

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Efient 5 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg prasugrel (as hydrochloride).

Excipient: Each tablet contains 2.7 mg lactose.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Yellow and double-arrow shaped tablets, debossed with “5 MG” on one side and “4760” on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Efient, co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of atherothrombotic events in 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

Efient should be initiated with a single 60 mg loading dose and then continued at 10 mg once a day. Patients taking Efient should also take ASA daily (75 mg to 325 mg).

In patients with acute coronary syndrome (ACS) who are managed with PCI, premature discontinuation of any antiplatelet agent, including Efient, could result in an increased risk of thrombosis, myocardial infarction or death due to the patient’s underlying disease. A treatment of up to 12 months is recommended unless the discontinuation of Efient is clinically indicated (see sections 4.4 and 5.1).

Patients \geq 75 years old

The use of Efient in patients \geq 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 \geq 75 years, then following a 60 mg loading dose a reduced maintenance dose of 5 mg should be prescribed. Patients \geq 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). The evidence for the 5 mg dose is based only on pharmacodynamic/pharmacokinetic analyses and no clinical data currently exist on the safety of this dose in the patients age group \geq 75 years.

Patients weighing $<$ 60 kg

Efient should be given as a single 60 mg loading dose and then continued at a 5 mg once daily dose. The 10 mg maintenance dose is not recommended. This is due to an increase in exposure to the active metabolite of prasugrel, and an increased risk of bleeding in patients with body weight $<$ 60 kg when

given a 10 mg once daily dose compared with patients ≥ 60 kg. Efficacy and safety of the 5 mg dose have not been prospectively assessed (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).

Children and adolescents

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

Method of administration

For oral use. Efient may be administered with or without food. Administration of the 60 mg prasugrel loading dose in the fasted state may provide most rapid onset of action (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.

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 key exclusion criteria included an increased risk of bleeding; anaemia; thrombocytopenia; a history of pathological intracranial findings. Patients with acute coronary syndromes undergoing PCI treated with Efient and ASA showed an increased risk of major and minor bleeding according to the TIMI classification system. Therefore, the use of Efient 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 Efient is required, platelet transfusion may be appropriate.

The use of Efient 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.

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, Efient 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.

Lactose

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

4.5 Interaction with other medicinal products and other forms of interaction

Warfarin: Concomitant administration of Efient 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 Efient should be co-administered with caution (see section 4.4).

Efient 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. Efient 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, Efient 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 Efient

Acetylsalicylic acid: Efient 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 Efient 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, Efient 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.

Effects of Efient 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 Efient 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 lactating women.

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

It is unknown whether prasugrel is excreted in human breast milk. Animal studies have shown excretion of prasugrel in breast milk. The use of prasugrel during breastfeeding is not recommended.

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

4.7 Effects on ability to drive and use machines

No studies on the effects on ability to drive and use machines have been performed. Prasugrel is expected to have no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

a. 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

In the phase 3 clinical trial, non-CABG-related TIMI major or minor bleeding rates for patients in two age groups were as follows:

Age	Prasugrel	Clopidogrel
≥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)

Patients < 60 kg

In the phase 3 clinical trial, non-CABG-related TIMI major or minor bleeding rates for patients in two weight groups were as follows:

Weight	Prasugrel	Clopidogrel
<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)

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).

b. 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 (≥ 1/1000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

Table 2: Haemorrhagic and Non-haemorrhagic adverse reactions

System Organ Class	Common	Uncommon	Rare	Not Known
Blood and Lymphatic System disorders	Anaemia		Thrombocytopaenia	Thrombotic thrombocytopenic 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		
<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.

4.9 Overdose

Overdose of Efiect 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.

Pharmacodynamics

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 ≥ 20% inhibition of platelet aggregation during maintenance dosing.

Platelet aggregation gradually returned to baseline values after treatment in 7 to 9 days after administration of a single 60 mg loading dose of prasugrel and in 5 days following discontinuation of

maintenance dosing at steady-state.

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

Efficacy and Safety in Acute Coronary Syndrome (ACS)

The phase 3 TRITON study compared Efient (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: Efient 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 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 = 6813) %	(N = 6795) %	0.812 (0.732, 0.902)	< 0.001
Primary Composite Outcome Events Cardiovascular (CV) death, non fatal MI, or non fatal stroke	9.4	11.5		
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	(N = 5044) %	(N = 5030) %		
Primary Composite Outcome Events 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	(N = 1769) %	(N = 1765) %		
Primary Composite Outcome Events 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 Efient 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 Efient 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 Efient, 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).

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. Efient was administered without regard to food in TRITON. Therefore, Efient 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%.

Metabolism

Prasugrel is not detected in plasma following oral administration. It is rapidly hydrolysed in the intestine to a thiolactone, which is then converted to the active metabolite by a single step of cytochrome P450 metabolism, primarily by CYP3A4 and CYP2B6 and to a lesser extent by CYP2C9 and CYP2C19. The active metabolite is further metabolised to two inactive compounds by S-methylation or conjugation with cysteine.

In healthy subjects, patients with stable atherosclerosis, and patients with ACS receiving Efient, 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).

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/1.73m²) and healthy subjects. Prasugrel-mediated inhibition of platelet aggregation was also similar in patients with ESRD who required haemodialysis compared to healthy subjects, although 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).

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.

Children and adolescents: 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 (E421)
Croscarmellose sodium

Hypromellose (E464)
Magnesium stearate

Film-Coat:

Lactose monohydrate
Hypromellose (E464)
Titanium dioxide (E171)
Triacetin (E1518)
Iron oxide yellow (E172)
Talc

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 temperature storage conditions. Store in the original package to protect from air and moisture.

6.5 Nature and contents of container

Aluminium foil blisters in cartons of 14, 28, 30, 30 (x1), 56, 84, 90 (x1) and 98 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland BV, Grootslag 1-5, NL-3991 RA Houten, The Netherlands.

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/503/001
EU/1/08/503/002
EU/1/08/503/003
EU/1/08/503/004
EU/1/08/503/005
EU/1/08/503/006
EU/1/08/503/007
EU/1/08/503/015

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25 February 2009

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

1. NAME OF THE MEDICINAL PRODUCT

Efient 10 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg prasugrel (as hydrochloride).

Excipient: Each tablet contains 2.1 mg lactose.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Beige and double-arrow shaped tablets, debossed with “10 MG” on one side and “4759” on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Efient, co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of atherothrombotic events in 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

Efient should be initiated with a single 60 mg loading dose and then continued at 10 mg once a day. Patients taking Efient should also take ASA daily (75 mg to 325 mg).

In patients with acute coronary syndrome (ACS) who are managed with PCI, premature discontinuation of any antiplatelet agent, including Efient, could result in an increased risk of thrombosis, myocardial infarction or death due to the patient's underlying disease. A treatment of up to 12 months is recommended unless the discontinuation of Efient is clinically indicated (see sections 4.4 and 5.1).

Patients \geq 75 years old

The use of Efient in patients \geq 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 \geq 75 years, then following a 60 mg loading dose a reduced maintenance dose of 5 mg should be prescribed. Patients \geq 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). The evidence for the 5 mg dose is based only on pharmacodynamic/pharmacokinetic analyses and no clinical data currently exist on the safety of this dose in the patients age group \geq 75 years.

Patients weighing $<$ 60 kg

Efient should be given as a single 60 mg loading dose and then continued at a 5 mg once daily dose. The 10 mg maintenance dose is not recommended. This is due to an increase in exposure to the active metabolite of prasugrel, and an increased risk of bleeding in patients with body weight $<$ 60 kg when

given a 10 mg once daily dose compared with patients ≥ 60 kg. Efficacy and safety of the 5 mg dose have not been prospectively assessed (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).

Children and adolescents

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

Method of administration

For oral use. Efient may be administered with or without food. Administration of the 60 mg prasugrel loading dose in the fasted state may provide most rapid onset of action (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.

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 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 Efient and ASA showed an increased risk of major and minor bleeding according to the TIMI classification system. Therefore, the use of Efient 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 Efient is required, platelet transfusion may be appropriate.

The use of Efient 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.

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, Efient 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.

Lactose

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

4.5 Interaction with other medicinal products and other forms of interaction

Warfarin: Concomitant administration of Efient 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 Efient should be co-administered with caution (see section 4.4).

Efient 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. Efient 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, Efient 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 Efient

Acetylsalicylic acid: Efient 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 Efient 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, Efient 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.

Effects of Efient 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 Efient 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 lactating women.

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

It is unknown whether prasugrel is excreted in human breast milk. Animal studies have shown excretion of prasugrel in breast milk. The use of prasugrel during breastfeeding is not recommended.

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

4.7 Effects on ability to drive and use machines

No studies on the effects on ability to drive and use machines have been performed. Prasugrel is expected to have no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

a. 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

In the phase 3 clinical trial, non-CABG-related TIMI major or minor bleeding rates for patients in two age groups were as follows:

Age	Prasugrel	Clopidogrel
≥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)

Patients < 60 kg

In the phase 3 clinical trial, non-CABG-related TIMI major or minor bleeding rates for patients in two weight groups were as follows:

Weight	Prasugrel	Clopidogrel
<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)

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).

b. 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 (≥ 1/1000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

Table 2: Haemorrhagic and Non-haemorrhagic adverse reactions

System Organ Class	Common	Uncommon	Rare	Not Known
<i>Blood and Lymphatic System disorders</i>	Anaemia		Thrombocytopaenia	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.

4.9 Overdose

Overdose of Efiect 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.

Pharmacodynamics

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 ≥ 20% inhibition of platelet aggregation during maintenance dosing.

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

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

Efficacy and Safety in Acute Coronary Syndrome (ACS)

The phase 3 TRITON study compared Efient (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: Efient 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 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 = 6813) %	(N = 6795) %	0.812 (0.732, 0.902)	< 0.001
Primary Composite Outcome Events Cardiovascular (CV) death, non fatal MI, or non fatal stroke	9.4	11.5		
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	(N = 5044) %	(N = 5030) %		
Primary Composite Outcome Events 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	(N = 1769) %	(N = 1765) %		
Primary Composite Outcome Events 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 Efient 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 Efient 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 Efient, 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).

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. Efient was administered without regard to food in TRITON. Therefore, Efient 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%.

Metabolism

Prasugrel is not detected in plasma following oral administration. It is rapidly hydrolysed in the intestine to a thiolactone, which is then converted to the active metabolite by a single step of cytochrome P450 metabolism, primarily by CYP3A4 and CYP2B6 and to a lesser extent by CYP2C9 and CYP2C19. The active metabolite is further metabolised to two inactive compounds by S-methylation or conjugation with cysteine.

In healthy subjects, patients with stable atherosclerosis, and patients with ACS receiving Efient, 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).

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/1.73m²) and healthy subjects. Prasugrel-mediated inhibition of platelet aggregation was also similar in patients with ESRD who required haemodialysis compared to healthy subjects, although 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).

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.

Children and adolescents: 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 (E421)
Croscarmellose sodium

Hypromellose (E464)
Magnesium stearate

Film-Coat:

Lactose monohydrate
Hypromellose (E464)
Titanium dioxide (E171)
Triacetin (E1518)
Iron oxide red (E172)
Iron oxide yellow (E172)
Talc

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 temperature storage conditions. Store in the original package to protect from air and moisture.

6.5 Nature and contents of container

Aluminium foil blisters in cartons of 14, 28, 30, 30 (x1), 56, 84, 90 (x1) and 98 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland BV, Grootslag 1-5, NL-3991 RA Houten, The Netherlands.

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/503/008
EU/1/08/503/009
EU/1/08/503/010
EU/1/08/503/011
EU/1/08/503/012
EU/1/08/503/013
EU/1/08/503/014
EU/1/08/503/016

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25 February 2009

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

ANNEX II

- A. MANUFACTURING AUTHORISATION HOLDER
RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OF THE MARKETING AUTHORISATION**

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Lilly S.A.
Avda de la Industria 30
E-28108 Alcobendas (Madrid)
Spain

B. CONDITIONS OF THE MARKETING AUTHORISATION

• CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER

Medicinal product subject to medical prescription.

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

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 5mg should be prescribed.
 - Patients weighing < 60 kg should have a reduced maintenance dose of 5mg
 - The evidence for a 5mg dose is based only on PK/PD analyses and no clinical data currently exist on the safety of this dose in the at risk sub groups.
- **OTHER CONDITIONS**

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance presented in Module 1.8.1. of the Marketing Authorisation is in place and functioning before and whilst the product is on the market.

Risk Management Plan

The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in Revision 1.4 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the EMEA

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF 5mg FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Efient 5 mg film-coated tablets
prasugrel

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 5 mg prasugrel (as hydrochloride)

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
28 film-coated tablets
30x1 film-coated tablet
56 film-coated tablets
84 film-coated tablets
90x1 film-coated tablet
98 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 REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package to protect from air and 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

Eli Lilly Nederland BV, Grootslag 1-5, NL-3991 RA Houten, The Netherlands.

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/503/001 14 film-coated tablets
EU/1/08/503/002 28 film-coated tablets
EU/1/08/503/003 30x1 film-coated tablet
EU/1/08/503/004 56 film-coated tablets
EU/1/08/503/005 84 film-coated tablets
EU/1/08/503/006 90x1 film-coated tablet
EU/1/08/503/007 98 film-coated tablets
EU/1/08/503/015 30 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Effient 5 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER OF 5 mg FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Efient 5 mg film-coated tablets
prasugrel

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Lilly

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

<MON, TUE, WED, THU, FRI, SAT, SUN>

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF 10 mg FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Effient 10 mg film-coated tablets
prasugrel

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 10 mg prasugrel (as hydrochloride)

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
28 film-coated tablets
30x1 film-coated tablet
56 film-coated tablets
84 film-coated tablets
90x1 film-coated tablet
98 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 REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package to protect from air and 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**

Eli Lilly Nederland BV, Grootslag 1-5, NL-3991 RA Houten, The Netherlands.

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/503/008 14 film-coated tablets
EU/1/08/503/009 28 film-coated tablets
EU/1/08/503/010 30x1 film-coated tablet
EU/1/08/503/011 56 film-coated tablets
EU/1/08/503/012 84 film-coated tablets
EU/1/08/503/013 90x1 film-coated tablet
EU/1/08/503/014 98 film-coated tablets
EU/1/08/503/016 30 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

16. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

Effient 10 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER OF 10 mg FILM-COATED TABLETS

1. NAME OF THE MEDICINAL PRODUCT

Effient 10 mg film-coated tablets
prasugrel

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Lilly

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot:

5. OTHER

<MON, TUE, WED, THU, FRI, SAT, SUN>

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Efient 10 mg film-coated tablets **Efient 5 mg film-coated tablets** Prasugrel

Read all of this leaflet carefully before you start taking this medicine.

- 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. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Efient is and what it is used for
2. Before you take Efient
3. How to take Efient
4. Possible side effects
5. How to store Efient
6. Further information

1. WHAT EFIENT IS AND WHAT IT IS USED FOR

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

Efient inhibits the clumping of platelets and so reduces the chance of a blood clot forming.

You have been prescribed Efient 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. Efient 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 anti-platelet agent.

2. BEFORE YOU TAKE EFIENT

Do not take Efient

- If you are allergic (hypersensitive) to prasugrel or any of the other ingredients of Efient. 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**.
- If you have a medical condition that is currently causing bleeding, such as bleeding from your stomach or intestines.
- If you have ever had a stroke or a transient ischaemic attack (TIA).
- If you have severe liver disease.

Take special care with Efient

You should tell your doctor before taking Efient 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 Efient 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 Efient 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 Efient. If you then take Efient 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 Efient:

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').

Taking other medicines

Please tell your doctor if you are taking or have recently taken 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), or "non steroidal anti inflammatory drugs" for pain and fever (such as ibuprofen, naproxen, etoricoxib). If given together with Efient these medicines may increase the risk of bleeding

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

Taking Efient with food and drink

Efient may be taken with or without food.

Pregnancy and breast-feeding

Tell your doctor if you become pregnant or are trying to become pregnant while you are taking Efient. You should use Efient 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

No studies on the effects of Efient on the ability to drive and use machines have been performed. Efient is unlikely to affect your ability to drive or use machines.

Important information about some of the ingredients of Efient

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

3. HOW TO TAKE EFIENT

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

Your doctor will tell you how many Efient tablets to take. The usual dose of Efient 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 Efient per day. Your doctor will also tell you to take acetylsalicylic acid- (s)he will tell you the exact dose to take (usually between 75 mg and 325 mg daily).

You may take Efient 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 Efient. Efient should not be used in children and adolescents below 18 years of age.

If you take more Efient 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 Efient.

If you forget to take Efient

If you miss your scheduled daily dose, take Efient when you remember. If you forget your dose for an entire day, just resume taking Efient at its usual dose the next day. Do not take two doses in one day. For the 14, 28, 56 84 and 98 tablet pack sizes, you can check the day on which you last took a tablet of Efient by referring to the calendar printed on the blister.

If you stop taking Efient

Do not stop taking Efient without consulting your doctor. It is especially important to discuss with your doctor before stopping Efient because both the risks and the benefits are based on regular use.

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

4. POSSIBLE SIDE EFFECTS

Like all medicines, Efient 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 Efient 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 'BEFORE YOU TAKE EFIENT')
- A rash, itching, or a swollen face, swollen lips/tongue, or shortness of breath. These may be signs of an allergic reaction (see section 2 'BEFORE YOU TAKE EFIENT')

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 Efient. Although uncommon, severe bleeding can be life-threatening.

Common side effects (affect 1 to 10 users in 100)

- 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 (affect 1 to 10 users in 1,000)

- 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 (affect 1 to 10 users in 10,000)

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

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.

5. HOW TO STORE EFIENT

Keep out of the reach and sight of children.

Do not use Efient after the expiry date, which is stated on the blister and carton after EXP. The expiry date refers to the last day of that month.

Store in the original package to protect from air and moisture.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Efient contains

- The active substance is prasugrel.
Efient 10 mg: Each tablet contains 10 mg of prasugrel (as hydrochloride).
Efient 5 mg: Each tablet contains 5 mg of prasugrel (as hydrochloride).

- The other ingredients are microcrystalline cellulose, mannitol (E421), croscarmellose sodium, hypromellose (E464) magnesium stearate, lactose monohydrate, titanium dioxide (E171), triacetin (E1518), iron oxide red (10 mg tablets only) (E172), iron oxide yellow (E172) and talc.

What Efient looks like and contents of the pack

Efient 10 mg: The tablets are beige and double-arrow shaped, with "10 MG" debossed on one side and "4759" on the other.

Efient 5 mg: The tablets are yellow and double-arrow-shaped, with "5 MG" debossed on one side and "4760" on the other.

Efient is available in packs of 14, 28, 30, 56, 84, 90 and 98 tablets.
Not all pack sizes may be marketed.

Marketing Authorisation Holder

Eli Lilly Nederland BV
Grootslag 1 – 5
NL-3991 RA, Houten
The Netherlands.

Manufacturer:

Lilly S.A.
Avda. de la Industria 30
28108 Alcobendas
Madrid
Spain.

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

Belgique/België/Belgien

Daiichi Sankyo Belgium N.V.-S.A
Tél/Tel: +32 (0) 10 48 95 95

България

ТП "Ели Лили Недерланд" Б.В. - България
тел. +359 2 491 41 40

Česká republika

ELI LILLY ČR, s.r.o.
Tel: +420 234 664 111

Danmark

Eli Lilly Danmark A/S
Tlf: +45 45 26 60 00

Deutschland

Daiichi Sankyo Deutschland GmbH
Tel. +49 (0) 69 50 98 53 41

Eesti

Eli Lilly Holdings Limited Eesti filiaal
Tel: +372 6 817 280

Ελλάδα

ΦΑΡΜΑΣΕΡΒ-ΛΙΛΛΥ Α.Ε.Β.Ε.
Τηλ: +30 210 629 4600

España

Daiichi Sankyo España, S.A.
Tel: +34 (0) 91 539 99 11

Luxembourg/Luxemburg

Daiichi Sankyo Belgium N.V.-S.A
Tél/Tel: +32 (0) 10 48 95 95

Magyarország

Lilly Hungária Kft.
Tel: + 36 1 328 5100

Malta

Charles de Giorgio Ltd.
Tel: +356 25600 500

Nederland

Daiichi Sankyo Nederland B.V.
Tel: +31 (0) 20 4 07 20 72

Norge

Eli Lilly Norge A.S.
Tlf: +47 22 88 18 00

Österreich

Daiichi Sankyo Austria GmbH
Tel: +43 (0) 1 481 06 45

Polska

Eli Lilly Polska Sp. z o.o.
Tel. +48 (0) 22 440 33 00

Portugal

Daiichi Sankyo Portugal, Lda.
Tel: +351 21 4232010

France

Daiichi Sankyo France SAS

Tél: +33 (0) 1 55 62 14 60

Ireland

Daiichi Sankyo UK Ltd

Tel: +44 (0) 1753 893 600

Ísland

Icepharma hf.

Sími: +354 540 8000

Italia

Daiichi Sankyo Italia S.p.A.

Tel: +39 (0) 06 85 2551

Κύπρος

Phadisco Ltd

Τηλ: +357 22 715000

Latvija

Eli Lilly Holdings Limited pārstāvniecība Latvijā

Tel: +371 67364000

Lietuva

Eli Lilly Holdings Limited atstovybė

Tel. +370 (5) 2649600

România

Eli Lilly România S.R.L.

Tel: +40 21 4023000

Slovenija

Eli Lilly farmacevtska družba, d.o.o.

Tel: +386 (0)1 580 00 10

Slovenská republika

Eli Lilly Slovakia, s.r.o.

Tel: +421 220 663 111

Suomi/Finland

Oy Eli Lilly Finland Ab

Puh/Tel: +358-(0) 9 85 45 250

Sverige

Eli Lilly Sweden AB

Tel: + 46 (0) 8 7378800

United Kingdom

Daiichi Sankyo UK Ltd

Tel: +44 (0) 1753 893 600

This leaflet was last approved in {MM/YYYY}.

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