

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Prasugrel Mylan 5 mg film-coated tablets
Prasugrel Mylan 10 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Prasugrel Mylan 5 mg:

Each tablet contains prasugrel besilate equivalent to 5 mg prasugrel.

Prasugrel Mylan 10 mg:

Each tablet contains prasugrel besilate equivalent to 10 mg prasugrel.

Excipient with known effect

Each tablet contains 0.016 mg of sunset yellow FCF aluminium lake (E110).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Prasugrel Mylan 5 mg:

Yellow film-coated, capsule shaped, biconvex tablet, of dimensions 8.15 mm × 4.15 mm, debossed with 'PH3' on one side and 'M' on the other side.

Prasugrel Mylan 10 mg:

Beige film-coated, capsule shaped, biconvex tablet, of dimensions 11.15 mm × 5.15 mm, debossed with 'PH4' on one side and 'M' on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prasugrel Mylan, 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 Mylan 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 Mylan 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 Mylan, 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 Mylan is clinically indicated (see sections 4.4 and 5.1).

Patients ≥ 75 years old

The use of Prasugrel Mylan 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 Mylan 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 Mylan is contraindicated in patients with severe hepatic impairment (Child Pugh class C).

Paediatric population

The safety and efficacy of Prasugrel Mylan 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

Prasugrel Mylan is for oral use. It 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). The tablets should not be crushed or broken.

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 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 (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 Mylan 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 periprocedural 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 Mylan 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 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 (see section 4.5).

Prasugrel Mylan 5 mg contains sodium

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

Prasugrel Mylan 10 mg contains sunset yellow FCF aluminium lake (E110) and sodium

Sunset yellow FCF aluminium lake is an azo colouring agent, which may cause allergic reactions.

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

4.5 Interaction with other medicinal products and other forms of interaction

Warfarin

Concomitant administration of Prasugrel Mylan 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 Mylan should be co-administered with caution (see section 4.4).

Prasugrel Mylan 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 Mylan 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 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 Mylan

Acetylsalicylic acid

Prasugrel Mylan 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 Mylan 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 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 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 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 Mylan 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 Mylan 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 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 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 Mylan 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

Prasugrel had no effect on fertility of male and female rats at oral doses up to an exposure 240 times the recommended daily human maintenance dose (based on mg/m²).

4.7 Effects on ability to drive and use machines

Prasugrel has 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 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 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=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 (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=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 (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 (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 list 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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1000$ to $< 1/100$); rare ($\geq 1/10,000$ 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
<i>Blood and Lymphatic System disorders</i>	Anaemia		Thrombocytopenia	Thrombotic thrombocytopenic purpura (TTP) – see section 4.4
<i>Immune system disorders</i>		Hypersensitivity including angioedema		
<i>Eye disorders</i>		Eye haemorrhage		
<i>Vascular Disorders</i>	Haematoma			
<i>Respiratory, thoracic and mediastinal disorders</i>	Epistaxis	Haemoptysis		

<i>Gastrointestinal disorders</i>	Gastrointestinal haemorrhage	Retroperitoneal haemorrhage Rectal haemorrhage Haematochezia Gingival bleeding		
<i>Skin and subcutaneous tissue disorders</i>	Rash Ecchymosis			
<i>Renal and urinary disorders</i>	Haematuria			
<i>General disorders and administration site conditions</i>	Vessel puncture site haematoma Puncture site haemorrhage			
<i>Injury, poisoning and procedural complications</i>	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=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 the national reporting system listed in [Appendix V](#).

4.9 Overdose

Overdose of Prasugrel Mylan 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: Antithrombotic agents, 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 µM ADP and 30 minutes with 20 µM ADP. The maximum inhibition by prasugrel of ADP-induced platelet aggregation is 83% with 5 µM ADP and 79% with 20 µM ADP, in both cases with 89% of healthy subjects and patients with stable atherosclerosis achieving at least 50% inhibition of platelet aggregation by 1 hour. Prasugrel-mediated inhibition of platelet aggregation exhibits low between-subject (9%) and within-subject (12%) variability with both 5 µM and 20 µM ADP. Mean steady-state inhibition of platelet aggregation was 74% and 69% respectively for 5 µM ADP and 20 µM ADP, and was achieved following 3 to 5 days of administration of the 10 mg prasugrel maintenance dose preceded by a 60 mg loading dose. More than 98% of subjects had $\geq 20\%$ 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 GP IIb/IIIa inhibitors, were administered at the discretion of the physician. Approximately 40% of patients (in each of the treatment groups) received GP IIb/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

Prasugrel showed superior efficacy compared to clopidogrel in reducing the primary composite outcome events as well as the pre-specified secondary outcome events, including stent thrombosis (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 GP IIb/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 GP IIb/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=6813) %	(N=6795) %		
Primary Composite Outcome Events				
Cardiovascular (CV) death, non fatal MI, or non fatal 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
Non fatal MI	7.0	9.1	0.757 (0.672, 0.853)	<0.001
Non fatal stroke	0.9	0.9	1.016 (0.712, 1.451)	0.930

UA/NSTEMI Primary Composite Outcome Events	(N=5044) %	(N=5030) %		
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
Non-fatal MI	7.1	9.2	0.761 (0.663,0.873)	<0.001
Non-fatal stroke	0.8	0.8	0.979 (0.633,1.513)	0.922
STEMI Primary Composite Outcome Events	(N=1769) %	(N=1765) %		
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
Non-fatal MI	6.7	8.8	0.746 (0.588,0.948)	0.016
Non-fatal 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, non-fatal 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 prasugrel was 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 1000 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 9326 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=3022) 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 4033 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=2037) 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=1996). 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 teste 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).

Pharmacokinetic 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 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 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/1.73 m²) 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, repeat-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/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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Microcrystalline cellulose
Mannitol
Crospovidone
Colloidal anhydrous silica
Magnesium stearate

Film-coating

Polyvinyl alcohol
Talc
Titanium dioxide (E171)
Glyceryl monocaprylocaprate
Sodium lauryl sulfate
Iron oxide yellow (E172)
Sunset yellow FCF aluminium lake (E110) [only Prasugrel Mylan 10 mg]
Iron oxide red (E172) [only Prasugrel Mylan 10 mg]

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Prasugrel Mylan 5 mg:

Do not store above 30°C. Store in the original package in order to protect from moisture.

Prasugrel Mylan 10 mg:

HDPE bottle: Do not store above 25°C. Store in the original package in order to protect from moisture.

Blister packs:

Do not store above 30°C. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Prasugrel Mylan 5 mg:

White opaque HDPE bottle closed with white opaque polypropylene screw cap and aluminium induction sealing liner wad. Each bottle contains a desiccant labelled “DO NOT EAT” and 28 or 30 film-coated tablets.

Each carton contains 1 bottle.

OPA/Aluminium/PE/Desiccant/PE- Aluminium blister packs containing 28, 30, 84 or 98 film-coated tablets.

Prasugrel Mylan 10 mg:

White opaque HDPE bottle closed with white opaque polypropylene screw cap and aluminium induction sealing liner wad. Each bottle contains a desiccant labelled “DO NOT EAT” and 28 or 30 film-coated tablets.

Each carton contains 1 bottle.

OPA/Aluminium/PE/Desiccant/PE- Aluminium blister packs containing 28, 30, 84, 90 or 98 film-coated tablets.

OPA/Aluminium/PE/Desiccant/PE- Aluminium perforated unit dose blister pack containing 30 x 1 or 90 x 1 film-coated tablets.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Mylan Pharmaceuticals Limited, Damastown Industrial Park, Mulhuddart, Dublin 15, DUBLIN, Ireland

8. MARKETING AUTHORISATION NUMBER(S)

Prasugrel Mylan 5 mg:

EU/1/18/1273/001

EU/1/18/1273/003

EU/1/18/1273/005

EU/1/18/1273/006

EU/1/18/1273/007

EU/1/18/1273/008

Prasugrel Mylan 10 mg:

EU/1/18/1273/002
EU/1/18/1273/004
EU/1/18/1273/009
EU/1/18/1273/010
EU/1/18/1273/011
EU/1/18/1273/012
EU/1/18/1273/013
EU/1/18/1273/014
EU/1/18/1273/015

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 May 2018

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

McDermott Laboratories t/a Gerard Laboratories t/a Mylan Dublin
35/36 Baldoyle Industrial Estate
Grange Road
Dublin 13
Ireland

Mylan Hungary Kft./Mylan Hungary Ltd.
Mylan utca 1
2900 Komarom
Hungary

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
 - Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.
- **Additional risk minimisation measures**

The MAH should provide educational material to all physicians who may be involved in treating patients with prasugrel. The format and means of dissemination, of this material should be discussed with the appropriate learned societies. The results of the discussion, and where appropriate the material, should be agreed with the national competent authority and be available prior to launch in each member state.

The educational material should include:

- A copy of the SPC
- Emphasis that:
 - Severe haemorrhagic events are more frequent in patients ≥ 75 years of age (including fatal events) or those weighing < 60 kg
 - Treatment with prasugrel is generally not recommended for patients of ≥ 75 years of age.
 - If, after a careful individual benefit/risk evaluation by the prescribing physician, treatment is deemed necessary in the ≥ 75 years age group then following a loading dose of 60 mg, a reduced maintenance dose of 5 mg should be prescribed.
 - Patients weighing < 60 kg should have a reduced maintenance dose of 5 mg

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND IMMEDIATE PACKAGING

BOTTLE CARTON AND BOTTLE LABEL OF 5 MG FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Prasugrel Mylan 5 mg film-coated tablets
prasugrel

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains prasugrel besilate equivalent to 5 mg prasugrel.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

28 film-coated tablets

30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C. Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

carton only:

Mylan Pharmaceuticals Limited, Damastown Industrial Park, Mulhuddart, Dublin 15, DUBLIN, Ireland

label only : Mylan Pharmaceuticals Limited

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1273/001

EU/1/18/1273/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

prasugrel Mylan 5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

carton only:

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

carton only:

PC

SN

NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND IMMEDIATE PACKAGING

BLISTER CARTON OF 5 MG FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Prasugrel Mylan 5 mg film-coated tablets
prasugrel

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains prasugrel besilate equivalent to 5 mg prasugrel.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

28 film-coated tablets
30 film-coated tablets
84 film-coated tablets
98 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C. Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Mylan Pharmaceuticals Limited, Damastown Industrial Park, Mulhuddart, Dublin 15, DUBLIN, Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1273/005
EU/1/18/1273/006
EU/1/18/1273/007
EU/1/18/1273/008

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

prasugrel Mylan 5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

carton only:
2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

carton only:

PC

SN

NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER CARTON OF 5 MG FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Prasugrel Mylan 5 mg film-coated tablets
Prasugrel

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Mylan Pharmaceuticals Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

BOTTLE CARTON AND BOTTLE LABEL OF 10 MG FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Prasugrel Mylan 10 mg film-coated tablets
prasugrel

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains prasugrel besilate equivalent to 10 mg prasugrel.

3. LIST OF EXCIPIENTS

Contains sunset yellow FCF aluminium lake (E110). See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

28 film-coated tablets
30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C. Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

carton only:

Mylan Pharmaceuticals Limited, Damastown Industrial Park, Mulhuddart, Dublin 15, DUBLIN, Ireland

label only : Mylan Pharmaceuticals Limited

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1273/002

EU/1/18/1273/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

prasugrel Mylan 10 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

carton only:

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

carton only:

PC

SN

NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

BLISTER CARTON OF 10 MG FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Prasugrel Mylan 10 mg film-coated tablets
prasugrel

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains prasugrel besilate equivalent to 10 mg prasugrel.

3. LIST OF EXCIPIENTS

Contains sunset yellow FCF aluminium lake (E110). See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

28 film-coated tablets
30 film-coated tablets
30 x 1 film-coated tablets
84 film-coated tablets
90 film-coated tablets
90 x 1 film-coated tablets
98 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C. Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Mylan Pharmaceuticals Limited, Damastown Industrial Park, Mulhuddart, Dublin 15, DUBLIN, Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1273/009
EU/1/18/1273/010
EU/1/18/1273/011
EU/1/18/1273/012
EU/1/18/1273/013
EU/1/18/1273/014
EU/1/18/1273/015

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

prasugrel Mylan 10 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

carton only:

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

carton only:

PC

SN

NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER CARTON OF 10 MG FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Prasugrel Mylan 10 mg film-coated tablets
Prasugrel

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Mylan Pharmaceuticals Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Prasugrel Mylan 5 mg film-coated tablets Prasugrel Mylan 10 mg film-coated tablets prasugrel

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 4.

What is in this leaflet

1. What Prasugrel Mylan is and what it is used for
2. What you need to know before you take Prasugrel Mylan
3. How to take Prasugrel Mylan
4. Possible side effects
5. How to store Prasugrel Mylan
6. Contents of the pack and other information

1. What Prasugrel Mylan is and what it is used for

Prasugrel Mylan, which contains the active substance prasugrel, belongs to a group of medicines called antiplatelet 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 Mylan inhibits the clumping of platelets and so reduces the chance of a blood clot forming.

You have been prescribed Prasugrel Mylan because you have already had a heart attack or unstable angina and you have been treated with a procedure to open blocked arteries in the heart. You may also have had one or more stents placed to keep open a blocked or narrowed artery supplying blood to the heart. Prasugrel Mylan reduces the chances of you having a further heart attack or stroke or of dying from one of these atherothrombotic events. Your doctor will also give you acetylsalicylic acid (e.g. aspirin), another antiplatelet agent.

2. What you need to know before you take Prasugrel Mylan

Do not take Prasugrel Mylan if you

- are allergic to prasugrel or any of the other ingredients of this medicine (listed in section 6). An allergic reaction may be recognised as a rash, itching, a swollen face, swollen lips or shortness of breath. If this has happened to you, tell your doctor immediately.
- have a medical condition that is currently causing bleeding, such as bleeding from your stomach or intestines.
- have ever had a stroke or a transient ischaemic attack (TIA).
- have severe liver disease.

Warnings and precautions

• **Before you take Prasugrel Mylan:**

Talk to your doctor before taking Prasugrel Mylan.

You should tell your doctor before taking Prasugrel Mylan if any of the situations mentioned below apply to you:

- If you have an increased risk of bleeding such as:
 - age of 75 years or older. Your doctor should prescribe a daily dose of 5 mg as there is a greater risk of bleeding in patients older than 75 years
 - a recent serious injury
 - recent surgery (including some dental procedures)
 - recent or recurrent bleeding from the stomach or intestines (e.g. a stomach ulcer or colon polyps) body weight of less than 60 kg. Your doctor should prescribe a daily dose of 5 mg of Prasugrel Mylan if you weigh less than 60 kg
 - renal (kidney) disease or moderate liver problems
 - taking certain types of medicines (see ‘Taking other medicines’ below)
 - planned surgery (including some dental procedures) in the next seven days. Your doctor may wish you to stop taking Prasugrel Mylan temporarily due to the increased risk of bleeding
- If you have had allergic reactions (hypersensitivity) to clopidogrel or any other anti-platelet agent please tell your doctor before starting treatment with Prasugrel Mylan. If you then take Prasugrel Mylan and experience allergic reactions that may be recognised as a rash, itching, a swollen face, swollen lips or shortness of breath you need to tell your doctor **immediately**.

• **While you are taking Prasugrel Mylan:**

You should tell your doctor immediately if you develop a medical condition called Thrombotic Thrombocytopenic Purpura (or TTP) that includes fever and bruising under the skin that may appear as red pinpoint dots, with or without unexplained extreme tiredness, confusion, yellowing of the skin or eyes (jaundice) (see section 4 ‘Possible side effects’).

Children and adolescents

Prasugrel Mylan should not be used in children and adolescents below 18 years of age.

Other medicines and Prasugrel Mylan

Tell your doctor if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription, dietary supplements and herbal remedies.

It is particularly important to tell your doctor if you are being treated with:

- clopidogrel (an anti-platelet agent),
- warfarin (an anti-coagulant),
- ‘non-steroidal anti-inflammatory drugs’ for pain and fever (such as ibuprofen, naproxen, etoricoxib).

If given together with Prasugrel Mylan these medicines may increase the risk of bleeding.

Tell your doctor if you are taking morphine or other opioids (used to treat severe pain).

Only take other medicines while you are on Prasugrel Mylan if your doctor tells you that you can.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Tell your doctor if you become pregnant or are trying to become pregnant while you are taking Prasugrel Mylan. You should use Prasugrel Mylan only after discussing with your doctor the potential benefits and any potential risks to your unborn child.

If you are breast-feeding, ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Prasugrel Mylan is unlikely to affect your ability to drive or use machines.

Prasugrel 5 mg Mylan contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

Prasugrel Mylan 10 mg contains sunset yellow FCF aluminium lake (E110) and sodium

Sunset yellow FCF aluminium lake is a colouring agent, which may cause allergic reactions. This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

3. How to take Prasugrel Mylan

Always take Prasugrel Mylan exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

The usual dose of prasugrel is 10 mg per day. You will start the treatment with a single dose of 60 mg. If you weigh less than 60 kg or are more than 75 years of age, the dose is 5 mg Prasugrel Mylan per day. Your doctor will also tell you to take acetylsalicylic acid, and (s)he will tell you the exact dose to take (usually between 75 mg and 325 mg daily).

You may take Prasugrel Mylan with or without food. Take your dose at around the same time every day. Do not break or crush the tablet.

It is important that you tell your doctor, dentist and pharmacist, that you are taking Prasugrel Mylan.

If you take more Prasugrel Mylan than you should

Contact your doctor or hospital straight away, as you may be at risk of excessive bleeding. You should show the doctor your pack of Prasugrel Mylan.

If you forget to take Prasugrel Mylan

If you miss your scheduled daily dose, take Prasugrel Mylan when you remember. If you forget your dose for an entire day, just resume taking Prasugrel Mylan at its usual dose the next day. Do not take two doses in one day.

If you stop taking Prasugrel Mylan

Do not stop taking Prasugrel Mylan without consulting your doctor; if you stop taking Prasugrel Mylan 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.

4. Possible side effects

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

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 Prasugrel Mylan in patients who have never had a stroke or transient ischaemic attack (TIA).

Also contact your doctor immediately if you notice any of the following:

- Fever and bruising under the skin that may appear as red pinpoint dots, with or without unexplained extreme tiredness, confusion, yellowing of the skin or eyes (jaundice). (see section 2 'What you need to know before you take Prasugrel Mylan')
- A rash, itching, or a swollen face, swollen lips/tongue, or shortness of breath. These may be signs of a severe allergic reaction (see section 2 'What you need to know before you take Prasugrel Mylan')

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 Prasugrel Mylan. Although uncommon, severe bleeding can be life-threatening.

Common side effects (may affect up to 1 in 10 people)

- 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 side effects (may affect up to 1 in 100 people)

- 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 side effects (may affect up to 1 in 1,000 people)

- Low blood platelet count
- Subcutaneous haematoma (bleeding under the skin causing a swelling)

Reporting of side effects

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell you doctor or pharmacist. You can also report side effects directly via the national reporting system listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Prasugrel Mylan

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the bottle and carton after EXP. The expiry date refers to the last day of that month.

Prasugrel Mylan 5 mg: Do not store above 30°C. Store in the original package in order to protect from moisture.

Prasugrel Mylan 10 mg: Do not store above 25°C. Store in the original package in order to protect from moisture.

Blister packs only: Do not store above 30°C. Store in the original package in order to protect from moisture.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Prasugrel Mylan contains

– The active substance is prasugrel.

Prasugrel Mylan 5 mg: Each tablet contains prasugrel besilate equivalent to 5 mg prasugrel.

Prasugrel Mylan 10 mg: Each tablet contains prasugrel besilate equivalent to 10 mg prasugrel.

– The other ingredients are:

Prasugrel Mylan 5 mg: microcrystalline cellulose, mannitol, crospovidone, silica colloidal anhydrous, magnesium stearate, polyvinyl alcohol, talc, titanium dioxide (E171), glyceryl monocaprylocaprate, sodium lauryl sulfate, iron oxide yellow (E172).

Prasugrel Mylan 10 mg: microcrystalline cellulose, mannitol, crospovidone, silica colloidal anhydrous, magnesium stearate, polyvinyl alcohol, talc, titanium dioxide (E171), glyceryl monocaprylocaprate, sodium lauryl sulfate, iron oxide yellow (E172), sunset yellow FCF aluminium lake (E110) (see section 2, 'Prasugrel Mylan 10 mg contains sunset yellow FCF aluminium lake'), iron oxide red (E172).

What Prasugrel Mylan looks like and contents of the pack

Prasugrel Mylan 10 mg film-coated tablets are beige film-coated, capsule shaped, biconvex tablets, of dimensions 11.15 mm × 5.15 mm, debossed with 'PH4' on one side of the tablet and 'M' on the other side.

This medicine is available in plastic bottles containing a desiccant and 28 or 30 film-coated tablets and in blister packs containing 28, 30, 84, 90, 98 and in perforated blister packs containing 30 x 1 and 90 x 1 film-coated tablets.

Prasugrel Mylan 5 mg film-coated tablets are yellow film-coated, capsule shaped, biconvex tablets, of dimensions 8.15 mm × 4.15 mm, debossed with 'PH3' on one side of the tablet and 'M' on the other side.

This medicine is available in plastic bottles containing a desiccant and 28 or 30 film-coated tablets and in blister packs containing 28, 30, 84 or 98 film-coated tablets.

Do not eat or remove the desiccant contained in the bottle

Not all pack sizes may be marketed.

Marketing Authorisation Holder

Mylan Pharmaceuticals Limited, Damastown Industrial Park, Mulhuddart, Dublin 15, DUBLIN, Ireland

Manufacturer

Mylan Hungary Kft
Mylan utca 1, Komárom, 2900, Hungary

McDermott Laboratories Limited t/a Gerard Laboratories
35/36 Baldoyle Industrial Estate, Grange State, Dublin 13, Ireland

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

België/Belgique/Belgien

Mylan bvba/sprl
Tél/Tel: + 32 (0)2 658 61 00

България

Майлан ЕООД
Тел: +359 2 44 55 400

Česká republika

Mylan Healthcare CZ s.r.o.
Tel: + 420 222 004 400

Danmark

Viatriis ApS
Tlf: +45 28 11 69 32

Deutschland

Viatriis Healthcare GmbH
Tel: +49 800 0700 800

Eesti

BGP Products Switzerland GmbH
Eesti filiaal
Tel: + 372 6363 052

Ελλάδα

Generics Pharma Hellas ΕΠΕ
Τηλ: +30 210 993 6410

España

Viatriis Pharmaceuticals, S.L.U.
Tel: + 34 900 102 712

France

Viatriis Santé
Tél : +33 4 37 25 75 00

Hrvatska

Mylan Hrvatska d.o.o.
Tel: +385 1 23 50 599

Lietuva

Mylan Healthcare UAB
Tel: +370 5 205 1288

Luxembourg/Luxemburg

Mylan bvba/sprl
Tel: + 32 (0)2 658 61 00
(Belgique/Belgien)

Magyarország

Mylan EPD Kft
Tel: + 36 1 465 2100

Malta

V.J. Salomone Pharma Ltd
Tel: + 356 21 22 01 74

Nederland

Mylan BV
Tel: +31 (0)20 426 3300

Norge

Viatriis AS
Tlf: + 47 66 75 33 00

Österreich

Arcana Arzneimittel GmbH
Tel: +43 1 416 2418

Polska

Mylan Healthcare Sp. z o.o.
Tel: + 48 22 546 64 00

Portugal

Mylan, Lda.
Tel: + 351 21 412 72 56

România

BGP Products SRL
Tel: + 40 372 579 000

Ireland

Mylan Ireland Limited
Tel: +353 1 8711600

Ísland

Icepharma hf
Sími: +354 540 8000

Italia

Mylan Italia S.r.l.
Tel: + 39 02 612 46921

Κύπρος

Varnavas Hadjipanayis Ltd
Τηλ: +357 2220 7700

Latvija

Mylan Healthcare SIA
Tel: +371 676 055 80

Slovenija

Mylan Healthcare d.o.o.
Tel: + 386 1 23 63 180

Slovenská republika

Viartis Slovakia s.r.o.
Tel: +421 2 32 199 100

Suomi/Finland

Viartis Oy
Puh/Tel: + 358 20 720 9555

Sverige

Viartis AB
Tel: + 46 (0)8 630 19 00

United Kingdom (Northern Ireland)

Mylan IRE Healthcare Limited
Tel: +353 18711600

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>.