Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ticagrelor Krka 90 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 90 mg ticagrelor.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Slightly brownish-yellow, round, biconvex, film-coated tablets marked with 90 on one side.
Tablet dimensions: approximately 9 mm diameter.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ticagrelor Krka , co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of atherothrombotic events in adult patients with
- acute coronary syndromes (ACS) or
- a history of myocardial infarction (MI) and a high risk of developing an atherothrombotic event (see sections 4.2 and 5.1).

4.2 Posology and method of administration

Posology

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

Acute coronary syndromes
Ticagrelor Krka treatment should be initiated with a single 180 mg loading dose (two tablets of 90 mg) and then continued at 90 mg twice daily. Treatment with Ticagrelor Krka 90 mg twice daily is recommended for 12 months in ACS patients unless discontinuation is clinically indicated (see section 5.1).

Discontinuation of ASA may be considered after 3 months in patients with ACS who have undergone a percutaneous coronary intervention (PCI) procedure and have an increased risk of bleeding. In that case, ticagrelor as single antiplatelet therapy should be continued for 9 months (see section 4.4).

History of myocardial infarction
Ticagrelor Krka 60 mg twice daily is the recommended dose when an extended treatment is required for patients with a history of MI of at least one year and a high risk of an atherothrombotic event (see section 5.1). Treatment may be started without interruption as continuation therapy after the initial one-year treatment with Ticagrelor Krka 90 mg or other adenosine diphosphate (ADP) receptor inhibitor therapy in ACS patients with a high risk of an atherothrombotic event. Treatment can also be initiated up to 2 years from the MI, or within one year after stopping previous ADP receptor inhibitor treatment. There are limited data on the efficacy and safety of ticagrelor beyond 3 years of extended treatment.

If a switch is needed, the first dose of Ticagrelor Krka should be administered 24 hours following the last dose of the other antiplatelet medication.

Missed dose
Lapses in therapy should also be avoided. A patient who misses a dose of Ticagrelor Krka should take only one tablet (their next dose) at its scheduled time.

Special populations Elderly
No dose adjustment is required in elderly (see section 5.2).

Renal impairment
No dose adjustment is necessary for patients with renal impairment (see section 5.2).

Hepatic impairment
Ticagrelor has not been studied in patients with severe hepatic impairment and its use in these patients is therefore contraindicated (see section 4.3). Only limited information is available in patients with moderate hepatic impairment. Dose adjustment is not recommended, but ticagrelor should be used with caution (see sections 4.4 and 5.2). No dose adjustment is necessary for patients with mild hepatic impairment (see section 5.2).

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

Method of administration
For oral use.
Ticagrelor Krka can be administered with or without food.
For patients who are unable to swallow the tablet(s) whole, the tablets can be crushed to a fine powder and mixed in half a glass of water and drunk immediately. The glass should be rinsed with a further half glass of water and the contents drunk. The mixture can also be administered via a nasogastric tube. For further information see section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 (see section 4.8).
- Active pathological bleeding.
- History of intracranial haemorrhage (see section 4.8).
- Severe hepatic impairment (see sections 4.2, 4.4 and 5.2).
- Co-administration of ticagrelor with strong CYP3A4 inhibitors (e.g. ketoconazole, clarithromycin, nefazodone, ritonavir and atazanavir), as co-administration may lead to a substantial increase in exposure to ticagrelor (see section 4.5).

4.4 Special warnings and precautions for use

Bleeding risk
The use of ticagrelor in patients at known increased risk for bleeding should be balanced against the benefit in terms of prevention of 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 a propensity to bleed (e.g. due to recent trauma, recent surgery, coagulation disorders, active or recent gastrointestinal bleeding) or who are at increased risk of trauma. The use of ticagrelor is contraindicated in patients with active pathological bleeding, in those with a history of intracranial haemorrhage, and in patients with severe hepatic impairment (see section 4.3).
- Patients with concomitant administration of medicinal products that may increase the risk of bleeding (e.g. non-steroidal anti-inflammatory drugs (NSAIDs), oral anticoagulants and/or fibrinolytics) within 24 hours of ticagrelor dosing.

In two randomised controlled studies (TICO and TWILIGHT) in patients with ACS who have undergone a PCI procedure with a drug-eluting stent, discontinuing ASA after 3 months dual antiplatelet therapy with ticagrelor and ASA (DAPT), and continuing with ticagrelor as single antiplatelet therapy (SAPT) for 9 and 12 months, respectively, has been shown to decrease the risk of bleeding with no observed increase in risk of major adverse cardiovascular events (MACE) compared with continued DAPT. The decision to discontinue ASA after 3 months and continue with ticagrelor as single antiplatelet therapy for 9 months in patients

with an increased risk of bleeding should be based on clinical judgment considering the risk of bleeding versus the risk of thrombotic events (see section 4.2).

Platelet transfusion did not reverse the antiplatelet effect of ticagrelor in healthy volunteers and is unlikely to be of clinical benefit in patients with bleeding. Since co-administration of ticagrelor with desmopressin did not decrease template-bleeding time, desmopressin is unlikely to be effective in managing clinical bleeding events (see section 4.5).

Antifibrinolytic therapy (aminocaproic acid or tranexamic acid) and/or recombinant factor VIIa therapy may increase haemostasis. Ticagrelor may be resumed after the cause of bleeding has been identified and controlled.

Surgery
Patients should be advised to inform physicians and dentists that they are taking ticagrelor before any surgery is scheduled and before any new medicinal product is taken.

In PLATO patients undergoing coronary artery bypass grafting (CABG), ticagrelor had more bleeding than clopidogrel when stopped within 1 day prior to surgery but a similar rate of major bleeds compared to clopidogrel after stopping therapy 2 or more days before surgery (see section 4.8). If a patient is to undergo elective surgery and antiplatelet effect is not desired, ticagrelor should be discontinued 5 days prior to surgery (see section 5.1).

Patients with prior ischaemic stroke
ACS patients with prior ischaemic stroke can be treated with ticagrelor for up to 12 months (PLATO study).
In PEGASUS, patients with history of MI with prior ischaemic stroke were not included. Therefore, in the absence of data, treatment beyond one year is not recommended in these patients.

Hepatic impairment
Use of ticagrelor is contraindicated in patients with severe hepatic impairment (see sections 4.2 and 4.3). There is limited experience with ticagrelor in patients with moderate hepatic impairment, therefore, caution is advised in these patients (see sections 4.2 and 5.2).

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

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

During the Holter substudy in PLATO, more patients had ventricular pauses $\geq$3 seconds with ticagrelor than with clopidogrel during the acute phase of their ACS. The increase in
Holter-detected ventricular pauses with ticagrelor was higher in patients with chronic heart failure (CHF) than in the overall study population during the acute phase of ACS, but not at one month with ticagrelor or compared to clopidogrel. There were no adverse clinical consequences associated with this imbalance (including syncope or pacemaker insertion) in this patient population (see section 5.1).

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

Dyspnoea
Dyspnoea was reported in patients treated with ticagrelor. Dyspnoea is usually mild to moderate in intensity and often resolves without need for treatment discontinuation. Patients with asthma/chronic obstructive pulmonary disease (COPD) may have an increased absolute risk of experiencing dyspnoea with ticagrelor. Ticagrelor should be used with caution in patients with history of asthma and/or COPD. The mechanism has not been elucidated. If a patient reports new, prolonged or worsened

dyspnoea this should be investigated fully and if not tolerated, treatment with ticagrelor should be stopped. For further details see section 4.8.

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

Creatinine elevations
Creatinine levels may increase during treatment with ticagrelor. The mechanism has not been elucidated. Renal function should be checked according to routine medical practice. In patients with ACS, it is recommended that renal function is also checked one month after initiating the treatment with ticagrelor, paying special attention to patients ≥75 years, patients with moderate/severe renal impairment and those receiving concomitant treatment with an angiotensin receptor blocker (ARB).

Uric acid increase
Hyperuricaemia may occur during treatment with ticagrelor (see section 4.8). Caution is advised in patients with history of hyperuricaemia or gouty arthritis. As a precautionary measure, the use of ticagrelor in patients with uric acid nephropathy is discouraged.

Thrombotic Thrombocytopenic Purpura (TTP)
Thrombotic Thrombocytopenic Purpura (TTP) has been reported very rarely with the use of ticagrelor. It is characterised by thrombocytopenia and microangiopathic haemolytic anaemia associated with either neurological findings, renal dysfunction or fever. TTP is a potentially fatal condition requiring prompt treatment including plasmapheresis.

Interference with platelet function tests to diagnose heparin induced thrombocytopenia (HIT)
In the heparin induced platelet activation (HIPA) test used to diagnose HIT, anti-platelet factor 4/heparin antibodies in patient serum activate platelets of healthy donors in the presence of heparin.
False negative results in a platelet function test (to include, but may not be limited to the HIPA test) for HIT have been reported in patients administered ticagrelor. This is related to inhibition of the P2Y12-receptor on the healthy donor platelets in the test by ticagrelor in the patient's sera/plasma. Information on concomitant treatment with ticagrelor is required for interpretation of HIT platelet function tests.
In patients who have developed HIT, the benefit-risk of continued treatment with ticagrelor should be assessed, taking both the prothrombotic state of HIT and the increased risk of bleeding with concomitant anticoagulant and ticagrelor treatment into consideration.

Other
Based on a relationship observed in PLATO between maintenance ASA dose and relative efficacy of ticagrelor compared to clopidogrel, co-administration of ticagrelor and high maintenance dose ASA (>300 mg) is not recommended (see section 5.1).

Premature discontinuation
Premature discontinuation with any antiplatelet therapy, including Ticagrelor Krka , could result in an increased risk of cardiovascular (CV) death, MI or stroke due to the patient's underlying disease. Therefore, premature discontinuation of treatment should be avoided.

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Ticagrelor is primarily a CYP3A4 substrate and a mild inhibitor of CYP3A4. Ticagrelor is also a P-glycoprotein (P-gp) substrate and a weak P-gp inhibitor and may increase the exposure of P-gp substrates. Ticagrelor is a breast cancer resistance protein (BCRP) inhibitor.

Effects of medicinal and other products on ticagrelor

CYP3A4 inhibitors

- *Strong CYP3A4 inhibitors* – Co-administration of ketoconazole with ticagrelor increased the ticagrelor C_{max} and AUC equal to 2.4-fold and 7.3-fold, respectively. The C_{max} and AUC of the active metabolite were reduced by 89% and 56%, respectively. Other strong inhibitors of CYP3A4 (clarithromycin, nefazodone, ritonavir and atazanavir)

would be 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 ticagrelor C_{max} by 69% and AUC to 2.7-fold and decreased the active metabolite C_{max} by 38% and AUC was unchanged. There was no effect of ticagrelor on diltiazem plasma levels. Other moderate CYP3A4 inhibitors (e.g. amprenavir, aprepitant, erythromycin and fluconazole) would be expected to have a similar effect and can as well be co-administered with ticagrelor.
- A 2-fold increase of ticagrelor exposure was observed after daily consumption of large quantities of grapefruit juice (3x200 ml). This magnitude of increased exposure is not expected to be clinically relevant to most patients.

CYP3A inducers

Co-administration of rifampicin with ticagrelor decreased ticagrelor C_{max} and AUC by 73% and 86%, respectively. The C_{max} of the active metabolite was unchanged and the AUC was decreased by 46%, respectively. Other CYP3A inducers (e.g. phenytoin, carbamazepine and phenobarbital) would be expected to decrease the exposure to ticagrelor as well. Co-administration of ticagrelor with potent CYP3A inducers may decrease exposure and efficacy of ticagrelor, therefore, their concomitant use with ticagrelor is discouraged.

Cyclosporine (P-gp and CYP3A inhibitor)

Co-administration of cyclosporine (600 mg) with ticagrelor increased ticagrelor C_{max} and AUC equal to 2.3-fold and 2.8-fold, respectively. The AUC of the active metabolite was increased by 32% and C_{max} was decreased by 15% in the presence of cyclosporine.

No data are available on concomitant use of ticagrelor with other active substances that also are potent P-gp inhibitors and moderate CYP3A4 inhibitors (e.g. verapamil, quinidine) that also may increase ticagrelor exposure. If the association cannot be avoided, their concomitant use should be made with caution.

Others

Clinical pharmacology interaction studies showed that co-administration of ticagrelor with heparin, enoxaparin and ASA or desmopressin did not have any effect on the pharmacokinetics of ticagrelor or the active metabolite or on ADP-induced platelet aggregation compared with ticagrelor alone. If clinically indicated, medicinal products that alter haemostasis should be used with caution in combination with ticagrelor.

A delayed and decreased exposure to oral $P2Y_{12}$ inhibitors, including ticagrelor and its active metabolite, has been observed in patients with ACS treated with morphine (35% reduction in ticagrelor exposure). This interaction may be related to reduced gastrointestinal motility and apply to other opioids. The clinical relevance is unknown, but data indicate the potential for reduced ticagrelor efficacy in patients co-administered ticagrelor and morphine. In patients with ACS, in whom morphine cannot be withheld and fast $P2Y_{12}$ inhibition is deemed crucial, the use of a parenteral $P2Y_{12}$ inhibitor may be considered.

Effects of ticagrelor on other medicinal products

Medicinal products metabolised by CYP3A4

- *Simvastatin* – Co-administration of ticagrelor with simvastatin increased simvastatin C_{max} by 81% and AUC by 56% and increased simvastatin acid C_{max} by 64% and AUC by 52% with some individual increases equal to 2- to 3-fold. Co-administration of ticagrelor with doses of simvastatin exceeding 40 mg daily could cause adverse reactions of simvastatin and should be weighed against potential benefits. There was no effect of simvastatin on ticagrelor plasma levels. Ticagrelor may have similar effect on lovastatin. The concomitant use of ticagrelor with doses of simvastatin or lovastatin greater than 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 considered clinically significant.
- A similar effect on other statins metabolised by CYP3A4 cannot be excluded. Patients in PLATO receiving ticagrelor took a variety of statins, with no concern of an association with statin safety among the 93% of the PLATO cohort taking these medicinal products.

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

P-gp substrates (including digoxin, cyclosporine)
Concomitant administration of ticagrelor increased the digoxin C_{max} by 75% and AUC by 28%. The mean trough digoxin levels were increased about 30% with ticagrelor co-administration with some individual maximum increases to 2-fold. In the presence of digoxin, the C_{max} and AUC of ticagrelor and its active metabolite were not affected. Therefore, appropriate clinical and/or laboratory monitoring is recommended when giving narrow therapeutic index P-gp dependent medicinal products like digoxin concomitantly with ticagrelor.

There was no effect of ticagrelor on cyclosporine blood levels. Effect of ticagrelor on other P-gp substrates has not been studied.

Medicinal products metabolised by CYP2C9
Co-administration of ticagrelor with tolbutamide resulted in no change in the plasma levels of either medicinal product, which suggests that ticagrelor is not a CYP2C9 inhibitor and unlikely to alter the CYP2C9 mediated metabolism of medicinal products like warfarin and tolbutamide.

Rosuvastatin (BCRP substrate)
Ticagrelor has been shown to increase rosuvastatin concentrations, which may result in increased risk of myopathy, including rhabdomyolysis. Consideration should be given to the benefits of prevention of major adverse cardiovascular events by use of rosuvastatin versus the risks with increased rosuvastatin plasma concentrations.

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

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

Other concomitant therapy
In clinical studies, ticagrelor was commonly administered with ASA, proton pump inhibitors, statins, beta-blockers, angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers as needed for concomitant conditions for long-term and also heparin, low molecular weight heparin and intravenous GpIIb/IIIa inhibitors for short durations (see section 5.1). No evidence of clinically significant adverse interactions with these medicinal products was observed.

Co-administration of ticagrelor with heparin, enoxaparin or desmopressin had no effect on activated partial thromboplastin time (aPTT), activated coagulation time (ACT) or factor Xa assays. However, due to potential pharmacodynamic interactions, caution should be exercised with the concomitant administration of ticagrelor with medicinal products known to alter haemostasis.

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
Women of childbearing potential should use appropriate contraceptive measures to avoid pregnancy during ticagrelor therapy.

Pregnancy
There are no or limited amount of data from the use of ticagrelor in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Ticagrelor is not recommended during pregnancy.

Breast-feeding
Available pharmacodynamic/toxicological data in animals have shown excretion of ticagrelor and its active metabolites in milk (see section 5.3). A risk to newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from ticagrelor therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility
Ticagrelor had no effect on male or female fertility in animals (see section 5.3).

4.7 Effects on ability to drive and use machines

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.

4.8 Undesirable 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 (see section 5.1).
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 (see section 4.4).

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 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 (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥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)

SOC	Very common	Common	Uncommon	Not known
Neoplasms benign, malignant and unspecified (including cysts and polyps)			Tumour bleedings[a]	
Blood and lymphatic system disorders	Blood disorder bleedings[b]			Thrombotic Thrombocytopenic Purpura[c]
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[m]	
Eye disorders			Eye haemorrhage[e]	
Ear and labyrinth disorders		Vertigo	Ear haemorrhage	
Cardiac disorders				Bradyarrhythmia, AV block[c]
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[d]		
Injury, poisoning and procedural complications		Post procedural haemorrhage, Traumatic bleedings[l]		

a e.g. bleeding from bladder cancer, gastric cancer, colon cancer
b e.g. increased tendency to bruise, spontaneous haematoma, haemorrhagic diathesis
c Identified in post-marketing experience
d Frequencies 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.
e e.g. conjunctival, retinal, intraocular bleeding
f e.g. epistaxis, haemoptysis
g e.g. gingival bleeding, rectal haemorrhage, gastric ulcer haemorrhage
h e.g. ecchymosis, skin haemorrhage, petechiae
i e.g. haemarthrosis, muscle haemorrhage
j e.g. haematuria, cystitis haemorrhagic
k e.g. vaginal haemorrhage, haematospermia, postmenopausal haemorrhage
l e.g. contusion, traumatic haematoma, traumatic haemorrhage
m i.e. spontaneous, procedure related or traumatic intracranial 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 (see section 4.4).

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 (see section 4.4).

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 Major or Minor and PLATO Major and PLATO Major or Minor bleeding categories (see Table 3). Discontinuation of treatment due to bleeding was more common with ticagrelor 60 mg compared to ASA therapy alone (6.2% and 1.5%, respectively). The majority of these bleedings were of less severity (classified as TIMI Requiring medical attention), e.g. epistaxis, bruising and haematomas.

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

Intracranial bleeding:
Spontaneous ICHs were reported in similar rates for ticagrelor 60 mg and ASA therapy alone (n=13, 0.2% in both treatment groups). Traumatic and procedural ICHs showed a minor increase with ticagrelor 60 mg treatment, (n=15, 0.2%) compared with ASA therapy alone (n=10, 0.1%). There were 6 fatal ICHs with ticagrelor 60 mg and 5 fatal ICHs with ASA therapy alone. The incidence of intracranial bleeding was low in both treatment groups given the significant comorbidity and CV risk factors of the population under study.

Dyspnoea
Dyspnoea, a sensation of breathlessness, is reported by patients treated with ticagrelor. In PLATO, dyspnoea adverse events (AEs) (dyspnoea, dyspnoea at rest, dyspnoea exertional, dyspnoea paroxysmal nocturnal and nocturnal dyspnoea), when combined, was reported by 13.8% of patients treated with ticagrelor and by 7.8% of patients treated with clopidogrel. In 2.2% of patients taking ticagrelor and by 0.6% taking clopidogrel investigators considered the dyspnoea causally related to treatment in the PLATO study and few were serious (0.14% ticagrelor; 0.02% clopidogrel), (see section 4.4). Most reported symptoms of dyspnoea were mild to moderate in intensity, and most were reported as a single episode early after starting treatment.

Compared with clopidogrel, patients with asthma/COPD treated with ticagrelor may have an increased risk of experiencing non-serious dyspnoea (3.29% ticagrelor versus 0.53% clopidogrel) and serious dyspnoea (0.38% ticagrelor versus 0.00% clopidogrel). In absolute terms, this risk was higher than in the overall PLATO population. Ticagrelor should be used with caution in patients with history of asthma and/or COPD (see section 4.4).

About 30% of episodes resolved within 7 days. PLATO included patients with baseline congestive heart failure, COPD or asthma; these patients, and the elderly, were more likely to report dyspnoea. For ticagrelor, 0.9% of patients discontinued study drug because of dyspnoea compared with 0.1% taking clopidogrel. The higher incidence of dyspnoea with ticagrelor is not associated with new or worsening heart or lung disease (see section 4.4). Ticagrelor does not affect tests of pulmonary function.

In PEGASUS, dyspnoea was reported in 14.2% of patients taking ticagrelor 60 mg twice daily and in 5.5% of patients taking ASA alone. As in PLATO, most reported dyspnoea was mild to moderate in intensity (see section 4.4). Patients who reported dyspnoea tended to be older and more frequently had dyspnoea, COPD or asthma at baseline.

Investigations
Uric acid elevations: In PLATO, serum uric acid increased to more than upper limit of normal in 22% of patients receiving ticagrelor compared to 13% of patients receiving clopidogrel. The corresponding numbers in PEGASUS were 9.1%, 8.8% and 5.5% for ticagrelor 90 mg, 60 mg and placebo, respectively. Mean serum uric acid increased approximately 15% with ticagrelor compared to approximately 7.5% with clopidogrel and after treatment was stopped, decreased to approximately 7% on ticagrelor but with no decrease observed for clopidogrel. In PEGASUS, a reversible increase in mean serum uric acid levels of 6.3% and 5.6% was found for ticagrelor 90 mg and 60 mg, respectively, compared to a 1.5% decrease in the placebo group. In PLATO, the frequency of gouty arthritis was 0.2% for ticagrelor vs. 0.1% for clopidogrel. The corresponding numbers for gout/gouty arthritis in PEGASUS were 1.6%, 1.5% and 1.1% for ticagrelor 90 mg, 60 mg and placebo, respectively.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance. Website: www.hpra.ie.

4.9 Overdose

Ticagrelor is well tolerated in single doses up to 900 mg. Gastrointestinal toxicity was dose-limiting in a single ascending dose study. Other clinically meaningful adverse reactions which may occur with overdose include dyspnoea and ventricular pauses (see section 4.8).

In the event of an overdose, the above potential adverse reactions could occur and 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). Treatment of overdose should follow local standard medical practice. The expected effect of excessive ticagrelor dosing is prolonged duration of bleeding risk associated with platelet inhibition. Platelet transfusion is unlikely to be of clinical benefit in patients with bleeding (see section 4.4). If bleeding occurs other appropriate supportive measures should be taken.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action
Ticagrelor Krka contains ticagrelor, a member of the chemical class cyclopentyltriazolopyrimidines (CPTP), which is an oral, direct acting, selective and reversibly binding $P2Y_{12}$ receptor antagonist that prevents ADP-mediated $P2Y_{12}$ dependent platelet activation and aggregation. Ticagrelor does not prevent ADP binding but when bound to the $P2Y_{12}$ receptor prevents ADP-induced signal transduction. Since platelets participate in the initiation and/or evolution of thrombotic complications of atherosclerotic disease, inhibition of platelet function has been shown to reduce the risk of CV events such as death, MI or stroke.

Ticagrelor also increases local endogenous adenosine levels by inhibiting the equilibrative nucleoside transporter-1 (ENT-1).

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

Pharmacodynamic effects
Onset of action
In patients with stable coronary artery disease (CAD) on ASA, ticagrelor demonstrates a rapid onset of pharmacological effect as demonstrated by a mean inhibition of platelet aggregation (IPA) for ticagrelor at 0.5 hours after 180 mg loading dose of about 41%, with the maximum IPA effect of 89% by 2-4 hours post dose, and maintained between 2-8 hours. 90% of patients had final extent IPA>70% by 2 hours post dose.

Offset of action
If a CABG procedure is planned, ticagrelor bleeding risk is increased compared to clopidogrel when discontinued within less than 96 hours prior to procedure.

Switching data
Switching from clopidogrel 75 mg to ticagrelor 90 mg twice daily results in an absolute IPA increase of 26.4% and switching from ticagrelor to clopidogrel results in an absolute IPA decrease of 24.5%. Patients can be switched from clopidogrel to ticagrelor without any interruption of antiplatelet effect (see section 4.2).

Clinical efficacy and safety
The clinical evidence for the efficacy and safety of ticagrelor is derived from two phase 3 trials:

- The PLATO [PLATelet Inhibition and Patient Outcomes] study, a comparison of ticagrelor to clopidogrel, both given in combination with ASA and other standard therapy.
- The PEGASUS TIMI-54 [PrEvention with TicaGrelor of SecondAry Thrombotic Events in High-RiSk AcUte Coronary Syndrome Patients] study, a comparison of ticagrelor combined with ASA to ASA therapy alone.

PLATO study (Acute Coronary Syndromes)

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

Clinical efficacy

On a background of daily ASA, ticagrelor 90 mg twice daily showed superiority to 75 mg daily clopidogrel in preventing the composite endpoint of CV death, MI or stroke, with the difference driven by CV death and MI. Patients received a 300 mg loading dose of clopidogrel (600 mg possible if having PCI) or 180 mg of ticagrelor.

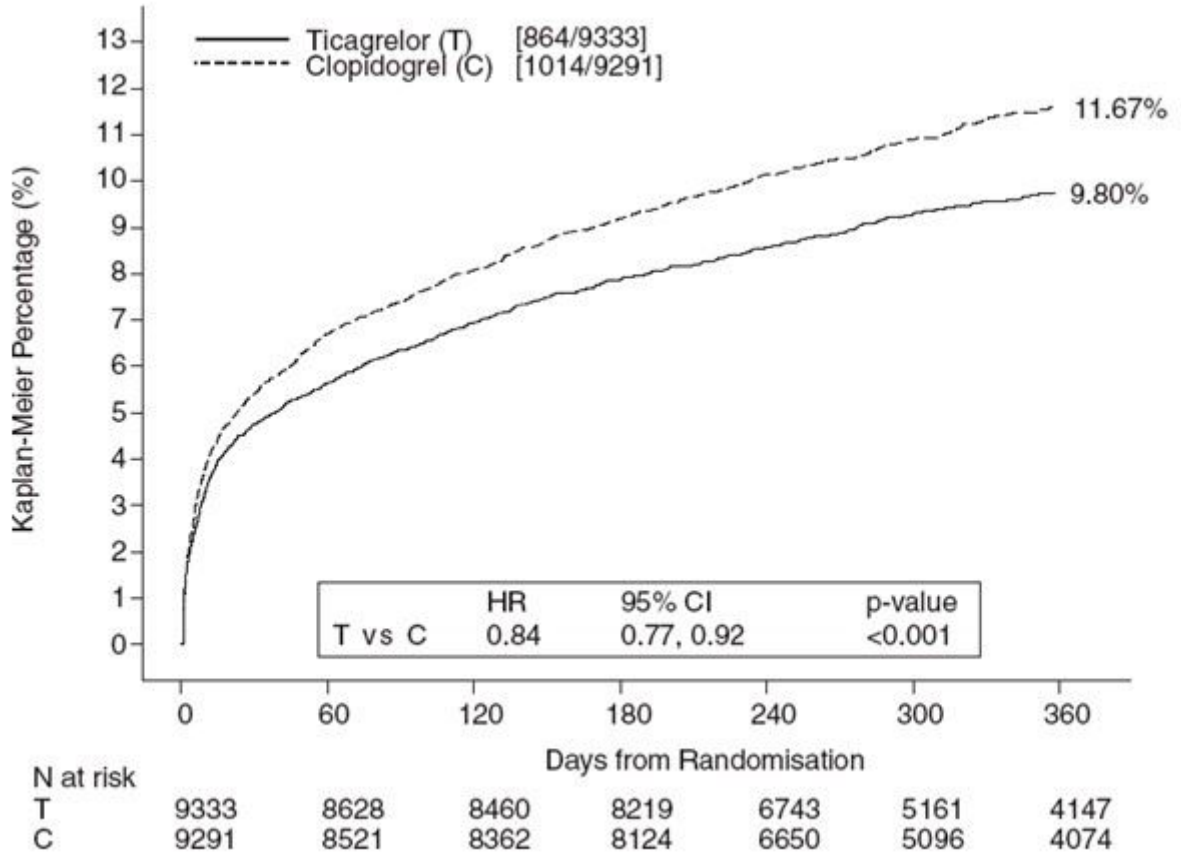
The result appeared early (absolute risk reduction [ARR] 0.6% and relative risk reduction [RRR] of 12% at 30 days), with a constant treatment effect over the entire 12-month period, yielding ARR 1.9% per year with RRR of 16%. This suggests it is appropriate to treat patients with ticagrelor 90 mg twice daily for 12 months (see section 4.2). Treating 54 ACS patients with ticagrelor instead of clopidogrel will prevent 1 atherothrombotic event; treating 91 will prevent 1 CV death (see Figure 1 and Table 4).

The treatment effect of ticagrelor over clopidogrel appears consistent across many subgroups, including weight; sex; medical history of diabetes mellitus, transient ischaemic attack or non-haemorrhagic stroke, or revascularisation; concomitant therapies including heparins, GpIIb/IIIa inhibitors and proton pump inhibitors (see section 4.5); final index event diagnosis (STEMI, NSTEMI or UA); and treatment pathway intended at randomisation (invasive or medical).

A weakly significant treatment interaction was observed with region whereby the hazard ratio (HR) for the primary endpoint favours ticagrelor in the rest of world but favours clopidogrel in North America, which represented approximately 10% of the overall population studied (interaction p-value=0.045). Exploratory analyses suggest a possible association with ASA dose such that reduced efficacy was observed with ticagrelor with increasing ASA doses. Chronic daily ASA doses to accompany ticagrelor should be 75-150 mg (see sections 4.2 and 4.4).

Figure 1 shows the estimate of the risk to the first occurrence of any event in the composite efficacy endpoint.

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



Ticagrelor reduced the occurrence of the primary composite endpoint compared to clopidogrel in both the UA/NSTEMI and STEMI population (Table 4). Thus, Ticagrelor Krka 90 mg twice daily together with low-dose ASA can be used in patients with ACS (unstable angina, non-ST elevation Myocardial Infarction [NSTEMI] or ST elevation Myocardial Infarction [STEMI]); including patients managed medically, and those who are managed with percutaneous coronary intervention (PCI) or coronary artery by-pass grafting (CABG).

Table 4 - Analysis of primary and secondary efficacy endpoints (PLATO)

	Ticagrelor 90 mgtwice daily (% patients with event) N=9333	Clopidogrel 75 mg once daily (% patients with event) N=9291	ARR[a] (%/yr)	RRR[a] (%) (95% CI)	*p*-value
CV death, MI (excl. silent MI) or stroke	9.3	10.9	1.9	16 (8, 23)	0.0003
Invasive intent	8.5	10.0	1.7	16 (6, 25)	0.0025
Medical intent	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 (excl. 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 (excl. silent MI) or stroke	9.7	11.5	2.1	16 (8, 23)	0.0001
CV death, total MI, stroke, SRI, RI, TIA or other ATE[c]	13.8	15.7	2.1	12 (5, 19)	0.0006
All-cause mortality	4.3	5.4	1.4	22 (11, 31)	0.0003[d]
Definite stent thrombosis	1.2	1.7	0.6	32 (8, 49)	0.0123[d]

a ARR = absolute risk reduction; RRR = relative risk reduction = (1-Hazard ratio) x 100%. A negative RRR indicates a relative risk increase.
b Excluding silent MI.
c SRI = serious recurrent ischaemia; RI = recurrent ischaemia; TIA = transient ischaemic attack; ATE = arterial thrombotic event. Total MI includes silent MI, with date of event set to date when discovered.
d Nominal significance value; all others are formally statistically significant by pre-defined hierarchical testing.

PLATO genetic substudy
CYP2C19 and ABCB1 genotyping of 10,285 patients in PLATO provided associations of genotype groups with PLATO outcomes. The superiority of ticagrelor over clopidogrel in reducing major CV events was not significantly affected by patient 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 clopidogrel in patients with one or more CYP2C19 loss of function alleles, but similar to clopidogrel in patients with no loss of function allele.

Combined efficacy and safety composite
A combined efficacy and safety composite (CV death, MI, stroke or PLATO-defined 'Total Major' bleeding) indicates that the benefit in efficacy of ticagrelor compared to clopidogrel is not offset by the major bleeding events (ARR 1.4%, RRR 8%, HR 0.92; p=0.0257) over 12 months after ACS.
Clinical safety

Holter substudy:
To study the occurrence of ventricular pauses and other arrhythmic episodes during PLATO, investigators performed Holter monitoring in a subset of nearly 3000 patients, of whom approximately 2000 had recordings both in the acute phase of their

ACS and after one month. The primary variable of interest was the occurrence of ventricular pauses ≥3 seconds. More patients had ventricular pauses with ticagrelor (6.0%) than with clopidogrel (3.5%) in the acute phase; and 2.2% and 1.6%, respectively, after 1 month (see section 4.4). The increase in ventricular pauses in the acute phase of ACS was more pronounced in ticagrelor patients with history of CHF (9.2% versus 5.4% in patients without CHF history; for clopidogrel patients, 4.0% in those with versus 3.6% in those without CHF history). This imbalance did not occur at one month: 2.0% versus 2.1% for ticagrelor patients with and without CHF history, respectively; and 3.8% versus 1.4% with clopidogrel. There were no adverse clinical consequences associated with this imbalance (including pacemaker insertions) in this population of patients.

PEGASUS study (History of Myocardial Infarction)

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

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

Patients were ineligible if there was planned use of a $P2Y_{12}$ receptor antagonist, dipyridamole, cilostazol, or anticoagulant therapy during the study period; if they had a bleeding disorder or a history of an ischaemic stroke or intracranial bleeding, a central nervous system tumour or an intracranial vascular abnormality; if they had had gastrointestinal bleeding within the previous 6 months or major surgery within the previous 30 days.

Clinical efficacy

Figure 2 - Analysis of primary clinical composite endpoint of CV death, MI and stroke (PEGASUS)

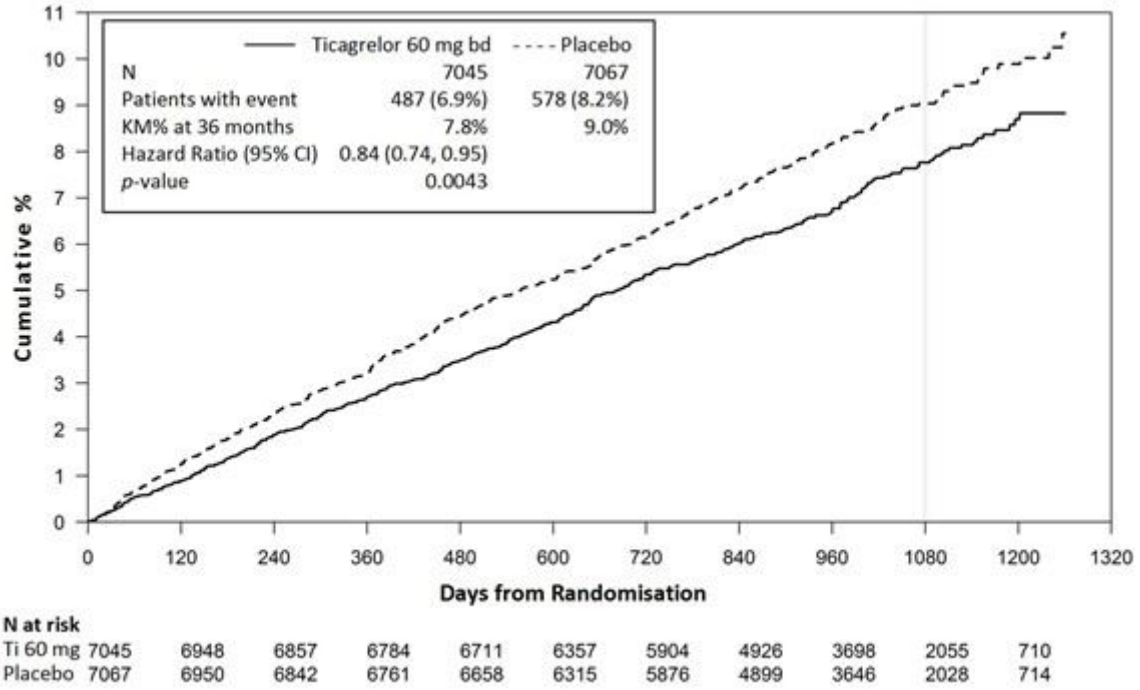


Table 5 - Analysis of primary and secondary efficacy endpoints (PEGASUS)

	Ticagrelor 60 mg twice daily +ASA N = 7045			**ASA alone N = 7067**		
Characteristic	**Patients with events**	**KM %**	**HR (95% CI)**	**Patients with events**	**KM %**	***p*-value**
Primary endpoint						
Composite of CV Death/MI/Stroke	487 (6.9%)	7.8%	0.84 (0.74, 0.95)	578 (8.2%)	9.0%	0.0043 (s)
CV death	174 (2.5%)	2.9%	0.83 (0.68, 1.01)	210 (3.0%)	3.4%	0.0676
MI	285 (4.0%)	4.5%	0.84 (0.72, 0.98)	338 (4.8%)	5.2%	0.0314
Stroke	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 vs. ASA therapy alone from Cox proportional hazards model with treatment group as the only explanatory variable.
KM percentage calculated at 36 months.
Note: the number of first events for the components CV death, MI and stroke are the actual number of first events for each component and do not add up to the number of events in the composite endpoint
(s) Indicates statistical significance.
CI = Confidence interval; CV = Cardiovascular; HR = Hazard ratio; KM = Kaplan-Meier; MI = Myocardial infarction; N = Number of patients.

Both 60 mg twice daily and 90 mg twice daily regimens of ticagrelor in combination with ASA were superior to ASA alone in the prevention of atherothrombotic events (composite endpoint: CV death, MI and stroke), with a consistent treatment effect over the entire study period, yielding a 16% RRR and 1.27% ARR for ticagrelor 60 mg and a 15% RRR and 1.19% ARR for ticagrelor 90 mg.

Although the efficacy profiles of 90 mg and 60 mg were similar, there is evidence that the lower dose has a better tolerability and safety profile in relation to risk of the bleeding and dyspnoea. Therefore, only Ticagrelor Krka 60 mg twice daily co-administered with ASA is recommended for the prevention atherothrombotic events (CV death, MI and stroke) in patients with a history of MI and a high risk of developing an atherothrombotic event.
Relative to ASA alone, ticagrelor 60 mg twice daily significantly reduced the primary composite endpoint of CV death, MI and stroke. Each of the components contributed to the reduction in the primary composite endpoint (CV death 17% RRR, MI 16% RRR and stroke 25% RRR).

The RRR for the composite endpoint from 1 to 360 days (17% RRR) and from 361 days and onwards (16% RRR) was similar. There are limited data on the efficacy and safety of ticagrelor beyond 3 years of extended treatment.

There was no evidence of benefit (no reduction in the primary composite endpoint of CV death, MI and stroke, but an increase in major bleeding) when ticagrelor 60 mg twice daily was introduced in clinically stable patients >2 years from the MI, or more than one year after stopping previous ADP receptor inhibitor treatment (see also section 4.2).

Clinical safety
The rate of discontinuations with ticagrelor 60 mg due to bleeding and dyspnoea was higher in patients >75 years (42%) than in younger patients (range: 23-31%), with a difference versus placebo higher than 10% (42% vs. 29%) in patients >75 years.

Paediatric population
In a randomised, double-blind, parallel-group Phase III study (HESTIA 3), 193 paediatric patients (ages 2 to less than 18 years) with sickle cell disease were randomised to receive either placebo or ticagrelor at doses of 15 mg to 45 mg twice daily depending on body weight. Ticagrelor resulted in a median platelet inhibition of 35% at pre-dose and 56% at 2 hours post-dose at steady state. Compared to placebo, there was no treatment benefit of ticagrelor on the rate of vaso-occlusive crises.

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

5.2 Pharmacokinetic properties

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

Absorption
Absorption of ticagrelor is rapid with a median t_{max} of approximately 1.5 hours. The formation of the major circulating metabolite AR-C124910XX (also active) from ticagrelor is rapid with a median t_{max} of approximately 2.5 hours. Following an oral ticagrelor 90 mg single dose under fasted conditions in healthy subjects, C_{max} is 529 ng/ml and AUC is 3451 ng*h/ml. The metabolite parent 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 that in the ACS population. Based on a population pharmacokinetic analysis of the PEGASUS study the median ticagrelor C_{max} was 391 ng/ml and AUC was 3801 ng*h/ml at steady state for ticagrelor 60 mg. For ticagrelor 90 mg C_{max} was 627 ng/ml and AUC was 6255 ng*h/ml at steady state.

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

Ticagrelor as crushed tablets mixed in water, given orally or administered through a nasogastric tube into the stomach, has a comparable bioavailability to whole tablets with regards to AUC and C_{max} for ticagrelor and the active metabolite. Initial exposure (0.5 and 1 hour post-dose) from crushed ticagrelor tablets mixed in water was higher compared to whole tablets, with a generally identical concentration profile thereafter (2 to 48 hours).

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

Biotransformation
CYP3A4 is the major enzyme responsible for ticagrelor metabolism and the formation of the active metabolite and their interactions with other CYP3A substrates ranges from activation through to inhibition.

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

Elimination
The primary route of ticagrelor elimination is via hepatic metabolism. When radiolabelled ticagrelor is administered, the mean recovery of radioactivity is approximately 84% (57.8% in faeces, 26.5% in urine). Recoveries of ticagrelor and the active metabolite in urine were both less than 1% of the dose. The primary route of elimination for the active metabolite is most likely via biliary secretion. The mean $t_{1/2}$ was approximately 7 hours for ticagrelor and 8.5 hours for the active metabolite.

Special populations

Elderly
Higher exposures to ticagrelor (approximately 25% for both C_{max} and AUC) and the active metabolite were observed in elderly (≥75years) ACS patients compared to younger patients by the population pharmacokinetic analysis. These differences are not considered clinically significant (see section 4.2).

Paediatric population
Limited data are available in children with sickle cell disease (see sections 4.2 and 5.1).

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, were administered ticagrelor as paediatric dispersible 15 mg tablets at doses of respectively 15, 30 and 45 mg twice daily. Based on population pharmacokinetic analysis, the mean AUC ranged from 1095 ng*h/mL to 1458 ng*h/mL and the mean Cmax ranged from 143 ng/mL to 206 ng/mL at steady state.

Gender
Higher exposures to ticagrelor and the active metabolite were observed in women compared to men. These differences are not considered clinically significant.

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

In patients with end stage renal disease on haemodialysis AUC and C_{max} of ticagrelor 90 mg administered on a day without dialysis were 38% and 51% higher compared to subjects with normal renal function. A similar increase in exposure was observed when ticagrelor was administered immediately prior to dialysis (49% and 61%, respectively) showing that ticagrelor is not dialysable. Exposure of the active metabolite increased to a lesser extent (AUC 13-14% and C_{max} 17-36%). The inhibition of platelet aggregation (IPA) effect of ticagrelor was independent of dialysis in patients with end stage renal disease and similar to subjects with normal renal function (see section 4.2).

Hepatic impairment
C_{max} and AUC for ticagrelor were 12% and 23% higher in patients with mild hepatic impairment compared to matched healthy subjects, respectively, however, the IPA effect of ticagrelor was similar between the two groups. No dose adjustment is needed for patients with mild hepatic impairment. Ticagrelor has not been studied in patients with severe hepatic impairment and there is no pharmacokinetic information in patients with moderate hepatic impairment. In patients that had moderate or severe

elevation in one or more liver function tests at baseline, ticagrelor plasma concentrations were on average similar or slightly higher as compared to those without baseline elevations. No dose adjustment is recommended in patients with moderate hepatic impairment (see sections 4.2 and 4.4).

Ethnicity
Patients of Asian descent have a 39% higher mean bioavailability compared to Caucasian patients. Patients self-identified as black had an 18% lower bioavailability of ticagrelor compared to Caucasian patients, in clinical pharmacology studies, the exposure (C_{max} and AUC) to ticagrelor in Japanese subjects was approximately 40% (20% after adjusting for body weight) higher compared to that in Caucasians. The exposure in patients self-identified as Hispanic or Latino was similar to that in Caucasians.

5.3 Preclinical safety data

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

Gastrointestinal irritation was observed in several animal species at clinical relevant exposure levels (see section 4.8).

In female rats, ticagrelor at high dose showed an increased incidence of uterine tumours (adenocarcinomas) and an increased incidence of hepatic adenomas. The mechanism for uterine tumours is likely hormonal imbalance which can lead to tumours in rats. The mechanism for the hepatic adenomas is likely due to a rodent-specific enzyme induction in the liver. Thus, the carcinogenicity findings are considered unlikely to be relevant for humans.

In rats, minor developmental anomalies were seen at a maternal toxic dose (safety margin of 5.1). In rabbits, a slight delay in hepatic maturity and skeletal development was seen in foetuses from dams at high dose without showing maternal toxicity (safety margin of 4.5).

Studies in rats and rabbits have shown reproductive toxicity, with slightly reduced maternal body weight gain and reduced neonatal viability and birth weight, with delayed growth. Ticagrelor produced irregular cycles (mostly extended cycles) in female rats, but did not affect overall fertility in male and female rats. Pharmacokinetic studies performed with radiolabelled ticagrelor have shown that the parent compound and its metabolites are excreted in the milk of rats (see section 4.6).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Microcrystalline cellulose (E460)
Calcium hydrogen phosphate dihydrate (E341)
Hypromellose 2910 (E464)
Croscarmellose sodium (E468)
Magnesium stearate (E470b)

Film coating:
Hypromellose (E464)
Titanium dioxide (E171)
Talc (E553b)
Propylene glycol (E1520)
Yellow iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Blister (PVC/PVDC//Alu): 14, 56, 60, 100 or 168 film-coated tablets, in a box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

For patients who are unable to swallow the tablet(s) whole, the tablets can be crushed to a fine powder and mixed in half a glass of water and drunk immediately. The glass should be rinsed with a further half glass of water and the contents drunk. The mixture can also be administered via a nasogastric tube (CH8 or greater). It is important to flush the nasogastric tube through two (2) times with 50 ml of water after administration of the mixture.

7 MARKETING AUTHORISATION HOLDER

KRKA, d.d., Novo mesto
Šmarješka cesta 6
8501 Novo mesto
Slovenia

8 MARKETING AUTHORISATION NUMBER

PA1347/102/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12th February 2021
Date of last renewal: 30th November 2025

10 DATE OF REVISION OF THE TEXT

June 2026