Prasugrel Tablets IP 5 &10 mg

MSN

PrasuSafe™ 5 & 10 प्रासुसेफ ५&१०

To be sold by retail on prescription of Cardiologist only

PRESCRIBING INFORMATION

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 recom mended, except in high-risk patients (diabetes or prior myocardial infarction [MI]), where its use may be considered**
- **Do not start Prasugrel in patients likely to undergo urgent cor onary artery bypass graft surgery (CABG). When possible, discon tinue Prasugrel at least 7 days prior to any surgery**
- **Additional risk factors for bleeding include: body weight <60 kg, propensity to bleed, concomitant use of medications that increase the risk of bleeding.**
- **Suspect bleeding in any patient who is hypotensive and has recently un dergone invasive or surgical procedures**
- **If possible, manage bleeding without discontinuing Prasugrel.**
- **Stopping Prasugrel increases the risk of subsequent cardiovascular events**

1. GENERIC NAME

Prasugrel Tablets IP 5 mg
Prasugrel Tablets IP 10 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Prasugrel Tablets IP 5 mg
Each film coated tablet contains:
Prasugrel Hydrochloride IP Equivalent to Prasugrel 5 mg
Colors : Titanium Dioxide IP

Prasugrel Tablets IP 10 mg
Each film coated tablet contains
Prasugrel Hydrochloride IP Equivalent to Prasugrel 10 mg
Colours: Titanium Dioxide IP
Ferric Oxide (Red) USP-NF

3. DOSAGE FORM AND STRENGTH

Prasugrel is available as film coated tablets 5 mg and 10 mg.

4. CLINICAL PARTICULARS

4.1. Indications

Prasugrel tablets are 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 infraction (NSTEMI).
- Patients with ST-elevation myocardial infraction (STEMI) when managed with primary or delayed PCI.

4.2. Posology and Method of Administration

Initiate Prasugrel treatment as a single 60 mg oral loading dose and then continue at 10 mg orally once daily. Patients taking Prasugrel should also take aspirin (75 mg to 325 mg) daily. Prasugrel may be administered with or without food.

Timing of Loading Dose

In the clinical trial that established the efficacy and safety of Prasugrel, the loading dose of Prasugrel was not administered until coronary anatomy was established in UA/NSTEMI patients and in STEMI patients presenting more than 12 hours after symptom onset. In STEMI patients presenting within 12 hours of symptom onset, the loading dose of Prasugrel was administered at the time of diagnosis, although most received Prasugrel at the time of PCI. For the small fraction of patients that required urgent CABG after treatment with Prasugrel, the risk of significant bleeding was substantial.

Dosing in Low Weight Patients

Compared to patients weighing ≥60 kg, patients weighing <60 kg have an increased exposure to the active metabolite of prasugrel and an increased risk of bleeding on a 10 mg once daily maintenance dose. 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.

4.3. Contraindications

- Hypersensitivity to the active substance or to prasugrel or any component of the product
- Active pathological bleeding: Prasugrel is contraindicated in patients with active pathological bleeding such as peptic ulcer or intracranial hemorrhage.
- History of stroke or transient ischaemic attack (TIA)
- Severe hepatic impairment (Child Pugh class C)

4.4. Special Warnings and Precautions for Use

General Risk of Bleeding

Thienopyridines, including Prasusafe, increase the risk of bleeding. With the dosing regimens, TIMI (Thrombolysis in Myocardial Infarction) Major (clinically overt bleeding associated with a fall in hemoglobin ≥5 g/dL, or intracranial hemorrhage) and TIMI Minor (overt bleeding associated with a fall in hemoglobin of ≥3 g/dL but <5 g/dL), bleeding events were more common on Prasusafe than on clopidogrel. Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, PCI, CABG, or other surgical procedures even if the patient does not have overt signs of bleeding. Do not use Prasusafe in patients with active bleeding, prior TIA or stroke.

Other risk factors for bleeding are:

- Age ≥75 years. Because of the risk of bleeding (including fatal bleeding) and uncertain effectiveness in patients ≥75 years of age, use of Prasusafe is generally not recommended in these patients, except in high-risk situations (patients with diabetes or history of myocardial infarction) where its effect appears to be greater and its use may be considered
- CABG or other surgical procedure
- Body weight <60 kg. Consider a lower (5 mg) maintenance dose
- Propensity to bleed (e.g., recent trauma, recent surgery, recent or recurrent gastrointestinal (GI) bleeding, active peptic ulcer disease, severe hepatic impairment, or moderate to severe renal impairment)
- Medications that increase the risk of bleeding (e.g., oral anticoagulants, chronic use of nonsteroidal anti-inflammatory drugs [NSAIDs], and fibrinolytic agents).

Thienopyridines inhibit platelet aggregation for the lifetime of the platelet (7-10 days), so withholding a dose will not be useful in managing a bleeding event or the risk of bleeding associated with an invasive procedure. Because the half-life of Prasugrel's active metabolite is short relative to the lifetime of the platelet, it may be possible to restore hemostasis by administering exogenous platelets; however, platelet transfusions within 6 hours of the loading dose or 4 hours of the maintenance dose may be less effective.

Coronary Artery Bypass Graft Surgery-Related Bleeding

The risk of bleeding is increased in patients receiving Prasugrel who undergo CABG. If possible, Prasugrel should be discontinued at least 7 days prior to CABG.

Do not start Prasugrel in patients likely to undergo urgent CABG. CABG-related bleeding may be treated with transfusion of blood products, including packed red blood cells and platelets; however, platelet transfusions within 6 hours of the loading dose or 4 hours of the maintenance dose may be less effective.

Discontinuation of Prasugrel

Discontinue thienopyridines, including Prasugrel, for active bleeding, elective surgery, stroke, or TIA. The optimal duration of thienopyridine therapy is unknown. In patients who are managed with PCI and stent placement, premature discontinuation of any antiplatelet medication, including thienopyridines, conveys an increased risk of stent thrombosis, myocardial infarction, and death. Patients who require premature discontinuation of a thienopyridine will be at increased risk for cardiac events. Lapses in therapy should be avoided, and if thienopyridines must be temporarily discontinued because of an adverse event(s), they should be restarted as soon as possible.

Thrombotic Thrombocytopenic Purpura (TTP)

TTP has been reported with the use of Prasugrel. TTP can occur after a brief exposure (<2 weeks). TTP is a serious condition that can be fatal and requires urgent treatment, including Plasmapheresis (plasma exchange). TTP is characterized by thrombocytopenia, microangiopathic hemolytic anemia (schistocytes [fragment red blood cells] seen on peripheral smear), neurological findings, renal dysfunction, and fever.

Hypersensitivity Including Angioedema

Hypersensitivity including angioedema has been reported in patients receiving Prasugrel, including patients with a history of hypersensitivity reaction to other thienopyridines.

4.5. Drug Interactions

Warfarin:

Concomitant administration of Prasusafe 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 Prasusafe should be co-administered with caution.

Prasusafe 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. Prasusafe 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, Prasusafe 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 Prasusafe

Acetylsalicylic acid:

Prasusafe 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 Prasusafe 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, Prasusafe 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 azol 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.

Morphine and other opioids:

A delayed and decreased exposure to oral P2Y12 inhibitors, including prasugrel and its active metabolite, has been observed in patients with acute coronary syndrome treated with morphine. This interaction may be related to reduced gastrointestinal motility and apply to other opioids. The clinical relevance is unknown, but data indicate the potential for reduced prasugrel efficacy in patients co-administered prasugrel and morphine. In patients with acute coronary syndrome, in whom morphine cannot be withheld and fast P2Y12 inhibition is deemed crucial, the use of a parenteral P2Y12 inhibitor may be considered.

Effects of Prasusafe 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 Prasusafe 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).

4.6. Use in Special Populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy

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, Prasusafe should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the foetus.

Breast-feeding

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.0

Fertility

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/m^2)

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Because of the risk of bleeding, and because effectiveness is uncertain in patients ≥75 years of age, use of Prasusafe 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

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. There is limited experience in patients with end stage renal disease, but such patients are generally at higher risk of bleeding.

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

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.

4.7. Effects on Ability to Drive and Use Machines

Prasugrel is expected to have no or negligible influence on the ability to drive and use machines

4.8. Undesirable Effects

Below table summarises haemorrhagic and non-haemorrhagic adverse reactions, classified by frequency and system organ class. Frequencies are defined as follows:

Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 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).

System Organ Class	Common	Uncommon	Rare	Not Known
Blood and Lymphatic System disorders	Anaemia	Thrombocy-topaenia	Thrombotic thrombocy-topaenic purpura (TTP) *-see section 4.4*	
Immune system disorders	Hypersensi-tivity including angioedema			
Eye disorders	Eye haemor-rhage			
Vascular Disorders	Haematoma			
Respiratory, thoracic and mediastinal disorders	Epistaxis	Haemoptysis		
Gastrointestinal disorders	Gastrointestinal haemorrhage	Retroperito-neal haemorrhage Rectal haem-orrhage Haemato-chezia Gingival bleeding		
Skin and subcutaneous tissue disorders	Rash Ecchymosis			
Renal and urinary disorders	Haematuria			
General disorders and administration site conditions	Vessel puncture site haematoma Puncture site haemorrhage			
Injury, poisoning and procedural complications	Contusion	Post-proce-dural haemorrhage	Subcuta-neous haematoma	

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. To report Suspected Adverse Reactions, contact MSN Laboratories Private Limited at pharmacovigilance@msnlabs.com or through company website www.msnlabs.com->Contact us->Medical Enquiry/ to report a side effect.

4.9. Overdose

Overdose of Prasusafe 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of action

Prasugrel is an inhibitor of platelet activation and aggregation through the irreversible binding of its active metabolite to the P2Y 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.

5.2 Pharmacodynamic Properties

Prasugrel produces inhibition of platelet aggregation to 20 µM or 5 µM ADP, as measured by light transmission aggregometry. Following a 60 mg loading dose of Prasusafe, approximately 90% of patients had at least 50% inhibition of platelet aggregation by 1 hour. Maximum platelet inhibition was about 80%. Mean steady-state inhibition of platelet aggregation was about 70% following 3 to 5 days of dosing at 10 mg daily after a 60 mg loading dose of Prasusafe.

Platelet aggregation gradually returns to baseline values over 5-9 days after discontinuation of prasugrel, this time course being a reflection of new platelet production rather than pharmacokinetics of prasugrel. Discontinuing clopidogrel 75 mg and initiating a prasugrel 10 mg maintenance dose with or without a prasugrel 60 mg loading dose results in a decrease of 14 percentage points in maximum platelet aggregation (MPA) by Day 7. This decrease in MPA is not greater than that typically produced by a 10 mg maintenance dose of prasugrel alone. The relationship between inhibition of platelet aggregation and clinical activity has not been established.

5 mg in Low Body Weight Patients

In patients with stable coronary artery disease, mean platelet inhibition in subjects <60 kg taking 5 mg prasugrel was similar to that of subjects ≥60 kg taking 10 mg prasugrel. The relationship between inhibition of platelet aggregation and clinical activity has not been established.

5.3 PHARMACOKINETIC PROPERTIES

Absorption

The absorption and metabolism of prasugrel are rapid, with peak plasma concentration (C_{max}) 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 C was decreased by 49% and the time to reach C (T_{max}) was increased from 0.5 to 1.5 hours. Prasusafe was administered without regard to food. Therefore, Prasusafe 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%.

Biotransformation

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 Smethylation or conjugation with cysteine. Patients with stable atherosclerosis, and patients with ACS receiving Prasusafe, 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).

6. NONCLINICAL PROPERTIES

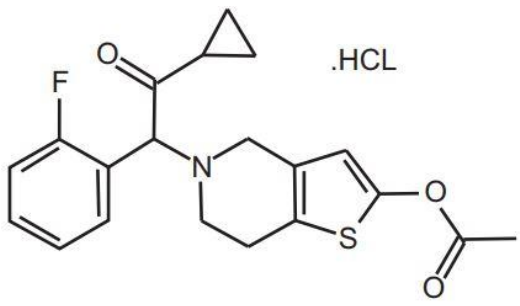
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, or toxicity to reproduction.

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of 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 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.

7. DESCRIPTION

Prasugrel is a 3rd generation thienopyridine class of anti-platelet drug. It blocks ADP (P2Y12) receptor on platelet membrane & inhibit platelet aggregation. Prasugrel is formulated as the hydrochloride salt, a racemate which is chemically designated as 5-[(1RS)-2-cyclopropyl-1-(2-fluorophenyl)-2oxoethhyl]-4, 5, 6, 7-tetrahydrothieno [3, 2 c] pyridine-2-yl acetate hydrochloride. Prasugrel hydrochloride has the formula $C_{20}H_{20}FNO_3S.HCl$ and molecular weight is of 409.9. The chemical structure is given below.



8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

None

8.2 Packing Information

Blister strip of 10 tablets

8.3 Storage and Handling Instructions

Store protected from moisture, at a temperature not exceeding 30°C.

9. PATIENT COUNSELING INFORMATION

Advise the patient to read the Prescribing information.

Administration

- Advise patients not to break Prasusafe tablets.
- Remind patients not to discontinue Prasusafe without first discussing it with the physician who prescribed Prasusafe.

Bleeding

- Inform patients that they:
- will bruise and bleed more easily.
- will take longer than usual to stop bleeding.
- should report any unanticipated, prolonged, or excessive bleeding, or blood in their stool or urine.

Thrombotic Thrombocytopenic Purpura

Inform patients that TTP is a rare but serious condition that has been reported with Prasusafe. Instruct patients to get prompt medical attention if they experience symptoms of TTP that cannot otherwise be explained.

Hypersensitivity

Inform patients that they may have hypersensitivity reactions and to seek immediate medical attention if any signs and symptoms of a hypersensitivity reaction occur. Patients who have had hypersensitivity reactions to other thienopyridines may have hypersensitivity reactions to Prasusafe.

Invasive Procedures

Instruct patients to:

- inform physicians and dentists that they are taking Prasusafe before any invasive procedure is scheduled.
- tell the doctor performing the invasive procedure to talk to the prescribing healthcare professional before stopping Prasusafe.

Concomitant Medications

Ask patients to list all prescription medications, over-the-counter medications, or dietary supplements they are taking or plan to take so the physician knows about other treatments that may affect bleeding risk (e.g., warfarin and NSAIDs).

10. DETAILS OF MANUFACTURER

MSN Laboratories Private Limited
(Formulations Division),
Plot No. 42, Anrich Industrial Estate,
Bollaram, Sangareddy District - 502 325,
Telangana, INDIA.

11. DETAILS OF MANUFACTURING LICENCE NUMBER

38/MD/AP/2007/F/CC

12. DATE OF REVISION

August 2021

™ Trade mark under registration

B3837-04