THINHET 60
(Ticagrelor 60 mg Film-Coated Tablets)
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1. NAME OF THE MEDICINAL PRODUCT
THINHET 60 (Ticagrelor 60 mg Film-Coated Tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains 60 mg of Ticagrelor.
*THINHET contains less than 1 mmol sodium (23 mg) per dose, i.e. is essentially 'sodium-free.'

3. PHARMACEUTICAL FORM
Film-coated tablet

3.1 Product description
Peach to light brown, round shaped, biconvex film-coated tablets with approx. diameter of 8.05mm debossed with "68" on one side and "V1" on other side.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
History of Myocardial Infarction (at least one year ago)
Ticagrelor 60mg, co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of atherothrombotic events (cardiovascular death, myocardial infarction and stroke) in adult patients with a history of myocardial infarction (MI) (MI occurred at least one year ago), and a high risk of developing an atherothrombotic event.

Coronary Artery Disease, Type 2 Diabetes Mellitus and History of Percutaneous Coronary Intervention
Ticagrelor 60mg, co-administered with low-dose acetylsalicylic acid (ASA: 75-150mg), is indicated to reduce the risk of a first myocardial infarction or stroke in patients with coronary artery disease (CAD), Type 2 Diabetes Mellitus (DM) and a history of percutaneous coronary intervention (PCI), who are also at high risk of developing an atherothrombotic events.

4.2 Posology and method of administration
Posology
History of Myocardial Infarction (at least one year ago)
Patients taking Ticagrelor 60 mg should also take a daily low maintenance dose of ASA 75-150 mg, unless specifically contraindicated.

Ticagrelor 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. Treatment may be started without interruption as continuation therapy after the initial one-year treatment with Ticagrelor 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 is limited data on the efficacy and safety of Ticagrelor 60 mg beyond 3 years of extended treatment. If a switch is needed, the first dose should be administered 24 hours following the last dose of the other antiplatelet medication.

Patients with Coronary Artery Disease (CAD) and Type 2 Diabetes Mellitus (DM) with a history of percutaneous coronary intervention (PCI)
Ticagrelor 60 mg twice daily is recommended dose for patients with CAD and type 2 DM with a history of PCI with no prior MI. No loading dose of Ticagrelor 60 mg is required. Patients may start treatment with Ticagrelor 60 mg twice daily, regardless of their previous antiplatelet regimen.

Treatment with Ticagrelor 60 mg should be continued in patients with CAD and type 2 DM for as long as the patient remains at high risk of an atherothrombotic events and low risk of bleeding, for a duration up to three years. Efficacy and safety data are insufficient to establish whether the benefits of Ticagrelor 60 mg still outweigh the risks after three years of treatment. If a switch is needed, the first dose of Ticagrelor 60 mg 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 60 mg should take only one tablet (their next dose) at its scheduled time.

Special populations
Elderly
No dose adjustment is required in elderly.

Renal impairment
No dose adjustment is necessary for patients with renal impairment.

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

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.

Method of administration
For oral use. Ticagrelor can be taken 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 (CH8 or greater). It is important to flush the nasogastric tube through with water after administration of the mixture.

4.3 Contraindications
- Hypersensitivity to the active substance or to any of the excipients listed.
- Active pathological bleeding.
- History of intracranial haemorrhage.
- Severe hepatic impairment.
- 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.

4.4 Special warning and precautions for use
Benefit- risk in patients with coronary artery disease (CAD) and type-2 diabetes mellitus (DM)
In the THEMIS trial, a positive benefit-risk profile was observed in the pre-specified subgroup of patients who have a history of percutaneous intervention (PCI), representing 58% of the overall THEMIS trial population. In the full THEMIS population, the benefit-risk profile was not considered favourable to support use of ticagrelor. Before initiating treatment in patients with CAD, type-2 diabetes and a history of PCI, it should be confirmed that a patient is at high risk of atherothombotic events and low risk of bleeding.

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. The treating physician should regularly reassess whether treatment with ticagrelor remains appropriate, particularly if there is a change in the factors associated with an increased risk of bleeding.

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.
- 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.

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

Antifibrinolytic therapy (aminocaproic acid or tranexamic acid) and/or recombinant factor VIIa therapy may 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. If a patient is to undergo elective surgery and antiplatelet effect is not desired, ticagrelor should be discontinued 5 days prior to surgery.

Patients with prior ischaemic stroke
In PEGASUS, (history of MI ≥ one year) and THEMIS (CAD and type 2 DM) trials, patients with prior ischaemic stroke were not included. Therefore, in the absence of data, treatment beyond one year is not recommended in these patients. Treatment in patients with CAD, type 2 DM and prior ischaemic stroke is also not recommended.

Hepatic impairment
Use of ticagrelor is contraindicated in patients with severe hepatic impairment. There is limited experience with ticagrelor in patients with moderate hepatic impairment, therefore, caution is advised in these patients.

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 atrioventricular (AV) block or bradycardic-related syncope) have been excluded from the main studies evaluating the safety and efficacy of ticagrelor as they may be at increased risk of developing bradyarrhythmias with ticagrelor. Therefore, due to the limited clinical experience, ticagrelor should be used with caution in these patients.

Bradyarrhythmic events, including 2nd and 3rd degree AV block, have however been reported in the post-marketing setting in patients with or without history of bradyarrhythmia, in most cases, shortly after initiation of treatment with ticagrelor. Therefore, ticagrelor should be used with caution and these patients should be closely monitored during the first few weeks on treatment.

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 and the PEGASUS trials during 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). In THEMIS, 73.8% of patients took beta blocker at study-entry.

During the Holter substudy in PLATO, more patients had ventricular pauses >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.

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 a 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.

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. 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.

Premature discontinuation
Premature discontinuation with any antiplatelet therapy, including Ticagrelor, 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.

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.
- 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 (3 x 200 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 P2Y12 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 effects of simvastatin and should be weighed against potential benefits. There was no effect of simvastatin on ticagrelor plasma levels. Ticagrelor may have a 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. The 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. Consideration should be given to the benefits of prevention of major adverse cardiovascular events by use of rosuvastatin and 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. 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. 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. 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. 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.

4.7 Effect 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 Side effects
Summary of the safety profile
The safety profile of ticagrelor has been evaluated in three large randomized phase 3 outcome trials (PLATO, PEGASUS and THEMIS) including more than 58,000 patients of which more than 32,000 patients were exposed to ticagrelor.

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. In the subgroup of THEMIS patients with history of PCI, discontinuation of study drug due to adverse events was higher for ticagrelor (21.3%) in combination with ASA versus ASA alone(13.0%) The most common adverse events leading to study discontinuation reported at higher rates with ticagrelor compared to ASA alone were dyspnoea, increased tendency to bruise, epistaxis and ecchymosis.

Tabulated list of adverse reactions
The following adverse reactions have been identified following studies or have been reported in postmarketing experience with ticagrelor.
Adverse reactions are listed by MedDRA System Organ Class (SOC). Within each SOC the adverse reactions are ranked by frequency categories. 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	
Vascular disorders		Hypotension		
Cardiac disorders				Bradyarrhythmia[c] AV block (2nd and 3rd degree)[c]
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 and connective tissue disorders			Muscular bleedings[i]	
Renal and urinary disorders		Urinary tract bleedings[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]		

AV = atrioventricular
[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/lifethreatening	5.8	5.8	0.6988
Non-CABG PLATO Major	4.5	3.8	0.0264
Non-Procedural PLATO Major	3.1	2.3	0.0058
PLATO total major + minor	16.1	14.6	0.0084
Non-procedural PLATO major + minor	5.9	4.3	<0.0001
TIMI-defined major	7.9	7.7	0.5669
TIMI-defined major + minor	11.4	10.9	0.3272

Bleeding category definitions:
Major Fatal/Life-threatening Bleed: Clinically apparent with >50 g/l decrease in haemoglobin or ≥4 red cell units transfused; or fatal; or intracranial; or intrapericardial with cardiac tamponade; or with hypovolaemic shock or severe hypotension requiring pressors or surgery.
Major Other: Clinically apparent with 30-50 g/L decrease in haemoglobin or 2-3 red cell units transfused; or significantly disabling.
Minor Bleed: Requires medical intervention to stop or treat bleeding.
TIMI Major Bleed: Clinically apparent with >50 g/l decrease in haemoglobin or intracranial haemorrhage.
TIMI Minor Bleed: Clinically apparent with 30-50 g/l decrease in haemoglobin.
*p-value calculated from Cox proportional hazards model with treatment group as the only explanatory variable.
Ticagrelor and clopidogrel did not differ in rates of PLATO Major Fatal/Life-threatening bleeding, PLATO total Major bleeding, TIMI Major bleeding, or TIMI Minor bleeding (Table 2). However, more PLATO combined Major + Minor bleeding occurred with ticagrelor compared with clopidogrel. Few patients in PLATO had fatal bleeds: 20 (0.2%) for ticagrelor and 23 (0.3%) for clopidogrel.
Age, sex, weight, race, geographic region, concurrent conditions, concomitant therapy, and medical history, including a previous stroke or transient ischaemic attack, all did not predict either overall or non-procedural PLATO Major bleeding. Thus, no particular group was identified at risk for any subset of bleeding.

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

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

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

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

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

		Ticagrelor 60 mg twice daily + ASA N = 6958		ASA alone N = 6996	
Safety endpoints		**KM%**	**Hazard Ratio (95% CI)**	**KM5**	***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 hospitalization, OR prompting evaluation.

Leaflet Size : 220 X 620 mm

Printing Colour
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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.

Bleeding findings in THEMIS patients who had undergone PCI

The primary safety endpoint in the THEMIS study was the 'TIMI Major Bleeding' events. The safety analysis included also the PLATO and BARC bleeding classifications.

In THEMIS, the rate of TIMI Major bleeding was higher for ticagrelor twice daily than for ASA alone (Kaplan-Meier estimate at 36 months: 2.2% vs. 1.2%, respectively, p < 0.0001). This higher incidence was characterized by a greater number of fatal bleedings (17 for ticagrelor vs. 10 for ASA) and intracranial haemorrhages (70 for ticagrelor vs. 46 for ASA alone). Most of the intracranial haemorrhages reported in the ticagrelor treatment arm were traumatic events (N = 41), most commonly reported in subdural location.

In the subgroup of patients with a history of PCI, the incidence of TIMI Major bleeding was also higher for ticagrelor compared to ASA alone (Table 4). There were few fatal bleeding events, 6 for ticagrelor in combination with ASA and 6 for ASA therapy alone. The number of patients with intracranial haemorrhages was 33 for ticagrelor in combination with ASA and 31 for ASA alone, corresponding to KM percentages of 0.7% and 0.6%, respectively, p = 0.4545. The rate of fatal bleeding and intracranial haemorrhage was however similar in both treatment arms. Among the cases of ICH reported with ticagrelor, 23 were traumatic and 10 were spontaneous. The observed increased risk of TIMI Major bleeding with ticagrelor was therefore primarily due to a higher frequency of events within the system organ class (SOC) gastrointestinal disorders; and injury, poisoning and procedural complications.

Table 4 – Analysis of bleeding events, Kaplan-Meier estimates of bleeding rates by treatment at 36 months in the THEMIS subgroup of patients with a history of PCI ("on treatment analysis")

	Ticagrelor twice daily with ASA N = 5536	ASA alone N = 5564	Hazard Ratio (95% CI)	*p*-value
Safety endpoints	**KM%**	**KM%**		
TIMI-defined bleeding categories				
TIMI major	2.4%	1.3%	2.03 (1.48, 2.76)	< 0.0001
TIMI major or minor	3.4%	1.7%	2.23 (1.70, 2.92)	< 0.0001
TIMI major or minor or requiring medical attention	13.1%	6.3%	2.28 (1.99, 2.62)	< 0.0001
PLATO-defined bleeding categories				
PLATO Major	3.8%	1.9%	2.22 (1.72, 2.86)	< 0.0001
Fatal/life-Othreatening	2.5%	1.3%	2.10 (1.54, 2.86)	< 0.0001
Other PLATO major	1.5%	0.6%	2.53 (1.64, 3.93)	< 0.0001

Bleeding category definitions:

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

If CABG related bleeding: fatal bleeding or perioperative intracranial bleeding or reoperation following closure of the sternotomy incision for the purpose of controlling bleeding or transfusion of ≥ 5 units of whole blood or PRBCs within a 48 hour period (cell saver transfusion was not counted in calculations of blood products) or chest tube output > 2 L within a 24 hour period.

TIMI Minor: Clinically apparent with 30-50 g/L decrease in Hgb or ≥ 10% to < 15% decrease in Hct, OR if no observed blood loss; ≥ 40 g/L decrease in Hgb concentration or ≥ 12% decrease in Hct.

TIMI Requiring medical attention: Requiring intervention, OR leading to hospitalization, 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 Hgb OR ≥ 4 red cell units transfused.

Discontinuation of study drug due to bleeding events in patients with a history of PCI was more common with ticagrelor compared to ASA alone (4.7% and 1.3%, respectively). Epistaxis and increased tendency to bruise were the most common bleeding events resulting in the discontinuation of ticagrelor treatment.

Bleeding in Patient Subpopulations: The bleeding profile of ticagrelor was generally consistent across multiple pre-defined subgroups (e.g., by age, gender, weight, ethnicity, geographic region, concurrent conditions, concomitant therapy, and medical history).

Other Adverse Events

In the THEMIS study protocol, adverse event collection was limited to serious adverse events, discontinuations due to adverse events and adverse events of interest. Adverse event data collected in the THEMIS trial appears consistent with data from PLATO and PEGASUS trials.

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. 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.

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. 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. Patients who reported dyspnoea tended to be older and more frequently had dyspnoea, COPD or asthma at baseline.

In THEMIS, patients who had undergone PCI, dyspnoea was reported in 22.0% of patients taking ticagrelor twice daily in combination with ASA and in 7.5% of patients taking ASA alone. Most reported dyspnoea was mild to moderate in intensity.

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.

4.9 Symptoms and treatment of 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.

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. 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. If bleeding occurs 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, a member of the chemical class cyclopentyl triazolopyrimidines (CPTP), which is an oral, direct acting, selective and reversibly binding $P2Y_{12}$ receptor antagonist that prevents ADP-mediated P2Y12 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 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.

Clinical efficacy and safety

The clinical evidence for the efficacy and safety of ticagrelor is derived from the PEGASUS TIMI54 [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 and the THEMIS [effect of Ticagrelor on Health outcomes in Diabetes Mellitus patients Intervention Study] study, a comparison of ticagrelor in combination with ASA to ASA alone in patients with CAD and type 2 DM.

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 P2Y12 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 gastrointestinal bleeding within the previous 6 months or major surgery within the previous 30 days.

Clinical efficacy

Figure 1 - Analysis of primary clinical composite endpoint of CV death, MI and stroke (PEGASUS)

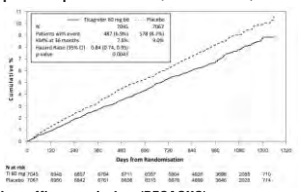


Table 5 - Analysis of primary and secondary efficacy endpoints (PEGASUS)

	Ticagrelor 60 mg twice daily + ASA N = 7045			ASA alone N = 7067		*p*-value
Characteristic	**Patients with events**	**KM%**	**HR (95% CI)**	**Patients with events**	**KM%**	
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 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.

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).

THEMIS study (Patients with Coronary Artery Disease (CAD) and Type 2 Diabetes Mellitus (DM) with History of Percutaneous Coronary Intervention (PCI))

Study Design

The THEMIS study was a 19,220 patient, event-driven, randomised, double-blind, placebo controlled, parallel group, international multi-centre study to assess the prevention of atherothrombotic events with ticagrelor combined with low dose ASA (75-150 mg) compared to ASA therapy alone in patients with CAD and type 2 DM. The median ticagrelor treatment duration was 33.2 months.

Patients were eligible to participate if they were aged 50 years or over, had CAD defined as history of PCI (58% of study population) or CABG (29%) or no history of coronary revascularisation, but angiographic evidence of ≥ 50% lumen stenosis of at least 1 coronary artery (20%) and type 2 DM treated with glucose-lowering medication for at least 6 months prior to study start.

Patients were ineligible to participate if they had a history of MI or stroke; if there was planned use of ADP receptor antagonists, ASA treatment > 150 mg od, dipyridamole, or cilostazol; if there was planned coronary, cerebrovascular, or peripheral arterial revascularization or anticipated use of CYP3A4 substrates with narrow therapeutic indices or strong CYP3A4 inhibitors; if they were at known increased risk for bleeding (e.g., need for chronic oral anticoagulants, known bleeding diathesis, coagulation disorder, recent major surgery, history of previous intracerebral bleed or GI bleeding within the past 6 months etc.) or bradycardic events unless treated with a pacemaker; if they had uncontrolled hypertension or renal failure requiring dialysis, or if they had any contraindications to receive ticagrelor treatment.

THEMIS study was conducted for a duration up to 57 months with mean (median) duration of exposure to ticagrelor of 29.2 months (33.2 months). With respect to duration of exposure to the study drug, 7322 (76.6%) patients were exposed to ticagrelor for 12 months, 6421 (67.2%) for 24 months and 4107 (43%) for 36 months. At 48 months, 1175 (12.3%) patients were exposed to ticagrelor. Patients were followed to study termination, irrespective of whether study drug had been discontinued.

Study Results

In the total THEMIS study population, ticagrelor twice daily in combination with ASA, compared to ASA alone, resulted in the prevention of atherothrombotic events (composite endpoint: CV death, MI and stroke), with a hazard ratio (HR) of 0.90 (95% CI: 0.81, 0.99, p = 0.0378), corresponding to a relative risk reduction (RRR) of 10% and an absolute risk reduction (ARR) of 0.73% (number needed to treat [NNT] of 138 after 36 months of treatment). The effect was driven by the individual components MI (HR 0.84, 95% CI: 0.71, 0.98) and stroke (HR 0.82, 95% CI: 0.67, 0.99), with no difference in CV deaths (HR 1.02, 95% CI: 0.88, 1.18). Of the secondary endpoints not assessed as part of the primary composite endpoint, ticagrelor reduced the number of ischaemic stroke events (HR 0.80, 95% CI: 0.64, 0.99) with no difference in all-cause death (HR 0.98, 95% CI 0.87, 1.10). The benefit-risk profile of ticagrelor in the total THEMIS study population was not considered favourable to support use of ticagrelor and therefore, an indication was not granted for the total study population.

In THEMIS patients with a history of PCI, which was a pre-specified subgroup corresponding to 58% of the total study population, treatment with ticagrelor in combination with ASA, compared to ASA alone, resulted in the prevention of atherothrombotic events (composite endpoint: CV death, MI and stroke) (see Table 6). Ticagrelor treatment yielded a 15% RRR, a 1.19% ARR (number needed to treat [NNT] of 84 after 36 months of treatment) and a more favourable benefit-risk profile than the total THEMIS study population. Again, the treatment benefit was driven by the MI and stroke components of the composite endpoint.

The baseline characteristics in the subgroup of patients with a history of PCI were comparable in both treatment arms.

Table 6 - Analysis of primary and secondary efficacy endpoints in the subgroup of THEMIS patients with a history of PCI (full analysis set)

	Ticagrelor twice daily + ASA N = 5558	ASA alone N = 5596	RRR%	Hazard Ratio (95% CI)	*p*-value[a]
Characteristic	**Patients with events**	**Patients with events**			
Primary endpoint					
Composite of CV Death/MI/Stroke	404 (7.3%)	480 (8.6%)	15%	0.85 (0.74, 0.97)	0.0133
CV death	174 (3.1%)	183 (3.3%)	4%	0.96 (1.78, 1.18)	0.6803
MI	171 (3.1%)	216 (3.9%)	20%	0.80 (0.65, 0.97)	0.0266
Stroke	96 (1.7%)	131 (2.3%)	26%	0.74 (0.57, 0.96)	0.0243
Secondary endpoint					
CV death	174 (3.1%)	183 (3.3%)	4%	0.96 (0.78, 1.18)	-
MI	171 (3.1%)	216 (3.9%)	20%	0.80 (0.65, 0.97)	-
Ischaemic Stroke	88% (91.6%)	113 (2.0%)	21%	0.79 (0.56, 1.04)	-
All-cause death[b]	282 (5.1%)	323 (5.8%)	12%	0.88 (0.75, 1.03)	-

Hazard ratio and p-values are calculated for ticagrelor twice daily + ASA vs ASA alone from Cox proportional hazards model with treatment as the only explanatory variable.

The number of first events for the components CV death, MI and stroke are the actual number of first events for each component and do not add up to the number of events in the composite endpoint

CI = Confidence interval; CV = Cardiovascular; HR = Hazard ratio; MI = Myocardial infarction.

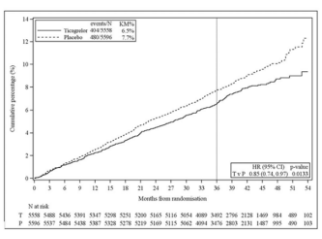
N = Number of patients in treatment group; RRR = Relative risk reduction.

[a] p-values are nominal.

[b] Includes deaths based on publicly available vital status data in patients who have withdrawn consent.

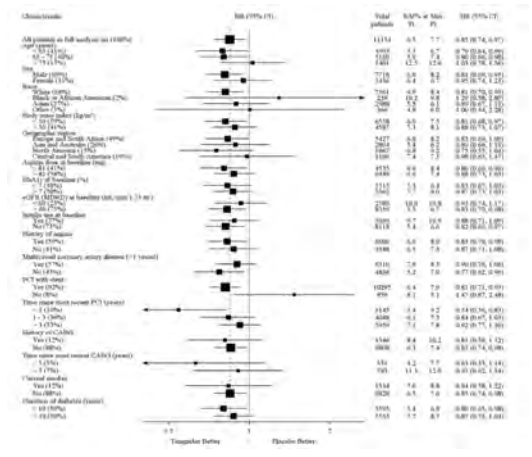
Treatment with ticagrelor should be continued in patients with CAD, type 2 DM and history of PCI for as long as the patient remains at high risk of an atherothrombotic event and low risk of bleeding, for a duration up to three years. Efficacy and safety data are insufficient to establish whether the benefits of ticagrelor still outweigh the risks after three years of extended treatment.

Figure 2 – Kaplan-Meier plot and analysis of primary clinical composite endpoint of CV death, MI and stroke in THEMIS patients with a history of PCI (full analysis set)



The treatment effect of TICAGRELOR across patient subgroups, based on patient characteristics including weight, gender, medical history, and geographic region, in THEMIS patients with a history of PCI is shown in Figure 3.

Figure 3: Hazard ratios and rates of the primary clinical composite end point of CV death, MI and stroke by patient subgroup in THEMIS PCI patients (full analysis set)



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, is bioequivalent 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 t1/2 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 (≥ 75 years) ACS patients compared to younger patients by the population pharmacokinetic analysis. These differences are not considered clinically significant.

Paediatric population

Limited data are available in 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, 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 C_{max} 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.

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. 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.

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.

6. PHARMACEUTICALS PARTICULARS

6.1 List of excipients

Tablet core: Mannitol (Pearlitol 160 C), Sodium starch Glycolate Type A (Primojel), Povidone (Kollidon 30 LP), Purified water, Mannitol (Pearlitol SD 200), Cellulose Microcrystalline (Emcocel 102), Magnesium stearate (Ligamed MF-2-V)

Film-coating: Instacoat universal Brown (A05E04420), Purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Packaging available

3 x 10's Clear PVC/PE/PVdC-Aluminium Blister Pack.

6.6 Special precautions for disposal and other handling

No special requirements for disposal

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

7. NAME AND ADDRESS OF MANUFACTURER

Annora Pharma Private Limited
Sy. No. 261, Annaram Village,
Gummadidala Mandal,
Sangareddy District, Telangana State,
502313, India.

8. PRODUCT REGISTRATION HOLDER

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Unit E-13A-02, Menara SUEZCAP 2, No. 2, KL Gateway,
Jalan Kerinchi, Gerbang Kerinchi Lestari,
59200 Kuala Lumpur, Malaysia.

9. DATE OF REVISION

22 September 2025