies in animals have shown reproductive toxicity (See Section 5.3). Ticagrelor is not recommended during pregnancy.

Lactation period

Pharmacodynamic/toxicological data from animals have shown that ticagrelor and its active metabolites are excreted in milk (see section 5.3). Risk for newborns/infants cannot be excluded. A decision should be made whether to discontinue breastfeeding or discontinue/avoid ticagrelor treatment, taking into account the benefits of breastfeeding for the child and the benefits of treatment for the woman.

Reproductive ability/Fertility

Ticagrelor has no effect on female or male fertility in experimental animals (See Section 5.3).

• Effects on ability to drive and use machines

Ticagrelor has no or negligible effects on the ability to drive and use machines. Dizziness and confusion have been reported during treatment with ticagrelor. Therefore, patients with these symptoms should be careful when driving or operating machinery.

• Undesirable effects

Safety profile summary

The safety profile of ticagrelor has been evaluated in two large phase 3 outcome studies (PLATO and PEGASUS) involving over 39,000 patients (see section 5.1).

In the PLATO study, patients receiving ticagrelor had a higher incidence of discontinuation due to adverse events than patients receiving clopidogrel (7.4% vs. 5.4%) In the PEGASUS study, the incidence of discontinuation due to adverse events was higher in patients treated with ticagrelor compared to ASA alone (16.1% for ticagrelor 60 mg + ASA vs 8.5% for ASA alone). The most commonly reported adverse reactions in patients treated with ticagrelor are bleeding and dyspnoea (see section 4.4).

Tabulated summary of adverse reactions

The following adverse reactions are described based on those reported following studies with ticagrelor or from post-marketing experience.

Adverse reactions are listed by MedDRA System Organ Class (SOC). Adverse reactions are listed by frequency category within each SOC and are presented in order of decreasing severity. Frequencies are defined as: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$); unknown (cannot be estimated from available data).

Benign, malignant and unspecified neoplasms (including cysts and polyps)

Uncommon: Tumor bleedinga

Blood and lymph system diseases

Very common: Bleeding blood diseaseb

Unknown: Thrombotic Thrombocytopenic Purpurac

Immune system diseases

Uncommon: Hypersensitivity reactions including angioedemac

Metabolism and nutritional diseases

Very common: Hyperuricemia

Common: Gout/Gouty arthritis

Psychiatric diseases

Uncommon: Confusion

Nervous system diseases

Common: Dizziness, syncope, headache

Uncommon: Intracranial haemorrhage

Eye diseases

Uncommon: Eye haemorrhage

Ear and inner ear diseases

Common: Vertigo

Uncommon: Ear haemorrhage

Cardiac diseases

Unknown: Bradyarrhythmia, AV blockade

Vascular diseases

Common: Hypotension

Respiratory, thoracic disorders and mediastinal diseases

Very common: Dyspnea

Common: Respiratory system bleeding

Gastrointestinal diseases

Common: Gastrointestinal haemorrhage, diarrhoea, nausea, dyspepsia, constipation

Uncommon: Retroperitoneal haemorrhage

Skin and subcutaneous tissue diseases

Common: Subcutaneous or skin bleeding, itching, rash

Musculoskeletal disorders, connective tissue and bone diseases

Uncommon: Bleeding in the muscle

Kidney and urinary tract diseases

Common: Bleeding in the urinary tract

Reproductive system and breast diseases

Uncommon: Reproductive system bleeding

Studies

Common: Increased blood creatinine level

Injury and poisoning and procedural complications

Common: Post-procedural haemorrhage, traumatic bleeding

e.g.; bleeding due to bladder cancer, gastric cancer, colon cancer.

b e.g.; Increased tendency to bruising, spontaneous hematoma, hemorrhagic diathesis.

c Diagnosed post-marketing experience
d Frequencies derived from laboratory observations (initially below the reference range or Increase in uric acid from the value within the reference range > upper limit of normal. from the beginning
>50% creatinine increases) and is not the crude adverse event reporting frequency.
e.g.; conjunctival, retinal, intraocular hemorrhage.
f e.g.; nosebleed, hemoptysis.
g e.g.; gum bleeding, rectal hemorrhage, gastric ulcer hemorrhage.
h e.g.; ecchymosis, skin haemorrhage, petechiae, e.g.; hemarthrosis, muscle hemorrhage.
j e.g.; hematuria, hemorrhagic cystitis.
k e.g.; vaginal hemorrhage, hematospermia, post-menopausal hemorrhage.
l e.g.; contusion, traumatic hematoma, traumatic hemorrhage.
m e.g.; spontaneous, procedural, or traumatic intracranial hemorrhage.
Description of selected adverse reactions
Bleeding
Bleeding findings in the PLATO study
The overall outcome of bleeding rates in the PLATO study is shown in Table 1.

Table 1 – Analysis of overall bleeding events, Kaplan-Meier estimates (PLATO) at 12 months

	Twice a day Tikagrelor 90 mg N=9235	Klopidogrel 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

Definitions of bleeding categories:

Major Fatal/Life-Threatening Bleeding: >50 g/L decrease in hemoglobin or Clinically evident with transfusion of ≥ 4 units of erythrocytes; or fatal; or intracranial; or intrapericardial with cardiac tamponade; or severe hypotension or hypovolemic shock requiring pressors or surgery.

Major Other: Clinically evident with a decrease in hemoglobin of 30-50 g/L or transfusion of 2-3 units of erythrocytes; or significantly disabling.

Minor Bleeding: Requiring medical attention to stop or treat bleeding.

TIMI Major Bleeding: Clinically evident or intracranial hemorrhage with >50 g/L decrease

in hemoglobin.

TIMI Minor Bleeding: Clinically evident with a decrease in hemoglobin of 30-50 g/L.

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

The rates of PLATO major fatal/life-threatening bleeding, PLATO total major bleeding, TIMI major bleeding, or TIMI minor bleeding (Table 1) are not different between ticagrelor and clopidogrel. However, total PLATO major + minor bleeding was higher with ticagrelor compared with clopidogrel. Fatal bleeding occurred in a small number of patients in PLATO; 20 (0.2%) for ticagrelor and 23 (0.3%) for clopidogrel (see section 4.4).

None of the factors including age, sex, weight, race, geographic region, concurrent conditions, concomitant treatment, and medical history of a previous stroke or transient ischemic attack were predictive of overall or nonprocedural PLATO major bleeding. Therefore, no specific risk group has been identified for any bleeding subgroup.

CABG-associated bleeding:

In PLATO, 1584 patients (cohort) who underwent coronary artery bypass graft (CABG) surgery

PLATO major fatal/life-threatening bleeding occurred in 42% of patients (12%), with no difference between treatment groups. Fatal CABG bleeding occurred in 6 people in each treatment group (See Section 4.4).

Non-CABG-related bleeding and non-procedural related bleeding:

Ticagrelor and clopidogrel did not differ in non-CABG PLATO major fatal/life-threatening bleeding; but PLATO total major, TIMI major, and TIMI major + minor bleeding occurred more frequently with ticagrelor. Similarly, when all procedure-related bleeding is excluded, the number of bleedings occurring with ticagrelor appears to be greater than with clopidogrel (Table 1). Discontinuations of treatment due to non-procedural bleeding occurred more frequently with ticagrelor (2.9%) than with clopidogrel (1.2%; $p < 0.001$).

Intracranial bleeding:

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

Bleeding findings in the PEGASUS study

The results for overall bleeding events in the PEGASUS study are shown in Table 2.

Table 2 - Analysis of overall bleeding events, Kaplan-Meier estimates at 36 months (PEGASUS)

	Twice a day Tikagrelor 60 mg + ASA N=6958		Only ASA N=6996	
Safety endpoints	%KM	Rate of dangerous (%95 GA)	%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
Intracranial Hemorrhage (IC)	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 a drop in hemoglobin (Hgb) of ≥ 50 g/L or hematocrit (Hct) when Hgb is not present

Clinically significant hemorrhage findings associated with 15% falls.

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

HR: Intracranial Hemorrhage (Intracranial hemorrhage).

Other TIMI Major: Non-fatal non-HR TIMI Major bleeding.

TIMI Minor: Clinically evident with a decrease in hemoglobin of 30-50 g/L.

TIMI requiring medical attention: Requiring intervention OR leading to hospitalization OR requiring evaluation.

PLATO Major Fatal/Life-threatening: Fatal bleeding OR any intracranial bleeding OR intrapericardial with cardiac tamponade OR hypovolemic shock or severe hypotension requiring pressor/inotrope or surgery OR hemoglobin

Clinically significant with a decrease of >50 g/L OR transfusion of ≥ 4 units of red blood cells.

PLATO Major Other: Significantly disabling OR clinically significant with a decrease in hemoglobin of 30-50 g/L OR transfusion of 2-3 units of red blood cells.

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

In the PEGASUS study, TIMI Major bleeding was higher for ticagrelor 60 mg twice daily than for ASA alone. There was no increased risk of bleeding for fatal bleeding and only a small increase in intracranial haemorrhages compared to ASA treatment alone. A small number of fatal bleeding events occurred, 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 is due to a higher frequency of other TIMI Major bleeding resulting from events in the primary gastrointestinal tract organ class.

Increased bleeding patterns similar to TIMI Major were seen for the TIMI Major or Minor and PLATO Major and PLATO Major or Minor bleeding categories (See Table 2).

Discontinuation of treatment due to bleeding was more common with ticagrelor 60 mg than

with ASA therapy alone (6.2% and 1.5%, respectively). The majority of these bleedings are less severe (classified as TIMI requiring medical attention), such as nosebleeds, bruising, and hematomas.

Bleeding profile of ticagrelor 60 mg across multiple predefined subgroups (e.g., age, sex, weight, race, geographic region, concurrent conditions, concomitant treatment, and medical history) for TIMI Major, TIMI Major or Minor, and PLATO Major bleeding events. was found to be consistent.

Intracranial bleeding:

Spontaneous intracranial hemorrhages were reported at similar rates for ticagrelor 60 mg and ASA therapy alone (n=13, 0.2% in both treatment groups). Traumatic and procedure-related intracranial hemorrhages showed a small increase with ticagrelor 60 mg treatment (n=15, 0.2%) compared to ASA treatment alone (n=10, 0.1%). 6 fatal intracranial bleeds occurred with ticagrelor 60 mg and 5 fatal intracranial bleeds occurred with ASA therapy alone. The incidence of intracranial hemorrhage was low in both treatment groups, taking into account significant comorbidity and cardiovascular risk factors of the population under investigation.

Dyspnea

Dyspnea, a type of feeling of breathlessness, has been reported in patients treated with ticagrelor. In the PLATO study, dyspnea adverse events (AEs) (dyspnea, dyspnea at rest, exertional dyspnea, paroxysmal nocturnal dyspnea, and nocturnal dyspnea) when combined were reported in 13.8% of patients receiving ticagrelor and 7.8% of patients receiving clopidogrel. In 2.2% of patients receiving ticagrelor and 0.6% of patients receiving clopidogrel, investigators considered dyspnea to be causally related to treatment in the PLATO study, and only a few were considered serious (0.14% ticagrelor; 0.02% clopidogrel) (See Section 4.4). Most dyspnea symptoms reported were mild to moderate in severity, and most were reported as a single episode early after initiation of treatment.

Compared with clopidogrel, asthma/COPD patients treated with ticagrelor may be at increased risk of experiencing non-severe dyspnea (3.29% with ticagrelor vs 0.53% with clopidogrel) and severe dyspnea (0.38% with ticagrelor vs 0.00% with clopidogrel). In absolute terms the risk may be higher than in the general PLATO population. Ticagrelor should be used with caution in patients with a history of asthma and/or COPD (see section 4.4).

Approximately 30% of episodes resolved within 7 days. The PLATO study included patients with congestive heart failure, COPD, or asthma at baseline; these patients and the elderly were more likely to report dyspnea. For ticagrelor, 0.9% of patients discontinued the study due to dyspnea, while this rate was 0.1% for those with clopidogrel. The higher incidence of dyspnea occurring with ticagrelor is not associated with new or worsening heart or lung disease (see section 4.4). Ticagrelor does not affect lung function tests.

In the PEGASUS study, dyspnea was reported in 14.2% of patients receiving ticagrelor 60 mg twice daily and in 5.5% of patients receiving ASA alone. The most commonly reported dyspnea events in the PLATO study were mild to moderate (see section 4.4). Patients reporting dyspnea tend to be older and more often have underlying dyspnea, COPD, or asthma.

Studies

Uric acid elevations: In the PLATO study, serum uric acid was elevated above the upper

limit of normal in 22% of patients receiving ticagrelor, compared with 13% of patients receiving clopidogrel. In the PEGASUS study, the corresponding values were 9.1%, 8.8% and 5.5% for ticagrelor 90 mg, 60 mg and placebo, respectively. Mean serum uric acid increased by approximately 15% with ticagrelor compared to approximately 7.5% with clopidogrel and decreased to approximately 7% on ticagrelor after treatment was stopped; However, no reduction was observed with clopidogrel. In the PEGASUS study, reversible increases in mean serum uric acid levels of 6.3% and 5.6% were found for ticagrelor 90 mg and 60 mg, respectively, compared to a 1.5% decrease in the placebo group. In the PLATO study, the frequency of gouty arthritis was 0.2% for ticagrelor versus 0.1% for clopidogrel. In the PEGASUS study, the corresponding values for gout/gouty arthritis were 1.6%, 1.5% and 1.1% for ticagrelor 90 mg, 60 mg and placebo, respectively.

Reporting of suspected adverse reactions

It is of great importance to report suspected drug adverse reactions after licensing. Reporting allows continuous monitoring of the benefit/risk balance of the drug. Healthcare professionals are required to report any suspected adverse reactions to the Turkish Pharmacovigilance Center (TÜFAM) (www.titck.gov.tr; e-mail: tufam@titck.gov.tr; tel: 0 800 314 00 08; fax: 0 312 218 35 99).

• Overdose and treatment

Ticagrelor is well tolerated in single doses up to 900 mg. Gastrointestinal toxicity was determined to be dose limiting in the single ascending dose study. Other clinically significant adverse effects that may occur with overdose include dyspnea and ventricular bradycardias (See Section 4.8).

In case of overdose, the above potential adverse reactions may occur, in which case ECG monitoring should be considered.

There is currently no known antidote to reverse the effects of ticagrelor and ticagrelor is not dialysable (see section 5.2). Local standard medical precautions should be taken in the treatment of overdose. In overdose of ticagrelor, the expected effect is a prolongation of bleeding risk due to platelet inhibition. Platelet transfusion is unlikely to provide clinical benefit in patients with bleeding (See Section 4.4). If bleeding is observed, appropriate supportive measures should be taken.

5. PHARMACOLOGICAL PROPERTIES

• Pharmacodynamic properties

Pharmacotherapeutic group: Platelet aggregation inhibitors (except Heparin)

ATC code: B01AC24

Mechanism of action

Ticagrelor contains ticagrelor, a member of the cyclopentyltriazolopyrimidine (SPTP) chemical class, which is an oral, direct-acting, selectively and reversibly binding P2Y₁₂

receptor antagonist and inhibits ADP-mediated P2Y₁₂-dependent platelet activation and aggregation. Ticagrelor does not block ADP binding to the receptor, but when bound to the P2Y₁₂ receptor, it blocks ADP-stimulated signaling. Because platelets participate in the initiation and/or development of thrombotic complications of atherosclerotic disease, inhibition of platelet function has been shown to reduce the risk of CV events such as death, MI, or stroke. Ticagrelor also increases local endogenous adenosine levels by inhibiting stabilizing nucleoside transporter-1 (ENT-1).

Ticagrelor has been documented to potentiate the following adenosine-stimulated effects in healthy subjects and ACS patients: vasodilation (measured by increases in coronary blood flow in healthy volunteers and ACS patients; headache), inhibition of platelet function (in human whole blood in vitro), and dyspnea. However, the link between observed adenosine increases and clinical outcomes (e.g., morbidity-mortality) has not been clearly established.

Pharmacodynamic effects

Onset of effect

In patients with stable coronary artery disease (CAD) receiving ASA therapy, ticagrelor is It showed a rapid onset of pharmacological effect with a mean platelet aggregation inhibition (TAI) value of approximately 41% after a 180 mg loading dose at 0.5 hours; The maximum TAI effect of 89% occurred 2-4 hours after the dose and lasted between 2-8 hours. At 2 hours post-dose, 90% of patients had a final comprehensive TAI > 70%.

End of effect

If a CABG procedure is planned, the risk of bleeding from ticagrelor is increased compared to clopidogrel if ticagrelor is discontinued less than 96 hours before the procedure.

Migration data

Switching from clopidogrel 75 mg to ticagrelor 90 mg twice daily results in a 26.4% absolute TAI increase, and switching from ticagrelor to clopidogrel results in a 24.5% absolute TAI reduction. Patients can be switched from clopidogrel to ticagrelor without interruption of antiplatelet effect (see section 4.2).

Clinical efficacy and safety

Clinical findings for the efficacy and safety of ticagrelor were obtained from two phase 3 studies:

- PLATO [PLATelet Inhibition and Patient Outcomes] study comparing ticagrelor with clopidogrel, both given in combination with ASA and other standard therapy
 - PEGASUS TIMI-54 [PrEvention with TicaGrelor of SecondAry Thrombotic Events in High-RiSk AcUte Coronary Syndrome Patients] study, comparing ticagrelor treatment in combination with ASA with ASA treatment alone
- PLATO study (Acute Coronary Syndromes)

The PLATO study included 18,624 patients with unstable angina (UA), non-ST elevation myocardial infarction (NSTEMI), or ST elevation myocardial infarction (STEMI) within 24 hours of symptom onset and treated primarily medically or with percutaneous coronary intervention (PCI) or CABG. .

Clinical effectiveness

In background therapy with ASA once daily, ticagrelor 90 mg twice daily was superior to clopidogrel 75 mg once daily in preventing the composite endpoint of CV death, MI, or stroke, with the difference driven by CV death and MI. Patients were given a loading dose of 300 mg clopidogrel (600 mg can also be given if PCI is to be performed) or 180 mg ticagrelor.

This result was evident early on (absolute risk reduction [MRA] 0.6% and relative risk reduction [RRA] 12% at 30 days), with a consistent treatment effect over the 12-month period, with an NRA of 16% and 1.9% per year. 1 MRA was provided. These results suggest that it is appropriate to treat patients with ticagrelor 90 mg twice daily for 12 months (see section 4.2). Treating 54 ACS patients with ticagrelor instead of clopidogrel will prevent 1 atherothrombotic event; Treating 91 patients will prevent 1 CV death (See Figure 1 and Table 3).

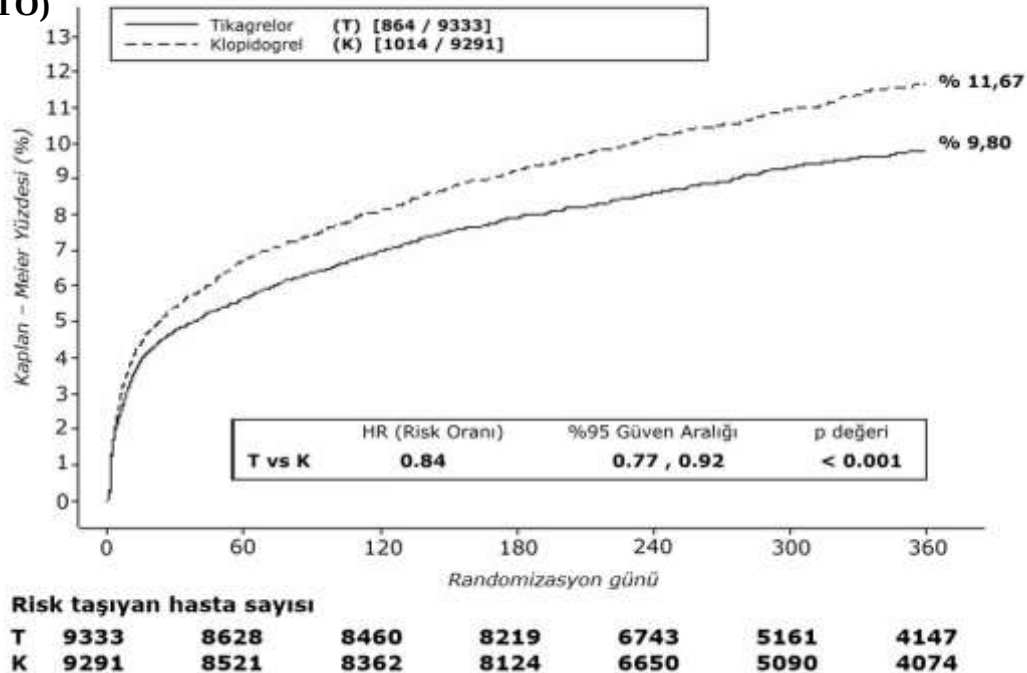
Treatment effect of ticagrelor compared to clopidogrel; weight, gender, medical history of diabetes, transient ischemic attack or nonhemorrhagic stroke or revascularization; concomitant treatments including heparins, GpIIb/IIIa inhibitors and proton pump inhibitors (see section 4.5); The final index is consistent across multiple subgroups, including case diagnosis (STEMI, NSTEMI, or UA) and treatment pathway targeted at randomization (invasive or medical).

The hazard ratio (HR) for the primary endpoint favored clopidogrel in North America; however, a low significant treatment interaction was observed in the rest of the world favoring ticagrelor, suggesting that this interaction was approximately

It was found to represent 10% (interaction p-value = 0.045). Exploratory analyzes suggest a possible relationship with ASA dose, as decreased efficacy with ticagrelor was observed with increasing ASA dose. Chronic daily ASA doses to be given with ticagrelor should be 75 – 150 mg (See Sections 4.2 and 4.4).

Figure 1 shows the estimated initial risk of any event occurring in the composite efficacy endpoint.

Figure 1 – Primary clinical composite endpoint analysis of CV death, MI and stroke (PLATO)



Ticagrelor reduces the occurrence of the primary composite endpoint in both the UA/NSTEMI and STEMI populations compared to clopidogrel (Table 3). Therefore, in patients with ACS (unstable angina, non-ST-elevation Myocardial Infarction [NSTEMI], and ST-elevation Myocardial Infarction [STEMI]), including patients on medical therapy and patients treated with percutaneous coronary intervention (PCI) or coronary bypass graft (CABG).) ticagrelor 90 mg twice daily can be used together with low dose ASA.

Table 3 – Analysis of primary and secondary efficacy endpoints (PLATO)

	Twice a day ticagrelor 90 mg (% of patients experiencing an event) N=9333	Once a day clopidogrel 75 mg (% of patients experiencing an event)N=9291	MRA ^a (%/year)	NRA ^a (%) (%95 GA)	<i>p</i> -value
CV death, MI (except silent MI) or stroke	9.3	10.9	1.9	16 (8, 23)	0.0003
invasive intervention	8.5	10.0	1.7	16 (6, 25)	0.0025
medical intervention	11.3	13.2	2.3	15 (0.3, 27)	0.0444 ^d
CV death	3.8	4.8	1.1	21 (9, 31)	0.0013
MI (except silent MI) ^b	5.4	6.4	1.1	16 (5, 25)	0.0045
Stroke	1.3	1.1	-0.2	-17 (-52, 9)	0.2249
All-cause mortality, MI (excluding silent MI) or stroke	9.7	11.5	2.1	16 (8, 23)	0.0001
CV death, total MI, stroke, CRI, RI, TIA or other ATOc	13.8	15.7	2.1	12 (5, 19)	0.0006
All	4.3	5.4	1.4	22 (11, 31)	0.0003 ^d
reasons	1.2	1.7	0.6	32 (8, 49)	0.0123 ^d

aMRA = absolute risk reduction; NRA = relative risk reduction = (1-Hazard ratio) x 100%. Negative NRA indicates relative risk increase.

^bExcept for silent MI.

^cCRI = Severe recurrent ischemia; RI = Recurrent ischemia; TIA = Transient ischemic attack; ATO = Arterial thrombotic event. Total MI includes silent MI and the date of the event is determined as the date it was discovered.

^dNominal significance value; all others are formally and statistically significant according to the predefined hierarchy test.

PLATO genetic substudy

Determination of CYP2C19 and ABCB1 genotypes of 10285 patients in the PLATO study revealed the relationships of genotype groups with PLATO results. The superiority of ticagrelor over clopidogrel in reducing major CV events was not significantly affected by the patient's CYP2C19 or ABCB1 genotype. Similar to the overall PLATO study, total PLATO major bleeding did not differ between ticagrelor and clopidogrel regardless of CYP2C19 or ABCB1 genotype. Non-CABG PLATO major bleeding was increased with ticagrelor compared with clopidogrel in patients with one or more CYP2C19 loss-of-function alleles; but is similar to clopidogrel in patients without the loss-of-function allele.

Combined combination of efficacy and safety

The combined efficacy and safety composite (CV death, MI, stroke, or PLATO-defined “overall major” bleeding) suggests that the benefit in efficacy of ticagrelor compared with clopidogrel was not offset by major bleeding events at 12 months after ACS (MRA 1.4%, NRA 8%, TO). 0.92; $p=0.0257$).

Clinical safety

Holter substudy:

To examine the occurrence of ventricular pauses and other arrhythmic episodes during the PLATO study, researchers conducted Holter monitoring in a subgroup of approximately 3,000 patients; Records are available for approximately 2000 of these patients, both during the acute phase of their ACS and one month later. The primary variable examined was the occurrence of ventricular pauses of ≥ 3 seconds. More patients had ventricular pauses with ticagrelor (6.0%) than with clopidogrel (3.5%) in the acute phase, compared with 2.2% and 1.6%, respectively, after 1 month (see section 4.4). The increase in ventricular pauses during the acute phase of ACS was more pronounced in ticagrelor patients with a history of CHF (9.2% versus 5.4% in patients without a history of CHF; 3.6% versus 4.0% in clopidogrel patients without a history of CHF). This imbalance did not occur at one month: 2.0% versus 2.1% for ticagrelor patients with and without a history of CHF, and 3.8% versus 1.4% with clopidogrel, respectively. There were no adverse clinical outcomes associated with this imbalance in this patient population (including pacemaker placement).

PEGASUS Study (History of Myocardial Infarction)

The PEGASUS TIMI-54 study compared low-dose ASA (75-150 mg) in combination with 2 doses (either 90 mg twice daily or 60 mg twice daily) compared with ASA therapy alone in patients with a history of MI and additional risk factors for atherothrombosis. This was a 21,162-patient, event-driven, randomised, double-blind, placebo-controlled, parallel-group, international multicenter study evaluating the prevention of atherothrombotic events with ticagrelor given 100 mg (mg).

Patients were eligible to participate in the study if they were 50 years of age or older, had a history of MI (1 to 3 years before randomization), and had at least one of the following atherothrombosis risk factors: age ≥ 65 years, diabetes mellitus requiring drug therapy, a second previous MI, multivessel CAD. Chronic renal dysfunction without symptoms or end stage.

Patients were found to be ineligible for participation in the study if: P2Y₁₂ receptor antagonist, dipyridamole, cilostazol or anticoagulant treatment was planned during the

study period;
if you have a coagulation disorder or a history of ischemic stroke or intracranial hemorrhage, a central nervous system tumor, or an intracranial vascular anomaly; have had gastrointestinal bleeding in the previous 6 months or major surgery within the previous 30 days.

Clinical effectiveness

Figure 2 – Primary clinical composite endpoint analysis of CV death, MI and stroke (PEGASUS)

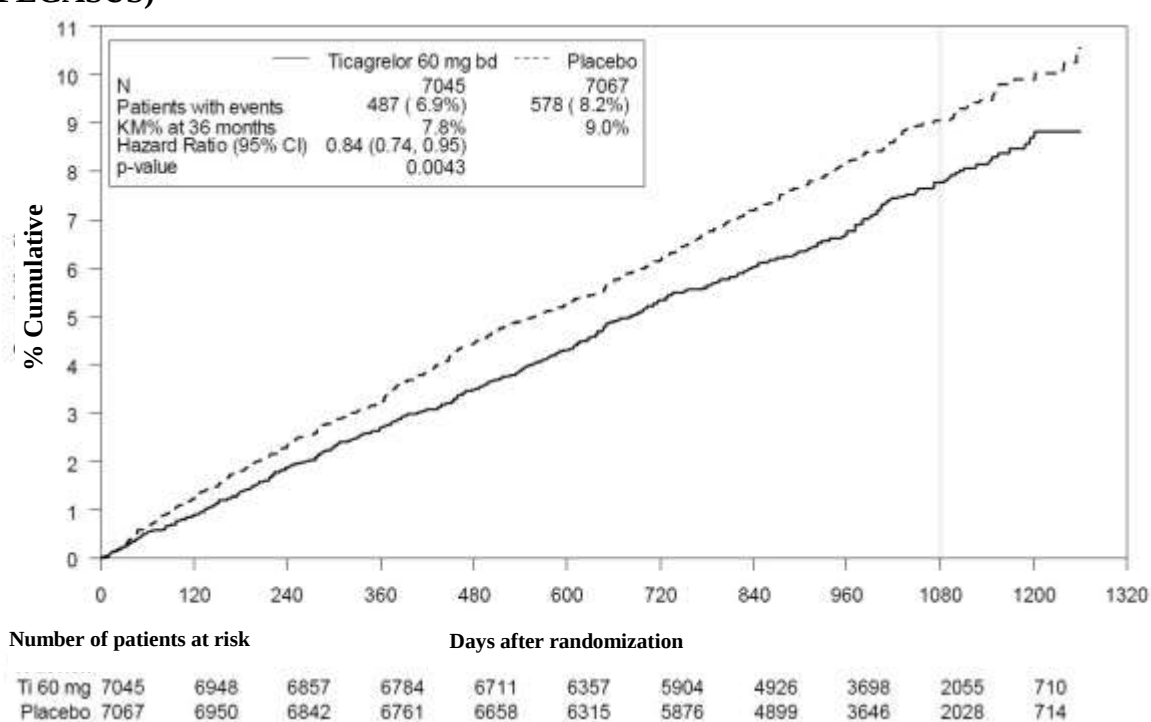


Table 4 – Analysis of Primary and Secondary Efficacy Endpoints (PEGASUS)

	Twice a day tikagrelor 60 mg + ASA N=7045			Only ASA N=7067		p- value
Features	Diseases that occur	%KM	TO (%95 GA)	Diseases that occur	%KM	
Primary endpoint						
KV	487 (%6.9)	%7.8	0.84 (0.74, 0.95)	578 (%8.2)	%9.0	0.0043 (s)
death/MI/Stroke composite	174 (%2.5)	%2.9	0.83 (0.68, 1.01)	210 (%3.0)	%3.4	0.0676
CV death	285 (%4.0)	%4.5	0.84 (0.72, 0.98)	338 (%4.8)	%5.2	0.0314
MI	91 (%1.3)	%1.5	0.75 (0.57, 0.98)	122 (%1.7)	%1.9	0.0337
Secondary Endpoint						

CV death	174 (%2.5)	%2.9	0.83 (0.68, 1.01)	210 (%3.0)	%3.4	-
All-cause mortality	289 (%4.1)	%4.7	0.89 (0.76, 1.04)	326 (%4.6)	%5.2	-

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

Kaplan-Meier percentage calculated at 36 months.

Note: For the CV death, MI and Stroke components, the number of first events is the actual number of first events for each component and is not added to the number of events in the composite endpoint.

(s) Indicates statistical significance.

CI=Confidence interval; CV=Cardiovascular; TO = Hazard rate; KM=Kaplan-Meier; MI = Myocardial infarction.

Both the 60 mg twice daily and 90 mg twice daily ticagrelor regimens in combination with ASA were superior to ASA alone in preventing atherothrombotic events (composite endpoint: CV death, MI, and stroke) with a consistent treatment effect throughout the study period. It gives a 16% relative risk reduction (RRA) and 1.27% absolute risk reduction (MRA) for ticagrelor 60 mg and a 15% NRA and 1.19% MRA for ticagrelor 90 mg.

Although the efficacy profile of 90 mg and 60 mg is similar, there is evidence that the lower dose has a better safety profile and tolerability in relation to the risk of bleeding and dyspnea. Therefore, ticagrelor 60 mg administered only twice daily with ASA is recommended for the prevention of atherothrombotic events (CV death, MI and stroke) in patients with a history of MI and at high risk of developing atherothrombotic events.

Ticagrelor 60 mg twice daily significantly reduces the primary composite endpoint of CV death, MI, and stroke relative to ASA alone. Each of the components contributed to a reduction in the primary composite endpoint (CV death 17% NRA, MI 16% NRA, and stroke 25% NRA).

Composite endpoint NRAs from day one to day 360 (17% NRA) and day 361 and beyond (16% NRA) were similar. Efficacy and safety data for ticagrelor after 3 years of extended treatment are limited.

There was no evidence of benefit when ticagrelor 60 mg twice daily was administered to patients who were clinically stable more than 2 years after MI or more than 1 year after discontinuing previous ADP receptor inhibitor therapy (the primary composite outcome of CV death, MI, and stroke). There is no decrease in bleeding, but there is an increase in major bleeding (see also Section 4.2).

Clinical safety

The rate of discontinuation of ticagrelor 60 mg due to bleeding and dyspnea was higher in patients >75 years of age (42%) compared to younger patients (range 23% to 31%).

In patients >75 years of age, the difference versus placebo was greater than 10% (42% versus 29%).

Pediatric population

In a randomized, double-blind, parallel-group Phase III study (HESTIA 3), 193 pediatric patients (ages 2 to under 18 years) with sickle cell disease were randomized to receive placebo or ticagrelor at doses of 15 mg to 45 mg twice daily, based on body weight. has been made. Ticagrelor resulted in a median platelet inhibition of 35% pre-dose and 56% at 2 hours post-dose at steady state.

Compared with placebo, ticagrelor had no beneficial therapeutic effect on the rate of vaso-occlusive crises.

The European Medicines Agency has waived the obligation to submit study results with ticagrelor in all subsets of the pediatric population with a history of acute coronary syndromes (ACS) and myocardial infarction (MI) (see section 4.2 for information on pediatric use).

5.2. Pharmacokinetic properties

General features

Absorption

Absorption of ticagrelor is rapid, with an average t_{max} of 1.5 hours. Formation of the major circulating metabolite of ticagrelor, AR-C124910XX (also the active metabolite), is rapid, with a mean t_{max} of approximately 2.5 hours. Following oral administration of 90 mg ticagrelor to healthy volunteers under fasting conditions, the C_{max} value is 529 ng/ml and the AUC value is 3451 ng*s/ml. The major metabolite ratios are 0.28 for C_{max} and 0.42 for AUC. The pharmacokinetics of ticagrelor and AR-C124910XX in patients with a history of MI were generally similar to those in the ACS population. Based on population pharmacokinetic analysis of the PEGASUS study, the median ticagrelor C_{max} was 391 ng/mL and the steady-state AUC for ticagrelor 60 mg was 3801 ng*h/mL. Steady-state C_{max} for ticagrelor 90 mg is 627 ng/mL and AUC is 6255 ng*h/mL.

The mean absolute bioavailability of ticagrelor is estimated to be 36%. High-fat diet had no effect on the C_{max} of ticagrelor and the AUC of the active metabolite, but caused a 21% increase in the AUC of ticagrelor and a 22% decrease in the C_{max} of the active metabolite. These minor changes are considered to be of minimal clinical significance, so ticagrelor can be taken with or without food. Ticagrelor and the active metabolite are P-gp substrates.

Crushed and watered ticagrelor tablets have a similar bioavailability as whole tablets in terms of AUC and C_{max} of ticagrelor and the active metabolite when administered orally or via a nasogastric tube into the stomach. Initial exposure from crushed and water-mixed ticagrelor tablets was higher (0.5 and 1 hour post-dose) than from whole tablets, with a generally similar concentration profile occurring thereafter (2 to 48 hours).

Distribution

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

Biotransformation

CYP3A4 is the major enzyme responsible for the metabolism of ticagrelor and the formation of the active metabolite enzyme, and its interactions with other CYP3A substrates can range from activation to inhibition.

The major metabolite of ticagrelor is AR-C124910XX, which was also found to be effective when assessed for in vitro binding to the platelet P2Y₁₂ ADP-receptor. Systemic exposure to the active metabolite is approximately 30-40% of that achieved for ticagrelor.

Elimination

The primary route of elimination of ticagrelor is hepatic metabolism. When radiolabeled ticagrelor is administered, the mean recovery of radioactivity is approximately 84% (57.8% in feces, 26.5% in urine). The recovery of ticagrelor and its active metabolite in urine is less than 1% of the dose. The primary elimination pathway for the active metabolite is predominantly biliary excretion. Mean $t_{1/2}$ is approximately 7 hours for ticagrelor and 8.5 hours for the active metabolite.

Linearity/non-linearity

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

Special Population:

Geriatric Population

By population pharmacokinetic analysis, elderly (≥ 75 years) ACS patients had higher exposures to ticagrelor and its active metabolite compared to younger patients (approximately for C_{max} and AUC). 25%) was observed. These differences are not thought to be clinically significant (see section 4.2).

Pediatric Population

Limited data are available on children with sickle cell disease.

In the HESTIA 3 study, patients aged 2 to less than 18 years, weighing ≥ 12 to ≤ 24 kg, >24 to ≤ 48 kg, and >48 kg received ticagrelor as pediatric dispersible 15 mg tablets at doses of 15, 30, and 45 mg twice daily, respectively. Based on population pharmacokinetic analysis, mean AUC at steady state ranged from 1095 ng*h/mL to 1458 ng*h/mL and mean C_{max} ranged from 143 ng/mL to 206 ng/mL.

Gender

Higher exposure to ticagrelor and the active metabolite was observed in women compared to men. These differences are not thought to be clinically significant.

Renal Failure

Exposure to ticagrelor is approximately 20% lower and exposure to the active metabolite is approximately 17% higher in patients with severe renal impairment (creatinine clearance < 30 mL/min) compared to subjects with normal renal function.

In patients with terminal stage renal disease undergoing hemodialysis, the AUC and C_{max} of ticagrelor 90 mg administered on a non-dialysis day were 38% and 51% higher than in subjects with normal renal function. A similar increase in exposure was observed when ticagrelor was administered immediately before dialysis (49% and 61%, respectively), indicating that ticagrelor is not dialysable. Exposure to the active metabolite increased to a lesser extent (AUC 13-14%, C_{max} 17-36%). The platelet aggregation inhibition (IPA) effect

of ticagrelor in patients with terminal renal disease appeared to be independent of dialysis and was similar to that in volunteers with normal renal function (see section 4.2).

Liver Failure

C_{max} and AUC values for ticagrelor were 12% and 23% higher, respectively, in patients with mild hepatic impairment compared with matched healthy volunteers; however, the TAI effect of ticagrelor was similar between the two groups. No dosage adjustment is necessary in patients with mild hepatic impairment. Ticagrelor has not been studied in patients with severe hepatic impairment and no pharmacokinetic information is available in patients with moderate hepatic impairment. Ticagrelor plasma concentrations in patients with moderate or severe elevations of one or more liver function tests at baseline were, on average, similar or slightly higher than in patients without elevations at baseline. No dosage adjustment is recommended in patients with moderate hepatic impairment (see sections 4.2 and 4.4).

Race

The mean bioavailability was 39% higher in Asian patients compared to Caucasian patients. The bioavailability of ticagrelor is 18% lower in black patients compared to white patients. In clinical pharmacology studies, exposure (C_{max} and AUC) to ticagrelor was approximately 40% (20% after adjustment for body weight) higher in Japanese patients compared to Caucasians.

5.3. Preclinical safety data

Preclinical data for ticagrelor and its major metabolite did not reveal an unacceptable risk of adverse events for humans based on conventional studies of safety pharmacology, single and repeated dose toxicity and genotoxic potential.

Gastrointestinal irritation has been observed in various animal species at clinically relevant exposure levels (See Section 4.8).

In female rats, high doses of ticagrelor showed an increased incidence of uterine tumors (adenocarcinomas) and hepatic adenomas. The mechanism of uterine tumors is likely hormone imbalance, which can cause tumors in rats. The mechanism of hepatic adenomas is probably due to rodent-specific enzyme induction in the liver. For these reasons, it is thought that the carcinogenicity findings may be relevant to humans.

Minor developmental anomalies were seen in rats at the maternally toxic dose (safety margin 5.1). In rabbits, a slight delay in hepatic maturity and skeletal development was seen in fetuses of females at the high dose, without evidence of maternal toxicity (safety margin 4.5).

Studies in rats and rabbits showed reproductive toxicity with a slight decrease in maternal body weight gain and a decrease in birth weight with delayed neonatal viability and growth. Ticagrelor caused irregular cycles (mostly prolonged cycles) in female rats but did not affect overall fertility in male or female rats. Pharmacokinetic studies with radiolabeled ticagrelor showed that the parent compound and its metabolites are excreted in the milk of rats (see section 4.6).

6. PHARMACEUTICAL PROPERTIES

• List of excipients

Mannitol (E421)
Dibasic calcium phosphate dihydrate
Microcrystalline cellulose pH 101
Hydroxypropyl cellulose
Croscarmellose sodium
Colloidal silica hydrate 244
Magnesium stearate
Hypromellose
Titanium dioxide
Talc
Polyethylene glycol 400
Yellow iron oxide

• Incompatibilities

There is no known incompatibility.

• Shelf life

24 months

• Special precautions for storage

Store below 25 °C.

• Nature and content of the packaging

Transparent PVC/PE/PVDC/Alu blister containing 56 or 168 film-coated tablets is presented in a cardboard box with instructions for use.

• Disposal of residues of the medicinal product for human use and other special measures

Unused products or waste materials must be disposed of in accordance with the "Medical Waste Control Regulation" and "Packaging Waste Control Regulations".

7. MARKETING AUTHORIZATION HOLDER

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Okmeydanı Boruçiçeği Sok. No:16 34382, Şişli - İstanbul
Tel: 0212 220 64 00
Fax: 0212 222 57 59

8. MARKETING AUTHORIZATION NUMBER(S)

2022/432

9. DATE OF FIRST APPROVAL/RENEWAL OF THE APPROVAL

Date of first authorization: 05.08.2022

Date of renewal of authorization: 05.08.2022

10. DATE OF REVISION OF THE SPC

05.08.2022