SUMMARY OF PRODUCT CHARACTERISTICS

TICALOR

(Ticagrelor Tablets 60 mg & 90 mg)

1. NAME OF THE MEDICINAL PRODUCT

TICALOR

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ticagrelor Tablets 60mg

Each film coated tablet contains:
Ticagrelor Ph. Eur. 60mg
Excipients q.s.

Ticagrelor Tablets 90mg

Each film coated tablet contains:
Ticagrelor Ph. Eur. 90mg
Excipients q.s.

For the full list of excipients, see **section 6.1.**

3. PHARMACEUTICAL FORM

Film Coated Tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ticagrelor, 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

4.2 Posology and method of administration

Posology

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

Acute coronary syndromes

Ticagrelor 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 90 mg twice daily is recommended for 12 months in ACS patients unless discontinuation is clinically indicated.

History of myocardial infarction
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 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 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 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 have been reported 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 reported. There is no relevant use of ticagrelor in children with sickle cell disease.

Method of administration

For oral use.
Ticagrelor 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 (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 of this product.
- 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 **section 4.8**). 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.

Platelet transfusion have not been reported to 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 have not been reported to 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 patients undergoing coronary artery bypass grafting (CABG), more bleeding has been reported with ticagrelor 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.

Patients with prior ischaemic stroke
ACS patients with prior ischaemic stroke can be treated with ticagrelor for up to 12 months.

Treatment beyond one year is not recommended in patients with history of MI with prior ischaemic stroke.

Hepatic impairment
Use of ticagrelor is contraindicated in patients with severe hepatic impairment (see (see **sections 4.2 and 4.3**). Caution is advised in moderate hepatic impairment patients (see **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.

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 has been reported 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**).

More patients had reported 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.

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 has been 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
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.

Sodium content
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say it is 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.

Effects of medicinal and other products on ticagrelor

CYP3A4 inhibitors

- Strong CYP3A4 inhibitors – Co-administration of ketoconazole with ticagrelor has been reported to increase 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 have been reported to reduce 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 has been reported to increase the ticagrelor C_{max} by 69% and AUC to 2.7-fold and decrease the active metabolite C_{max} by 38% and AUC was unchanged. There was no effect of ticagrelor reported 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 has been reported after daily consumption of large quantities of grapefruit juice (3x 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 has been reported to decrease ticagrelor C_{max} and AUC by 73% and 86%, respectively. The C_{max} of the active metabolite has been reported to be 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 has been reported to increase ticagrelor C_{max} and AUC equal to 2.3-fold and 2.8-fold, respectively. The AUC of the active metabolite has been reportedly increased by 32% and C_{max} was decreased by 15% in the presence of cyclosporine.

No data have been reported 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
Co-administration of ticagrelor with heparin, enoxaparin and ASA or desmopressin have been reported to 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 reported 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 reported 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 has been reported to increase 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 has been reported to increase atorvastatin acid C_{max} by 23% and AUC by 36%. Similar increases in AUC and C_{max} were reported for all atorvastatin acid metabolites. These increases are not considered clinically significant.
- A similar effect on other statins metabolised by CYP3A4 cannot be excluded.

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 and digoxin has been reported to increase 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.

No effect of ticagrelor on cyclosporine blood levels have been reported. Effect of ticagrelor on other P-gp substrates has not been studied.

Medicinal products metabolised by CYP2C9
Co-administration of ticagrelor with tolbutamide reported to result 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
Ticagrelor might affect renal excretion of rosuvastatin, increasing the risk for rosuvastatin accumulation. Although the exact mechanism is not known, in some cases, concomitant use of ticagrelor and rosuvastatin led to renal function decrease, increased CPK level and rhabdomyolysis.

Oral contraceptives
Co-administration of ticagrelor and levonorgestrel and ethinyl estradiol have been reported to increase 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 has been reported 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 reported 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 has been reported.

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 reported from the use of ticagrelor in pregnant women. Reported studies in animals have shown reproductive toxicity (see **section 5.3**). Ticagrelor is not recommended during pregnancy.

Lactation
Reported 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
No effect on male or female fertility in animals has been reported (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
In one reported study, patients treated with ticagrelor had reported to have a higher incidence of treatment discontinuation due to adverse events than clopidogrel (7.4% vs. 5.4%). In another reported study, patients on ticagrelor had reported to have 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 reported with ticagrelor (Table below). 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: Adverse reactions by frequency and system organ class (SOC)

SOC	Very common	Common	Uncommon	Unknown
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		Gastrointestinal	Retroperitoneal	

SOC	Very common	Common	Uncommon	Unknown
disorders		haemorrhage[g], Diarrhoea, Nausea, Dyspepsia, Constipation	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 reported Study 1

Overall outcome of bleeding rates in the reported study 1 are shown in Table below.

Table: Analysis of overall bleeding events, Kaplan-Meier estimates at 12 months (Reported Study 1)

	Ticagrelor 90 mg twice daily	Clopidogrel	p-value*
Total Major	11.6	11.2	0.4336
Major Fatal/Life-Threatening	5.8	5.8	0.6988
Non-CABG Major	4.5	3.8	0.0264
Non-Procedural Major	3.1	2.3	0.0058
Total Major + Minor	16.1	14.6	0.0084
Non-Procedural 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 Major Fatal/Life-threatening bleeding, total Major bleeding, TIMI Major bleeding, or TIMI Minor bleeding. However, more combined Major + Minor bleeding have been reported with ticagrelor compared with clopidogrel. Few patients reported to 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 major bleeding. Thus, no particular group was identified at risk for any subset of bleeding.

CABG-related bleeding: In patients (12% of cohort) who underwent coronary artery bypass graft (CABG) surgery reported a Major Fatal/Life-threatening bleeding with no difference between treatment groups. Fatal CABG bleeding has been reported 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 -defined Major Fatal/Life-threatening bleeding, but -defined Total Major, TIMI Major, and TIMI Major + Minor bleeding were more common with ticagrelor. Similarly, when removing all procedure related bleeds, more bleeding were reported with ticagrelor than with clopidogrel. Discontinuation of treatment due to non-procedural bleeding was reported more common for ticagrelor (2.9%) than for clopidogrel (1.2%; p<0.001).

Intracranial bleeding: There were more intracranial non-procedural bleeds reported 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 reported Study 2
Overall outcome of bleeding events in the reported Study 2 are shown in Table below.

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

	Ticagrelor 60 mg twice daily + ASA		**ASA alone**	
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
Reported Study 1-defined bleeding categories				
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 Major	1.1	3.37 (1.95, 5.83)	0.3	<0.0001
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.
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.
Major Other: Significantly disabling, OR clinically apparent with 30-50 g/L decrease in haemoglobin, OR 2-3 red cell units transfused.
Minor: Requires medical intervention to stop or treat bleeding.

TIMI Major bleeding for ticagrelor 60 mg twice daily has been reported to be higher than for ASA alone. No increased bleeding risk has been reported for fatal bleeding and only a minor increase has been reported in intracranial haemorrhages, as compared to ASA therapy alone. There were few fatal bleeding events reported, 11 (0.3%) for ticagrelor 60 mg and 12 (0.3%) for ASA therapy alone. The reported 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 reported for TIMI Major or Minor and reported Study 1 Major and reported Study 1 Major or Minor bleeding categories. Discontinuation of treatment due to bleeding was reported to be 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 has been reported to be 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 reported Study 1 Major bleeding events.

Intracranial bleeding: Spontaneous ICHs has been reported in similar rates for ticagrelor 60 mg and ASA therapy alone (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 reported with ticagrelor 60 mg and 5 fatal ICHs with ASA therapy alone. The incidence of intracranial bleeding was reported to be 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. 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 study 1 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 population of reported Study 1. 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. The reported Study 1 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 active substance 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 another reported study, Study 2, 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 reported study 1, 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 reported study 1, serum uric acid has been reported to increase to more than upper limit of normal in 22% of patients receiving ticagrelor compared to 13% of patients receiving clopidogrel. The corresponding numbers in reported study 2, has been reported to be 9.1%, 8.8% and 5.5% for ticagrelor 90 mg, 60 mg and placebo, respectively. Mean serum uric acid has been reported to increase 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 reported study 2, a reversible increase in mean serum uric acid levels of 6.3% and 5.6% has been reported for ticagrelor 90 mg and 60 mg, respectively, compared to a 1.5% decrease in the placebo group. In study 1, the

frequency of gouty arthritis has been reported to be 0.2% for ticagrelor *vs*. 0.1% for clopidogrel. The corresponding numbers for gout/gouty arthritis in study 2 have been reported as 1.6%, 1.5% and 1.1% for ticagrelor 90 mg, 60 mg and placebo, respectively.

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, 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 reported 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 have been reported to result 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**).

5.2 Pharmacokinetics properties

Ticagrelor has been reported to demonstrate 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 reported to be 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. The pharmacokinetics of ticagrelor and AR-C124910XX in patients with a history of MI have been reported to be generally similar to that in the ACS population. In the reported Study 2, the median ticagrelor C_{max} has been reported to be 391 ng/ml and AUC was 3801 ng*h/ml at steady state for ticagrelor 60 mg. In another reported study for ticagrelor 90 mg, C_{max} has been reported to be 627 ng/ml and AUC has been reported to be 6255 ng*h/ml at steady state.

The mean absolute bioavailability of ticagrelor has been reported to be estimated to be 36%. Ingestion of a high-fat meal has been reported to result 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. Ticagrelor as well as the active metabolite are P-gp substrates.

Distribution
The steady state volume of distribution of ticagrelor is reported to be 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 reported to be approximately 30-40% of that obtained for ticagrelor.

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

Special populations

Elderly
Higher exposures to ticagrelor (approximately 25% for both C_{max} and AUC) and the active metabolite have been reported 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**).

In the reported 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 reported

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 have been reported in women compared to men. These differences are not considered clinically significant.

Renal impairment
Exposure to ticagrelor has been reported to be approximately 20% lower and exposure to the active metabolite has been reported to be 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 have been reported as 38% and 51% higher compared to subjects with normal renal function. A similar increase in exposure has been reported when ticagrelor 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 has been reported to be independent of dialysis in patients with end stage renal disease and similar to subjects with normal renal function (see **sections 4.2**).

Hepatic impairment
C_{max} and AUC for ticagrelor has been reported to be 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 reported 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
Mean bioavailability of ticagrelor in patients of Asian descent have been reported to be 39% higher compared to Caucasian patients. Patients self-identified as black had an 18% lower bioavailability of ticagrelor compared to Caucasian patients, in reported 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 has been reported to be similar to that in Caucasians.

5.3 Preclinical safety data

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

Gastrointestinal irritation has been reported in several animal species at clinical relevant exposure levels (see **section 4.8**).

In female rats, ticagrelor at high dose reported 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 reported carcinogenicity findings are considered unlikely to be relevant for humans.

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

Reported 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. Reported 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

Lactose, Microcrystalline cellulose (PH 101), Hydroxypropyl cellulose, Croscarmellose Sodium, Magnesium stearate, Hypromellose, Titanium Dioxide, Macrogol, Talc, Ferrosoferric Oxide, Iron oxide Yellow & Iron oxide Red.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

3 PVC/PVDC blisters of 10's Tablets

6.6 Special precautions for disposal and other handling

This medicinal product does not require any special storage conditions.

7. MARKETING AUTHORISATION HOLDER

Sun Pharmaceutical Industries Limited,
Sun House, 201 B/1, Western Express Highway,
Gurgaon (East), Mumbai, 400063, India

8. MARKETING AUTHORISATION NUMBER(S)

Not applicable

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Not applicable

10. DATE OF REVISION OF THE TEXT

January 2023

REFERENCES

- Summary of Product Characteristics of Brilique 60 mg and 90 mg Film-coated Tablets, AstraZeneca UK Limited, November 2022.