SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
Ticagrelor Tablets
COROLOR

2. QUALITATIVA AND QUANTITATIVE COMPOSITION
Each film coated tablet contains: Ticagrelor ..... 90 mg
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Tablet
Yellow, round, biconvex film coated tablets debossed with 'T' above '90' on one face and plain on other face.

Prescription only medicine

4. CLINICAL PARTICULARS
4.1 Therapeutic indications:
Ticagrelor is indicated to reduce the rate of cardiovascular death, myocardial infarction, and stroke in patients with acute coronary syndrome (ACS) or a history of myocardial infarction (MI). For at least the first 12 months following ACS, it is superior to clopidogrel.

Ticagrelor also reduces the rate of stent thrombosis in patients who have been stented for treatment of ACS.

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

History of myocardial infarction
Ticagrelor 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.
Renal impairment
No dose adjustment is necessary for patients with renal impairment. No information is available concerning treatment of patients on renal dialysis and therefore Ticagrelor is not recommended in these patients.
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. No data are available.

Method of administration
For oral use
The medicinal product can be taken with/without food

4.3 Contraindications:
History of Intracranial Hemorrhage
Ticagrelor is contraindicated in patients with a history of intracranial hemorrhage (ICH) because of a high risk of recurrent ICH in this population.

Active Bleeding
Ticagrelor is contraindicated in patients with active pathological bleeding such as peptic ulcer or intracranial hemorrhage.

Hypersensitivity
Ticagrelor is contraindicated in patients with hypersensitivity (e.g., angioedema) to Ticagrelor or any component of the product.

4.4 Special warning and precautions:
General Risk of Bleeding
Drugs that inhibit platelet function including Ticagrelor increase the risk of bleeding.
If possible, manage bleeding without discontinuing Ticagrelor. Stopping Ticagrelor increases the risk of subsequent cardiovascular events.

Concomitant Aspirin Maintenance Dose
In PLATO the use of Ticagrelor with maintenance doses of aspirin above 100 mg decreased the effectiveness of Ticagrelor. Therefore, after the initial loading dose of aspirin, use Ticagrelor A with a maintenance dose of aspirin of 75-100 mg.

Dyspnea

In clinical trials, about 14% of patients treated with Ticagrelor developed dyspnea. Dyspnea was usually mild to moderate in intensity and often resolved during continued treatment, but led to study drug discontinuation in 0.9% of Ticagrelor and 0.1% of clopidogrel patients in PLATO and 4.3% of Ticagrelor 60 mg and 0.7% on aspirin alone patients in PEGASUS.

In a sub study of PLATO, 199 subjects underwent pulmonary function testing irrespective of whether they reported dyspnea. There was no indication of an adverse effect on pulmonary function assessed after one month or after at least 6 months of chronic treatment.

If a patient develops new, prolonged, or worsened dyspnea that is determined to be related to Ticagrelor, no specific treatment is required; continue Ticagrelor without interruption if possible. In the case of intolerable dyspnea requiring discontinuation of Ticagrelor, consider prescribing another antiplatelet agent.

Discontinuation of Ticagrelor
Discontinuation of Ticagrelor will increase the risk of myocardial infarction, stroke, and death. If Ticagrelor must be temporarily discontinued (e.g., to treat bleeding or for significant surgery), restart it as soon as possible. When possible, interrupt therapy with Ticagrelor for five days prior to surgery that has a major risk of bleeding. Resume Ticagrelor as soon as hemostasis is achieved.

Bradyarrhythmia
Ticagrelor can cause ventricular pauses. Bradyarrhythmia including AV block have been reported in the postmarketing setting. Patients with a history of sick sinus syndrome, 2nd or 3rd degree AV block or bradycardia-related syncope not protected by a pacemaker were excluded from clinical studies and may be at increased risk of developing bradyarrhythmia with ticagrelor.

Severe Hepatic Impairment
Avoid use of Ticagrelor in patients with severe hepatic impairment. Severe hepatic impairment is likely to increase serum concentration of Ticagrelor. There are no studies of Ticagrelor patients with severe hepatic impairment

Geriatric Use
In PLATO and PEGASUS, about half of patients in each study were ≥65 years of age and about 15% were ≥75 years of age. No overall differences in safety or effectiveness were observed between elderly and younger patients.

Hepatic Impairment
Ticagrelor is metabolized by the liver and impaired hepatic function can increase risks for bleeding and other adverse events. Avoid use of Ticagrelor in patients with severe hepatic impairment. There is limited experience with Ticagrelor in patients with moderate hepatic impairment; consider the risks and benefits of treatment, noting the probable increase in exposure to Ticagrelor. No dosage adjustment is needed in patients with mild hepatic impairment.

Renal Impairment
No dosage adjustment is needed in patients with renal impairment. Patients receiving dialysis have not been studied

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

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 $P2Y_{12}$-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.

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).

4.5 Interactions with Other Medicaments
Strong CYP3A Inhibitors
Strong CYP3A inhibitors substantially increase Ticagrelor exposure and so increase the risk of dyspnea, bleeding, and other adverse events. Avoid use of strong inhibitors of CYP3A (e.g.,

ketoconazole, itraconazole, voriconazole, clarithromycin, nefazodone, ritonavir, Saquinavir, nelfinavir, indinavir, Atazanavir and telithromycin)

Strong CYP3A Inducers
Strong CYP3A inducers substantially reduce Ticagrelor exposure and so decrease the efficacy of Ticagrelor. Avoid use with strong inducers of CYP3A (e.g., rifampin, phenytoin, carbamazepine and phenobarbital).

Aspirin
Use of Ticagrelor with aspirin maintenance doses above 100 mg reduced the effectiveness of Ticagrelor.

Simvastatin, Lovastatin
Ticagrelor increases serum concentrations of simvastatin and lovastatin because these drugs are metabolized by CYP3A4. Avoid simvastatin and lovastatin doses greater than 40 mg.

Digoxin
Ticagrelor inhibits the P-glycoprotein transporter; monitor digoxin levels with initiation of or change in Ticagrelor therapy

4.6 Pregnancy and lactation:
Pregnancy
This medicinal product is not recommended during pregnancy
There are no adequate and well-controlled studies of Ticagrelor use in pregnant women. In animal studies, Ticagrelor caused structural abnormalities at maternal doses about 5 to 7 times the maximum recommended human dose (MRHD) based on body surface area. Ticagrelor should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation
It is not known whether Ticagrelor or its active metabolites are excreted in human milk. Ticagrelor is excreted in rat milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from Ticagrelor, a decision should be made whether to discontinue nursing or to discontinue Ticagrelor.
Fertility
Ticagrelor had no effect on male or female fertility in animals

4.7 Effects on ability to drive and use machine:
Ticagrelor has no or negligible influence on the ability to drive and use machines. During treatment with ticagrelor, dizziness and confusion have been reported. Therefore, patients who experience these symptoms should be cautious while driving or using machines.

4.8 Undesirable effects:
Summary of the safety profile
The safety profile of Ticagrelor has been evaluated in two large phase 3 outcome trials (PLATO and PEGASUS) including more than 39,000 patients.
In PLATO, patients on Ticagrelor had a higher incidence of discontinuation due to adverse events than clopidogrel (7.4% vs. 5.4%). In PEGASUS, patients on Ticagrelor had a higher incidence of discontinuation due to adverse events compared to ASA therapy alone (16.1% for

Ticagrelor 60 mg with ASA vs. 8.5% for ASA therapy alone). The most commonly reported adverse reactions in patients treated with Ticagrelor were bleeding and dyspnoea.

Tabulated list of adverse reactions
The following adverse reactions have been identified following studies or have been reported in post-marketing experience with Ticagrelor (Table 1).
Adverse reactions are listed by MedDRA and System Organ Class (SOC). Within each SOC the adverse reactions are ranked by frequency category. Frequency categories are defined according to the following conventions: Very common (≥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)

System Organ Classification	**Very Common**	**Common**	**Uncommon**
Neoplasms benign, malignant and unspecified (including cysts and polyps)			Tumour bleedings[a]
Blood and lymphatic system disorders	Blood disorder bleedings[b]		
Immune system disorders			Hypersensitivity including
Metabolism and nutrition disorders	Hyperuricaemia[d]	Gout/Gouty Arthritis	
Psychiatric disorders			Confusion
Nervous system disorders		Dizziness, Syncope, Headache	Intracranial haemorrhage
Eye disorders			Eye haemorrhage[e]
Ear and labyrinth disorders		Vertigo	Ear haemorrhage
Vascular disorders		Hypotension	
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Respiratory system bleedings[f]	
Gastrointestinal disorders		Gastrointestinal haemorrhage[g], Diarrhoea, Nausea, Dyspepsia, Constipation	Retroperitoneal haemorrhage
Skin and subcutaneous tissue disorders		Subcutaneous or dermal bleeding[h], Rash, Pruritus	

Musculoskeletal connective tissue and bone			Muscular bleedings[i]
Renal and urinary disorders		Urinary tract bleeding[j]	
Reproductive system and breast disorders			Reproductive system bleedings[k]
Investigations		Blood creatinine increased[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, petechial
[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

Description of selected adverse reactions
Bleeding
Bleeding findings in PLATO
Overall outcome of bleeding rates in the PLATO study are shown in Table 2.

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

	Ticagrelor 90 mg twice daily N=9235	**Clopidogrel N=9186**	***p*-value***
PLATO Total Major	11.6	11.2	0.4336
PLATO Major Fatal/Life-Threatening	5.8	5.8	0.6988
Non-CABG PLATO Major	4.5	3.8	0.0264
Non-Procedural PLATO Major	3.1	2.3	0.0058
PLATO Total Major + Minor	16.1	14.6	0.0084

Non-Procedural PLATO Major + Minor	5.9	4.3	<0.0001
TIMI-defined Major	7.9	7.7	0.5669
TIMI-defined Major + Minor	11.4	10.9	0.3272

***Bleeding category definitions*:**
Major Fatal/Life-threatening Bleed: Clinically apparent with >50 g/l decrease in haemoglobin or ≥4 red cell units transfused; or fatal; or intracranial; or intrapericardial with cardiac tamponade; or with hypovolaemic shock or severe hypotension requiring pressors or surgery.
Major Other: Clinically apparent with 30-50 g/L decrease in haemoglobin or 2-3 red cell units transfused; or significantly disabling.

Minor Bleed: Requires medical intervention to stop or treat bleeding.
TIMI Major Bleed: Clinically apparent with >50 g/l decrease in haemoglobin or intracranial haemorrhage.

TIMI Minor Bleed**:** Clinically apparent with 30-50 g/l decrease in haemoglobin.
**p*-value calculated from Cox proportional hazards model with treatment group as the only explanatory variable.

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

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

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

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

Intracranial bleeding: There were more intracranial non-procedural bleeds with ticagrelor (n=27 bleeds in 26 patients, 0.3%) than with clopidogrel (n=14 bleeds, 0.2%), of which 11 bleeds with ticagrelor and 1 with clopidogrel were fatal. There was no difference in overall fatal bleeds.
Bleeding findings in PEGASUS
Overall outcome of bleeding events in the PEGASUS study are shown in Table 3.

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

	Ticagrelor 60 mg twice daily + ASA N=6958		**ASA alone N=6996**	
Safety Endpoints	**KM%**	**Hazard Ratio (95% CI)**	**KM%**	***p*-value**
TIMI-defined bleeding categories				
TIMI Major	2.3	2.32 (1.68, 3.21)	1.1	<0.0001
Fatal	0.3	1.00 (0.44, 2.27)	0.3	1.0000
ICH	0.6	1.33 (0.77, 2.31)	0.5	0.3130
Other TIMI Major	1.6	3.61 (2.31, 5.65)	0.5	<0.0001
TIMI Major or Minor	3.4	2.54 (1.93, 3.35)	1.4	<0.0001
TIMI Major or Minor or Requiring medical attention	16.6	2.64 (2.35, 2.97)	7.0	<0.0001
PLATO-defined bleeding categories				
PLATO Major	3.5	2.57 (1.95, 3.37)	1.4	<0.0001
Fatal/Life-threatening	2.4	2.38 (1.73, 3.26)	1.1	<0.0001
Other PLATO Major	1.1	3.37 (1.95, 5.83)	0.3	<0.0001
PLATO Major or Minor	15.2	2.71 (2.40, 3.08)	6.2	<0.0001

Bleeding category definitions:
TIMI Major: Fatal bleeding, OR any intracranial bleeding, OR clinically overt signs of haemorrhage associated with a drop in haemoglobin (Hgb) of ≥50 g/L, or when Hgb is not available, a fall in haematocrit (Hct) of 15%.
Fatal: A bleeding event that directly led to death within 7 days.
ICH: Intracranial haemorrhage.

Other TIMI Major: Non-fatal non-ICH TIMI major bleeding.
TIMI Minor: Clinically apparent with 30-50 g/L decrease in haemoglobin.
TIMI Requiring medical attention: Requiring intervention, OR leading to hospitalisation, OR prompting evaluation.

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

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

PLATO Minor: Requires medical intervention to stop or treat bleeding.
In PEGASUS, TIMI Major bleeding for ticagrelor 60 mg twice daily was higher than for ASA alone. No increased bleeding risk was seen for fatal bleeding and only a minor increase was observed in intracranial haemorrhages, as compared to ASA therapy alone. There were few fatal bleeding events in the study, 11 (0.3%) for ticagrelor 60 mg and 12 (0.3%) for ASA therapy alone. The observed increased risk of TIMI Major bleeding with ticagrelor 60 mg was primarily due to a higher frequency of Other TIMI Major bleedings driven by events in the gastrointestinal SOC.

Increased bleeding patterns similar to TIMI Major were seen for TIMI Major or Minor and PLATO Major and PLATO Major or Minor bleeding categories. Discontinuation of treatment due to bleeding was more common with ticagrelor 60 mg compared to ASA therapy alone (6.2% and 1.5%, respectively). The majority of these bleedings were of less severity (classified as TIMI Requiring medical attention), e.g. epistaxis, bruising and haematomas.
The bleeding profile of ticagrelor 60 mg was consistent across multiple pre-defined subgroups (e.g. by age, gender, weight, race, geographic region, concurrent conditions, concomitant therapy, and medical history) for TIMI Major, TIMI Major or Minor and PLATO Major bleeding events.

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

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

4.9 Overdose:
There is currently no known treatment to reverse the effects of Ticagrelor, and ticagrelor is not expected to be dialyzable. Treatment of overdose should follow local standard medical practice. Bleeding is the expected pharmacologic effect of overdosing. If bleeding occurs, appropriate supportive measures should be taken.
Other effects of overdose may include gastrointestinal effects (nausea, vomiting, and diarrhea) or ventricular pauses. Monitor the ECG.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic Properties:
Pharmacotherapeutic group: Platelet aggregation inhibitors excluding heparin, ATC code: B01AC24

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

Ticagrelor also increases local endogenous adenosine levels by inhibiting the equilibrative nucleoside transporter-1 (ENT-1).
Ticagrelor has been documented to augment the following adenosine-induced effects in healthy subjects and in patients with ACS: vasodilation (measured by coronary blood flow increases in healthy volunteers and ACS patients; headache), inhibition of platelet function (in human whole blood *in vitro*) and dyspnea. However, a link between the observed increases in adenosine and clinical outcomes (e.g. morbidity-mortality) has not been clearly elucidated.

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

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

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

5.2 Pharmacokinetic Properties:

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

Absorption
Absorption of ticagrelor is rapid with a median t_{max} of approximately 1.5 hours. The formation of the major circulating metabolite AR-C124910XX (also active) from ticagrelor is rapid with a median t_{max} of approximately 2.5 hours. Following an oral ticagrelor 90 mg single dose under fasted conditions in healthy subjects, C_{max} is 529 ng/ml and AUC is 3451 ng*h/ml. The metabolite parent ratios are 0.28 for C_{max} and 0.42 for AUC. The pharmacokinetics of ticagrelor and AR-C124910XX in patients with a history of MI were generally similar to that in the ACS population. Based on a population pharmacokinetic analysis of the PEGASUS study the median ticagrelor C_{max} was 391 ng/ml and AUC was 3801 ng*h/ml at steady state for ticagrelor 60 mg. For ticagrelor 90 mg C_{max} was 627 ng/ml and AUC was 6255 ng*h/ml at steady state.

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

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

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

Biotransformation
CYP3A4 is the major enzyme responsible for ticagrelor metabolism and the formation of the active metabolite and their interactions with other CYP3A substrates ranges from activation through to inhibition.
The major metabolite of ticagrelor is AR-C124910XX, which is also active as assessed by *in vitro* binding to the platelet $P2Y_{12}$ ADP-receptor. The systemic exposure to the active metabolite is approximately 30-40% of that obtained for ticagrelor.

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

Special populations
Elderly

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

Paediatric population

Ticagrelor has not been evaluated in a Paediatric population.

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.

Hepatic impairment

C_{max} and AUC for ticagrelor were 12% and 23% higher in patients with mild hepatic impairment compared to matched healthy subjects, respectively; however, the IPA effect of ticagrelor was similar between the two groups. No dose adjustment is needed for patients with mild hepatic impairment. Ticagrelor has not been studied in patients with severe hepatic impairment and there is no pharmacokinetic information in patients with moderate hepatic impairment. In patients that had moderate or severe elevation in one or more liver function tests at baseline, ticagrelor plasma concentrations were on average similar or slightly higher as compared to those without baseline elevations. No dose adjustment is recommended in patients with moderate hepatic impairment.

Ethnicity

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

5.3 Preclinical safety Data:

Carcinogenesis

Ticagrelor was not carcinogenic in the mouse at doses up to 250 mg/kg/day or in the male rat at doses up to 120 mg/kg/day (19 and 15 times the MRHD of 90 mg twice daily on the basis of AUC, respectively). Uterine carcinomas, uterine adenocarcinomas and hepatocellular adenomas were seen in female rats at doses of 180 mg/kg/day (29-fold the maximally recommended dose of 90 mg twice daily on the basis of AUC), whereas 60 mg/kg/day (8-fold the MRHD based on AUC) was not carcinogenic in female rats.

Mutagenesis

Ticagrelor did not demonstrate genotoxicity when tested in the Ames bacterial mutagenicity test, mouse lymphoma assay and the rat micronucleus test. The active O-demethylated metabolite did not demonstrate genotoxicity in the Ames assay and mouse lymphoma assay.

Impairment of Fertility

Ticagrelor had no effect on male fertility at doses up to 180 mg/kg/day or on female fertility at doses up to 200 mg/kg/day (>15-fold the MRHD on the basis of AUC). Doses of ≥10 mg/kg/day given to female rats caused an increased incidence of irregular duration estrus cycles (1.5-fold the MRHD based on AUC).

Reproductive toxicology
In reproductive toxicology studies, pregnant rats received ticagrelor during organogenesis at doses from 20 to 300 mg/kg/day. 20 mg/kg/day is approximately the same as the MRHD of 90 mg twice daily for a 60 kg human on a mg/m2 basis. Adverse outcomes in offspring occurred at doses of 300 mg/kg/day (16.5 times the MRHD on a mg/m2 basis) and included supernumerary liver lobe and ribs, incomplete ossification of sternebrae, displaced articulation of pelvis, and misshapen/misaligned sternebrae. At the mid-dose of 100 mg/kg/day, delayed development of liver and skeleton was seen. When pregnant rabbits received ticagrelor during organogenesis at doses from 21 to 63 mg/kg/day, fetuses exposed to the highest maternal dose of 63 mg/kg/day (6.8 times the MRHD on a mg/m2 basis) had delayed gall bladder development and incomplete ossification of the hyoid, pubis and sternebrae occurred.
In a prenatal/postnatal study, pregnant rats received ticagrelor at doses of 10 to 180 mg/kg/day during late gestation and lactation. Pup death and effects on pup growth were observed at 180 mg/kg/day (approximately 10 times the MRHD on a mg/m2 basis). Relatively minor effects such as delays in pinna unfolding and eye opening occurred at doses of 10 and 60 mg/kg (approximately one-half and 3.2 times the MRHD on a mg/m2 basis).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients:
Mannitol {Mannogem)
Dicalcium Phosphate Dihydrate (Calipharm D)
Croscarmellose Sodium
Hydroxy propyl cellulose
Magnesium Stearate
Opadry Yellow-036520034

6.2 Incompatibilities:
Not applicable

6.3 Shelf life:
3 years.

6.4 Special precautions for storage:
Do not store above 30°C. Keep away from the reach of children

6.5 Nature and contents of container:
Alu/Alu blister packaging

6.6 Special precautions for disposal and other handling
Any unused product or waste material should be disposed in accordance with local requirements.

7. Marketing Authorization Holder:
Micro labs Limited

31, Race course road
Bangalore-560001

8. Marketing Authorization Numbers
TAN 21 HM 0469

9. Date of first authorization
26/11/2021

10. Date of revision of the text