Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Prasugrel Rowex 10 mg Film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg prasugrel (as besylate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Dark-beige double-arrow shaped tablets, debossed with "10" on one side, 11.02±0.1mm in length, 5.20±0.1mm in width, 3.95±0.4mm in thickness.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Prasugrel Rowex, co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of atherothrombotic events in adult patients with acute coronary syndrome (i.e. unstable angina, non-ST segment elevation myocardial infarction [UA/NSTEMI] or ST segment elevation myocardial infarction [STEMI]) undergoing primary or delayed percutaneous coronary intervention (PCI).

For further information, please refer to section 5.1.

4.2 Posology and method of administration

Posology

Adults

Prasugrel Rowex 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 (see sections 4.4, 4.8 and 5.1). Patients taking Prasugrel Rowex should also take ASA daily (75 mg to 325 mg).

In patients with acute coronary syndrome (ACS) who are managed with PCI, premature discontinuation of any antiplatelet agent, including prasugrel, could result in an increased risk of thrombosis, myocardial infarction or death due to the patient's underlying disease. A treatment of up to 12 months is recommended unless the discontinuation of Prasugrel Rowex is clinically indicated (see sections4.4 and 5.1).

Patients ≥ 75 years old

The use of prasugrel in patients ≥ 75 years of age is generally not recommended. If, after a careful individual benefit/risk evaluation by the prescribing physician (see section 4.4), 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 (see sections 4.4, 4.8, 5.1 and 5.2).

Patients weighing < 60 kg

Prasugrel Rowex 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 (see sections 4.4, 4.8 and 5.2).

Renal impairment

No dose adjustment is necessary for patients with renal impairment, including patients with end stage renal disease (see section 5.2). There is limited therapeutic experience in patients with renal impairment (see section 4.4).

Hepatic impairment
No dose adjustment is necessary in subjects with mild to moderate hepatic impairment (Child Pugh class A and B) (see section 5.2). There is limited therapeutic experience in patients with mild and moderate hepatic dysfunction (see section 4.4). Prasugrel is contraindicated in patients with severe hepatic impairment (Child Pugh class C).

Paediatric population
The safety and efficacy of prasugrel in children below age 18 has not been established. Limited data are available in children with sickle cell anaemia (see section 5.1).

Method of administration
For oral use. Prasugrel Rowex 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 (see section 5.2). Do not crush or break the tablet.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Active pathological bleeding.
History of stroke or transient ischaemic attack (TIA).
Severe hepatic impairment (Child Pugh class C).

4.4 Special warnings and precautions for use

Bleeding risk
In the phase 3 clinical trial (TRITON) 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 prasugrelin 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 (see sections 4.2 and 4.8). 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 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 (see sections 4.2 and 4.8).

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 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 (see sections 4.2, 4.8 and 5.1).

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 Rowex 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 (see section 4.8). 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 (see section 4.8).

Thrombotic Thrombocytopaenic 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 (see section 4.5).

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially 'sodium-free'

4.5 Interaction with other medicinal products and other forms of interactions

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 (see section 4.4).

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 (see section 4.4).

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 H_2blockers. Although not studied in specific interaction studies, prasugrel has been co-administered in the phase 3 clinical trial with low molecular weight heparin, bivalirudin, and GP IIb/IIIa inhibitors (no information available regarding the type of GP IIb/IIIa inhibitor used) without evidence of clinically significant adverse interactions.

Effects of other medicinal products on prasugrel
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 coadministered 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 H_2 blocker) or lansoprazole (a proton pump inhibitor) did not change the prasugrel active metabolite's AUC and T_{max}, but decreased the C_{max} by 14% and 29%, respectively. In the phase 3 clinical trial, prasugrel was administered without regard to co-administration of a proton pump inhibitor or H_2blocker.
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 T_{max}, but decreased the C_{max} 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 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 (see section 4.4).

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 coadministered 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 lactation

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 (see section 5.3). 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 breast-feeding is not recommended.

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).

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

Summary of the safety profile

Safety in patients with acute coronary syndrome undergoing PCI was evaluated in one clopidogrel-controlled study (TRITON) in which 6,741 patients were treated with prasugrel (60 mg loading dose and 10 mg once daily maintenance dose) for a median of 14.5 months (5,802 patients were treated for over 6 months, 4,136 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 Table 1. 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).

Table 1: Incidence of Non-CABG related bleeding[a] (% Patients)

Event	**All ACS**		**UA/NSTEMI**		**STEMI**	
	Prasugrel[b] +ASA (N = 6,741)	**Clopidogrel[b] +ASA (N = 6,716)**	**Prasugrel[b] +ASA (N = 5,001)**	**Clopidogrel[b] +ASA (N = 4,980)**	**Prasugrel[b] +ASA (N = 1,740)**	**Clopidogrel[b] +ASA (N = 1,736)**
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=1,785)*	9.0% (1.0% fatal)	6.9% (0.1% fatal)
<75 years (N=11,672)*	3.8% (0.2% fatal)	2.9% (0.1% fatal)

<75 years (N=7,180)**	2.0% (0.1% fatal) [a]	1.3% (0.1% fatal)
	Prasugrel **5 mg**	Clopidogrel 75 mg
≥75 years (N=2,060) **	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 (see 5.1):*
[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=12,672)*	4.2% (0.3% fatal)	3.3% (0.1% fatal)
≥60 kg (N=7,845)**	2.2% (0.2% fatal) [a]	1.6% (0.2% fatal)
	Prasugrel **5 mg**	Clopidogrel 75 mg
<60kg (N=1,391)**	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 (see 5.1):*
[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 the 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 (see section 4.4).

Bleeding Risk Associated with Timing of Loading Dose in NSTEMI
In a 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 (see sections 4.2 and 4.4). Non-CABG- related TIMI bleeding rates through 7 days for patients were as follows:

Adverse Reaction	**Prasugrel Prior to Coronary Angiography[a] (N=2,037) %**	**Prasugrel At time of PCI[a] (N=1,996) %**
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
Table 2 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 (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to <1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

Table 2: 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) *-see section 4.4*
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 Rectal haemorrhage Haematochezia 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-procedural haemorrhage	Subcutaneous haematoma	

In patients with or without a history of TIA or stroke, the incidence of stroke in the phase 3 clinical trial was as follows (see section 4.4):

History of TIA or stroke	Prasugrel	Clopidogrel
Yes (N=518)	6.5% (2.3% ICH*)	1.2% (0% ICH*)
No (N=13,090)	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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

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 Pharmacodynamic properties

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 $P2Y_{12}$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 microM ADP and 30 minutes with 20 microM ADP. The maximum inhibition by prasugrel of ADP-induced platelet aggregation is 83% with 5 microM ADP and 79% with 20 microM ADP, in both cases with 89% of healthy subjects and patients with stable atherosclerosis achieving at least 50% inhibition of platelet aggregation by 1 hour. Prasugrel-mediated inhibition of platelet aggregation exhibits low between-subject (9%) and within-subject (12%) variability with both 5 microM and 20 microM ADP. Mean steady-state inhibition of platelet aggregation was 74% and 69% respectively for 5 microM ADP and 20 microM ADP, and was achieved following 3 to 5 days of administration of the 10 mg prasugrel maintenance dose preceded by a 60 mg loading dose. More than 98% of subjects had ≥ 20% inhibition of platelet aggregation during maintenance dosing.

Platelet aggregation gradually returned to baseline values after treatment in 7 to 9 days after administration of a single 60 mg loading dose of prasugrel and in 5 days following discontinuation of maintenance dosing at steady-state.

Switching data: Following administration of 75 mg clopidogrel once daily for 10 days, 40 healthy subjects were switched to prasugrel 10 mg once daily with or without a loading dose of 60 mg. Similar or higher inhibition of platelet aggregation was observed with prasugrel. Switching directly to prasugrel 60 mg loading dose resulted in the most rapid onset of higher platelet inhibition. Following administration of a 900 mg loading dose of clopidogrel (with ASA), 56 subjects with ACS were treated for 14 days with either prasugrel 10 mg once daily or clopidogrel 150 mg once daily, and then switched to either clopidogrel 150 mg or prasugrel 10 mg for another 14 days. Higher inhibition of platelet aggregation was observed in patients switched to prasugrel 10 mg compared with those treated with clopidogrel 150 mg. In a study of 276 ACS patients managed with PCI, switching from an initial loading dose of 600 mg clopidogrel or placebo administered upon presentation to the hospital prior to coronary angiography to a 60 mg loading dose of prasugrel administered at the time of percutaneous coronary intervention, resulted in a similar increased inhibition of platelet aggregation for the 72 hour duration of the study.

Clinical efficacy and safety

Acute Coronary Syndrome (ACS)

The phase 3 TRITON study compared prasugrel with clopidogrel, both co-administered with ASA and other standard therapy. TRITON was a 13,608 patient, multicentre international, randomised, double blind, parallel group study. Patients had ACS with moderate to high risk UA, NSTEMI, or STEMI and were managed with PCI.

Patients with UA/NSTEMI within 72 hours of symptoms or STEMI between 12 hours to 14 days of symptoms were randomised after knowledge of coronary anatomy. Patients with STEMI within 12 hours of symptoms and planned for primary PCI could be

randomised without knowledge of coronary anatomy. For all patients, the loading dose could be administered anytime between randomisation and 1 hour after the patient left the catheterisation lab.

Patients randomised to receive prasugrel (60 mg loading dose followed by 10 mg once daily) or clopidogrel (300 mg loading dose followed by 75 mg once daily) were treated for a median of 14.5 months (maximum of 15 months with a minimum of 6 months follow-up). Patients also received ASA (75 mg to 325 mg once daily). Use of any thienopyridine within 5 days before enrolment was an exclusion criterion. Other therapies, such as heparin and GPIIb/IIIa inhibitors, were administered at the discretion of the physician. Approximately 40% of patients (in each of the treatment groups) received GPIIb/IIIa inhibitors in support of PCI (no information available regarding the type of GP IIb/IIIa inhibitor used). Approximately 98% of patients (in each of the treatment groups) received antithrombins (heparin, low molecular weight heparin, bivalirudin, or other agent) directly in support of PCI.

The trial's primary outcome measure was the time to first occurrence of cardiovascular (CV) death, non-fatal myocardial infarction (MI), or non-fatal stroke. Analysis of the composite endpoint in the All ACS population (combined UA/NSTEMI and STEMI cohorts) was contingent on showing statistical superiority of prasugrel versus clopidogrel in the UA/NSTEMI cohort ($p < 0.05$).

All ACS population: Prasugrelshowed superior efficacy compared to clopidogrel in reducing the primary composite outcome events as well as the pre-specified secondary outcome events, including stent thrombosis (see Table 3). The benefit of prasugrel was apparent within the first 3 days and it persisted to the end of study. The superior efficacy was accompanied by an increase in major bleeding (see sections 4.4 and 4.8). The patient population was 92% Caucasian, 26% female, and 39% ≥ 65 years of age. The benefits associated with prasugrel were independent of the use of other acute and long-term cardiovascular therapies, including heparin/low molecular weight heparin, bivalirudin, intravenous GPIIb/IIIa inhibitors, lipid-lowering medicinal products, beta-blockers, and angiotensin converting enzyme inhibitors. The efficacy of prasugrel was independent of the ASA dose (75 mg to 325 mg once daily). The use of oral anticoagulants, non-study antiplatelet medicinal products and chronic NSAIDs was not allowed in TRITON. In the All ACS population, prasugrel was associated with a lower incidence of CV death, non-fatal MI, or non-fatal stroke compared to clopidogrel, regardless of baseline characteristics such as age, sex, body weight, geographical region, use of GPIIb/IIIa inhibitors, and stent type. The benefit was primarily due to a significant decrease in non-fatal MI (see Table 3). Subjects with diabetes had significant reductions in the primary and all secondary composite endpoints.

The observed benefit of prasugrel in patients ≥ 75 years was less than that observed in patients < 75 years. Patients ≥ 75 years were at increased risk of bleeding, including fatal (see sections 4.2, 4.4, and 4.8). Patients ≥ 75 years in whom the benefit with prasugrel was more evident included those with diabetes, STEMI, higher risk of stent thrombosis, or recurrent events.

Patients with a history of TIA or a history of ischaemic stroke more than 3 months prior to prasugrel therapy had no reduction in the primary composite endpoint.

Table 3: Patients with Outcome Events in TRITON Primary Analysis

Outcome Events	**Prasugrel + ASA**	**Clopidogrel +ASA**	**Hazard Ratio (HR) (95% CI)**	**p-value**
All ACS	**(N = 6,813) %**	**(N = 6,795) %**		
Primary Composite Outcome Events Cardiovascular (CV) death, nonfatal MI, or nonfatal stroke	9.4	11.5	0.812 (0.732, 0.902)	< 0.001
Primary Individual Outcome Events				
CV death	2.0	2.2	0.886 (0.701, 1.118)	0.307
Nonfatal MI	7.0	9.1	0.757 (0.672, 0.853)	< 0.001
Nonfatal stroke	0.9	0.9	1.016 (0.712, 1.451)	0.930
UA/NSTEMI Primary Composite Outcome Events	**(N = 5,044) %**	**(N = 5,030) %**		
CV death, nonfatal MI, or nonfatal stroke	9.3	11.2	0.820 (0.726, 0.927)	0.002
CV death	1.8	1.8	0.979 (0.732,1.309)	0.885
Nonfatal MI	7.1	9.2	0.761 (0.663,0.873)	< 0.001

Nonfatal stroke	0.8	0.8	0.979 (0.633,1.513)	0.922
STEMI **Primary Composite Outcome Events**	**(N = 1,769)** **%**	**(N = 1,765)** **%**		
CV death, nonfatal MI, or nonfatal stroke	9.8	12.2	0.793 (0.649, 0.968)	0.019
CV death	2.4	3.3	0.738 (0.497,1.094)	0.129
Nonfatal MI	6.7	8.8	0.746 (0.588,0.948)	0.016
Nonfatal stroke	1.2	1.1	1.097 (0.590,2.040)	0.770

In the All ACS population, analysis of each of the secondary endpoints showed a significant benefit ($p < 0.001$) for prasugrel versus clopidogrel. These included definite or probable stent thrombosis at study end (0.9% vs 1.8%; HR 0.498; CI 0.364, 0.683); CV death, nonfatal MI, or urgent target vessel revascularisation through 30 days (5.9% vs 7.4%; HR 0.784; CI 0.688,0.894); all cause death, nonfatal MI, or nonfatal stroke through study end (10.2% vs 12.1%; HR 0.831; CI 0.751, 0.919); CV death, nonfatal MI, nonfatal stroke or rehospitalisation for cardiac ischaemic event through study end (11.7% vs 13.8%; HR 0.838; CI 0.762, 0.921). Analysis of all cause death did not show any significant difference between prasugrel and clopidogrel in the All ACS population (2.76% vs 2.90%), in the UA/NSTEMI population (2.58% vs 2.41%), and in the STEMI population (3.28% vs 4.31%).

Prasugrel was associated with a 50% reduction in stent thrombosis through the 15 month follow-up period. The reduction in stent thrombosis with prasugrelwas observed both early and beyond 30 days for both bare metal and drug eluting stents.

In an analysis of patients who survived an ischaemic event, prasugrel was associated with a reduction in the incidence of subsequent primary endpoint events (7.8% for prasugrel vs 11.9% for clopidogrel).

Although bleeding was increased with prasugrel, an analysis of the composite endpoint of death from any cause, nonfatal myocardial infarction, nonfatal stroke, and non-CABG-related TIMI major haemorrhage favoured prasugrel compared to clopidogrel (Hazard ratio, 0.87; 95% CI, 0.79 to 0.95; $p = 0.004$). In TRITON, for every 1,000 patients treated with prasugrel, there were 22 fewer patients with myocardial infarction, and 5 more with non–CABG-related TIMI major haemorrhages, compared with patients treated with clopidogrel.

Results of a pharmacodynamic/pharmacogenomic study in 720 Asian ACS PCI patients demonstrated that higher levels of platelet inhibition are achieved with prasugrel compared to clopidogrel, and that prasugrel 60-mg loading dose/10-mg maintenance dose is an appropriate dose regimen in Asian subjects who weigh at least 60 kg and are less than 75 years of age (see section 4.2).

In a 30 month study (TRILOGY–ACS) in 9,326 patients with UA/NSTEMI ACS medically managed without revascularisation (non-licensed indication), prasugrel did not significantly reduce the frequency of the composite endpoint of CV death, MI or stroke compared to clopidogrel. Rates of TIMI major bleeding (including life threatening, fatal and ICH) were similar in prasugrel and clopidogrel treated patients. Patients ≥75 years old or those below 60 kg (N=3,022) were randomized to 5 mg prasugrel. As in the < 75 years old and ≥60 kg patients treated with 10 mg prasugrel, there was no difference between 5 mg prasugrel and 75 mg clopidogrel in CV outcomes. Rates of major bleeding were similar in patients treated with 5 mg prasugrel and those treated with 75 mg clopidogrel. Prasugrel 5 mg provided greater antiplatelet effect than clopidogrel 75 mg. Prasugrel should be used with caution in patients ≥ 75 years old and in patients weighing <60 kg (see sections 4.2, 4.4 and 4.8).

In a 30-day study (ACCOAST) in 4,033 patients with NSTEMI with elevated troponin who were scheduled for coronary angiography followed by PCI within 2 to 48 hours after randomization, subjects who received prasugrel 30 mg loading dose on average 4 hours prior to coronary angiography followed by a 30 mg loading dose at the time of PCI (n=2,037) 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 (n=1,996). Specifically, prasugrel did not significantly reduce the frequency of the composite endpoint of cardiovascular (CV) death, myocardial infarction (MI), stroke, urgent revascularization (UR), or glycoprotein (GP) IIb/IIIa inhibitor bailout through 7 days from randomization in subjects receiving prasugrel prior to coronary angiography compared to patients receiving the full loading dose of prasugrel at the time of PCI, and the rate of the key safety objective for all TIMI major bleeding (CABG and non-CABG events) through 7 days from randomization in all treated subjects was significantly higher in subjects receiving prasugrel prior to coronary angiography versus patients receiving the full loading dose of prasugrel 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. (See sections 4.2, 4.4, and 4.8)

Paediatric population

Study TADO tested the use of prasugrel (n=171) vs placebo (n=170) in patients, ages 2 to less than 18 years of age, with sickle cell anaemia for reduction of vaso occlusive crisis in a phase III study. The study failed to meet any of the primary or secondary endpoints. Overall, no new safety findings were identified for prasugrel as monotherapy in this patient population.

5.2 Pharmacokinetic properties

Prasugrel is a prodrug and is rapidly metabolised *in vivo* to an active metabolite and inactive metabolites. The active metabolite's exposure (AUC) has moderate to low between-subject (27%) and within-subject (19%) variability. Prasugrel's pharmacokinetics 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 (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_{max} was decreased by 49% and the time to reach C_{max} (T_{max}) 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 (see section 4.2).

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 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).

Special Populations
Elderly: In a study of healthy subjects between the ages of 20 and 80 years, age had no significant effect on pharmacokinetics of prasugrel or its inhibition of platelet aggregation. In the large phase 3 clinical trial, the mean estimated exposure (AUC) of the active metabolite was 19% higher in very elderly patients (≥ 75 years of age) compared to subjects < 75 years of age. Prasugrel should be used with caution in patients ≥ 75 years of age due to the potential risk of bleeding in this population (see sections 4.2 and 4.4). 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 (see section 4.3).

Renal impairment: No dose 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/1.73m^2) and healthy subjects. Prasugrel-mediated inhibition of platelet aggregation was also similar in patients with ESRD who required haemodialysis compared to healthy subjects, although C_{max} 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 (see section 4.4). In a 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 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 (see section 4.2).

5.3 Preclinical safety data

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^2 basis) that caused effects on maternal body weight and/or food consumption, there was a slight decrease in offspring body weight (relative to controls). In pre- and post-natal rat studies, maternal treatment had no effect on the behavioural or reproductive development of the offspring at doses up to an exposure 240 times the recommended daily human maintenance dose (based on mg/m^2).

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Cellulose, Microcrystalline
Mannitol (E421)
Croscarmellose sodium
Hypromellose
Sodium Laurylsulphate (SLS) (E487)
Colloidal Silicon Dioxide
Magnesium stearate

Coating
Coating medium (orange) consisting of:
Hypromellose
Hydroxypropylcellulose
Talc
Titanium dioxide (E171)
Iron oxide red (E172)
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

OPA/ALU/PE/DESICCANT/PE - ALU/PE foil blisters in cartons of 10, 14, 28, 30, 56, 84, 90, 98 and 100 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Rowex Ltd
Newtown
Bantry
Co. Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0711/282/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17th August 2018

10 DATE OF REVISION OF THE TEXT

August 2019