For the use of a Cardiologist only

PRAX
(Prasugrel Hydrochloride Tablets 5,10mg)

PRASUGREL HYDROCHLORIDE TABLETS

WARNING : BLEEDING RISK

Prasugrel can cause significant, sometimes fatal, bleeding. Do not use Prasugrel in patients with active pathological bleeding or a history of transient ischemic attack or stroke. In patients 75 years of age, Prasugrel is generally not recommended, because of the increased risk of fatal and intracranial bleeding and uncertain benefit, except in high-risk situations (patients with diabetes or a history of prior MI) where its effect appears to be greater and its use may be considered. Do not start Prasugrel in patients likely to undergo urgent coronary artery bypass graft surgery (CABG). When possible, discontinue the drug at least 7 days prior to any surgery.

Additional risk factor for bleeding include:

- Body weight < 60 kg.
- Propensity to bleed.
- Concomitant use of medications that increase the risk of bleeding (e.g., warfarin, heparin, fibrinolytic therapy, chronic use of non-steroidal anti-inflammatory drugs (NSAIDS). Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, percutaneous coronary intervention (PCI), CABG, or other surgical procedures in the setting of Prasugrel.

If possible, manage bleeding without discontinuing Prasugrel Hydrochloride Tablets. Stopping Prasugrel Hydrochloride Tablets, particularly in the first few weeks after acute coronary syndrome, increases the risk of subsequent cardiovascular events.

GENERIC NAME

Prasugrel Hydrochloride Tablets

COMPOSITION

PRAX 5

Each film coated tablet contains:
Prasugrel Hydrochloride equivalent to Prasugrel 5 mg
Colour: Titanium Dioxide I.P.

PRAX 10

Each film coated tablet contains:
Prasugrel Hydrochloride equivalent to Prasugrel 10 mg
Colours : Red Oxide of Iron and Titanium Dioxide I.P.

DOSAGE FORM

Film Coated Tablet for oral use

DESCRIPTION

Prasugrel Hydrochloride Tablets, a thienopyridine class inhibitor of platelet activation and aggregation mediated by the P2Y12 ADP receptor. Prasugrel Hydrochloride Tablets is formulated as the hydrochloride salt, a racemate, which is chemically designated as 5-[2-cyclopropyl-1-(2fluorophenyl)-2-oxoethyl]-4,5,6,7-tetrahydrothien[3,2-c]pyridin-2-ylacetate hydrochloride. Prasugrel Hydrochloride has the empirical formula $C_{20}H_{20}FNO_3S$•HCl representing a molecular weight of 409.90.

Prasugrel Hydrochloride is a white to off white colour powder. It is soluble at pH 2, slightly soluble at pH 3 to 4, and practically insoluble at pH 6 to 7.5. It also dissolves freely in methanol.

INDICATIONS

Prasugrel Hydrochloride Tablets is indicated to reduce the rate of thrombotic cardiovascular (CV) events (including stent thrombosis) in patients with acute coronary syndrome (ACS) who are to be managed with percutaneous coronary intervention (PCI) as follows:

- Patients with unstable angina (UA) or non-ST-elevation myocardial infarction (NSTEMI).
- Patients with ST-elevation myocardial infarction (STEMI) when managed with primary or delayed PCI.

DOSE AND METHOD OF ADMINISTRATION

Posology

Adults

Prasugrel Hydrochloride Tablets should be initiated with a single 60 mg loading dose and then continued at 10 mg once a day. Patients taking Prasugrel Hydrochloride Tablets should also take ASA daily (75 mg to 325 mg). In patients with acute coronary syndrome (ACS) who are managed with PCI, premature discontinuation of any antiplatelet agent, including Prasugrel Hydrochloride Tablets, could result in an increased risk of thrombosis, myocardial infarction or death due to the patient's underlying disease. A treatment of up to 12 months is recommended, unless the discontinuation of Prasugrel Hydrochloride Tablets is clinically indicated.

Renal impairment

No dose adjustment is necessary for patients with renal impairment, including patients with end stage renal disease. There is limited therapeutic experience in patients with renal impairment).

Hepatic impairment

No dose adjustment is necessary in subjects with mild to moderate hepatic impairment (Child-Pugh class A and B). There is limited therapeutic experience in patients with mild and moderate hepatic dysfunction).

Children and adolescents

Prasugrel Hydrochloride Tablets is not recommended for use in children below age 18 due to a lack of data on safety and efficacy.

Method of administration

For oral use. Prasugrel Hydrochloride Tablets may be administered with or without food. Administration of the 60 mg Prasugrel Hydrochloride Tablets loading dose in the fasted state may provide most rapid onset of action. Do not crush or break the tablet.

CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients. Active pathological bleeding. Prasugrel Hydrochloride Tablets is contraindicated in patients with active pathological bleeding such as peptic ulcer or intracranial. Prior Transient Ischemic Attack or Stroke Prasugrel Hydrochloride Tablets is contraindicated in patients with a history of prior transient ischemic attack (TIA) or stroke. In TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel), patients with a history of TIA or ischemic stroke (> 3 months prior to enrollment) had a higher rate of stroke on Prasugrel (6.5%; of which 4.2% were thrombotic stroke and 2.3% were intracranial hemorrhage[ICH]) than on Clopidogrel (1.2%; all thrombotic). In patients without such a history, the incidence of stroke was 0.9% (0.2% ICH) and 1.0% (0.3% ICH) with Prasugrel and Clopidogrel, respectively. Patients with a history of ischemic stroke within 3 months of screening and patients with a history of hemorrhagic stroke at any time were excluded from TRITON-TIMI 38. Patients who experience a stroke or TIA while on Prasugrel generally should have therapy discontinued. Severe hepatic impairment (Child-Pugh class C).

SPECIAL WARNINGS AND PRECAUTIONS

Warning: BLEEDING RISK

Prasugrel Hydrochloride Tablets can cause significant, sometimes fatal, bleeding. Do not use Prasugrel Hydrochloride Tablets in patients with active pathological bleeding or a history of transient ischemic attack or stroke.

In the phase 3 clinical trial, key exclusion criteria included an increased risk of bleeding; anaemia; thrombocytopenia; a history of pathological intracranial findings. Patients with acute coronary syndromes undergoing PCI treated with Prasugrel Hydrochloride Tablets and ASA showed an increased risk of major and minor bleeding according to the TIMI classification system. Therefore, the use of Prasugrel Hydrochloride Tablets in patients at increased risk of bleeding should only be considered when the benefits in terms of prevention of ischaemic events are deemed to outweigh the risk of serious bleedings. This concern applies especially to patients:

- 75 years of age.
- With a propensity to bleed (e.g., due to recent trauma, recent surgery, recent or recurrent gastrointestinal bleeding, or active peptic ulcer disease). With body weight < 60 kg. In these patients the 10mg maintenance dose is not recommended. A 5 mg maintenance dose should be used.
- With concomitant administration of medicinal products that may increase the risk of bleeding, including oral anticoagulants, Clopidogrel, non-steroidal anti-inflammatory drugs (NSAIDs), and fibrinolytics.

The use of Prasugrel Hydrochloride Tablets in patients' 75 years of age is generally not recommended, and should only be undertaken with caution after a careful individual benefit/risk evaluation by the prescribing physician indicates that benefits in terms of prevention of ischaemic events outweigh the risk of serious bleedings. In the phase 3 clinical trial these

patients were at greater risk of bleeding, including fatal bleeding, compared to patients < 75 years of age. If prescribed, a lower maintenance dose of 5 mg should be used; the 10 mg maintenance dose is not recommended. Therapeutic experience with Prasugrel is limited in patients with renal impairment (including ESRD) and in patients with moderate hepatic impairment. These patients may have an increased bleeding risk. Therefore, Prasugrel should be used with caution in these patients. Therapeutic experience with Prasugrel is limited in Asian patients. Therefore, Prasugrel should be used with caution in these patients. For patients with active bleeding for whom reversal of the pharmacological effects of Prasugrel Hydrochloride Tablets is required, platelet transfusion may be appropriate. Patients should be told that it might take longer than usual to stop bleeding when they take Prasugrel (in combination with Acetyl Salicylic acid), and that they should report any unusual bleeding (site or duration) to their physician.

Surgery
Patients should be advised to inform physicians and dentists that they are taking Prasugrel before any surgery is scheduled, and before any new medicinal product is taken. If a patient is to undergo elective surgery, and an antiplatelet effect is not desired, Prasugrel Hydrochloride Tablets should be discontinued at least 7 days prior to surgery. Increased frequency (3-fold) and severity of bleeding may occur in patients undergoing CABG surgery within 7 days of discontinuation of Prasugrel. The benefits and risks of Prasugrel should be carefully considered in patients in whom the coronary anatomy has not been defined, and urgent CABG is a possibility.

Thrombotic Thrombocytopenic Purpura (TTP)
TTP has been reported with the use of other thienopyridines. TTP is a serious condition and requires prompt treatment. Prasugrel Hydrochloride Tablets was not associated with TTP in clinical trials supporting registration.

Lactose
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take Prasugrel Hydrochloride Tablets.

Interaction with other medicinal products and other forms of interaction
Warfarin: Concomitant administration of Prasugrel Hydrochloride Tablets with Coumarin derivatives other than Warfarin has not been studied. Because of the potential for increased risk of bleeding, warfarin (or other coumarin derivatives) and Prasugrel should be co-administered with caution. *Non-steroidal anti-inflammatory drugs* (NSAIDs):

Concomitant administration with chronic NSAIDs has not been studied. Because of the potential for increased risk of bleeding, chronic NSAIDs (including COX-2 inhibitors) and Prasugrel Hydrochloride Tablets should be co-administered with caution. Prasugrel Hydrochloride Tablets can be concomitantly administered with medicinal products metabolised by cytochrome P450 enzymes (including statins), or medicinal products that are inducers or inhibitors of cytochrome P450 enzymes. Prasugrel Hydrochloride Tablets can also be concomitantly administered with ASA, heparin, digoxin, and medicinal products that elevate gastric pH, including proton pump inhibitors and H2 blockers. Although not studied in specific interaction studies, Prasugrel

Hydrochloride Tablets has been co-administered in the phase 3 clinical trial with low molecular weight Heparin, Bivalirudin, and GP IIb/IIIa inhibitors (no information available regarding the type of GP IIb/IIIa inhibitor used) without evidence of clinically significant adverse interactions.

Effects of other medicinal products on Prasugrel Tablet:
Acetylsalicylic acid: Prasugrel Hydrochloride Tablets is to be administered concomitantly with acetylsalicylic acid (ASA). Although a pharmacodynamic interaction with ASA leading to an increased risk of bleeding is possible, the demonstration of the efficacy and safety of Prasugrel comes from patients concomitantly treated with ASA.

Heparin: A single intravenous bolus dose of unfractionated heparin (100 U/kg) did not significantly alter the prasugrel-mediated inhibition of platelet aggregation. Likewise, Prasugrel did not significantly alter the effect of heparin on measures of coagulation. Therefore, both medicinal products can be administered concomitantly. An increased risk of bleeding is possible when Prasugrel Tablet is co-administered with heparin.

Statins: Atorvastatin (80 mg daily) did not alter the pharmacokinetics of Prasugrel and its inhibition of platelet aggregation. Therefore, statins that are substrates of CYP3A are not anticipated to have an effect on the pharmacokinetics of Prasugrel or its inhibition of platelet aggregation.

Medicinal products that elevate gastric pH: Daily co-administration of ranitidine (an H2 blocker) or Lansoprazole (a proton pump inhibitor) did not change the Prasugrel active metabolite's AUC and Tmax, but decreased the Cmax by 14% and 29%, respectively. In the phase 3 clinical trial, Prasugrel Hydrochloride Tablets was administered without regard to co-administration of a proton pump inhibitor or H2 blocker. Administration of the 60 mg. Prasugrel loading dose without concomitant use of proton pump inhibitors may provide most rapid onset of action.

Inhibitors of CYP3A: Ketoconazole (400 mg daily), a selective and potent inhibitor of CYP3A4 and CYP3A5, did not affect Prasugrel-mediated inhibition of platelet aggregation or the Prasugrel active metabolite's AUC and Tmax, but decreased the Cmax by 34% to 46%. Therefore, CYP3A inhibitors such as Azole antifungals, HIV protease inhibitors, Clarithromycin, Telithromycin, Verapamil, Diltiazem, Indinavir, Ciprofloxacin, and grapefruit juice are not anticipated to have a significant effect on the pharmacokinetics of the active metabolite.

Inducers of cytochromes P450: Rifampicin (600 mg daily), a potent inducer of CYP3A and CYP2B6, and an inducer of CYP2C9, CYP2C19, and CYP2C8, did not significantly change the pharmacokinetics of Prasugrel. Therefore, known CYP3A inducers such as Rifampicin, Carbamazepine, and other inducers of cytochromes P450 are not anticipated to have significant effect on the pharmacokinetics of the active metabolite.

Effects of Prasugrel Hydrochloride Tablets on other medicinal products:
Digoxin: Prasugrel has no clinically significant effect on the pharmacokinetics of Digoxin. Medicinal products metabolised by CYP2C9: Prasugrel did not inhibit CYP2C9, as it did not

affect the pharmacokinetics of S warfarin. Because of the potential for increased risk of bleeding, warfarin and Prasugrel Hydrochloride Tablets should be co-administered with caution.

Medicinal products metabolised by CYP2B6: Prasugrel is a weak inhibitor of CYP2B6. In healthy subjects, Prasugrel decreased exposure to hydroxybupropion, a CYP2B6- mediated metabolite of Bupropion, by 23%. This effect is likely to be of clinical concern only when Prasugrel is co-administered with medicinal products for which CYP2B6 is the only metabolic pathway, and have a narrow therapeutic window (e.g., Cyclophosphamide, Efavirenz).

Pregnancy and lactation
No clinical study has been conducted in pregnant or lactating women. Animal studies do not indicate direct harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Because animal reproduction studies are not always predictive of a human response, Prasugrel Hydrochloride Tablets should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the foetus. It is unknown whether Prasugrel is excreted in human breast milk. Animal studies have shown excretion of Prasugrel in breast milk. The use of Prasugrel during breastfeeding is not recommended. Prasugrel had no effect on fertility of male and female rats at oral doses up to an exposure 240-times the recommended daily human maintenance dose (based on mg/m2). Pharmacodynamics of Prasugrel in patients with severe hepatic disease has not been studied, but such patients are generally at higher risk of bleeding.

Metabolic Status
In healthy subjects, patients with stable atherosclerosis, and patients with ACS receiving Prasugrel, there was no relevant effect of genetic variation in CYP2B6, CYP2C9, CYP2C19, or CYP3A5 on the pharmacokinetics of Prasugrel's active metabolite or its inhibition of platelet aggregation.

USE IN SPECIAL POPULATION
Pregnancy
Pregnancy Category B
There are no adequate and well-controlled studies of Prasugrel use in pregnant women. Reproductive and developmental toxicology studies in rats and rabbits at doses of up to 30 times the recommended therapeutic exposures in humans (based on plasma exposures to the major circulating human metabolite) revealed no evidence of fetal harm. Prasugrel should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Nursing Mothers
It is not known whether Prasugrel is excreted in human milk; however, metabolites of Prasugrel were found in rat milk. Because many drugs are excreted in human milk, Prasugrel should be used during nursing only if the potential benefit to the mother justifies the potential risk to the nursing infant.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

Geriatric Use
In TRITON-TIMI 38, 38.5% of patients were 65 years of age and 13.2% were 75 years of age. The risk of bleeding increased with advancing age in both treatment groups, although the relative risk of bleeding (Prasugrel compared with Clopidogrel) was similar across age groups. Patients' 75 years of age who received Prasugrel had an increased risk of fatal bleeding events (1.0%) compared to patients who received Clopidogrel (0.1%). In patients' 75 years of age, symptomatic intracranial hemorrhage occurred in 7 patients (0.8%) who received Prasugrel and in 3 patients (0.3%) who received Clopidogrel.

Because of the risk of bleeding, and because effectiveness is uncertain in patients 75 years of age, use of Prasugrel is generally not recommended in these patients, except in high-risk situations (diabetes and past history of myocardial infarction) where its effect appears to be greater and its use may be considered.

Low Body Weight
In TRITON-TIMI 38, 4.6% of patients treated with Prasugrel had body weight < 60 kg. Individuals with body weight < 60 kg had an increased risk of bleeding and an increased exposure to the active metabolite of Prasugrel. Consider lowering the maintenance dose to 5 mg in patients < 60 kg. The effectiveness and safety of the 5 mg dose have not been prospectively studied.

Renal Impairment
No dosage adjustment is necessary for patients with renal impairment.

Hepatic Impairment
No dosage adjustment is necessary in patients with mild to moderate hepatic impairment (Child-Pugh Class A and B). The pharmacokinetics and pharmacodynamics of Prasugrel in patients with severe hepatic disease have not been studied, but such patients are generally at higher risk of bleeding.

Metabolic Status
In healthy subjects, patients with stable atherosclerosis, and patients with ACS receiving Prasugrel, there was no relevant effect of genetic variation in CYP2B6, CYP2C9, CYP2C19, or CYP3A5 on the pharmacokinetics of Prasugrel's active metabolite or its inhibition of platelet aggregation.

ADVERSE REACTIONS
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials cannot be directly compared with the rates observed in other clinical trials of another drug and may not reflect the rates observed in practice.

Drug Discontinuation
The rate of study drug discontinuation because of adverse reactions was 7.2% for Prasugrel and 6.3% for Clopidogrel. Bleeding was the most common adverse reaction leading to study drug discontinuation for both drugs (2.5% for Prasugrel and 1.4% for Clopidogrel).

Bleeding
Bleeding Reported as Adverse Reactions - Hemorrhagic events reported as adverse reactions were, for Prasugrel and Clopidogrel, respectively: epistaxis (6.2%, 3.3%), gastrointestinal hemorrhage (1.5%, 1.0%), hemoptysis (0.6%, 0.5%), subcutaneous hematoma (0.5%, 0.2%), post-procedural hemorrhage (0.5%, 0.2%), retroperitoneal hemorrhage (0.3%, 0.2%), and retinal hemorrhage (0.0%, 0.1%).

Malignancies
During TRITON-TIMI 38, newly diagnosed malignancies were reported in 1.6% and 1.2% of patients treated with Prasugrel and Clopidogrel, respectively.

Other Adverse Events
Common and other important non-hemorrhagic adverse events were, for Prasugrel and Clopidogrel, respectively: severe thrombocytopenia (0.06%, 0.04%), anemia (2.2%, 2.0%), abnormal hepatic function (0.22%, 0.27%), allergic reactions (0.36%, 0.36%), and angioedema (0.06%, 0.04%). Table summarizes the adverse events reported by at least 2.5% of patients.

UNDESIRABLE EFFECTS
Safety in patients with acute coronary syndrome undergoing PCI was evaluated in one Clopidogrel-controlled study (TRITON) in which 6741 patients were treated with Prasugrel (60 mg loading dose and 10 mg once daily maintenance dose) for a median of 14.5 months (5802 patients were treated for over 6 months, 4136 patients were treated for more than 1 year). The rate of study drug discontinuation due to adverse events was 7.2% for Prasugrel and 6.3% for Clopidogrel. Of these, bleeding was the most common adverse reaction for both drugs leading to study drug discontinuation (2.5 % for Prasugrel and 1.4% for Clopidogrel).

OVERDOSE
Overdose of Prasugrel Hydrochloride Tablets may lead to prolonged bleeding time and subsequent bleeding complications. No data are available on the reversal of the pharmacological effect of Prasugrel; however, if prompt correction of prolonged bleeding time is required, platelet transfusion and/or other blood products may be considered.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamics
Prasugrel is an inhibitor of platelet activation and aggregation through the reversible binding of its active metabolite to the P2Y12 class of ADP receptors on platelets. Since platelets participate in the initiation and/or evolution of thrombotic complications of atherosclerotic disease, inhibition of platelet function can result in the reduction of the rate of cardiovascular events such as death, myocardial infarction, or stroke. Following a 60 mg loading dose of prasugrel, inhibition of ADP-induced platelet aggregation occurs at 15 minutes with 5 μM ADP and 30

minutes with 20 μM ADP. The maximum inhibition by Prasugrel of ADP-induced platelet aggregation is 83% with 5 μM ADP and 79% with 20 μM ADP, in both cases with 89% of healthy subjects and patients with stable atherosclerosis achieving at least 50% inhibition of platelet aggregation by 1 hour. Prasugrel-mediated inhibition of platelet aggregation exhibits low between-subject (12%) and within-subject (9%) variability with both 5 μM and 20 μM ADP.

Mean steady-state inhibition of platelet
aggregation was 74% and 69% respectively for 5 μM ADP and 20 μM ADP, and was achieved following 3 to 5 days of administration of the 10 mg Prasugrel maintenance dose preceded by a 60 mg loading dose. More than 98% of subjects had 20% inhibition of platelet aggregation during maintenance dosing. Platelet aggregation gradually returned to baseline values after treatment in 7 to 9 days after administration of a single 60 mg loading dose of Prasugrel, and in 5 days following discontinuation of maintenance dosing at steady-state.

Clopidogrel: Following administration of 75 mg Clopidogrel once daily for 10 days, 40 healthy subjects were switched to Prasugrel 10 mg once daily with or without a loading dose of 60 mg. Similar or higher inhibition of platelet aggregation was observed with Prasugrel. Switching directly to Prasugrel 60 mg loading dose resulted in the most rapid onset of higher platelet inhibition. Following administration of a 900 mg loading dose of Clopidogrel (with ASA), 56 subjects with ACS were treated for 14 days with either Prasugrel 10 mg once daily or Clopidogrel 150 mg once daily, and then switched to either Clopidogrel 150 mg or Prasugrel 10 mg for another 14 days. Higher inhibition of platelet aggregation was observed in patients switched to Prasugrel 10 mg compared with those treated with Clopidogrel 150 mg. No data are available on switching from a Clopidogrel loading dose directly to a Prasugrel loading dose.

Efficacy and Safety in Acute Coronary Syndrome (ACS)
The phase 3 TRITON study compared Prasugrel Tablet (Prasugrel) with Clopidogrel, both co-administered with ASA and other standard therapy. TRITON was a 13,608 patient, multi-centre international, randomised, double-blind, parallel group study. Patients had ACS with moderate to high risk UA, NSTEMI, or STEMI and were managed with PCI.

Patients with UA/NSTEMI within 72 hours of symptoms or STEMI between 12 hours to 14 days of symptoms were randomised after knowledge of coronary anatomy. Patients with STEMI within 12 hours of symptoms and planned for primary PCI could be randomized without knowledge of coronary anatomy. For all patients, the loading dose could be administered any time between randomisation and 1 hour after the patient left the catheterisation lab. Patients randomised to receive Prasugrel (60 mg loading dose followed by 10 mg once daily) or Clopidogrel (300 mg loading dose followed by 75 mg once daily) were treated for a median of 14.5 months (maximum of 15 months with a minimum of 6 months follow-up). Patients also received ASA (75 mg to 325 mg once daily). Use of any thienopyridine within 5 days before enrolment was an exclusion criterion. Other therapies, such as heparin and GPIIb/IIIa inhibitors, were administered at the discretion of the physician. Approximately 40% of patients (in each of the treatment groups) received GPIIb/IIIa inhibitors in support of PCI (no information available regarding the type of GPIIb/ IIIa inhibitor used). Approximately 98% of patients (in each of the treatment groups) received antithrombins (heparin, low molecular weight heparin, Bivalirudin, or other agent) directly in support of PCI. The trial's primary outcome measure was the time to first

occurrence of cardiovascular (CV) death, non-fatal myocardial infarction (MI), or non-fatal stroke. Analysis of the composite endpoint in the All ACS population (combined UA/NSTEMI and STEMI cohorts) was contingent on showing statistical superiority of Prasugrel versus Clopidogrel in the UA/NSTEMI cohort ($p < 0.05$).

All ACS population: Prasugrel Hydrochloride Tablets showed superior efficacy compared to Clopidogrel in reducing the primary composite outcome events as well as the pre-specified secondary outcome events, including stent thrombosis. The benefit of Prasugrel was apparent within the first 3 days and it persisted to the end of study. The superior efficacy was accompanied by an increase in major bleeding. The patient population was 92% Caucasian, 26% female, and 39% 65 years of age. The benefits associated with Prasugrel were independent of the use of other acute and long-term cardiovascular therapies, including heparin/low molecular weight heparin, Bivalirudin, intravenous GPIIb/IIIa inhibitors, lipid-lowering medicinal products, beta-blockers, and angiotensin converting enzyme inhibitors. The efficacy of Prasugrel was independent of the ASA dose (75 mg to 325 mg once daily). The use of oral anticoagulants, non-study antiplatelet medicinal products and chronic NSAIDs was not allowed in TRITON. In the All ACS population, Prasugrel was associated with a lower incidence of CV death, non-fatal MI, or non-fatal stroke compared to Clopidogrel, regardless of baseline characteristics such as age, sex, body weight, geographical region, use of GPIIb/IIIa inhibitors, and stent type. The benefit was primarily due to a significant decrease in non-fatal MI. Subjects with diabetes had significant reductions in the primary, and all secondary composite endpoints.

The observed benefit of Prasugrel in patients 75 years was less than that observed in patients < 75 years. Patients 75 years were at increased risk of bleeding, including fatal. Patients' 75 years in whom the benefit with Prasugrel was more evident included those with diabetes, STEMI, higher risk of stent thrombosis, or recurrent events.

PHARMACOKINETIC PROPERTIES

Prasugrel is a prodrug and is rapidly metabolised in vivo to an active metabolite and inactive metabolites. The active metabolite's exposure (AUC) has moderate to low between-subject (27%) and within-subject (19%) variability. Prasugrel's pharmacokinetics is similar in healthy subjects, patients with stable atherosclerosis, and patients undergoing percutaneous coronary intervention.

Absorption

The absorption and metabolism of Prasugrel are rapid, with peak plasma concentration (Cmax) of the active metabolite occurring in approximately 30 minutes. The active metabolite's exposure (AUC) increases proportionally over the therapeutic dose range. In a study of healthy subjects, AUC of the active metabolite was unaffected by a high fat, high calorie meal, but Cmax was decreased by 49% and the time to reach Cmax (Tmax) was increased from 0.5 to 1.5 hours. Prasugrel Hydrochloride Tablets was administered without regard to food in TRITON. Therefore, Prasugrel Hydrochloride Tablets can be administered without regard to food; however, the administration of Prasugrel loading dose in the fasted state may provide most rapid onset of action.

Distribution
Active metabolite binding to human serum albumin (4% buffered solution) was 98%.

Metabolism
Prasugrel is not detected in plasma following oral administration. It is rapidly hydrolysed in the intestine to a Thiolactone, which is then converted to the active metabolite by a single step of cytochrome P450 metabolism, primarily by CYP3A4 and CYP2B6, and to a lesser extent by CYP2C9 and CYP2C19. The active metabolite is further metabolised to two inactive compounds by S-methylation, or conjugation with cysteine. In healthy subjects, patients with stable atherosclerosis, and patients with ACS receiving Prasugrel Hydrochloride Tablets, there was no relevant effect of genetic variation in CYP3A5, CYP2B6, CYP2C9, or CYP2C19 on the pharmacokinetics of Prasugrel or its inhibition of platelet aggregation.

Elimination
Approximately 68% of the Prasugrel dose is excreted in the urine and 27% in the faeces, as inactive metabolites. The active metabolite has an elimination half-life of about 7.4 hours (range 2 to 15 hours).

Special Populations:
Elderly: In a study of healthy subjects between the ages of 20 and 80 years, age had no significant effect on pharmacokinetics of Prasugrel or its inhibition of platelet aggregation. In the large phase 3 clinical trial, the mean estimated exposure (AUC) of the active metabolite was 19% higher in very elderly patients (75 years of age) compared to subjects <75 years of age. Prasugrel should be used with caution in patients 75 years of age due to the potential risk of bleeding in this population.

Hepatic impairment: No dose adjustment is necessary for patients with mild to moderate impaired hepatic function (Child-Pugh class A and B). Pharmacokinetics of Prasugrel and its inhibition of platelet aggregation were similar in subjects with mild to moderate hepatic impairment compared to healthy subjects. Pharmacokinetics and pharmacodynamics of Prasugrel in patients with severe hepatic impairment have not been studied. Prasugrel must not be used in patients with severe hepatic impairment.

Renal impairment: No dosage adjustment is necessary for patients with renal impairment, including patients with end stage renal disease (ESRD). Pharmacokinetics of Prasugrel and its inhibition of platelet aggregation are similar in patients with moderate renal impairment (GFR 30-<50 ml/min/1.73m2) and healthy subjects. Prasugrel-mediated inhibition of platelet aggregation was also similar in patients with ESRD who required haemodialysis compared to healthy subjects, although Cmax and AUC of the active metabolite decreased 51% and 42%, respectively, in ESRD patients.

Body weight:
The mean exposure (AUC) of the active metabolite of Prasugrel is approximately 30 to 40% higher in healthy subjects and patients with a body weight of < 60 kg compared to those weighing 60 kg. Prasugrel Hydrochloride Tablets should be used with caution in patients with a body weight of <60 kg due to the potential risk of bleeding in this population.

Ethnicity: In clinical pharmacology studies, after adjusting for body weight, the AUC of the active metabolite was approximately 19% higher in Chinese, Japanese, and Korean subjects compared to that of Caucasians, predominantly related to higher exposure in Asian subjects <60 kg. There is no difference in exposure among Chinese, Japanese, and Korean subjects. Exposure in subjects of African and Hispanic descent is comparable to that of Caucasians. No dose adjustment is recommended based on ethnicity alone.

Gender: In healthy subjects and patients, the pharmacokinetics of Prasugrel is similar in men and women.

Children and adolescents: Pharmacokinetics and pharmacodynamics of Prasugrel have not been evaluated in a paediatric population.

PRECLINICAL SAFETY DATA
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeat-dose toxicity, genotoxicity, carcinogenic potential, or toxicity to reproduction. Effects in non-clinical studies were observed only at exposures considered sufficiently in excessof the maximum human exposure indicating little relevance to clinical use. Embryo-foetal developmental toxicology studies in rats and rabbits showed no evidence of malformations due to Prasugrel. At a very high dose (>240-times the recommended daily human maintenance dose on a mg/m^2 basis) that caused effects on maternal body weight and/or food consumption, there was a slight decrease in offspring body weight (relative to controls). In pre- and post-natal rat studies, maternal treatment had no effect on the behavioural or reproductive development of the offspring at doses up to an exposure 240-times the recommended daily human maintenance dose (based on mg/m^2).

No compound-related tumours were observed in a 2-year rat study with Prasugrel exposures ranging to greater than 75-times the recommended therapeutic exposures in humans (based on plasma exposures to the active and major circulating human metabolites). There was an increased incidence of tumours (hepatocellular adenomas) in mice exposed for 2 years to high doses (>75-times human exposure), but this was considered secondary to Prasugrel-induced enzyme induction. The rodent-specific association of liver tumours and drug-induced enzyme induction is well documented in the literature. The increase in liver tumours with Prasugrel administration in mice is not considered a relevant human risk.

INCOMPATIBILITIES
Not applicable

EXPIRY DATE
Do not use later than expiry date.

STORAGE
Store at a temperature not exceeding 30^oC, protected from moisture. Keep out of reach of children.

PRESENTATION
Prax 5 and Prax 10 are available as blister pack of 10 tablets.

MARKETED BY

TORRENT PHARMACEUTICALS LTD.
Torrent House, Off Ashram Road,
Ahmedabad-380 009, INDIA

IN/PRAX 5,10mg/SEPT-15/01/PI