**For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory Only**

# PRAX A 75

**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 è75 years of age, Prasugrel is generally not recommended, 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 coronary artery bypass graft surgery (CABG). When possible, discontinue 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 undergone invasive or surgical procedures.**
- **If possible, manage bleeding without discontinuing Prasugrel. Stopping prasugrel increases the risk of subsequent cardiovascular events.**

1. **Generic Name**

   Prasugrel Hydrochloride and Aspirin Capsules

2. **Qualitative and quantitative composition**

   Each hard gelatin capsule contains:

   Prasugrel Hydrochloride U.S.P.

   Equivalent to Prasugrel…….10 mg

   (As film coated tablet)

   Colours: Red Oxide of Iron and Titanium Dioxide I.P.

   Aspirin I.P……....75 mg

   (As enteric coated tablets)

   Colours: Yellow Oxide of Iron

   Approved colours used in hard gelatin capsules shells.

   The excipients used are Talc, Mannitol, Microcrystalline cellulose, Hydroxy propyl methylcellulose, Croscarmellose Sodium, Magnesium Stearate, Lactose Monohydrate, Triacetin, Titanium Dioxide, Ferric Oxide Red, Iso Propyl Alcohol, Methylene Chloride, Stearic Acid, Ethyl Cellulose, Diethyl Phthalate, Meth.Acid & Eth. Acr, Triethyl Citrate.

3. **Dosage form and strength**

   **Dosage form:** Hard gelatin capsule

**Strength**: Prasugrel: 10 mg and Aspirin: 75 mg

## 4. Clinical particulars

### 4.1 Therapeutic indication

It is indicated for the treatment of percutaneous coronary intervention (PCI).

### 4.2 Posology and method of administration

**Aspirin**

**Posology**

Patients should seek the advice of a doctor before commencing therapy for the first time. Physician decides the usual dosage of the medication. Should be used with caution in elderly patients who are more prone to adverse events. Treatment should be reviewed at regular intervals.

*Children*

Do not give to children aged under 16 years, unless specifically indicated (e.g. for Kawasaki's disease).

**Dose**: As directed by the Physician.

**Method of administration**

For oral administration only.

Take the capsules with water, do not cut, chew or crush the capsules. Swallow completely.

**Prasugrel**

**Posology**

*Adults*

Efient should be initiated with a single 60 mg loading dose and then continued at 10 mg once a day. In UA/NSTEMI patients, where coronary angiography is performed within 48 hours after admission, the loading dose should only be given at the time of PCI. Patients taking Efient 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 Efient, 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 Efient is clinically indicated.

*Patients ≥ 75 years old*

The use of Efient in patients ≥ 75 years of age is generally not recommended. If, after a careful individual benefit/risk evaluation by the prescribing physician, treatment is deemed necessary in the patients age group ≥ 75 years, then following a 60 mg loading dose a reduced maintenance dose of 5 mg should be prescribed. Patients ≥ 75 years of age have greater sensitivity to bleeding and higher exposure to the active metabolite of prasugrel.

*Patients weighing < 60 kg*

Efient should be given as a single 60 mg loading dose and then continued at a 5 mg once daily dose. The 10 mg maintenance dose is not recommended. This is due to an

increase in exposure to the active metabolite of prasugrel, and an increased risk of bleeding in patients with body weight < 60 kg when given a 10 mg once daily dose compared with patients ≥ 60 kg.

*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. Efient is contraindicated in patients with severe hepatic impairment (Child Pugh class C).

*Pediatric population*

The safety and efficacy of Efient in children below age 18 has not been established. Limited data are available in children with sickle cell anaemia.

**Method of administration**

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

## 4.3 Contraindications

- Hypersensitivity to salicylic acid compounds or prostaglandin synthetase inhibitors (e.g. certain asthma patients who may suffer an attack or faint and certain patients who may suffer from bronchospasm, rhinitis and urticaria), or to any other active ingredients or excipients.
- Active or history of peptic ulceration and/or gastric/intestinal haemorrhage, or other kinds of bleeding such as cerebrovascular haemorrhages.
- Active bleeding at other sites.
- Haemorrhagic diathesis; coagulation disorders such as haemophilia and or thrombocytopenia concurrent anticoagulant therapy.
- Patients who are suffering from gout.
- Severe hepatic impairment.
- Severe renal impairment.
- Do not give to children aged under 16 years, unless specifically indicated (e.g. for Kawasaki's disease).
- Doses >100 mg/day of aspirin during the third trimester of pregnancy; Methotrexate used at doses >15mg/week
- History of stroke or transient ischaemic attack (TIA).
- Severe hepatic impairment (Child Pugh class C).

## 4.4 Special warnings and precautions for use

**Aspirin**

Aspirin 75 mg is not suitable for use as an anti-inflammatory/ analgesic/ antipyretic. Caution should be exercised in patients with allergic disease, impairment hepatic or renal function (avoid if severe) and dehydration, since the use of NSAIDs may result

in deterioration of renal function. Liver function tests should be performed regularly in patients presenting slight or moderate hepatic insufficiency. Aspirin may also precipitate bronchospasm, induce attacks of asthma in susceptible subjects, or promote other hypersensitivity reactions. Risk factors are existing asthma, hay fever, nasal polyps or chronic respiratory diseases. The same applies for patients who also show allergic reaction to other substances (e.g. with skin reactions, itching or urticaria). Serious skin reactions, including Steven-Johnsons syndrome, have rarely been reported in association with the use of acetylsalicylic acid. Aspirin should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity. The elderly may be more susceptible to the toxic effects of salicylates. Continuous prolonged use of aspirin should be avoided in the elderly because of the risk of gastrointestinal bleeding and perforation which may be fatal. Where prolonged therapy is required, patients should be reviewed regularly. Caution should be taken in patients with glucose-6-phosphate dehydrogenase deficiency as haemolytic anaemia may occur. Aspirin 75 mg is not recommended during menorrhagia where it may increase menstrual bleeding. Aspirin prolongs bleeding time, mainly by inhibiting platelet aggregation and therefore it should be discontinued several days before scheduled surgical procedures. Haematological and haemorrhagic effects can occur, and may be severe. Use with caution before surgery, including tooth extraction. Patients should report any unusual bleeding symptoms to their physician. Care is advised when stopping antiplatelet therapy after stent insertion either after a fixed period of time or in preparation for a planned surgical procedure, as the balance between stent thrombosis and excessive bleeding has to be carefully assessed.

There is a possible association between aspirin and Reye's Syndrome when given to children. Reye's syndrome is a very rare disease, which affects the brain and liver, and can be fatal. For this reason aspirin should not be given to children aged under 16 years unless specifically indicated (e.g. for Kawasaki's disease). Aspirin is to be used with caution in cases of hypertension and patients with a stomach ulcer or a history of stomach ulcers or duodenal ulcer or haemorrhagic episodes or undergoing therapy with anticoagulants. Patients should report any unusual bleeding symptoms to their physician. If gastrointestinal bleeding or ulceration occurs the treatment should be withdrawn. Before commencing long term aspirin therapy for the management of cardiovascular or cerebrovascular disease patients should consult their doctor who can advise on the relative benefits versus the risks for the individual patient.

Concomitant treatment with Aspirin and other drugs that alter haemostasis (i.e. anticoagulants such as warfarin, thrombolytic and antiplatelet agents, anti-inflammatory drugs and selective serotonin reuptake inhibitors) is not recommended, unless strictly indicated, because they may enhance the risk of haemorrhage. If the combination cannot be avoided, close observation for signs of bleeding is recommended. Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration, such as oral corticosteroids, selective serotonin-reuptake inhibitors and deferasirox. Acetylsalicylic acid in low doses reduces uric acid excretion. Due to this fact, patients who tend to have reduced uric acid excretion may experience gout attacks.

The risk of hypoglycaemic effect with sulfonylureas and insulins may be potentiated with Aspirin taken at over dosage.

Aspirin should be avoided in late pregnancy and generally during breast feeding. This medicine contains lactose. Patients with rare hereditary problems of galactose

intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

**Prasugrel**

***Bleeding risk***

In the reported data in the phase 3 clinical trial key exclusion criteria included an increased risk of bleeding; anaemia; thrombocytopaenia; a history of pathological intracranial findings. Patients with acute coronary syndromes undergoing PCI treated with Prasugrel and ASA showed an increased risk of major and minor bleeding according to the TIMI classification system. Therefore, the use of Prasugrel 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 (see below).

- 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 10 mg 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.

For patients with active bleeding for whom reversal of the pharmacological effects of Prasugrel is required, platelet transfusion may be appropriate.

The use of Prasugrel 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 reported 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.

Patients should be told that it might take longer than usual to stop bleeding when they take prasugrel (in combination with ASA), and that they should report any unusual bleeding (site or duration) to their physician.

**Bleeding Risk Associated with Timing of Loading Dose in NSTEMI**

In a reported clinical trial of NSTEMI patients (the ACCOAST study), where patients were scheduled to undergo coronary angiography within 2 to 48 hours after randomization, a prasugrel loading dose given on average 4 hours prior to coronary angiography increased the risk of major and minor peri-procedural bleeding compared with a prasugrel loading dose at the time of PCI. Therefore, in UA/NSTEMI patients, where coronary angiography is performed within 48 hours after admission, the loading dose should be given at the time of PCI.

***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 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.

***Hypersensitivity including angioedema***

Hypersensitivity reactions including angioedema have been reported in patients receiving prasugrel, including in patients with a history of hypersensitivity reaction to clopidogrel. Monitoring for signs of hypersensitivity in patients with a known allergy to thienopyridines is advised.

**Thrombotic Thrombocytopenic Purpura (TTP)**

TTP has been reported with the use of prasugrel. TTP is a serious condition and requires prompt treatment.

**Morphine and other opioids**

Reduced prasugrel efficacy has been seen in patients co-administered prasugrel and morphine.

**4.5 Drugs interactions**

**ASPIRIN**

**Contraindicated combinations**

*Methotrexate (used at doses >15 mg/week)*:

The combined drugs, methotrexate and acetylsalicylic acid, enhance haematological toxicity of methotrexate due to the decreased renal clearance of methotrexate by acetylsalicylic acid. Therefore, the concomitant use of methotrexate (at doses >15 mg/week) with Aspirin 75 mg is contraindicated.

**Not recommended combinations**

*Uricosuric agents, e.g. probenecid and sulfinpyrazone*:

Salicylates reverse the effect of probenecid and sulfinpyrazone. The combination should be avoided.

**Combinations requiring precautions for use or to be taken into account**

*Anticoagulants e.g. coumarin, heparin, warfarin and phenindione*:

Increased risk of bleeding due to inhibited thrombocyte function, injury of the duodenal mucosa and displacement of oral anticoagulants from their plasma protein binding sites. The bleeding time should be monitored.

*Anti-platelet agents (e.g clopidogrel and dipyridamole) and selective serotonin re-uptake inhibitors (SSRIs; such as sertraline or paroxetine)*:

Increased risk of gastrointestinal bleeding.

*Antidiabetics, e.g. sulphonylureas*:

Salicylics may increase the hypoglycaemic effect of sulphonylureas.

*Digoxin and lithium*:

Acetylsalicylic acid impairs the renal excretion of digoxin and lithium, resulting in increased plasma concentrations. Monitoring of plasma concentrations of digoxin and lithium is recommended when initiating and terminating treatment with acetylsalicylic acid. Dose adjustment may be necessary.

*Diuretics and antihypertensives*:

NSAIDs may decrease the antihypertensive effects of diuretics and other antihypertensive agents. Patients with hypertension should be carefully monitored. As for other NSAIDs concomitant administration with ACE-inhibitors increases the risk of acute renal insufficiency.

Diuretics: Risk of acute renal failure due to the decreased glomerular filtration via decreased renal prostaglandin synthesis. Hydrating the patient and monitoring renal function at the start of the treatment is recommended.

*Other non-steroidal anti-inflammatory drugs (NSAIDs)*:

Concurrent administration can increase side effects. Use of two or more NSAIDs increases risk of gastrointestinal haemorrhage.

*Ibuprofen*:

Reported experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use.

*Ciclosporin, tacrolimus*:

Concomitant use of NSAIDs and ciclosporin or tacrolimus may increase the nephrotoxic effect of ciclosporin and tacrolimus. The renal function should be monitored in case of concomitant use of these agents and acetylsalicylic acid.

*Systemic Corticosteroids*:

The risk of gastrointestinal bleeding and ulceration is increased when acetylsalicylic acid and corticostetoids are coadministered. Corticosteroids reduce the plasma salicylate concentration and salicylate toxicity may occur following withdrawal of corticosteroids.

*Methotrexate (used at doses <15 mg/week)*:

The combined drugs, methotrexate and acetylsalicylic acid, may increase haematological toxicity of methotrexate due to decreased renal clearance of methotrexate by acetylsalicylic acid. Weekly blood count checks should be done during the first weeks of the combination. Enhanced monitoring should take place in the presence of even mildly impaired renal function, as well, as in elderly.

*Carbonic anhydrase inhibitors*:

Reduced excretion of acetazolamide; salicylate intoxication has occurred in patients on high dose salicylate regimes and carbonic anhydrase inhibitors. Concurrent administration of carbonic anhydrase inhibitors such as acetazolamide and salicylates may result in severe acidosis and increased central nervous system toxicity.

*Antacids and adsorbents*:

The excretion of aspirin is increased in alkaline urine; kaolin possibly reduces absorption. Antacids will reduce the effect of aspirin. Principle incompatibilities are iron salts, carbonates and alkali hydroxides.

*Mifepristone*:

The manufacturer of mifepristone recommends that aspirin should be avoided until eight to twelve days after mifepristone has been discontinued.

*Alcohol*:

Concomitant administration of alcohol and acetylsalicylic acid increases the risk of gastrointestinal bleeding.

*Antiemetics*:

Metoclopramide enhances the effects of aspirin by increasing the rate of absorption.

*Anti-epileptics*:

Salicylate diminishes the binding of phenytoin to plasma albumin. This may lead to decreased total phenytoin levels in plasma, but increased free phenytoin fraction. The unbound concentration, and thereby the therapeutic effect, does not appear to be significantly altered. Acetylsalicylic acid has been reported to decrease the binding of valproate to serum albumin, thereby increasing its free plasma concentrations at steady state.

*Leukotriene antagonists*:

The plasma concentration of zafirlukast is increased.

*Antibacterials***:**

The toxicity of sulphonamides may be increased.

*Thyroid function tests*:

Aspirin may interfere with thyroid function tests.

**PRASUGREL**

*Warfarin:*

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

Prasugrel 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 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 has been co-administered in the phase 3 reported 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**

*Acetylsalicylic acid*:

Prasugrel 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 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 reported clinical trial, Prasugrel 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 reported 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 Prasugrel 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 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 Fertility, pregnancy and Breast feeding

**Aspirin**

**Pregnancy**

During the first and second trimester of pregnancy, acetylsalicylic acid should not be given unless clearly necessary. If acetylsalicylic acid is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:

- Cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension)
- Renal dysfunction, which may progress to renal failure with oligo-hydroamniosis; the mother and the neonate, at the end of pregnancy
- Possible prolongation of bleeding time, an anti-aggregating effect that may occur even at very low doses
- Inhibition of uterine contractions resulting in delayed or prolonged labour Consequently, acetylsalicylic acid at doses of 100 mg/day and higher is contraindicated during the third trimester of, pregnancy.

**Breast-feeding**

As aspirin is excreted in breast milk, patients who are breast-feeding, as there is a risk of Reye's syndrome in the infant should not take Aspirin. High maternal doses may impair platelet function in the infant.

**Prasugrel**

No clinical study has been conducted in pregnant or breast-feeding women.

**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, Prasugrel 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.

**Fertility**

In reported study, 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 $mg/m^2$).

## 4.7 Effects on ability to drive and use machines

PRAX A is expected to have no or negligible influence on the ability to drive and use machines.

## 4.8 Undesirable effects

**Aspirin**

Side effects are grouped on the basis of System Organ Class. Within each system organ class the frequencies are defined as: 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) and not known (cannot be estimated from the available data).

| | |
|---|---|
| **Blood and lymphatic system disorders** | *Common*:<br>Increased bleeding tendencies.<br>*Rare*:<br>Thrombocytopenia, granulocytosis, aplastic anaemia.<br>*Not known*:<br>Cases of bleeding with prolonged bleeding time such as epistaxis, haematuria, purpura, ecchymoses, haemoptysis, haematoma, cerebral haemorrhage and gingival bleeding.<br>Symptoms may persist for a period of 4–8 days after acetylsalicylic acid discontinuation. As a result there may be an increased risk of bleeding during surgical procedures.<br>Aspirin decreases platelet adhesiveness and, in large doses, may cause hypoprothrombinaemia.<br>Existing (haematemesis, melaena) or occult gastrointestinal bleeding, which may lead to iron deficiency anaemia (more common at higher doses).<br>Haemolytic anaemia can occur in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. |
| **Immune system disorders** | *Rare:*<br>Hypersensitivity reactions, skin rashes, urticarial, asthma, bronchospasm, angio-oedema, allergic oedema, anaphylactic reactions including shock. |

| | |
|---|---|
| **Metabolism and digestive system disorders** | *Not known:*<br>Hyperuricemia. |
| **Nervous system disorders** | *Rare:*<br>Intracranial haemorrhage.<br>*Not known:*<br>Headache, vertigo. |
| **Ear and labyrinth disorders** | *Not known:*<br>Reduced hearing ability; tinnitus. |
| **Vascular disorders** | *Rare:*<br>Hemorrhagic vasculitis. |
| **Respiratory, thoracic and mediastinal disorders** | *Uncommon:*<br>Rhinitis, dyspnoea.<br>*Rare:*<br>Bronchospasm, asthma attacks. |
| **Reproductive System and mammary disorders** | *Rare:*<br>Menorrhagia. |
| **Gastrointestinal disorders** | *Common:*<br>Dyspepsia.<br>*Rare:*<br>Severe gastrointestinal haemorrhage, nausea, vomiting, gastritis.<br>*Not known:*<br>Gastric or duodenal ulcers and perforation, diarrhoea. |
| **Hepatobiliary disorders** | *Not known:*<br>Hepatic insufficiency. |
| **Skin and subcutaneous tissue disorders** | *Uncommon:*<br>Urticaria.<br>*Rare:*<br>Steven-Johnsons syndrome, Lyells syndrome, purpura, erythema nodosum, erythema multiforme. |
| **Renal and urinary tract disorders** | *Not known:*<br>Impaired renal function, salt and water retention, urate kidney stones. |

**Prasugrel**

***Summary of the safety profile***

Safety in patients with acute coronary syndrome undergoing PCI was evaluated in one reported study clopidogrel-controlled study 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).

**Bleeding**

Non-Coronary Artery Bypass Graft (CABG) related bleeding

In TRITON, the frequency of patients experiencing a non-CABG related bleeding event is shown in below table. The incidence of Non-CABG-related TIMI major bleeding, including life-threatening and fatal, as well as TIMI minor bleeding, was statistically significantly higher in subjects treated with prasugrel compared to clopidogrel in the UA/NSTEMI and All ACS populations. No significant difference was seen in the STEMI population. The most common site of spontaneous bleeding was the gastrointestinal tract (1.7% rate with prasugrel and 1.3% rate with clopidogrel); the most frequent site of provoked bleeding was the arterial puncture site (1.3% rate with prasugrel and 1.2% with clopidogrel).

**Incidence of Non-CABG related bleeding[a] (% Patients)**

| Event | All ACS | | UA/NSTEMI | | STEMI | |
|---|---|---|---|---|---|---|
| | **Prasugrel[b] +ASA (N=6741)** | **Clopidogrel[b] +ASA (N=6716)** | **Prasugrel[b] +ASA (N=5001)** | **Clopidogrel[b] +ASA (N=4980)** | **Prasugrel[b] +ASA (N=1740)** | **Clopidogrel[b] +ASA (N=1736)** |
| **TIMI major bleeding[c]** | 2.2 | 1.7 | 2.2 | 1.6 | 2.2 | 2.0 |
| **Life-threatening[d]** | 1.3 | 0.8 | 1.3 | 0.8 | 1.2 | 1.0 |
| **Fatal** | 0.3 | 0.1 | 0.3 | 0.1 | 0.4 | 0.1 |
| **Symptomatic ICH[e]** | 0.3 | 0.3 | 0.3 | 0.3 | 0.2 | 0.2 |
| **Requiring inotropes** | 0.3 | 0.1 | 0.3 | 0.1 | 0.3 | 0.2 |
| **Requiring surgical intervention** | 0.3 | 0.3 | 0.3 | 0.3 | 0.1 | 0.2 |
| **Requiring transfusion (≥ 4 units)** | 0.7 | 0.5 | 0.6 | 0.3 | 0.8 | 0.8 |
| **TIMI minor bleeding[f]** | 2.4 | 1.9 | 2.3 | 1.6 | 2.7 | 2.6 |

*a Centrally adjudicated events defined by the Thrombolysis in Myocardial Infarction (TIMI) Study Group criteria.*

*b Other standard therapies were used as appropriate.*

*c Any intracranial haemorrhage or any clinically overt bleeding associated with a fall in haemoglobin ≥ 5 g/dL.*

*d Life-threatening bleeding is a subset of TIMI major bleeding and includes the types indented below. Patients may be counted in more than one row.*

*e ICH=intracranial haemorrhage.*

*f Clinically overt bleeding associated with a fall in haemoglobin of ≥ 3 g/dL but < 5 g/dL.*

Patients ≥ 75 years old

Non-CABG-related TIMI major or minor bleeding rates:

| Age | **Prasugrel 10 mg** | **Clopidogrel 75 mg** |
|---|---|---|
| **≥ 75 years (N=1785)*** | 9.0% (1.0% fatal) | 6.9% (0.1% fatal) |
| **<75 years (N=11672)*** | 3.8% (0.2% fatal) | 2.9% (0.1% fatal) |
| **< 75 years (N=7180)**** | 2.0% (0.1% fatal) a | 1.3% (0.1% fatal) |
| | Prasugrel 5 mg | Clopidogrel 75 mg |
| **≥ 75 years (N=2060)**** | 2.6% (0.3% fatal) | 3.0% (0.5% fatal) |

**TRITON study in ACS patients undergoing PCI*

***TRILOGY-ACS study in patients not undergoing PCI:*

[a] *10 mg prasugrel; 5 mg prasugrel if < 60 kg*

Patients < 60 kg

Non-CABG-related TIMI major or minor bleeding rates:

| **Weight** | **Prasugrel 10 mg** | **Clopidogrel 75 mg** |
|---|---|---|
| **< 60 kg (N=664)*** | 10.1% (0% fatal) | 6.5% (0.3% fatal) |
| **≥ 60 kg (N=12672)*** | 4.2% (0.3% fatal) | 3.3% (0.1% fatal) |
| **≥ 60 kg (N=7845)**** | 2.2% (0.2% fatal)[a] | 1.6% (0.2% fatal) |
| | Prasugrel 5 mg | Clopidogrel 75 mg |
| **< 60 kg (N=1391)**** | 1.4% (0.1% fatal) | 2.2% (0.3% fatal) |

**TRITON study in ACS patients undergoing PCI*

***TRILOGY-ACS study in patients not undergoing PCI:*

[a] *10 mg prasugrel; 5 mg prasugrel if ≥ 75 years of age*

Patients ≥ 60 kg and age < 75 years

In patients ≥ 60 kg *and* age < 75 years, non-CABG-related TIMI major or minor bleeding rates were 3.6% for prasugrel and 2.8% for clopidogrel; rates for fatal bleeding were 0.2% for prasugrel and 0.1% for clopidogrel.

CABG-related bleeding

In reported phase 3 clinical trial, 437 patients underwent CABG during the course of the study. Of those patients, the rate of CABG-related TIMI major or minor bleeding was 14.1% for the prasugrel group and 4.5% in the clopidogrel group. The higher risk for bleeding events in subjects treated with prasugrel persisted up to 7 days from the most recent dose of study drug. For patients who received their thienopyridine within 3 days prior to CABG, the frequencies of TIMI major or minor bleeding were 26.7% (12 of 45 patients) in the prasugrel group, compared with 5.0% (3 of 60 patients) in the clopidogrel group. For patients who received their last dose of thienopyridine within 4 to 7 days prior to CABG, the frequencies decreased to 11.3% (9 of 80 patients) in the prasugrel group and 3.4% (3 of 89 patients) in the clopidogrel group. Beyond 7 days

after drug discontinuation, the observed rates of CABG-related bleeding were similar between treatment groups.

Bleeding Risk Associated with Timing of Loading Dose in NSTEMI

In reported clinical study of NSTEMI patients (the ACCOAST study), where patients were scheduled to undergo coronary angiography within 2 to 48 hours after randomization, patients given a 30 mg loading dose on average 4 hours prior to coronary angiography followed by a 30 mg loading dose at the time of PCI had an increased risk of non-CABG peri-procedural bleeding and no additional benefit compared to patients receiving a 60 mg loading dose at the time of PCI. Non-CABG-related TIMI bleeding rates through 7 days for patients were as follows:

| **Adverse Reaction** | **Prasugrel Prior to Coronary Angiography[a] (N=2037) %** | **Prasugrel At time of PCI[a] (N=1996) %** |
|---|---|---|
| **TIMI Major bleeding[b]** | 1.3 | 0.5 |
| **Life-threatening[c]** | 0.8 | 0.2 |
| **Fatal** | 0.1 | 0.0 |
| **Symptomatic ICH[d]** | 0.0 | 0.0 |
| **Requiring inotropes** | 0.3 | 0.2 |
| **Requiring surgical intervention** | 0.4 | 0.1 |
| **Requiring transfusion (≥ 4 units)** | 0.3 | 0.1 |
| **TIMI Minor bleeding[e]** | 1.7 | 0.6 |

[a]*Other standard therapies were used as appropriate. The clinical study protocol provided for all patients to receive aspirin and a daily maintenance dose of prasugrel.*

[b]*Any intracranial haemorrhage or any clinically overt bleeding associated with a fall in haemoglobin ≥ 5 g/dL.*

[c]*Life-threatening is a subset of TIMI Major bleeding and includes the types indented below. Patients may be counted in more than one row.*

[d]*ICH=intracranial haemorrhage.*

[e]*Clinically overt bleeding associated with a fall in haemoglobin of ≥ 3 g/dL but < 5 g/dL.*

***Tabulated summary of adverse reactions***

Below table summarises haemorrhagic and non-haemorrhagic adverse reactions in TRITON, or that were spontaneously reported, 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).

**Haemorrhagic and Non-haemorrhagic adverse reactions**

| System Organ Class | Common | Uncommon | Rare | Not Known |
|---|---|---|---|---|
| ***Blood and Lymphatic System disorders*** | Anaemia | | Thrombocytopaenia | Thrombotic thrombocytopaenic purpura (TTP) |
| ***Immune system disorders*** | | Hypersensitivity including angioedema | | |
| ***Eye disorders*** | | Eye haemorrhage | | |
| ***Vascular Disorders*** | Haematoma | | | |
| ***Respiratory, thoracic and mediastinal disorders*** | Epistaxis | Haemoptysis | | |
| ***Gastrointestinal disorders*** | Gastrointestinal haemorrhage | Retroperitoneal haemorrhage<br>Rectal haemorrhage<br>Haematochezia<br>Gingival bleeding | | |
| ***Skin and subcutaneous tissue disorders*** | Rash<br>Ecchymosis | | | |
| ***Renal and urinary disorders*** | Haematuria | | | |
| ***General disorders and administration site conditions*** | Vessel puncture site haematoma<br>Puncture site haemorrhage | | | |
| ***Injury, poisoning and procedural complications*** | Contusion | Post-procedural haemorrhage | Subcutaneous haematoma | |

In patients with or without a history of TIA or stroke, the incidence of stroke in the reported phase 3 clinical trial was as follows:

| History of TIA or stroke | Prasugrel | Clopidogrel |
|---|---|---|
| Yes (N=518) | 6.5% (2.3% ICH*) | 1.2% (0% ICH*) |
| No (N=13090) | 0.9% (0.2% ICH*) | 1.0% (0.3% ICH*) |

** ICH=intracranial haemorrhage.*

**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. Healthcare professionals are asked to report any suspected adverse reactions

via any point of contact of Torrent Pharma available at https://torrentpharma.com/index.php/site/info/adverse_event_reporting.

## 4.9 Overdose

**Aspirin**

Salicylate poisoning is usually associated with plasma concentrations >350 mg/L (2.5 mmol/L). Most adult deaths occur in patients whose concentrations exceed 700 mg/L (5.1 mmol/L). Single doses less than 100 mg/kg are unlikely to cause serious poisoning.

**Symptoms**

Common features include vomiting, dehydration, tinnitus, vertigo, deafness, and sweating, warm extremities with bounding pulses, increased respiratory rate and hyperventilation.

Some degree of acid-base disturbance is present in most cases. A mixed respiratory alkalosis and metabolic acidosis with normal or high arterial pH (normal or reduced hydrogen ion concentration) is usual in adults or children over the age of four years. In children aged four years or less, a dominant metabolic acidosis with low arterial pH (raised hydrogen ion concentration) is common. Acidosis may increase salicylate transfer across the blood brain barrier. Uncommon features include haematemesis, hyperpyrexia, hypoglycaemia, hypokalaemia, thrombocytopenia, increased INR/PTR, intravascular coagulation, renal failure and non-cardiac pulmonary oedema. Central nervous system features including confusion, disorientation, coma and convulsions are less common in adults than in children.

**Treatment**

Give activated charcoal if an adult presents within one hour of ingestion of more than 250 mg/kg. The plasma salicylate concentration should be measured, although the severity of poisoning cannot be determined from this alone and the clinical and biochemical features must be taken into account. Elimination is increased by urinary alkalinisation, which is achieved by the administration of 1.26% sodium bicarbonate.

The urine pH should be monitored. Correct metabolic acidosis with intravenous 8.4% sodium bicarbonate (first check serum potassium). Forced diuresis should not be used since it does not enhance salicylate excretion and may cause pulmonary oedema. Haemodialysis is the treatment of choice for severe poisoning and should be considered in patients with plasma salicylate concentrations >700 mg/L (5.1 mmol/L) or lower concentrations associated with severe clinical or metabolic features. Patients under ten years or over 70 have increased risk of salicylate toxicity and may require dialysis at an earlier stage.

**Prasugrel**

Overdose of prasugrel 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

**Aspirin**

Aspirin (acetylsalicylic acid) irreversibly acetylates platelet cyclo-oxygenase thereby inhibiting the biosynthesis of thromboxane, a potent vasoconstrictor and inducer of

platelet aggregation. It also inhibits the action of cyclo-oxygenase in the vascular endothelial wall preventing the synthesis of prostacyclin, a potent vasodilator and inhibitor of platelet aggregation.

**Prasugrel**

Prasugrel is an inhibitor of platelet activation and aggregation through the irreversible 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.

## 5.2 Pharmacodynamic properties

**Aspirin**

Pharmacotherapeutic group: Platelet Aggregation Inhibitor excl. Heparin, ATC code: B01AC06

The antiplatelet effect of aspirin is largely unrelated to its systemic bioavailability and its duration of effect does not correlate with the presence of intact salicylic acid in the circulation. The antiplatelet effect is considered to be largel presystemic, associated with acetylation of platelet cyclo-oxygenase in the portal circulation.

Aspirin (acetylsalicylic acid) irreversibly acetylates platelet cyclo-oxygenase thereby inhibiting the biosynthesis of thromboxane, a potent vasoconstrictor and inducer of platelet aggregation. It also inhibits the action of cyclo-oxygenase in the vascular endothelial wall preventing the synthesis of prostacyclin, a potent vasodilator and inhibitor of platelet aggregation. However, as the endothelial cell is capable of synthesising new cyclo-oxygenase, whereas the platelet is not, the effect on thromboxane is longer lasting. Due to the low dose, enteric-coated formulation of Aspirin 75mg is slowly released into the portal circulation and is deacetylated by the liver to inactive salicylate before reaching the systemic circulation. It is postulated that platelets passing through the portal circulation are exposed to acetylsalicylic acid concentrations sufficient to achieve effective thromboxane inhibition, while systemic prostacyclin synthesis remains essentially unaffected.

Reported experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. In one study, when a single dose of ibuprofen 400mg was taken within 8 hours before or within 30 minutes after immediate release aspirin dosing (81mg), a decreased effect of aspirin on the formation of thromboxane or platelet aggregation occurred. However, the limitations of these data and the uncertainties regarding extrapolation of *exvivo* data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use.

**Prasugrel**

Pharmacotherapeutic group: Platelet aggregation inhibitors excluding heparin, ATC code: B01AC22.

**Mechanism of action / Pharmacodynamic effects**

Prasugrel is an inhibitor of platelet activation and aggregation through the irreversible 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 μMADP and 30 minutes with 20 μM ADP.

## 5.3 Pharmacokinetic properties

### Aspirin

**Aspirin is rapidly absorbed after oral administration of conventional release** preparations, with some hydrolysis to salicylate before absorption. Absorption is delayed by the presence of food and is impaired in patients suffering migraine attacks.

Absorption is more rapid in patients with achlorhydria and following administration of polysorbates and antacids. Plasma concentrations of the drug increase disproportionately to the dose; e.g. a 325 mg dose having a half-life of 2-3hours and higher doses showing lower plasma concentrations in the presence of an increased half-life due to a disproportionate increase in the volume of distribution.

Aspirin is found in saliva, milk, plasma and synovial fluid at concentrations less than in blood and crosses the placenta. Salicylate/protein binding extensive. Aspirin/protein binding to a small extent. In the blood, rapid hydrolysis to salicylic acid; glucuronic acid/glycine conjugation to form glucuronides and salicyluronic acid. Salicylate reabsorbed by renal tubules in acid urine, and alkaline diuresis will increase the rate of excretion; 85% of dose excreted as free salicylate. The absolute bioavailability of aspirin from Aspirin (compared with intravenous aspirin solution) is approximately 25%.

### Prasugrel

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 are 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 was administered without regard to food in TRITON. Therefore, Prasugrel 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.

### 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 CYP3A4and 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, 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).

**Pharmacokinetics in 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 reported 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. In a study in subjects with stable atherosclerosis, the mean AUC of the active metabolite in patients ≥ 75 years old taking 5 mg prasugrel was approximately half that in patients < 65 years old taking 10 mg prasugrel, and the antiplatelet effect of 5 mg was reduced but was non-inferior compared to 10 mg.

***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 should be used with caution in patients with a body weight of < 60 kg due to the potential risk of bleeding in this population. In ab study in subjects with stable atherosclerosis, the mean AUC of the active metabolite in patients < 60 kg taking 5 mg prasugrel was 38% lower than in patients ≥ 60 kg taking 10 mg prasugrel, and the antiplatelet effect of 5 mg was similar to 10 mg.

***Ethnicity:***

In reported 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 are similar in men and women.

***Paediatric population:***

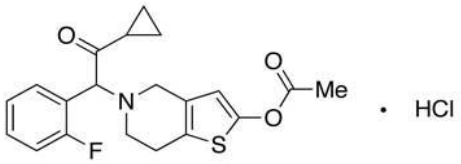
Pharmacokinetics and pharmacodynamics of prasugrel have not been evaluated in a paediatric population.

## 6. Nonclinical properties

Reported 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 reported 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/m2 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/m2). 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 Hydrochloride is Ethanone, 2-[2-(acetyloxy)-6,7 –dihydrothieno[3,2-c]pyridin-5(4H)-yl]-1- cyclopropyl-2-(2-fluorophenyl)-hydrochloride 5-[2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4,5,6,7-te-trahydrothieno[3,2-c]pyridin-2-yl acetate hydrochloride .Having molecular formula C20H20FNO3S.HCland molecular weight 409.9

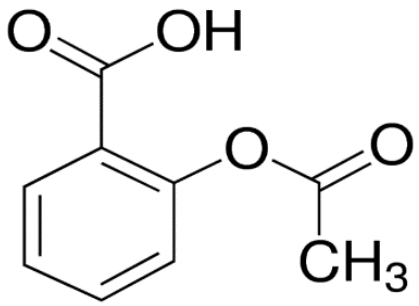



Prasugrel Hydrochloride is a white to almost white powder.

Solubility: Soluble in water; slightly soluble in acetonitrile and practically insoluble in ethyl acetate.

**Aspirin-** Acetylsalicylic acid

Aspirin is 2- acetoxybenzoic acid. Having molecular formula C9H8O4 and molecular weight 180.2




Aspirin is colourless crystals or a white, crystalline powder; odourless or almost odourless.

Solubility: Freely soluble in alcohol, soluble in chloroform and in ether, slightly soluble in water.

## 8. Pharmaceutical particulars

### 8.1 Incompatibilities

Not applicable

### 8.2 Shelf-life

Do not use later than date of expiry

### 8.3 Packaging information

**PRAX A 75** is packed in 10 blister strips of 10 Capsules each

### 8.4 Storage and handing instructions

- Store at A Temperature Not Exceeding $25^0$C, Protected From Moisture.
- Keep out of reach of children

## 9. Patient counselling information

**PRAX A 75**

**Prasugrel Hydrochloride and Aspirin Capsules**

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 9.4.

**What is in this leaflet?**



## 9.1 What PRAX A 75 is and what it is used for

PRAX A 75 is combination of Aspirin and Prasugrel. Aspirin belongs to a group of medicines called antiplatelet agents that help prevent your blood cells sticking together and forming a blood clot. Prasugrel belongs to a group of medicines called anti-platelet agents. Platelets are very small cell particles that circulate in the blood. When a blood vessel is damaged, for example if it is cut, platelets clump together to help form a blood clot (thrombus). Therefore, platelets are essential to help stop bleeding. If clots form within a hardened blood vessel such as an artery they can be very dangerous as they can cut off the blood supply, causing a heart attack (myocardial infarction), stroke or death. Clots in arteries supplying blood to the heart may also reduce the blood supply, causing unstable angina (a severe chest pain). Prasugrel inhibits the clumping of platelets and so reduces the chance of a blood clot forming.

PRAX A 75 is indicated for the treatment of percutaneous coronary intervention (PCI).

## 9.2 What you need to know before you take PRAX A 75

Do not take **PRAX A 75**

- If you are allergic to any of the ingredients of this medicine
- If you have ever had a bad reaction to aspirin, Prasugrel or any other nonsteroidal anti-inflammatory medicines (you have ever had asthma, swelling of the lips or face, itchy skin or runny nose after taking them)
- If you have, or ever had, an ulcer in your stomach or intestine
- If you are under 16 years old, unless your doctor tells you to
- if you have, or ever had, a bleed in your stomach or intestines (you may have been sick and it contained blood or dark particles that looked like coffee grounds and/or passed blood in your stools or passed black tarry stools)

- If you have had other types of bleeding like a stroke
- If you have a blood clotting disorder (e.g. haemophilia or thrombocytopenia) or are taking medicines to thin your blood
- If you have gout
- If you have severe kidney or liver problems
- If you are in your last 3 months of pregnancy; you must not use higher doses than 100mg per day (see section "Pregnancy and breast-feeding")
- If you are taking a medicine called methotrexate (e.g. for cancer or rheumatoid arthritis) in doses higher than 15mg per week
- If you have ever had a stroke or a transient ischaemic attack (TIA).
- If you have severe liver disease.

**Warnings and precautions**

- Talk to your doctor before taking Capsules:
- If you are asthmatic, have hay fever, nasal polyps or other chronic respiratory diseases; aspirin may induce asthma attack
- If you have other kidney, liver or heart problems
- If you have high blood pressure (your doctor may want to monitor you closely) if you are dehydrated
- if you have a condition called glucose-6-phosphate dehydrogenase deficiency
- If you are elderly (your doctor may want to monitor you closely)
- If you have or have ever had problems with your stomach or small intestine
- if you have heavy menstrual periods You must immediately seek medical advice, if your symptoms get worse or if you experience severe or unexpected side effects e.g. unusual bleeding symptoms, serious skin reactions or any other sign of serious allergy.

Inform your doctor if you are planning to have an operation (even a minor one, such as tooth extraction). You should take care not to become dehydrated (you may feel thirsty with a dry mouth) since the use of Aspirin at the same time may result in deterioration of kidney function. This medicinal product is not suitable as a painkiller or fever reducer. If any of the above applies to you, or if you are not sure, speak to your doctor or pharmacist.

**Children and adolescents**

Aspirin may cause Reye's syndrome when given to children. Reye's syndrome is a very rare disease which affects the brain and liver and can be life threatening. For this reason, Aspirin should not be given to children aged under 16 years, unless on the advice of a doctor.

**Other medicines and PRAX A 75**

**Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, particularly the following:**

- Warfarin or other blood thinners

- Medicines for depression
- Methotrexate (for cancer, skin problems, rheumatic problems, Crohn's disease)
- Ciclosporin or tacrolimus (given after transplant surgery, or psoriasis or rheumatism)
- Mifepristone (for termination of pregnancy) - do not take this medicine for 8 to 12 day after taking mifepristone
- Other non-steroidal anti-inflammatory medicines, like ibuprofen (to relieve pain, reduce swollen joints, muscles and ligaments)
- Corticosteroids like prednisolone (used for many conditions such as pain, swelling, allergy, asthma, rheumatism and skin problems)
- Phenytoin and sodium valproate (for epilepsy)
- Medicines for diabetes, such as glibenclamide, glipizide
- (sulphonylureas) or insulin
- Medicines used to treat high blood pressure like ACE inhibitors (e.g. ramipril, captopril)
- Water Capsules (diuretics e.g. spironolactone and acetazolamide)
- Metoclopramide (for feeling sick or being sick)
- Probenecid and sulfinpyrazone (for gout)
- Lithium (for severe mental problems)
- Medicines for heart problems (e.g. digoxin)
- Sulphonamide antibiotics (e.g. co-trimoxazole)
- Acetazolamide (for glaucoma)
- Zafirlukst (for asthma)
- Antacids (for indigestion) or adsorbents (e.g. kaolin for diarrhoea)

Aspirin may affect the results of thyroid function tests. Tell your doctor or nurse if you are taking these Capsules. Taking this medicine with alcohol

**Do Not drink alcohol whilst taking this medicine. Drinking alcohol** may possibly increase the risk of gastrointestinal bleeding and prolong bleeding time

**Pregnancy and breast-feeding**

- Ask your doctor or pharmacist for advice before taking any medicine.
- Pregnant women should not take aspirin during pregnancy unless advised by their doctor.
- You should not take Aspirin if you are in the last 3 month of pregnancy, unless you are advised to do so by your doctor and then the daily dose should not exceed 100mg. Regular or high doses of this medicinal product during late pregnancy can cause serious complications in the mother or baby.
- Breast-feeding women should not take Aspirin unless advised by their doctor.

**Driving and using machines**

These Capsules do not usually affect the ability to drive or operate machinery. PRAX A 75 contains lactose.

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

## 9.3 How to take PRAX A 75

Always take this medicine exactly as described in this leaflet or as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

- This medicine should be swallowed whole with a drink of water, do not cut, crush or chew the Capsules.
- Do not take any medications for indigestion either immediately before or after taking this medicine.

**Dosage: As prescribed by physician**

Do not give to children aged under 16 years unless on the advice of doctor. There is a possible association between aspirin and Reye's syndrome when given to children. Reye's syndrome is a very rare disease, which can be fatal. Do not take more than the recommended dose.

**If you take more PRAX A 75 than you should**

It is important to keep to the dose on the label or follow the instructions above. Taking **more t**han this could make you ill. If an overdose is taken, DO NOT DELAY, ask your doctor what to do or contact your nearest accident and emergency department. Common symptoms of overdose include: vomiting, dehydration, ringing in the ears, vertigo (dizziness), deafness, sweating, warm arms, legs or hands with racing pulse, rapid and deep breathing (hyperventilation) and increased breathing rate.

**If you forget to take PRAX A 75**

If you miss a dose, wait and take your next dose at the usual time. Do not take a double dose to make up for a forgotten dose. If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

**If you stop taking PRAX A 75**

Do not stop taking the drug without consulting your doctor; if you stop taking drug too soon, your risk of a heart attack may be higher.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

## 9.4 Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

**STOP TAKING** this medicine and tell your doctor immediately if you suffer from any of the following:

- Sudden wheezing, swelling of your lips, face or body, rash, fainting or difficulties swallowing (severe allergic reaction), shock

- Reddening of the skin with blisters or peeling and may be associated with a high fever and joint pains. This could be erythema multiforme, Stevens -Johnson syndrome or Lyell's syndrome

Unusual bleeding, such as coughing up blood, blood in your vomit or urine, or a stroke due to bleeding in brain or black stools

**Contact your doctor immediately if you notice any of the following:**

- Sudden numbness or weakness of the arm, leg or face, especially if only on one side of the body.
- Sudden confusion, difficulty speaking or understanding others.
- Sudden difficulty in walking or loss of balance or co-ordination.
- Sudden dizziness or sudden severe headache with no known cause.
- All of the above may be signs of a stroke. Stroke is an uncommon side effect of PRAX A 75 in patients who have never had a stroke or transient ischaemic attack (TIA)

Tell your doctor **promptly** if you notice any of the following:

- Blood in your urine.
- Bleeding from your rectum, blood in your stools or black stools.
- Uncontrollable bleeding, for example from a cut.
- All of the above may be signs of bleeding, the most common side effect with the drug. Although uncommon, severe bleeding can be life threatening.

**Other side effects**

**Common: may affect up to 1 in 10 people**

- Indigestion
- Increased tendency for bleeding
- Bleeding in the stomach or bowels
- Bleeding from a needle puncture site
- Nose bleeds
- Skin rash
- Small red bruises on the skin (ecchymoses)
- Blood in urine
- Haematoma (bleeding under the skin at the site of an injection, or into a muscle, causing swelling)
- Low haemoglobin or red blood cell count (anaemia)
- Bruising

**Uncommon: may affect up to 1 in 100 people**

- Hives
- Runny nose

- Breathing difficulty
- Allergic reaction (rash, itching, swollen lips/tongue, or shortness of breath)
- Spontaneous bleeding from the eye, rectum, gums or in the abdomen around the internal organs
- Bleeding after surgery
- Coughing up blood
- Blood in stools

**Rare: may affect up to 1 in 1,000 people**

- Severe bleeding in the stomach or intestines, brain haemorrhage; altered number of blood cells
- Inflammation of the stomach lining
- Nausea and vomiting
- Cramps in the lower respiratory tract, asthma attack
- Inflammation in the blood vessels
- Abnormal heavy or prolonged menstrual period
- Low blood platelet count
- Subcutaneous haematoma (bleeding under the skin causing a swelling)

**Not known: frequency cannot be estimated from the available data**

- Ringing in your ears (tinnitus) or reduced hearing ability
- Headache
- Vertigo
- Ulcers in stomach or small intestine and perforation
- Diarrhoea
- Increased bleeding time, e.g. when you have a nose bleed, bleeding gums (if bleeding is severe or lasts for a long time, talk to your doctor straight away)
- Impaired kidney function
- Salt and water retention
- Impaired liver function
- High level of uric acid in the blood
- Anaemia (a reduction in the number of red blood cells, which can make you look pale and feel tired) may occur due to bleeding
- Kidney stones (sharp stabbing pains in the stomach or back, with blood in the urine)

**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. Healthcare professionals are asked to report any suspected adverse reactions via any point of contact of Torrent Pharma available at https://torrentpharma.com/index.php/site/info/adverse_event_reporting.

**9.5 How to store PRAX A 75**

- Store at A Temperature Not Exceeding $25^0$C, Protected From Moisture.
- Keep out of reach of children.

**9.6 Contents of the pack and other information**

Each hard gelatin capsule contains:

Prasugrel 10 mg and Aspirin 75 mg

The excipients used are Talc, Mannitol, Microcrystalline cellulose, Hydroxy propyl methylcellulose, Croscarmellose Sodium, Magnesium Stearate, Lactose Monohydrate, Triacetin, Titanium Dioxide, Ferric Oxide Red, Iso Propyl Alcohol, Methylene Chloride, Stearic Acid, Ethyl Cellulose, Diethyl Phthalate, Meth.Acid&Eth.Acr, Triethyl Citrate.

**10 Details of manufacturer**

**Manufactured by:**

TORRENT PHARMACEUTICALS LTD.

Indrad-382721, Dist. Mehsana, INDIA.

At: 19,20,21 Sector- 6A, I.I.E;

SIDCUL, Ranipur, Haridwar-249403

**11 Details of permission or licence number with date**

5/UA/LL/2014 issued on 15.10.2018

**12 Date of revision**

**MAY 2021**

**MARKETED BY**

TORRENT PHARMACEUTICALS LTD.

Torrent House, Off Ashram Road,

Ahmedabad-380 009, INDIA

**IN/PRAX A 75 mg/MAY 21/04/PI**