Drug Discontinuation

The rate of study drug discontinuation due to adverse events was 7.2% for prasugrel and 6.3% for clopidogrel (OR 1.150; 95% CI, 1.005, 1.317; p=0.042). 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; OR 1.872; 95% CI, 1.448, 2.421; p<0.001).

Bleeding

Non-CABG-related Bleeding – In TRITON, the frequency of patients experiencing a non-CABG-related bleeding event is shown in Table 4. 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 non-CABG-related Thrombolysis in Myocardial Infarction (TIMI) Major or Minor bleeding was the GI 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 4: TRITON Incidence of Non-CABG-Related Bleeding[a] (% Patients) for All ACS

Event	Prasugrel[b] + Aspirin (N=6741)	Clopidogrel[b] + Aspirin (N=6716)
TIMI major bleeding[c]	2.2	1.7
Life-threatening[d]	1.3	0.8
Fatal	0.3	0.1
Symptomatic ICH[e]	0.3	0.3
Requiring inotropes	0.3	0.1
Requiring surgical intervention	0.3	0.3
Requiring transfusion (>4 units)	0.7	0.5
TIMI Minor bleeding[f]	2.4	1.9

[a]Centrally adjudicated events defined by the TIMI Study Group criteria.
[b]Other standard therapies were used as appropriate. The TRITON protocol provided for all patients to receive aspirin.
[c]Any intracranial haemorrhage or any clinically overt bleeding associated with a fall in haemoglobin ≥5 g/dL.
[d]Life-threatening 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.

Table 5 shows the incidence of non-CABG-related bleeding by UA/NSTEMI and STEMI subgroups.

Table 5: TRITON Incidence of Non-CABG-Related Bleeding[a] (% Patients) for UA/NSTEMI and STEMI

	UA/NSTEMI		STEMI	
Event	Prasugrel[b] (N=5001)	Clopidogrel[b] (N=4980)	Prasugrel[b] (N=1740)	Clopidogrel[b] (N=1736)
TIMI major bleeding[c]	2.2	1.6	2.2	2.0
Life-threatening[d]	1.3	0.8	1.2	1.0
Fatal	0.3	0.1	0.4	0.1
Symptomatic ICH[e]	0.3	0.3	0.2	0.2
Requiring inotropes	0.3	0.1	0.3	0.2
Requiring surgical intervention	0.3	0.3	0.1	0.2
Requiring transfusion (>4 units)	0.6	0.3	0.8	0.8
TIMI Minor bleeding[f]	2.3	1.6	2.7	2.6

[a]Centrally adjudicated events defined by the TIMI Study Group criteria.
[b]Other standard therapies were used as appropriate. The TRITON protocol provided for all patients to receive aspirin.
[c]Any intracranial haemorrhage or any clinically overt bleeding associated with a fall in haemoglobin ≥5 g/dL.
[d]Life-threatening 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 <60 kg

In TRITON, among prasugrel-treated patients, non-CABG-related TIMI major or minor bleeding for patients in two weight groups were as follows:

Weight	Prasugrel	Clopidogrel	HR (95% CI)	p-value
<60 kg (N=664)	10.0% (0% fatal)	6.5% (0.3% fatal)	1.570 (0.915, 2.694)	0.099
≥60 kg (N=12 672)	4.2% (0.3% fatal)	3.3% (0.1% fatal)	1.293 (1.078, 1.551)	0.005

Very elderly patients (≥75 years)

In TRITON, among prasugrel-treated patients, non-CABG-related TIMI major or minor bleeding for patients in two age groups were as follows:

Age	Prasugrel	Clopidogrel	HR (95% CI)	p-value
≥75 years (N=1 785)	9.0% (1.0% fatal)	6.9% (0.1% fatal)	1.346 (0.966, 1.877)	0.078
<75 years (N=11 672)	3.8% (0.2% fatal)	2.9% (0.1% fatal)	1.320 (1.081, 1.612)	0.006

Patients ≥75 years of age also had a higher risk of stroke compared to those <75 years. The incidence of stroke in patients ≥75 years of age treated with prasugrel was 2.89% compared to 1.43% with clopidogrel while for patients <75 years the rate of stroke was 0.83% with prasugrel and 0.99% with clopidogrel (see **Clinical Trials**).

Prior TIA or Stroke

In TRITON, among prasugrel-treated patients, non-CABG-related TIMI major or minor bleeding for patients with and without a history of TIA or stroke were as follows:

	Prasugrel	Clopidogrel	HR (95% CI)	P-Value
Prior TIA or Stroke	7.8 % (1.2% fatal)	4.0% (0% fatal)	2.082 (0.972, 4.456)	0.054
Without Prior TIA or Stroke	4.4% (0.3% fatal)	3.4% (0.1% fatal)	1.282 (1.076, 1.529)	0.005

In TRITON, in patients with or without a history of TIA or stroke, the incidence of stroke was as follows:

History of TIA or Stroke	Prasugrel	Clopidogrel
Yes (N=518)	6.5% (2.3% ICH*)	1.2% (0% ICH*)
No (N=13 090)	0.9% (0.2% ICH*)	1.0% (0.3% ICH*)

* ICH = intracranial haemorrhage

CABG-Related Bleeding – In TRITON, 437 patients underwent CABG during the course of the study (see Table 6). 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 (OR 3.587; 95% CI, 1.702, 7.557; p<0.001). The higher risk for bleeding events in patients 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 3.3% (3 of 90 patients) in the clopidogrel group. Beyond 7 days after drug discontinuation, the observed rates of CABG-related bleeding were similar between treatment groups (see **Precautions**).

Table 6: TRITON Incidence of CABG-Related Bleeding[a] (% Patients) for All ACS

	Prasugrel (%) (N=213)	Clopidogrel (%) (N=224)
TIMI Major or Minor bleeding	14.1	4.5
TIMI Major bleeding	11.3	3.6
Fatal	0.9	0
Reoperation	3.8	0.5
Transfusion of ≥5 units	6.6	2.2
Intracranial hemorrhage	0	0
TIMI Minor bleeding	2.8	0.9

[a] Patients may be counted in more than one row

Bleeding Reported as Adverse Events – Table 7 shows the incidence of common (≥1/100 to <1/10) and uncommon (≥1/1000 to <1/100) haemorrhagic adverse events in TRITON.

Table 7: Haemorrhagic Adverse Reactions

System Organ Class	MedDRA Preferred Term	Prasugrel	Clopidogrel
Injury, poisoning and procedural complications	Contusion	6.9	3.9
	Post-procedural haemorrhage	0.5	0.2
	Subcutaneous haematoma	0.5	0.2
Vascular Disorders	Haematoma	6.5	5.6
Respiratory, thoracic and mediastinal disorders	Epistaxis	6.2	3.3
	Haemoptysis	0.6	0.5
Skin and subcutaneous tissue disorders	Ecchymosis	2.2	1.7
General disorders and administration site conditions	Vessel Puncture Site Haematoma	2.0	1.6
	Puncture Site Haemorrhage	1.8	1.3
Renal and urinary disorders	Haematuria	1.5	1.3
GI disorders	GI Haemorrhage[a]	1.5	1.0
	Retroperitoneal haemorrhage	0.3	0.2
	Rectal haemorrhage	0.6	0.3
	Gingival bleeding	0.5	0.6
	Haematochezia	0.5	0.4
Eye disorders	Eye haemorrhage	0.2	0.1

[a]Approximately 50% of patients experiencing GI bleeding had GI pathology.

Other Clinical Studies

In a clinical study of NSTEMI (the ACCOAST study) patients given a 30 mg loading dose of prasugrel a median of approximately 4 hours prior to coronary angiography followed by 30 mg of prasugrel at the time of PCI had an increased risk of non-CABG peri-procedural bleeding compared to patients receiving a prasugrel loading dose of 60 mg at the time of PCI (see **Precautions** and **Dosage and Administration**).

Other Adverse Events

In TRITON, common and other important non-haemorrhagic adverse events for prasugrel and clopidogrel respectively were: severe thrombocytopenia (0.06%, 0.04%), anaemia (2.2%,2.0%), abnormal hepatic function (0.22%, 0.27%), allergic reactions (0.36%, 0.36%), angioedema (0.06%, 0.04%) and neoplasm (1.4%, 1.2%)[a,b]. Table 8 shows common non-haemorrhagic adverse events reported by at least 2.5% of patients.
[a] when colorectal neoplasms are excluded, reporting rates are 1.1% and 1.0% for prasugrel and clopidogrel respectively. In each treatment group, the evaluation of GI bleeding or anaemia led to the diagnosis in 80% of colorectal cancers. The diagnosis of colorectal cancers is related to GI bleeding in TRITON-TIMI 38.
[b] newly diagnosed only

Table 8: Common Non-Haemorrhagic Adverse Events reported by at least 2.5% of patients in either group in TRITON

MedDRA Preferred Term	Prasugrel (%) (N=6741)	Clopidogrel (%) (N=6716)
Hypertension	7.5	7.1
Hypercholesterolemia/Hyperlipidemia	7.0	7.4
Headache	5.5	5.3
Back Pain	5.0	4.5
Dyspnoea	4.9	4.5
Nausea	4.6	4.3
Dizziness	4.1	4.6
Cough	3.9	4.1
Hypotension	3.9	3.8
Fatigue	3.7	4.8
Non-cardiac chest pain	3.1	3.5
Atrial fibrillation	2.9	3.1
Bradycardia	2.9	2.4
Leukopenia (<4 x 10^9 WBC/L)	2.8	3.5
Rash	2.8	2.4
Pyrexia	2.7	2.2
Peripheral oedema	2.7	3.0
Pain in extremity	2.6	2.6
Diarrhoea	2.3	2.6

Spontaneous Data

Blood and lymphatic system disorders: Very rare (<0.01%): Thrombotic thrombocytopenic purpura (TTP) (see **Precautions**).
Immune system disorders: Rare (>0.01% and <0.1%): Hypersensitivity including angioedema (see **Precautions**).

DOSAGE AND ADMINISTRATION

General

Use in Adults (≥ 18 years)
EFFIENT should be initiated with a single 60 mg loading dose (LD) and then continued at a 10 mg once daily dose maintenance dose (MD). In NSTEMI patients, the loading dose should generally be given at the time of PCI (see **Precautions** and **Adverse Effects**). Patients taking prasugrel should also take aspirin (75 mg to 325 mg) daily.

EFFIENT may be taken with or without food (see **Pharmacology**).

Use in Elderly (≥ 75 years)
EFFIENT is generally not recommended in patients ≥75 years of age (see **Precautions**). EFFIENT should be given as a single 60 mg LD and consideration may be given to a 5 mg once daily maintenance dose. The 10 mg MD is not recommended. The evidence for the 5 mg dose is based on pharmacodynamic/pharmacokinetic analyses only and no clinical data currently exist on the safety and efficacy of this dose.

Patients Weighing <60 kg
EFFIENT should be given as a single 60 mg LD and then continued at a 5 mg once daily maintenance dose. The 10 mg MD is not recommended. The evidence for the 5 mg dose is based on pharmacodynamic/pharmacokinetic analyses only and no clinical data currently exist on the safety and efficacy of this dose (see **Precautions**).

Use in Children and Adolescents
The safety and efficacy of prasugrel has not been established in paediatric patients.

Use in Renal Impairment
No dosage adjustment is necessary for patients with renal impairment; including patients with end stage renal disease (ESRD). As ESRD significantly impacts both the AUC and C_{max} of the active metabolite of prasugrel, the use of prasugrel needs to be closely monitored in this class of patient (see **Pharmacokinetics – Special Populations**).

Use in Hepatic Impairment
No dosage adjustment is necessary in patients with mild to moderate hepatic impairment (Child Pugh Class A and B). The pharmacokinetics and pharmacodynamics of prasugrel in patients with severe hepatic disease (Child-Pugh Class C) have not been studied (see **Contraindications, Precautions and Pharmacokinetics – Special Populations**).

Use in Asian Populations
No dosage adjustment is necessary based on ethnicity alone. In clinical pharmacology studies the AUC of the active metabolite of prasugrel was higher in Chinese, Japanese, and Korean subjects compared to Caucasian subjects. Therapeutic experience with prasugrel is limited in Asian patients therefore; the use of prasugrel needs to be closely monitored in these patients (see **Pharmacokinetics – Special Populations**).

OVERDOSAGE

Overdose following prasugrel administration may lead to prolonged bleeding time and subsequent bleeding complications. In rats, lethality was observed only after administration of the very high dose of 2000 mg/kg. Symptoms of acute toxicity in dogs included emesis, increased serum alkaline phosphatase, and hepatocellular atrophy. Symptoms of acute toxicity in rats included mydriasis, irregular respiration, decreased locomotor activity, ptosis, staggering gait, and lacrimation. Consistent with known pharmacologic activity, platelet aggregation was inhibited in dogs.

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 at the discretion of the treating physician.

In case of overdose, immediately contact the Poisons Information Centre (in Australia, call 13 11 26; in New Zealand call 0800 764 766) for advice.

PRESENTATION AND STORAGE CONDITIONS

Film coated tablets containing 5 mg or 10 mg prasugrel (as hydrochloride) are supplied in blister packs of 6 and 28.

10 mg tablets are beige, double arrow-shaped, not scored and debossed with "10 MG" on one side and with "4759" on the other side.

5 mg tablets are yellow, double arrow-shaped, not scored and debossed with "5 MG" on one side and "4760" on the other side.

Storage

Store below 30°C. Store in the original package. Do not crush or break the tablet.

NAME AND ADDRESS OF SPONSOR

Eli Lilly Australia Pty. Limited,
112 Wharf Road, West Ryde, NSW 2114 AUSTRALIA

Eli Lilly and Company (NZ) Limited Level 1, 123 Ormiston Road Botany South Auckland 2016 NEW ZEALAND Telephone (NZ): 0800 500 056

POISON SCHEDULE OF THE MEDICINE

S4 – Prescription only medicine

EFFIENT® is a registered trademark of Eli Lilly and Company.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS

11 JUNE 2009

DATE OF MOST RECENT AMENDMENT

27 September 2013

AUEFF0031511 ELD282. 11/13. GHG.

Effient® (prasugrel) tablets

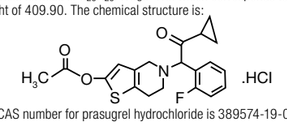
NAME OF THE MEDICINE

EFFIENT® (prasugrel hydrochloride)

The active ingredient is prasugrel hydrochloride.

DESCRIPTION

Prasugrel, an adenosine diphosphate (ADP) receptor antagonist of the thienopyridine class, is a potent inhibitor of platelet activation and aggregation mediated by the $P2Y_{12}$ ADP receptor. Chemically, prasugrel hydrochloride is (±)-2-[2-acetyloxy-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl]-1-cyclopropyl-2-(2-fluorophenyl)ethanone hydrochloride. The empirical formula is $C_{20}H_{20}FNO_3S$•HCl which corresponds to a molecular weight of 409.90. The chemical structure is:



The CAS number for prasugrel hydrochloride is 389574-19-0.

It is a white to light brown solid. Prasugrel hydrochloride is soluble at pH 2, slightly soluble at pH 3 to 4, and practically insoluble at pH 6 to 7.5. It also dissolves freely in methanol and is slightly soluble in 1- and 2-propanol and acetone. It is practically insoluble in diethyl ether and ethyl acetate.

Prasugrel is available for oral administration as a 5 mg or 10 mg double-arrow shaped, film-coated, not scored tablet, debossed on each side. Each beige 10 mg tablet is manufactured with 10.98 mg prasugrel hydrochloride, equivalent to 10 mg of prasugrel and each yellow 5 mg tablet with 5.49 mg prasugrel hydrochloride, equivalent to 5 mg of prasugrel. Other ingredients include mannitol, hypromellose, croscarmellose sodium, cellulose - microcrystalline, and vegetable magnesium stearate. The colour coatings contain lactose, hypromellose, titanium dioxide, glycerol triacetate, iron oxide yellow CI77492, and iron oxide red CI77491.

PHARMACOLOGY

Mechanism of Action

Prasugrel is an inhibitor of platelet activation and aggregation through the irreversible binding of its active metabolite to the $P2Y_{12}$ class of ADP receptors on platelets. A variety of drugs that inhibit platelet function have been shown to decrease morbid events in people with established atherosclerotic disease. 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 death and the rate of ischaemic cardiovascular events such as myocardial infarction or stroke.

Pharmacodynamics

Inhibition of platelet aggregation (IPA) induced by 5 or 20 µM ADP (termed "platelet inhibition" in the remainder of this document) measured by light transmission aggregometry has been assessed in clinical pharmacology studies in healthy subjects and patients with stable atherosclerosis for both prasugrel and clopidogrel with or without aspirin. Following a 60 mg loading dose (LD) of prasugrel, IPA occurs at 15 minutes for 5 µM ADP and 30 minutes for 20 µM ADP (see Figure 1). This rapid onset of action is a result of the rapid biotransformation of prasugrel to its active metabolite which is responsible for the IPA.

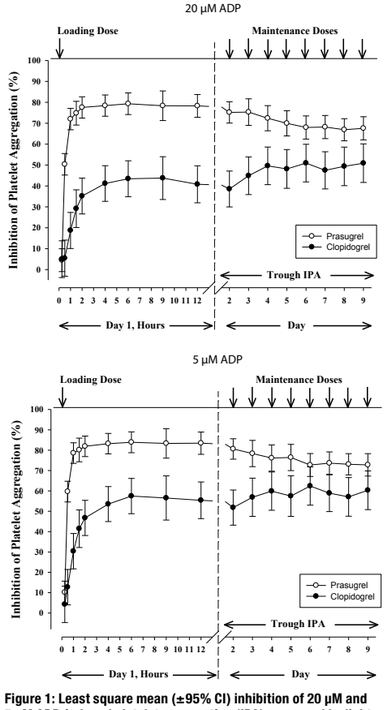


Figure 1: Least square mean (±95% CI) inhibition of 20 µM and 5 µM ADP-induced platelet aggregation (IPA) measured by light transmission aggregometry after prasugrel 60 mg/10 mg (○) LD and maintenance dose (MD) and clopidogrel 300 mg/75 mg (•), respectively. Arrows (↓) indicate day of dose administration.

The mean maximum IPA after a 60 mg LD of prasugrel was 79% and 83%, respectively for 20 µM and 5 µM ADP, with at least 89% of all healthy subjects and patients with stable atherosclerosis achieving at least 50% IPA by 1 hour for both ADP concentrations. Prasugrel-mediated IPA exhibits low between-subject (9%) and within-subject (12%) variability with both 5 µM and 20 µM ADP.

Mean steady state IPA was 69% and 74%, respectively for 20 µM and 5 µM ADP, and was achieved following 3 to 5 days of 10 mg maintenance dosing with a preceding LD of prasugrel. Greater than 98% of subjects had ≥20% IPA during maintenance dosing. The extent of IPA is dependent on the dose of prasugrel and exposure to the active metabolite.

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

Pharmacokinetics

Prasugrel is a prodrug and is rapidly metabolised to a pharmacologically 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 (PCI).

Absorption

Following oral administration, ≥79% of the dose is absorbed. The absorption and metabolism are rapid, with peak plasma concentrations (C_{max}) of the active metabolite occurring approximately 30 minutes after dosing. The active metabolite's exposure (AUC) increases proportionally over the therapeutic dose range. In a study of healthy subjects, AUC of the active metabolite was unaffected by a high fat, high calorie meal, but C_{max} was decreased by 49% and the time to reach C_{max} (T_{max}) was increased from 0.5 to 1.5 hours. Prasugrel was administered without regard to food in the large Phase 3 clinical trial. Therefore, EFFIENT can be administered without regard to food.

Distribution

In a sodium phosphate buffer (pH 7.4), active metabolite binding to 4% human serum albumin was 98%. Prasugrel metabolites have limited penetration into red blood cells.

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 Acute Coronary Syndromes (ACS) receiving EFFIENT, there was no relevant effect of genetic variation in CYP3A, CYP2B6, CYP2C9, or CYP2C19 on the pharmacokinetics of prasugrel or its IPA.

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).

In healthy subjects, patients with stable atherosclerosis, and patients with ACS receiving prasugrel, there was no relevant effect of genetic variation in CYP3A5, CYP2B6, CYP2C9, or CYP2C19 on the pharmacokinetics of prasugrel or its IPA.

Special Populations

Elderly

In a study of 32 healthy subjects between the ages of 20 and 80 years, age had no significant effect on pharmacokinetics of prasugrel or its IPA. 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 patients <75 years of age (See **Dosage and Administration, Precautions** and **Adverse Events**).

Paediatric

Pharmacokinetics and pharmacodynamics of prasugrel have not been evaluated in a paediatric population (see **Dosage and Administration**).

Gender and Ethnicity

In healthy subjects and patients, the pharmacokinetics of prasugrel are similar in men and women.

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 Caucasian subjects. 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.

Body Weight

The mean exposure (AUC) of the active metabolite is approximately 30 to 40% higher in healthy subjects with a body weight of <60 kg (132 pounds) and patients with a body weight of <60 kg compared to those weighing ≥60 kg (see **Dosage and Administration, Precautions** and **Adverse Effects**).

Smoking

Pharmacokinetics of prasugrel are similar in smokers and non-smokers.

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 IPA are similar in patients with moderate renal impairment (CrCL=30 to 50 mL/min) and healthy subjects. Prasugrel-mediated IPA 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.

Hepatic Impairment

Pharmacokinetics of prasugrel and its IPA were similar in patients with mild to moderate hepatic impairment (Child-Pugh Class A and B) compared to healthy subjects. No dose adjustment is thus necessary for these patients.

Pharmacokinetics and pharmacodynamics of prasugrel in patients with severe hepatic disease have not been studied. Prasugrel should not be used in patients with severe hepatic disease due to the potential risk of bleeding in this population (see **Contraindications** and **Precautions**).

CLINICAL TRIALS

TRITON Study

The clinical evidence for the efficacy of prasugrel is derived from a large Phase 3 clinical trial (the TRITON study), comparing prasugrel to clopidogrel, with both given in combination with aspirin and other standard therapy.

The TRITON study was a 13,608-patient, multicenter, international, randomised, double-blind, double dummy and parallel-group study. The patients randomised had Acute Coronary Syndrome (ACS) with moderate to high risk unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI), or ST-segment elevation myocardial infarction (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 coronary angiography. Patients with STEMI within 12 hours of symptoms and planned for primary PCI could be randomised prior to coronary angiography. For all patients, the loading dose (LD) could be administered anytime between randomisation and 1 hour after the patient left the catheterisation lab. If patients with STEMI were treated with thrombolytic therapy, randomisation could not occur until after 24 hours for fibrin specific lytic therapy or 48 hours for nonfibrin specific lytic therapy.

Patients were randomised to receive prasugrel (60 mg LD followed by 10 mg once daily) or clopidogrel (300 mg LD followed by 75 mg once daily) and were to be followed for a maximum of 15 months and a minimum of 6 months (actual median 14.5 months). Patients also received aspirin (75 mg to 325 mg once daily). 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) and 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 was the composite of cardiovascular (CV) death, nonfatal MI, or nonfatal stroke. Analysis of the composite endpoint in the all ACS population (combined UA/NSTEMI and STEMI cohorts) was contingent upon showing statistical superiority of prasugrel versus clopidogrel in the UA/NSTEMI cohort (p<0.05).

Analysis of the All ACS Population

In TRITON, prasugrel showed superior efficacy compared to clopidogrel in reducing the primary composite outcome events and the pre-specified secondary outcome events, including stent thrombosis (see Table 1). The superior efficacy was accompanied by an increase in major bleeding (see **Precautions** and **Adverse Effects**).

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 drugs, beta-blockers, and angiotensin converting enzyme inhibitors. The efficacy of prasugrel was independent of aspirin dose (75 mg to 325 mg once daily). The use of oral anticoagulants, non-study antiplatelet drugs, and chronic NSAIDs was not allowed in TRITON.

Table 1: Patients with Outcome Events in TRITON Primary Analysis (All ACS Population)

Outcome Events	Prasugrel (+aspirin) (N=6813) (%)	Clopidogrel (+aspirin) (N=6795) (%)	Relative Risk Reduction (%)[a] (95% CI)	Absolute Risk Reduction (%)	Hazard Ratio (95% CI)	p-value
Primary Outcome Events						
Primary Composite Outcome Events CV death, nonfatal MI, or nonfatal stroke	9.4	11.5	18.8 (9.8, 26.8)	2.1	0.812 (0.732, 0.902)	<0.001
Primary Individual Outcome Events CV death	2.0	2.2	11.4 (-11.8, 29.9)	0.2	0.886 (0.701, 1.118)	0.307
Nonfatal MI	7.0	9.1	24.3 (14.7, 32.8)	2.1	0.757 (0.672, 0.853)	<0.001
Nonfatal stroke	0.9	0.9	-1.6 (-45.1, 28.8)	0	1.016 (0.715, 1.451)	0.930
Secondary Outcome Events						
CV death, nonfatal MI, or nonfatal stroke through 90 days	6.8	8.4	20.3 (9.9, 29.5)	1.6	0.797 (0.705, 0.901)	<0.001
CV death, nonfatal MI, or nonfatal stroke through 30 days	5.7	7.4	23.3 (12.4, 32.8)	1.7	0.767 (0.672, 0.876)	<0.001
CV death, nonfatal MI, or urgent target vessel revascularisation (UTVR) through 90 days	6.9	8.7	20.6 (10.4, 29.7)	1.8	0.794 (0.703, 0.896)	<0.001
CV death, nonfatal MI, or UTVR through 30 days	5.9	7.4	21.6 (10.6, 31.2)	1.5	0.784 (0.688, 0.894)	<0.001
All cause death, nonfatal MI, or nonfatal stroke through study end	10.2	12.1	16.9 (8.1, 24.9)	1.9	0.831 (0.751, 0.919)	<0.001
CV death, nonfatal MI, nonfatal stroke, or rehospitalisation for cardiac ischaemic event through study end	11.7	13.8	16.2 (7.9, 23.8)	2.1	0.838 (0.762, 0.921)	<0.001
Definite or probable stent thrombosis through study end[b]	0.9	1.8	50.2 (31.7, 63.6)	0.9	0.494 (0.361, 0.677)	<0.001

[a] Values with a negative Relative Risk Reduction indicate a relative risk increase.
[b] N=6422 for prasugrel and N=6422 for clopidogrel.

The Kaplan-Meier curve shows the primary composite endpoint of CV death, nonfatal MI, or nonfatal stroke over time in the all ACS population (see Figure 2). The all ACS event curves separated as early as 3 days and continued to diverge over the 15 month follow-up period. Prasugrel demonstrated a relative risk reduction of 18% and an absolute risk reduction of 0.9% in the primary composite endpoint from 0-3 days (4.7% in the prasugrel group and 5.6% in the clopidogrel group; HR 0.825; 95% CI, 0.711, 0.957; p=0.011). Prasugrel demonstrated a relative risk reduction of 20% and an absolute risk reduction of 1.2% in the primary composite endpoint from 3 days to the end of the study (5.2% in the prasugrel group and 6.4% in the clopidogrel group; HR 0.805; 95% CI, 0.698, 0.927; p=0.003). Primary individual outcome events showed an absolute risk reduction of 2.1% and relative risk reduction of 24.3% in nonfatal MI with prasugrel compared to clopidogrel. A 0.2% absolute risk reduction and 11.4% relative risk reduction in CV death was seen in the prasugrel group compared to clopidogrel while for nonfatal stroke, there was no difference between the prasugrel and clopidogrel treated groups (see Table 1).

Incidence of non-CABG-related major bleeding, including life threatening and fatal, as well as TIMI minor bleeding was higher in prasugrel-treated patients compared to clopidogrel-treated patients (4.5% for prasugrel and 3.4% for clopidogrel; HR 1.314; 95% CI, 1.107, 1.559; p=0.002). In the prasugrel group, the incidence of fatal bleeding was 0.3% compared to 0.1% in clopidogrel-treated patients (HR 4.664; 95% CI, 1.341, 16.230; p=0.008). Study drug discontinuation due to bleeding events was 2.5% in the prasugrel arm and 1.4% for clopidogrel (OR 1.872; 95% CI, 1.448, 2.421; p<0.001) (see **Adverse Effects**).

Prasugrel demonstrated a relative risk reduction of 50.2% and an absolute risk reduction of 0.9% in stent thrombosis through the 15 month follow-up period (see Table 2). The reduction in stent thrombosis with prasugrel was observed both early and beyond 30 days for both bare metal and drug eluting stents.

Table 2: Patients with Definite or Probable Stent Thrombosis in the TRITON study

	Prasugrel (+ aspirin) (%)	Clopidogrel (+ aspirin) (%)	Relative Risk Reduction (%) (95% CI)	Absolute Risk Reduction (%)	p-value
UA/NSTEMI	N=4798	N=4789			
Definite or probable stent thrombosis	0.8	1. 7	50.2 (26.8, 66.1)	0.9	<0.001
STEMI	N=1624	N=1633			
Definite or probable stent thrombosis	1.2	2. 5	50.2 (13.5, 71.3)	1.3	0.011
All ACS	N=6422	N=6422			
Definite or probable stent thrombosis	0.9	1.8	50.2 (31.7, 63.6)	0.9	<0.001

For patients who survived an on-study stroke or myocardial infarction, prasugrel-treated patients demonstrated a relative risk reduction of 33% and an absolute risk reduction of 4.1% in the incidence of subsequent primary endpoint events compared to clopidogrel-treated patients (7.8% for prasugrel and 11.9% for clopidogrel, HR 0.67; 95% CI, 0.45, 0.98, p=0.037). An analysis of the composite endpoint of death from any cause, nonfatal MI, nonfatal stroke, or non-Coronary Artery Bypass Graft (CABG)-related TIMI major haemorrhage favoured prasugrel compared to clopidogrel (11.5% in the prasugrel group and 13.1% in the clopidogrel group; HR, 0.87; 95% CI, 0.79 to 0.95; p=0.004). In TRITON, for every 1000 patients treated with prasugrel, there were 22 fewer patients with MI, and 5 more with non–CABG-related TIMI major haemorrhages, compared with patients treated with clopidogrel.

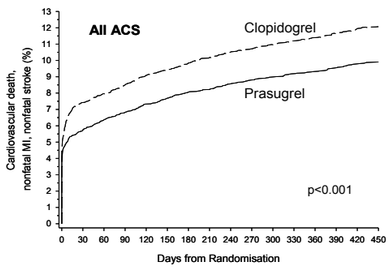


Figure 2: Primary Endpoint for the All ACS Population.

Analyses were performed to assess the effect of demographics, baseline characteristics, and medical history on the incidence of the primary endpoint of CV death, nonfatal MI, or nonfatal stroke by patients randomised to prasugrel or clopidogrel. The treatment benefit associated with prasugrel was preserved across the major pre-specified subgroups in all 3 populations (UA/NSTEMI, STEMI and All ACS) as shown in Figure 3.

Analysis of Patients with Diabetes

Patients with diabetes treated with prasugrel had a greater treatment benefit with respect to the primary composite efficacy endpoint when compared to those with diabetes treated with clopidogrel. In the All ACS population, the relative risk reduction with prasugrel compared to clopidogrel in 3146 patients with diabetes was 11.42% versus 15.80%; (HR=0.705; 95% CI, 0.582, 0.854; p<.001) while for patients without diabetes (N=10462) it was 8.84% versus 10.20%; (HR=0.861; 95% CI, 0.761, 0.976; p=.019). A similar pattern was seen for the UA/NSTEMI and STEMI populations. There were also reductions in Urgent Target Vessel Revascularistion (UTVR) and stent thrombosis in patients with diabetes treated with prasugrel.

The incidence of TIMI major or minor bleeding was similar in patients with and without diabetes. TIMI major or minor bleeding in patients with diabetes treated with prasugrel was 4.9% compared to 3.8% with clopidogrel (HR 1.297; 95% CI, 0.923, 1.822; p=0.133) and for patients without diabetes, TIMI major or minor bleeding was 4.4% for prasugrel and 3.3% with clopidogrel (HR 1.320; 95% CI, 1.083, 1.609; p=0.006).

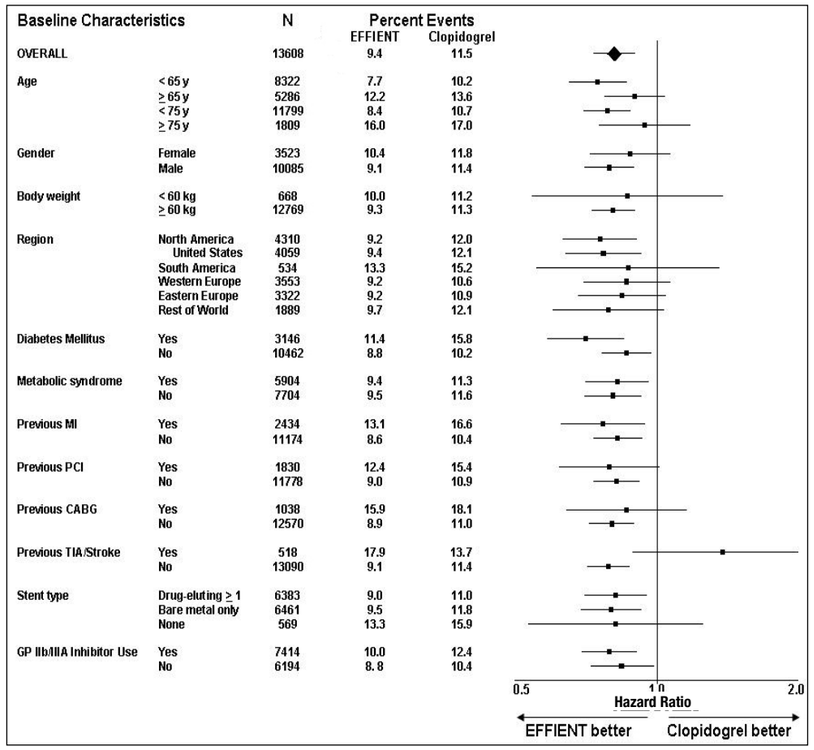


Figure 3: Hazard Ratio (95% CI) for Composite CV Death, Nonfatal MI, or Nonfatal Stroke in the TRITON Study for All ACS.

Analysis of Patients According to Age

In the All ACS population, the event rate with prasugrel compared to clopidogrel for patients aged <75 years was 8.44% versus 10.65%; (HR=0.784; 95% CI, 0.687, 0.881; p<.001) while for patients aged ≥75 years it was 15.98% versus 16.96%; (HR=0.940; 95% CI 0.749, 1.181; p=.596). Similar results were seen in the UA/NSTEMI and STEMI populations.

In the elderly (≥75 years of age) there was an increased risk of non-CABG related bleeding compared to patients <75 years of age, including an increased risk of both life-threatening and fatal bleeding. Life-threatening bleeding in patients <75 years treated with prasugrel was 1.06% (0.2% fatal) compared to 0.72% (0.1% fatal) with clopidogrel (HR=1.475; 95% CI, 0.997, 2.182; p=0.051) and for patients ≥75 years of age it was 2.58% (1.0% fatal) with prasugrel versus 1.57% (0.1% fatal) with clopidogrel (HR=1.694; 95% CI, 0.870, 3.298); p=0.117) (see **Precautions** and **Adverse Effects**). Patients ≥75 years of age also had a higher rate of stroke with prasugrel compared to clopidogrel (2.89% versus 1.43%; HR 2.117; 95% CI, 1.087, 4.125; p=0.024) while for patients aged <75 years the rate of stroke was 0.83% with prasugrel and 0.99% with clopidogrel (HR 0.841; 95% CI, 0.575, 1.230; p=0.371).

Analysis of Patients by Body Weight

In the All ACS population, the event rate with prasugrel compared to clopidogrel for patients with body weight ≥60 kg was 8.6% versus 10.7%; (HR=0.80; 95% CI, 0.71, 0.90; p<0.001) while for patients with body weight <60 kg it was 14.4% versus 16.4%; (HR=0.860; 95% CI, 0.66, 1.121; p=0.255). In patients with low body weight (<60 kg) there was an increased risk of non-CABG related bleeding compared to patients ≥60 kg (see **Precautions** and **Adverse Effects**).

Analysis of Patients with Prior TIA/Stroke

In the All ACS population, there was an increase in the incidence of the primary composite endpoint with prasugrel compared to clopidogrel in patients with prior TIA or stroke (17.94% versus 13.67%; HR=1.375; p=0.153). This was primarily due to an increase in all stroke in patients with prior TIA or stroke randomised to prasugrel compared to clopidogrel (6.49% versus 1.17%; HR=5.643; p=0.002). There was also an increased risk of non-CABG related bleeding in patients with a history of prior TIA or stroke compared to those not in this population (see **Contraindications** and **Adverse Effects**).

Analysis of the UA/NSTEMI and STEMI Populations

As shown in Table 3, prasugrel reduced the occurrence of the primary composite endpoint compared to clopidogrel in both the UA/NSTEMI and STEMI populations.

Table 3: Patients with Outcome Events in TRITON (UA/NSTEMI and STEMI)

	Prasugrel (+ aspirin)[a] (%)	Clopidogrel (+ aspirin)[a] (%)	Relative Risk Reduction (%) (95% CI)	Absolute Risk Reduction (%)	p-value
UA/NSTEMI	N=5044	N=5030			
CV death, nonfatal MI, or nonfatal stroke	9.3	11.2	18.0 (7.3, 27.4)	1.9	0.002
STEMI	N=1769	N=1765			
CV death, nonfatal MI, or nonfatal stroke	9.8	12.2	20.7 (3.2, 35.1)	2.4	0.019

[a]Other standard therapies were used as appropriate. The TRITON protocol provided for all patients to receive aspirin.

The secondary endpoint data for the UA/NSTEMI and STEMI populations are similar to those for the all ACS population.

The Kaplan-Meier curves show the primary composite endpoint of CV death, nonfatal MI, or nonfatal stroke over time (see Figures 4 and 5) in the UA/NSTEMI population and the STEMI population. The UA/NSTEMI event curve (see Figure 4) separated as early as 3 days and continued to diverge over the 15 month follow-up period. The STEMI event curve (see Figure 5) separated as early as 3 days and remained separate over the 15 month follow-up period.

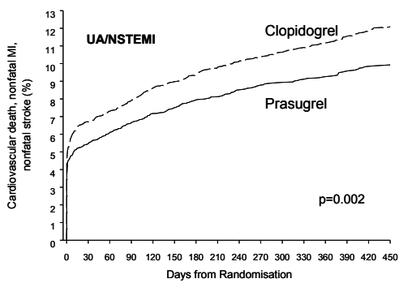


Figure 4: Cumulative Event Rate for Composite CV Death, Nonfatal MI, or Nonfatal Stroke in the TRITON Study in the UA/NSTEMI Population.

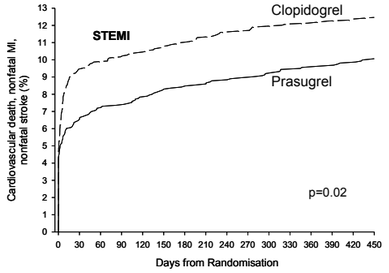


Figure 5: Cumulative Event Rate for Composite CV Death, Nonfatal MI, or Nonfatal Stroke in the TRITON Study in the STEMI Population.

INDICATIONS

EFFIENT, co-administered with aspirin, is indicated for the prevention of atherothrombotic events (myocardial infarction, stroke and cardiovascular death) in patients with acute coronary syndromes (moderate to high risk unstable angina (UA), non ST-segment elevation myocardial infarction (NSTEMI) or ST-segment elevation myocardial infarction (STEMI)) who are to undergo percutaneous coronary intervention (PCI).

CONTRAINDICATIONS

EFFIENT is contraindicated in patients with:
- active pathological bleeding;
- a known history of transient ischaemic attack (TIA) or stroke;
- severe hepatic impairment (Child-Pugh Class C);
- a known hypersensitivity or allergy to any ingredient of the product.

PRECAUTIONS

Prior TIA or Stroke

In the Phase 3 clinical trial, prasugrel-treated patients with a history of TIA or a history of ischaemic stroke more than 3 months prior to drug therapy had a higher rate of the primary composite endpoint, including ischaemic or haemorrhagic stroke compared to clopidogrel. The rate of TIMI major or minor bleeding was also increased in these patients compared to patients without a history of TIA or stroke. Patients with a history of ischaemic stroke within 3 months of drug therapy or haemorrhagic stroke were excluded from the Phase 3 clinical trial (see **Adverse Effects** and **Clinical Trials**).

Prasugrel has not been studied without aspirin in patients with prior history of TIA or stroke.

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 prasugrel showed an increased risk of major and minor bleeding according to the TIMI classification system. Therefore use of prasugrel in patients at increased risk of bleeding should only be considered when the benefits in terms of prevention of ischaemic events are deemed to outweigh the risk of serious bleeding. In particular, caution is necessary in patients:

- ≥75 years of age. In the Phase 3 clinical trial patients ≥75 years of age taking prasugrel were at a greater risk of bleeding, including fatal bleeding, compared to patients <75 years of age. A 5 mg maintenance dose (MD) should be considered for patients ≥75 years of age (see **Use in Elderly, Adverse Effects** and **Dosage and Administration**)
- with a propensity to bleed (e.g. due to recent trauma, recent surgery, recent or recurrent gastrointestinal (GI) bleeding, active peptic ulcer disease, severe hepatic impairment, severe renal impairment, or moderate to severe renal impairment)
- with body weight <60 kg. In these patients, a 5 mg MD is recommended (see **Body Weight, Adverse Effects** and **Dosage and Administration**)
- with concomitant administration of medications that may increase the risk of bleeding, including oral anticoagulants, non steroidal anti-inflammatory drugs (NSAIDs), and fibrinolytics

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

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

Bleeding Risk Associated with Timing of Loading Dose in NSTEMI

In a clinical trial of NSTEMI patients (the ACCOAST study), patients given a 30 mg loading dose of prasugrel a median of approximately 4 hours prior to coronary angiography followed by 30 mg at the time of PCI had an increased risk of major and minor peri-procedural bleeding and no additional benefit compared to patients receiving a loading dose of 60 mg at the time of PCI. Therefore in NSTEMI patients the 60 mg loading dose should generally be given at the time of PCI (see **Dosage and Administration**).

Use in Elderly

Of the total number of prasugrel-treated patients in TRITON, 38.5% were ≥65 years of age and 13.2% were ≥75 years of age. The event rate of the primary composite endpoint with prasugrel compared to clopidogrel for patients aged ≥75 years was 15.98% versus 16.96%; (HR=0.940; 95% CI, 0.749, 1.181; p=0.596). Individuals ≥75 years of age had an increased risk of TIMI major or minor bleeding (including life-threatening and fatal bleeding) due to greater sensitivity to bleeding and higher exposure to the active metabolite of prasugrel in patients ≥75 years of age compared to patients <75 years of age. There was also an increase in the incidence of stroke in patients ≥75 years compared to those <75 years of age. The use of prasugrel in patients ≥75 years of age is generally not recommended and should be used with caution only 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 bleeding. Consideration should be given to a 5 mg once daily MD, the 10 mg MD is not recommended for these patients (see **Dosage and Administration, Bleeding Risk, Adverse Effects and Pharmacology**).

Body Weight

Of the total number of prasugrel patients in the TRITON study, 4.6% had body weight <60 kg. Individuals with body weight <60 kg had an increased risk of TIMI major or minor bleeding and an increased exposure to the active metabolite of prasugrel. Prasugrel should be used 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 bleeding. For patients <60 kg, a 5 mg once daily MD should be used, the 10 mg MD is not recommended for these patients (see **Dosage and Administration, Bleeding Risk, Adverse Effects** and **Pharmacology**).

Surgery

Patients should be advised to inform physicians and dentists that they are taking prasugrel before any surgery is scheduled and before any new medicinal product is taken. If a patient is to undergo elective surgery and an antiplatelet effect is not desired, prasugrel should be discontinued at least 7 days prior to surgery. Increased frequency (3 fold) and severity of bleeding may occur in patients undergoing CABG surgery within 7 days of discontinuation of prasugrel. The benefits and risks of prasugrel should be carefully considered in patients in whom the coronary anatomy has not been defined and urgent CABG is a possibility.

Discontinuation of prasugrel

In patients with ACS who are managed with PCI, premature discontinuation of any antiplatelet medication, including prasugrel, could result in an increased risk of thrombosis, MI, or death. Patients who require premature discontinuation of prasugrel (e.g. secondary to active bleeding) should be monitored for cardiac events. Once the patient is stabilised, at the discretion of the patient's treating physician, restarting antiplatelet treatment may be considered.

Neoplasms

In TRITON, the incidence of newly diagnosed neoplasms was higher for prasugrel-treated patients compared to clopidogrel-treated patients (1.4% (94/6741) to 1.2% (80/6716) respectively, p=0.30). The higher incidence appeared to be related to a higher incidence of colorectal neoplasms (19 prasugrel vs 10 clopidogrel). This imbalance may have resulted from the more potent antiplatelet effect of prasugrel bringing more events to medical attention. The non-clinical studies were negative for carcinogenicity and tumour stimulation (see **Precautions – Carcinogenicity**). Bleeding in patients taking antiplatelet therapy warrants diagnostic investigation since it may unmask a previously unsuspected lesion (e.g. tumour, ulcer).

Thrombotic Thrombocytopenic Purpura (TTP)

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

Hypersensitivity

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.

Effects on Fertility

Animal studies did not indicate direct harmful effects with respect to fertility. Prasugrel had no effect on fertility of male or female rats at oral doses up to 300 mg/kg per day, corresponding to an active metabolite exposure (based on AUC) of approximately 1500 times that anticipated at the recommended human maintenance dose.

Use in Pregnancy

Pregnancy Category B1.

There are no adequate and well-controlled studies in pregnant women.

Because animal reproduction studies are not always predictive of a human response, prasugrel should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the foetus.

Embryo foetal developmental toxicology studies in rats and rabbits showed no evidence of malformations at doses corresponding to more than 100 times the active metabolite exposure anticipated in humans at the maintenance dose of 10 mg daily (based on AUC) of prasugrel. Only minor decreases in maternal body weight gain (3%) and offspring body weight (3 to 5%) were observed relative to controls. In prenatal and postnatal rat studies, a similar dose exposure had no effect on the behavioural or reproductive development of offspring.

Use in Lactation

There are no clinical studies in lactating women.

A study in rats has shown that prasugrel metabolites are excreted in the animals' milk. It is not known whether prasugrel is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the benefit of the drug to the nursing woman.

Carcinogenicity

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. Therefore, the increase in liver tumours with prasugrel administration in mice is not considered a relevant human risk.

Genotoxicity

Assays for gene mutations (Ames test) and chromosomal damage (Chinese Hamster Ovary cells in vitro, mouse micronucleus in vivo test) did not provide any evidence of a genotoxic potential for prasugrel.

Paediatric Use

Safety and effectiveness in paediatric patients has not been established (see **Pharmacology**).

Renal Impairment

No dosage adjustment is necessary for patients with renal impairment; including patients with end-stage renal diseasee (see **Dosage and Administration, Bleeding Risk** and **Pharmacology**).

Use in Hepatic Impairment

No dosage adjustment is necessary in patients with mild to moderate hepatic impairment (Child-Pugh Class A and B). The pharmacokinetics and pharmacodynamics of prasugrel in patients with severe hepatic disease have not been studied. Prasugrel should not be used in patients with severe hepatic disease due to the potential risk of bleeding in this population (see **Precautions and Pharmacology**).

Effects on Ability to Drive and Use Machines

No studies on 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.

Lactose

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

Interactions with Other Medicines

Prasugrel can be concomitantly administered with medicinal products metabolised by cytochrome P450 enzymes (including statins), or medicinal products that are inducers or inhibitors of cytochrome P450 enzymes. Prasugrel can also be concomitantly administered with ASA, heparin, digoxin, and medicinal products that elevate gastric pH, including proton pump inhibitors and H_2 blockers. Although not studied in specific interaction studies, prasugrel was co-administered in the Phase 3 clinical trial with low molecular weight heparin, bivalirudin, and GPIIb/IIIa inhibitors (no information is available regarding the type of GPIIb/IIIa inhibitor used) without evidence of clinically significant adverse interactions.

Potential for Other Drugs to Affect Prasugrel

Inhibitors of CYP3A:
Ketoconazole (400 mg daily), a selective and potent inhibitor of CYP3A4 and CYP3A5, did not affect prasugrel-mediated IPA or the active metabolite's AUC and T_{max}, but decreased the C_{max} by 34% to 46%. Therefore, CYP3A inhibitors such as verapamil, diltiazem, indinavir, ciprofloxacin, clarithromycin, 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 and its IPA. 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.

Drugs that Elevate Gastric pH:
Daily co-administration of ranitidine (an H_2 receptor blocker) or lansoprazole (a proton pump inhibitor) did not change the metabolite's AUC and T_{max}, but decreased the C_{max} by 14% and 29%, respectively. In the pivotal Phase 3 trial, prasugrel was administered without regard to co-administration of a proton pump inhibitor (PPI) or H_2 receptor blocker, and the reduction in the primary endpoint from 0-3 days was consistent for patients taking prasugrel with and without concomitant use of a PPI or H_2 receptor blocker.

Statins:
Atorvastatin (80 mg daily) did not alter the pharmacokinetics of prasugrel or its IPA. Therefore, statins that are substrates of CYP3A are not anticipated to have an effect on the pharmacokinetics of prasugrel or its IPA.

Heparin:
A single intravenous dose of unfractionated heparin (100 U/kg) did not significantly alter the prasugrel-mediated IPA. Likewise, prasugrel did not significantly alter the effect of heparin on measures of coagulation. An increased risk of bleeding is possible when prasugrel is co-administered with heparin.

Aspirin:
Aspirin (150 mg daily with an additional single 900 mg) did not alter prasugrel-mediated IPA. Although a pharmacodynamic interaction with aspirin leading to an increased risk of bleeding is possible, the demonstration of the efficacy and safety of prasugrel comes from patients concomitantly treated with aspirin.

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 and prasugrel should be co-administered with caution.

Clopidogrel:
Following administration of 75 mg clopidogrel daily for 10 days, healthy subjects were switched to 10 mg of prasugrel once daily, with or without a 60 mg LD. Throughout the study, all subjects were concurrently taking 81 mg of aspirin once daily. Higher IPA was observed with prasugrel compared to clopidogrel.

Potential for Prasugrel to Affect Other Drugs

Drugs Metabolised by CYP2C9 and CYP2C19:
Prasugrel did not inhibit CYP2C9 or CYP2C19, as it did not affect the pharmacokinetics of S-warfarin or R-warfarin. Because of the potential for increased risk of bleeding, warfarin and prasugrel should be co-administered with caution.

Drugs 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%, which is not considered to be clinically significant. 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).

Effect on Digoxin:
Prasugrel has no clinically significant effect on the pharmacokinetics of digoxin. When prasugrel was co-administered with digoxin, a substrate of P-glycoprotein transporter, the AUC of digoxin was not altered, while C_{max} decreased by 17%.

ADVERSE EFFECTS

During clinical development, 7681 patients with atherosclerosis with or without ACS who did or did not undergo PCI were exposed to prasugrel in 5 studies using clopidogrel as the comparator. Safety in patients with ACS undergoing PCI was evaluated in a clopidogrel-controlled study, TRITON, in which 6741 patients were treated with prasugrel (60 mg LD and 10 mg once daily MD) for a median of 14.5 months (5802 patients were treated for over 6 months; 4136 patients were treated for more than 1 year).