

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Effient safely and effectively. See full prescribing information for Effient.

EFFIENT (prasugrel) tablets

Initial U.S. Approval: 2009

### WARNING: BLEEDING RISK

See full prescribing information for complete boxed warning

Effient can cause significant, sometimes fatal, bleeding (5.1, 5.2, and 6.1).

Do not use Effient in patients with active pathological bleeding or a history of transient ischemic attack or stroke (4.1 and 4.2).

In patients  $\geq 75$  years of age, Effient is generally not recommended because of the increased risk of fatal and intracranial bleeding and uncertain benefit, except in high-risk patients (diabetes or prior MI), where its effect appears to be greater and its use may be considered (8.5).

Do not start Effient in patients likely to undergo urgent coronary artery bypass graft surgery (CABG). When possible, discontinue Effient at least 7 days prior to any surgery.

Additional risk factors for bleeding include:

- body weight  $< 60$  kg
- propensity to bleed
- concomitant use of medications that increase the risk of bleeding

Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, percutaneous coronary intervention (PCI), CABG, or other surgical procedures in the setting of Effient.

If possible, manage bleeding without discontinuing Effient. Stopping Effient, particularly in the first few weeks after acute coronary syndrome, increases the risk of subsequent cardiovascular events (5.3).

### INDICATIONS AND USAGE

Effient is a P2Y<sub>12</sub> platelet inhibitor indicated for the reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with acute coronary syndrome who are to be managed with PCI as follows:

- Patients with unstable angina or, non-ST-elevation myocardial infarction (NSTEMI) (1.1).
- Patients with ST-elevation myocardial infarction (STEMI) when managed with either primary or delayed PCI (1.1).

### DOSAGE AND ADMINISTRATION

- Initiate treatment with a single 60-mg oral loading dose (2).
- Continue at 10 mg once daily with or without food. Consider 5 mg once daily for patients  $< 60$  kg (2).
- Patients should also take aspirin (75 mg to 325 mg) daily (2).

### DOSAGE FORMS AND STRENGTHS

5 mg and 10 mg tablets (3)

### CONTRAINDICATIONS

- Active pathological bleeding (4.1)
- Prior transient ischemic attack or stroke (4.2)

### WARNINGS AND PRECAUTIONS

- CABG-related bleeding: Risk increases in patients receiving Effient who undergo CABG (5.2).
- Discontinuation of Effient: Premature discontinuation increases risk of stent thrombosis, MI, and death (5.3).

### ADVERSE REACTIONS

Bleeding, including life-threatening and fatal bleeding, is the most commonly reported adverse reaction (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-545-5979 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 04/2010

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## FULL PRESCRIBING INFORMATION

### WARNING: BLEEDING RISK

Effient can cause significant, sometimes fatal, bleeding [see *Warnings and Precautions (5.1 and 5.2) and Adverse Reactions (6.1)*].

Do not use Effient in patients with active pathological bleeding or a history of transient ischemic attack or stroke [see *Contraindications (4.1 and 4.2)*].

In patients  $\geq 75$  years of age, Effient is generally not recommended, because of the increased risk of fatal and intracranial bleeding and uncertain benefit, except in high-risk situations (patients with diabetes or a history of prior MI) where its effect appears to be greater and its use may be considered [see *Use in Specific Populations (8.5)*].

Do not start Effient in patients likely to undergo urgent coronary artery bypass graft surgery (CABG). When possible, discontinue Effient at least 7 days prior to any surgery.

Additional risk factors for bleeding include:

- body weight  $< 60$  kg
- propensity to bleed
- concomitant use of medications that increase the risk of bleeding (e.g., warfarin, heparin, fibrinolytic therapy, chronic use of non-steroidal anti-inflammatory drugs [NSAIDs])

Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, percutaneous coronary intervention (PCI), CABG, or other surgical procedures in the setting of Effient.

If possible, manage bleeding without discontinuing Effient. Discontinuing Effient, particularly in the first few weeks after acute coronary syndrome, increases the risk of subsequent cardiovascular events [see *Warnings and Precautions (5.3)*].

## 1 INDICATIONS AND USAGE

### 1.1 Acute Coronary Syndrome

Effient<sup>®</sup> is indicated to reduce the rate of thrombotic cardiovascular (CV) events (including stent thrombosis) in patients with acute coronary syndrome (ACS) who are to be managed with percutaneous coronary intervention (PCI) as follows:

- Patients with unstable angina (UA) or non-ST-elevation myocardial infarction (NSTEMI).
- Patients with ST-elevation myocardial infarction (STEMI) when managed with primary or delayed PCI.

Effient has been shown to reduce the rate of a combined endpoint of cardiovascular death, nonfatal myocardial infarction (MI), or nonfatal stroke compared to clopidogrel. The difference between treatments was driven predominantly by MI, with no difference on strokes and little difference on CV death [see *Clinical Studies (14)*].

It is generally recommended that antiplatelet therapy be administered promptly in the management of ACS because many cardiovascular events occur within hours of initial presentation. In the clinical trial that established the efficacy of Effient, Effient and the control drug were not administered to UA/NSTEMI patients until coronary anatomy was established. For the small fraction of patients that required urgent CABG after treatment with Effient, the risk of significant bleeding was substantial [see *Warnings and Precautions (5.2)*]. Because the large majority of patients are managed without CABG, however, treatment can be considered before determining coronary anatomy if need for CABG is considered unlikely. The advantages of earlier treatment with Effient must then be balanced against the increased rate of bleeding in patients who do need to undergo urgent CABG.

## 2 DOSAGE AND ADMINISTRATION

Initiate Effient treatment as a single 60-mg oral loading dose and then continue at 10 mg orally once daily. Patients taking Effient should also take aspirin (75 mg to 325 mg) daily [see *Drug Interactions (7) and Clinical Pharmacology (12.3)*]. Effient may be administered with or without food [see *Clinical Pharmacology (12.3) and Clinical Studies (14)*].

### Dosing in Low Weight Patients

Compared to patients weighing  $\geq 60$  kg, patients weighing  $< 60$  kg have an increased exposure to the active metabolite of prasugrel and an increased risk of bleeding on a 10 mg once daily maintenance dose. Consider lowering the maintenance dose to 5 mg in patients  $< 60$  kg. The effectiveness and safety of the 5 mg dose have not been prospectively studied.

## 3 DOSAGE FORMS AND STRENGTHS

Effient 5 mg is a yellow, elongated hexagonal, film-coated, non-scored tablet debossed with “5121” on one side and 3 parallel arched lines followed by a “5” on the other.

Effient 10 mg is a beige, elongated hexagonal, film-coated, non-scored tablet debossed with “5123” on one side and 3 parallel arched lines followed by a “10” on the other.

## 4 CONTRAINDICATIONS

### 4.1 Active Bleeding

Effient is contraindicated in patients with active pathological bleeding such as peptic ulcer or intracranial hemorrhage [see *Warnings and Precautions (5.1) and Adverse Reactions (6.1)*].

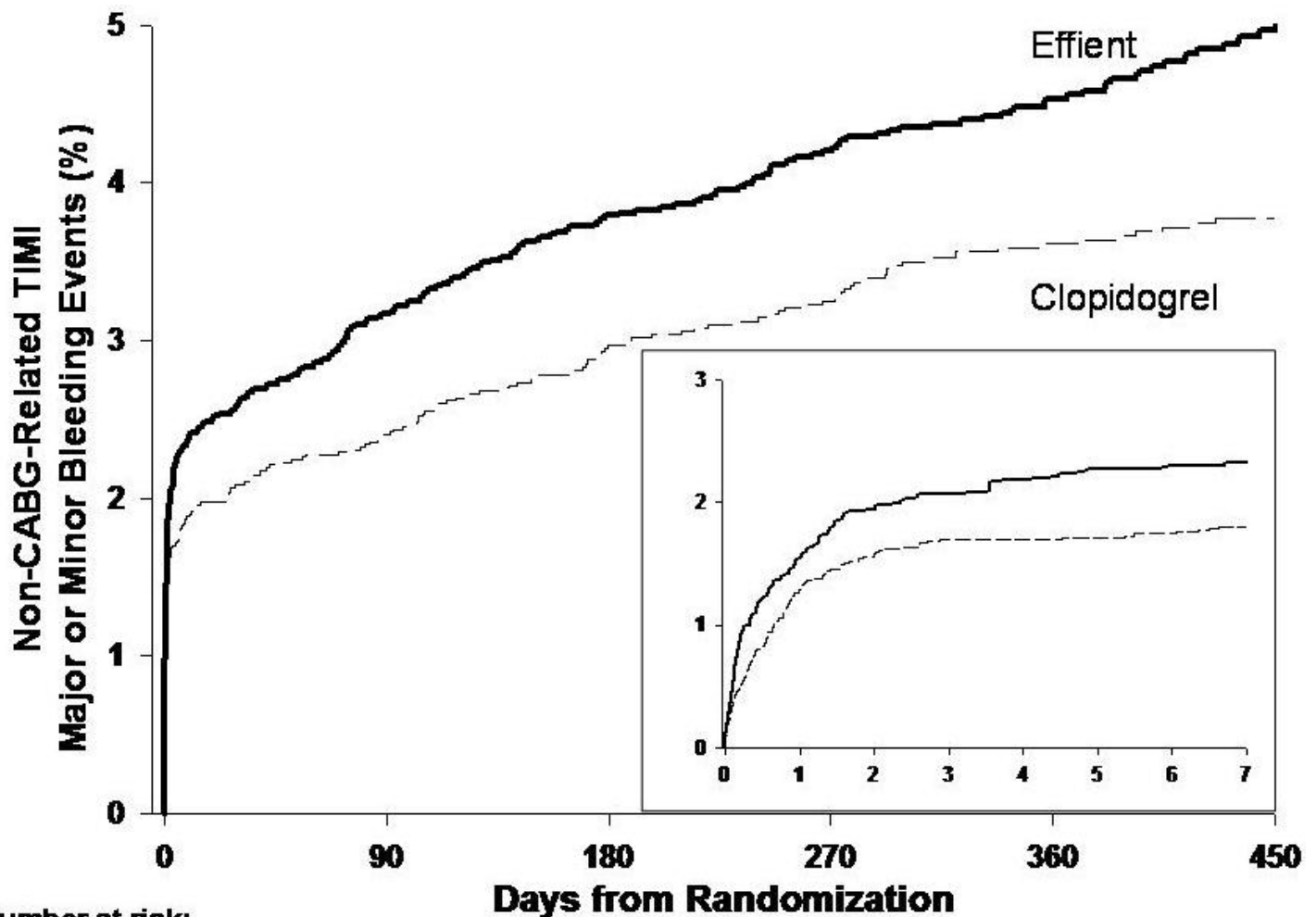
### 4.2 Prior Transient Ischemic Attack or Stroke

Effient is contraindicated in patients with a history of prior transient ischemic attack (TIA) or stroke. In TRITON-TIMI 38 (TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel), patients with a history of TIA or ischemic stroke (>3 months prior to enrollment) had a higher rate of stroke on Effient (6.5%; of which 4.2% were thrombotic stroke and 2.3% were intracranial hemorrhage [ICH]) than on clopidogrel (1.2%; all thrombotic). In patients without such a history, the incidence of stroke was 0.9% (0.2% ICH) and 1.0% (0.3% ICH) with Effient and clopidogrel, respectively. Patients with a history of ischemic stroke within 3 months of screening and patients with a history of hemorrhagic stroke at any time were excluded from TRITON-TIMI 38. Patients who experience a stroke or TIA while on Effient generally should have therapy discontinued [see Adverse Reactions (6.1) and Clinical Studies (14)].

**5 WARNINGS AND PRECAUTIONS**

**5.1 General Risk of Bleeding**

Thienopyridines, including Effient, increase the risk of bleeding. With the dosing regimens used in TRITON-TIMI 38, TIMI (Thrombolysis in Myocardial Infarction) Major (clinically overt bleeding associated with a fall in hemoglobin  $\geq 5$  g/dL, or intracranial hemorrhage) and TIMI Minor (overt bleeding associated with a fall in hemoglobin of  $\geq 3$  g/dL but  $< 5$  g/dL) bleeding events were more common on Effient than on clopidogrel [see Adverse Reactions (6.1)]. The bleeding risk is highest initially, as shown in Figure 1 (events through 450 days; inset shows events through 7 days).



Number at risk:						
Effient	6741	6042	5707	4813	4078	2747
Clopidogrel	6716	6023	5764	4883	4138	2792

Figure 1: Non-CABG-Related TIMI Major or Minor Bleeding Events.

Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, PCI, CABG, or other surgical procedures even if the patient does not have overt signs of bleeding.

Do not use Effient in patients with active bleeding, prior TIA or stroke [see Contraindications (4.1 and 4.2)].

Other risk factors for bleeding are:

- Age  $\geq 75$  years. Because of the risk of bleeding (including fatal bleeding) and uncertain effectiveness in patients  $\geq 75$  years of age, use of Effient is generally not recommended in these patients, except in high-risk situations (patients with diabetes

81 or history of myocardial infarction) where its effect appears to be greater and its use may be considered [see *Adverse*  
82 *Reactions (6.1), Use in Specific Populations (8.5), Clinical Pharmacology (12.3), and Clinical Trials (14)*].

- 83 • CABG or other surgical procedure [see *Warnings and Precautions (5.2)*].
- 84 • Body weight <60 kg. Consider a lower (5 mg) maintenance dose [see *Dosage and Administration (2), Adverse*  
85 *Reactions (6.1), Use in Specific Populations (8.6)*].
- 86 • Propensity to bleed (e.g., recent trauma, recent surgery, recent or recurrent gastrointestinal (GI) bleeding, active peptic  
87 ulcer disease, or severe hepatic impairment) [see *Adverse Reactions (6.1) and Use in Specific Populations (8.8)*].
- 88 • Medications that increase the risk of bleeding (e.g., oral anticoagulants, chronic use of non-steroidal anti-inflammatory  
89 drugs [NSAIDs], and fibrinolytic agents). Aspirin and heparin were commonly used in TRITON-TIMI 38 [see *Drug*  
90 *Interactions (7), Clinical Studies (14)*].

91 Thienopyridines inhibit platelet aggregation for the lifetime of the platelet (7-10 days), so withholding a dose will not be  
92 useful in managing a bleeding event or the risk of bleeding associated with an invasive procedure. Because the half-life of prasugrel's  
93 active metabolite is short relative to the lifetime of the platelet, it may be possible to restore hemostasis by administering exogenous  
94 platelets; however, platelet transfusions within 6 hours of the loading dose or 4 hours of the maintenance dose may be less effective.

## 95 **5.2 Coronary Artery Bypass Graft Surgery-Related Bleeding**

96 The risk of bleeding is increased in patients receiving Effient who undergo CABG. If possible, Effient should be discontinued  
97 at least 7 days prior to CABG.

98 Of the 437 patients who underwent CABG during TRITON-TIMI 38, the rates of CABG-related TIMI Major or Minor  
99 bleeding were 14.1% in the Effient group and 4.5% in the clopidogrel group [see *Adverse Reactions (6.1)*]. The higher risk for  
100 bleeding events in patients treated with Effient persisted up to 7 days from the most recent dose of study drug. For patients receiving a  
101 thienopyridine within 3 days prior to CABG, the frequencies of TIMI Major or Minor bleeding were 26.7% (12 of 45 patients) in the  
102 Effient group, compared with 5.0% (3 of 60 patients) in the clopidogrel group. For patients who received their last dose of  
103 thienopyridine within 4 to 7 days prior to CABG, the frequencies decreased to 11.3% (9 of 80 patients) in the prasugrel group and  
104 3.4% (3 of 89 patients) in the clopidogrel group.

105 Do not start Effient in patients likely to undergo urgent CABG. CABG-related bleeding may be treated with transfusion of  
106 blood products, including packed red blood cells and platelets; however, platelet transfusions within 6 hours of the loading dose or 4  
107 hours of the maintenance dose may be less effective.

## 108 **5.3 Discontinuation of Effient**

109 Discontinue thienopyridines, including Effient, for active bleeding, elective surgery, stroke, or TIA. The optimal duration of  
110 thienopyridine therapy is unknown. In patients who are managed with PCI and stent placement, premature discontinuation of any  
111 antiplatelet medication, including thienopyridines, conveys an increased risk of stent thrombosis, myocardial infarction, and death.  
112 Patients who require premature discontinuation of a thienopyridine will be at increased risk for cardiac events. Lapses in therapy  
113 should be avoided, and if thienopyridines must be temporarily discontinued because of an adverse event(s), they should be restarted as  
114 soon as possible [see *Contraindications (4.1 and 4.2) and Warnings and Precautions (5.1)*].

## 115 **5.4 Thrombotic Thrombocytopenic Purpura**

116 Thrombotic thrombocytopenic purpura (TTP) has been reported with the use of other thienopyridines, sometimes after a brief  
117 exposure (<2 weeks). TTP is a serious condition that can be fatal and requires urgent treatment, including plasmapheresis (plasma  
118 exchange). TTP is characterized by thrombocytopenia, microangiopathic hemolytic anemia (schistocytes [fragment red blood cells]  
119 seen on peripheral smear), neurological findings, renal dysfunction, and fever.

# 120 **6 ADVERSE REACTIONS**

## 121 **6.1 Clinical Trials Experience**

122 The following serious adverse reactions are also discussed elsewhere in the labeling:

- 123 • Bleeding [see *Boxed Warning and Warnings and Precautions (5.1, 5.2)*]
- 124 • Thrombotic thrombocytopenic purpura [see *Warnings and Precautions (5.4)*]

125 Safety in patients with ACS undergoing PCI was evaluated in a clopidogrel-controlled study, TRITON-TIMI 38, in which  
126 6741 patients were treated with Effient (60-mg loading dose and 10 mg once daily) for a median of 14.5 months (5802 patients were  
127 treated for over 6 months; 4136 patients were treated for more than 1 year). The population treated with Effient was 27 to 96 years of  
128 age, 25% female, and 92% Caucasian. All patients in the TRITON-TIMI 38 study were to receive aspirin. The dose of clopidogrel in  
129 this study was a 300-mg loading dose and 75 mg once daily.

130 Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials  
131 cannot be directly compared with the rates observed in other clinical trials of another drug and may not reflect the rates observed in  
132 practice.

### 133 Drug Discontinuation

134 The rate of study drug discontinuation because of adverse reactions was 7.2% for Effient and 6.3% for clopidogrel. Bleeding  
135 was the most common adverse reaction leading to study drug discontinuation for both drugs (2.5% for Effient and 1.4% for  
136 clopidogrel).

### 137 Bleeding

138 *Bleeding Unrelated to CABG Surgery* - In TRITON-TIMI 38, overall rates of TIMI Major or Minor bleeding adverse  
139 reactions unrelated to coronary artery bypass graft surgery (CABG) were significantly higher on Effient than on clopidogrel, as shown  
140 in Table 1.  
141  
142

**Table 1: Non-CABG-Related Bleeding<sup>a</sup> (TRITON-TIMI 38)**

	<b>Effient (%) (N=6741)</b>	<b>Clopidogrel (%) (N=6716)</b>	<b>p-value</b>
TIMI Major or Minor bleeding	4.5	3.4	p=0.002
TIMI Major bleeding <sup>b</sup>	2.2	1.7	p=0.029
Life-threatening	1.3	0.8	p=0.015
Fatal	0.3	0.1	
Symptomatic intracranial hemorrhage (ICH)	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 <sup>b</sup>	2.4	1.9	p=0.022

143 <sup>a</sup> Patients may be counted in more than one row.

144 <sup>b</sup> See 5.1 for definition.

145  
146 Figure 1 demonstrates non-CABG related TIMI Major or Minor bleeding. The bleeding rate is highest initially, as shown in  
147 Figure 1 (inset: Days 0 to 7) [see *Warnings and Precautions* (5.1)].

148 Bleeding rates in patients with the risk factors of age ≥75 years and weight <60 kg are shown in Table 2.  
149

**Table 2: Bleeding Rates for Non-CABG-Related Bleeding by Weight and Age (TRITON-TIMI 38)**

	<b>Major/Minor</b>		<b>Fatal</b>	
	<b>Effient (%)</b>	<b>Clopidogrel (%)</b>	<b>Effient (%)</b>	<b>Clopidogrel (%)</b>
Weight <60 kg (N=308 Effient, N=356 clopidogrel)	10.1	6.5	0.0	0.3
Weight ≥60 kg (N=6373 Effient, N=6299 clopidogrel)	4.2	3.3	0.3	0.1
Age <75 years (N=5850 Effient, N=5822 clopidogrel)	3.8	2.9	0.2	0.1
Age ≥75 years (N=891 Effient, N=894 clopidogrel)	9.0	6.9	1.0	0.1

151  
152 *Bleeding Related to CABG* - In TRITON-TIMI 38, 437 patients who received a thienopyridine underwent CABG during the  
153 course of the study. The rate of CABG-related TIMI Major or Minor bleeding was 14.1% for the Effient group and 4.5% in the  
154 clopidogrel group (Table 3). The higher risk for bleeding adverse reactions in patients treated with Effient persisted up to 7 days from  
155 the most recent dose of study drug.  
156

**Table 3: CABG-Related Bleeding<sup>a</sup> (TRITON-TIMI 38)**

	<b>Effient (%) (N=213)</b>	<b>Clopidogrel (%) (N=224)</b>
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

158 <sup>a</sup> Patients may be counted in more than one row.

159  
160 *Bleeding Reported as Adverse Reactions* - Hemorrhagic events reported as adverse reactions in TRITON-TIMI 38 were, for  
161 Effient and clopidogrel, respectively: epistaxis (6.2%, 3.3%), gastrointestinal hemorrhage (1.5%, 1.0%), hemoptysis (0.6%, 0.5%),  
162 subcutaneous hematoma (0.5%, 0.2%), post-procedural hemorrhage (0.5%, 0.2%), retroperitoneal hemorrhage (0.3%, 0.2%), and  
163 retinal hemorrhage (0.0%, 0.1%).

164 Malignancies

165 During TRITON-TIMI 38, newly-diagnosed malignancies were reported in 1.6% and 1.2% of patients treated with prasugrel  
166 and clopidogrel, respectively. The sites contributing to the differences were primarily colon and lung. It is unclear if these  
167 observations are causally-related or are random occurrences.

168 Other Adverse Events

169 In TRITON-TIMI 38, common and other important non-hemorrhagic adverse events were, for Effient and clopidogrel,  
170 respectively: severe thrombocytopenia (0.06%, 0.04%), anemia (2.2%, 2.0%), abnormal hepatic function (0.22%, 0.27%), allergic  
171 reactions (0.36%, 0.36%), and angioedema (0.06%, 0.04%). Table 4 summarizes the adverse events reported by at least 2.5% of  
172 patients.  
173

174 **Table 4: Non-Hemorrhagic Treatment Emergent Adverse Events Reported by at Least 2.5% of Patients in Either Group**

	Effient (%) (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
Dyspnea	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 <sup>9</sup> WBC/L)	2.8	3.5
Rash	2.8	2.4
Pyrexia	2.7	2.2
Peripheral edema	2.7	3.0
Pain in extremity	2.6	2.6
Diarrhea	2.3	2.6

175  
176 **7 DRUG INTERACTIONS**

177 **7.1 Warfarin**

178 Coadministration of Effient and warfarin increases the risk of bleeding [see *Warnings and Precautions (5.1) and Clinical*  
179 *Pharmacology (12.3)*].

180 **7.2 Non-Steroidal Anti-Inflammatory Drugs**

181 Coadministration of Effient and NSAIDs (used chronically) may increase the risk of bleeding [see *Warnings and Precautions*  
182 *(5.1)*].

183 **7.3 Other Concomitant Medications**

184 Effient can be administered with drugs that are inducers or inhibitors of cytochrome P450 enzymes [see *Clinical*  
185 *Pharmacology (12.3)*].

186 Effient can be administered with aspirin (75 mg to 325 mg per day), heparin, GPIIb/IIIa inhibitors, statins, digoxin, and drugs  
187 that elevate gastric pH, including proton pump inhibitors and H<sub>2</sub> blockers [see *Clinical Pharmacology (12.3)*].

188 **8 USE IN SPECIFIC POPULATIONS**

189 **8.1 Pregnancy**

190 Pregnancy Category B - There are no adequate and well-controlled studies of Effient use in pregnant women. Reproductive  
191 and developmental toxicology studies in rats and rabbits at doses of up to 30 times the recommended therapeutic exposures in humans  
192 (based on plasma exposures to the major circulating human metabolite) revealed no evidence of fetal harm; however, animal studies  
193 are not always predictive of a human response. Effient should be used during pregnancy only if the potential benefit to the mother  
194 justifies the potential risk to the fetus.

195 In embryo fetal developmental toxicology studies, pregnant rats and rabbits received prasugrel at maternally toxic oral doses  
196 equivalent to more than 40 times the human exposure. A slight decrease in pup body weight was observed; but, there were no  
197 structural malformations in either species. In prenatal and postnatal rat studies, maternal treatment with prasugrel had no effect on the  
198 behavioral or reproductive development of the offspring at doses greater than 150 times the human exposure [see *Nonclinical*  
199 *Toxicology (13.1)*].

200 **8.3 Nursing Mothers**

201 It is not known whether Effient is excreted in human milk; however, metabolites of Effient were found in rat milk. Because  
202 many drugs are excreted in human milk, prasugrel should be used during nursing only if the potential benefit to the mother justifies  
203 the potential risk to the nursing infant.

204 **8.4 Pediatric Use**

205 Safety and effectiveness in pediatric patients have not been established [see *Clinical Pharmacology (12.3)*].

206 **8.5 Geriatric Use**

207 In TRITON-TIMI 38, 38.5% of patients were  $\geq 65$  years of age and 13.2% were  $\geq 75$  years of age. The risk of bleeding  
208 increased with advancing age in both treatment groups, although the relative risk of bleeding (Effient compared with clopidogrel) was  
209 similar across age groups.

210 Patients  $\geq 75$  years of age who received Effient had an increased risk of fatal bleeding events (1.0%) compared to patients who  
211 received clopidogrel (0.1%). In patients  $\geq 75$  years of age, symptomatic intracranial hemorrhage occurred in 7 patients (0.8%) who  
212 received Effient and in 3 patients (0.3%) who received clopidogrel. Because of the risk of bleeding, and because effectiveness is  
213 uncertain in patients  $\geq 75$  years of age [see *Clinical Studies (14)*], use of Effient is generally not recommended in these patients, except  
214 in high-risk situations (diabetes and past history of myocardial infarction) where its effect appears to be greater and its use may be  
215 considered [see *Warnings and Precautions (5.1)*, *Clinical Pharmacology (12.3)*, and *Clinical Studies (14)*].

216 **8.6 Low Body Weight**

217 In TRITON-TIMI 38, 4.6% of patients treated with Effient had body weight  $< 60$  kg. Individuals with body weight  $< 60$  kg had  
218 an increased risk of bleeding and an increased exposure to the active metabolite of prasugrel [see *Dosage and Administration (2)*,  
219 *Warnings and Precautions (5.1)*, and *Clinical Pharmacology (12.3)*]. Consider lowering the maintenance dose to 5 mg in patients  
220  $< 60$  kg. The effectiveness and safety of the 5 mg dose have not been prospectively studied.

221 **8.7 Renal Impairment**

222 No dosage adjustment is necessary for patients with renal impairment. There is limited experience in patients with end-stage  
223 renal disease [see *Clinical Pharmacology (12.3)*].

224 **8.8 Hepatic Impairment**

225 No dosage adjustment is necessary in patients with mild to moderate hepatic impairment (Child-Pugh Class A and B). The  
226 pharmacokinetics and pharmacodynamics of prasugrel in patients with severe hepatic disease have not been studied, but such patients  
227 are generally at higher risk of bleeding [see *Warnings and Precautions (5.1)* and *Clinical Pharmacology (12.3)*].

228 **8.9 Metabolic Status**

229 In healthy subjects, patients with stable atherosclerosis, and patients with ACS receiving prasugrel, there was no relevant  
230 effect of genetic variation in CYP2B6, CYP2C9, CYP2C19, or CYP3A5 on the pharmacokinetics of prasugrel's active metabolite or  
231 its inhibition of platelet aggregation.

232 **10 OVERDOSAGE**

233 **10.1 Signs and Symptoms**

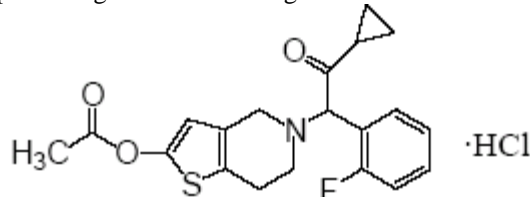
234 Platelet inhibition by prasugrel is rapid and irreversible, lasting for the life of the platelet, and is unlikely to be increased in the  
235 event of an overdose. In rats, lethality was observed after administration of 2000 mg/kg. Symptoms of acute toxicity in dogs included  
236 emesis, increased serum alkaline phosphatase, and hepatocellular atrophy. Symptoms of acute toxicity in rats included mydriasis,  
237 irregular respiration, decreased locomotor activity, ptosis, staggering gait, and lacrimation.

238 **10.2 Recommendations about Specific Treatment**

239 Platelet transfusion may restore clotting ability. The prasugrel active metabolite is not likely to be removed by dialysis.

240 **11 DESCRIPTION**

241 Effient contains prasugrel, a thienopyridine class inhibitor of platelet activation and aggregation mediated by the P2Y<sub>12</sub> ADP  
242 receptor. Effient is formulated as the hydrochloride salt, a racemate, which is chemically designated as 5-[(1RS)-2-cyclopropyl-1-(2-  
243 fluorophenyl)-2-oxoethyl]-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl acetate hydrochloride. Prasugrel hydrochloride has the  
244 empirical formula C<sub>20</sub>H<sub>20</sub>FNO<sub>3</sub>S·HCl representing a molecular weight of 409.90. The chemical structure of prasugrel hydrochloride is:



245 Prasugrel hydrochloride is a white to practically white solid. It is soluble at pH 2, slightly soluble at pH 3 to 4, and practically  
246 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  
247 insoluble in diethyl ether and ethyl acetate.

248 Effient is available for oral administration as 5 mg or 10 mg elongated hexagonal, film-coated, non-scored tablets, debossed  
249 on each side. Each yellow 5 mg tablet is manufactured with 5.49 mg prasugrel hydrochloride, equivalent to 5 mg prasugrel and each  
250 beige 10 mg tablet with 10.98 mg prasugrel hydrochloride, equivalent to 10 mg of prasugrel. Other ingredients include mannitol,  
251 hypromellose, low-substituted hydroxypropyl cellulose, microcrystalline cellulose, sucrose stearate, and glyceryl behenate. The color  
252 coatings contain lactose, hypromellose, titanium dioxide, triacetin, iron oxide yellow, and iron oxide red (only in Effient 10 mg tablet).  
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## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Prasugrel is an inhibitor of platelet activation and aggregation through the irreversible binding of its active metabolite to the P2Y<sub>12</sub> class of ADP receptors on platelets.

### 12.2 Pharmacodynamics

Prasugrel produces inhibition of platelet aggregation to 20  $\mu$ M or 5  $\mu$ M ADP, as measured by light transmission aggregometry. Following a 60-mg loading dose of Effient, approximately 90% of patients had at least 50% inhibition of platelet aggregation by 1 hour. Maximum platelet inhibition was about 80% (see Figure 2). Mean steady-state inhibition of platelet aggregation was about 70% following 3 to 5 days of dosing at 10 mg daily after a 60-mg loading dose of Effient.

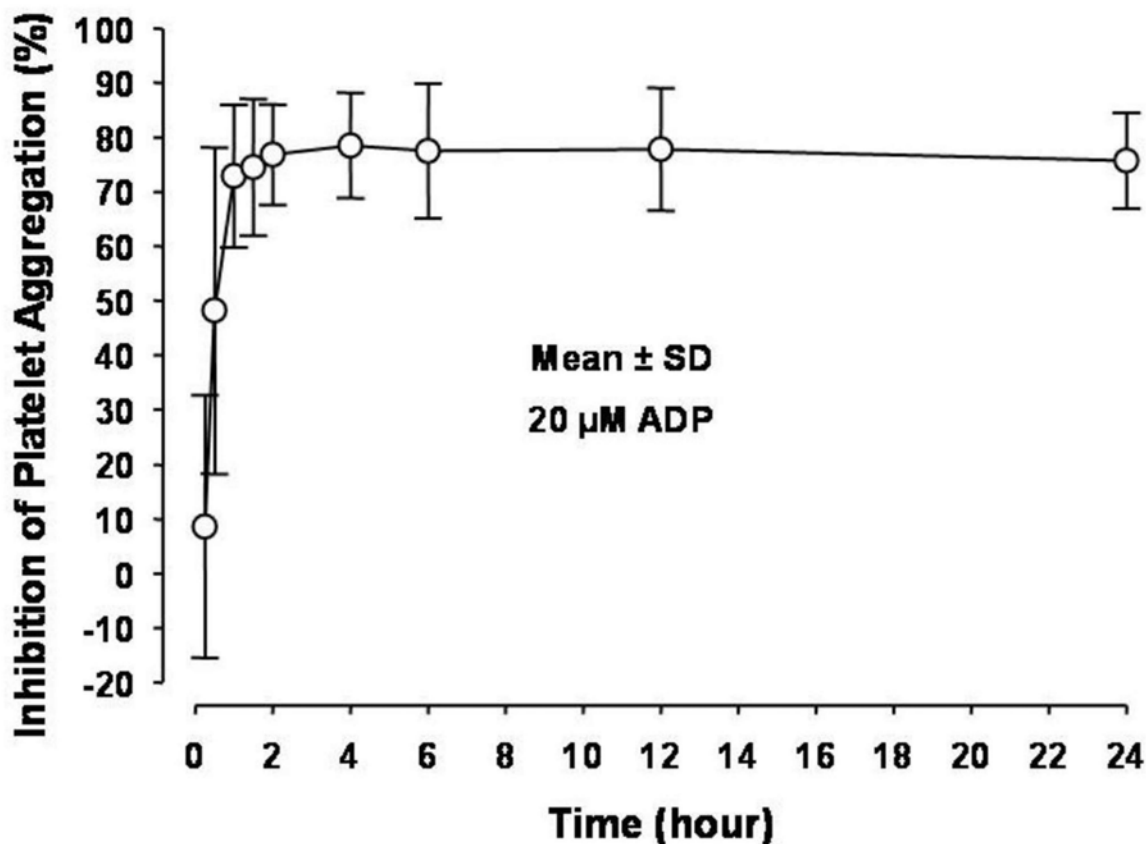


Figure 2: Inhibition (Mean $\pm$ SD) of 20  $\mu$ M ADP-induced Platelet Aggregation (IPA) Measured by Light Transmission Aggregometry after Prasugrel 60 mg.

Platelet aggregation gradually returns to baseline values over 5-9 days after discontinuation of prasugrel, this time course being a reflection of new platelet production rather than pharmacokinetics of prasugrel. Discontinuing clopidogrel 75 mg and initiating prasugrel 10 mg with the next dose resulted in increased inhibition of platelet aggregation, but not greater than that typically produced by a 10-mg maintenance dose of prasugrel alone. The relationship between inhibition of platelet aggregation and clinical activity has not been established.

### 12.3 Pharmacokinetics

Prasugrel is a prodrug and is rapidly metabolized to a pharmacologically active metabolite and inactive metabolites. The active metabolite has an elimination half-life of about 7 hours (range 2-15 hours). Healthy subjects, patients with stable atherosclerosis, and patients undergoing PCI show similar pharmacokinetics.

**Absorption and Binding** - Following oral administration,  $\geq 79\%$  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 slightly more than proportionally over the dose range of 5 to 60 mg. Repeated daily doses of 10 mg do not lead to accumulation of the active metabolite. In a study of healthy subjects given a single 15 mg dose, the AUC of the active metabolite was unaffected by a high fat, high calorie meal, but  $C_{max}$  was decreased by 49% and  $T_{max}$  was increased from 0.5 to 1.5 hours. Effient can be administered without regard to food. The active metabolite is bound about 98% to human serum albumin.

**Metabolism and Elimination** - Prasugrel is not detected in plasma following oral administration. It is rapidly hydrolyzed in the intestine to a thiolactone, which is then converted to the active metabolite by a single step, primarily by CYP3A4 and CYP2B6 and to a lesser extent by CYP2C9 and CYP2C19. The estimates of apparent volume of distribution of prasugrel's active metabolite ranged

from 44 to 68 L and the estimates of apparent clearance ranged from 112 to 166 L/hr in healthy subjects and patients with stable atherosclerosis. The active metabolite is metabolized to two inactive compounds by S-methylation or conjugation with cysteine. The major inactive metabolites are highly bound to human plasma proteins. Approximately 68% of the prasugrel dose is excreted in the urine and 27% in the feces as inactive metabolites.

#### Specific Populations

*Pediatric* - Pharmacokinetics and pharmacodynamics of prasugrel have not been evaluated in a pediatric population [see *Use in Specific Populations* (8.4)].

*Geriatric* - In a study of 32 healthy subjects between the ages of 20 and 80 years, age had no significant effect on pharmacokinetics of prasugrel's active metabolite or its inhibition of platelet aggregation. In TRITON-TIMI 38, the mean exposure (AUC) of the active metabolite was 19% higher in patients  $\geq 75$  years of age than in patients  $< 75$  years of age [see *Warnings and Precautions* (5.1), *Adverse Reactions* (6.1), and *Use in Specific Populations* (8.5)].

*Body Weight* - The mean exposure (AUC) to the active metabolite is approximately 30 to 40% higher in subjects with a body weight of  $< 60$  kg than in those weighing  $\geq 60$  kg [see *Dosage and Administration* (2), *Warnings and Precautions* (5.1), *Adverse Reactions* (6.1), and *Use in Specific Populations* (8.6)].

*Gender* - Pharmacokinetics of prasugrel's active metabolite are similar in men and women.

*Ethnicity* - Exposure in subjects of African and Hispanic descent is similar to that in Caucasians. 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 than in Caucasian subjects.

*Smoking* - Pharmacokinetics of prasugrel's active metabolite are similar in smokers and nonsmokers.

*Renal Impairment* - Pharmacokinetics of prasugrel's active metabolite and its inhibition of platelet aggregation are similar in patients with moderate renal impairment (CrCL=30 to 50 mL/min) and healthy subjects. In patients with end-stage renal disease, exposure to the active metabolite (both  $C_{max}$  and AUC (0- $t_{last}$ )) was about half that in healthy controls and patients with moderate renal impairment [see *Use in Specific Populations* (8.7)].

*Hepatic Impairment* - Pharmacokinetics of prasugrel's active metabolite and inhibition of platelet aggregation were similar in patients with mild to moderate hepatic impairment compared to healthy subjects. The pharmacokinetics and pharmacodynamics of prasugrel's active metabolite in patients with severe hepatic disease have not been studied [see *Warnings and Precautions* (5.1) and *Use in Specific Populations* (8.8)].

#### Drug 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 inhibition of platelet aggregation 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 expected to have a significant effect on the pharmacokinetics of the active metabolite of prasugrel [see *Drug Interactions* (7.3)].

*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's active metabolite or its inhibition of platelet aggregation. Therefore, known CYP3A inducers such as rifampicin, carbamazepine, and other inducers of cytochromes P450 are not expected to have significant effect on the pharmacokinetics of the active metabolite of prasugrel [see *Drug Interactions* (7.3)].

*Drugs that Elevate Gastric pH* - Daily coadministration of ranitidine (an H<sub>2</sub> blocker) or lansoprazole (a proton pump inhibitor) decreased the  $C_{max}$  of the prasugrel active metabolite by 14% and 29%, respectively, but did not change the active metabolite's AUC and  $T_{max}$ . In TRITON-TIMI 38, Effient was administered without regard to coadministration of a proton pump inhibitor or H<sub>2</sub> blocker [see *Drug Interactions* (7.3)].

*Statins* - Atorvastatin (80 mg daily), a drug metabolized by CYP450 3A4, did not alter the pharmacokinetics of prasugrel's active metabolite or its inhibition of platelet aggregation [see *Drug Interactions* (7.3)].

*Heparin* - A single intravenous dose of unfractionated heparin (100 U/kg) did not significantly alter coagulation or the prasugrel-mediated inhibition of platelet aggregation; however, bleeding time was increased compared with either drug alone [see *Drug Interactions* (7.3)].

*Aspirin* - Aspirin 150 mg daily did not alter prasugrel-mediated inhibition of platelet aggregation; however, bleeding time was increased compared with either drug alone [see *Drug Interactions* (7.3)].

*Warfarin* - A significant prolongation of the bleeding time was observed when prasugrel was coadministered with 15 mg of warfarin [see *Drug Interactions* (7.1)].

##### *Potential for Prasugrel to Affect Other Drugs*

*In vitro* metabolism studies demonstrate that prasugrel's main circulating metabolites are not likely to cause clinically significant inhibition of CYP1A2, CYP2C9, CYP2C19, CYP2D6, or CYP3A, or induction of CYP1A2 or CYP3A.

*Drugs Metabolized 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%, an amount not considered clinically significant. Prasugrel is not anticipated to have significant effect on the pharmacokinetics of drugs that are primarily metabolized by CYP2B6, such as halothane, cyclophosphamide, propofol, and nevirapine.

*Effect on Digoxin* - The potential role of prasugrel as a Pgp substrate was not evaluated. Prasugrel is not an inhibitor of Pgp, as digoxin clearance was not affected by prasugrel coadministration [see *Drug Interactions* (7.3)].

## **12.5 Pharmacogenomics**

347 There is no relevant effect of genetic variation in CYP2B6, CYP2C9, CYP2C19, or CYP3A5 on the pharmacokinetics of  
348 prasugrel's active metabolite or its inhibition of platelet aggregation.

### 349 **13 NONCLINICAL TOXICOLOGY**

#### 350 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

351 *Carcinogenesis* - No compound-related tumors were observed in a 2-year rat study with prasugrel at oral doses up to  
352 100 mg/kg/day (>100 times the recommended therapeutic exposures in humans (based on plasma exposures to the major circulating  
353 human metabolite). There was an increased incidence of tumors (hepatocellular adenomas) in mice exposed for 2 years to high doses  
354 (>250 times the human metabolite exposure).

355 *Mutagenesis* - Prasugrel was not genotoxic in two *in vitro* tests (Ames bacterial gene mutation test, clastogenicity assay in  
356 Chinese hamster fibroblasts) and in one *in vivo* test (micronucleus test by intraperitoneal route in mice).

357 *Impairment of Fertility* - Prasugrel had no effect on fertility of male and female rats at oral doses up to 300 mg/kg/day (80  
358 times the human major metabolite exposure at daily dose of 10 mg prasugrel).

### 359 **14 CLINICAL STUDIES**

360 The clinical evidence for the effectiveness of Effient is derived from the TRITON-TIMI 38 (TRial to Assess Improvement in  
361 Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel) study, a 13,608-patient, multicenter, international,  
362 randomized, double-blind, parallel-group study comparing Effient to a regimen of clopidogrel, each added to aspirin and other  
363 standard therapy, in patients with ACS (UA, NSTEMI, or STEMI) who were to be managed with PCI. Randomization was stratified  
364 for UA/NSTEMI and STEMI.

365 Patients with UA/NSTEMI presenting within 72 hours of symptom onset were to be randomized after undergoing coronary  
366 angiography. Patients with STEMI presenting within 12 hours of symptom onset could be randomized prior to coronary angiography.  
367 Patients with STEMI presenting between 12 hours and 14 days of symptom onset were to be randomized after undergoing coronary  
368 angiography. Patients underwent PCI, and for both UA/NSTEMI and STEMI patients, the loading dose was to be administered  
369 anytime between randomization and 1 hour after the patient left the catheterization lab. If patients with STEMI were treated with  
370 thrombolytic therapy, randomization could not occur until at least 24 hours (for tenecteplase, reteplase, or alteplase) or 48 hours (for  
371 streptokinase) after the thrombolytic was given.

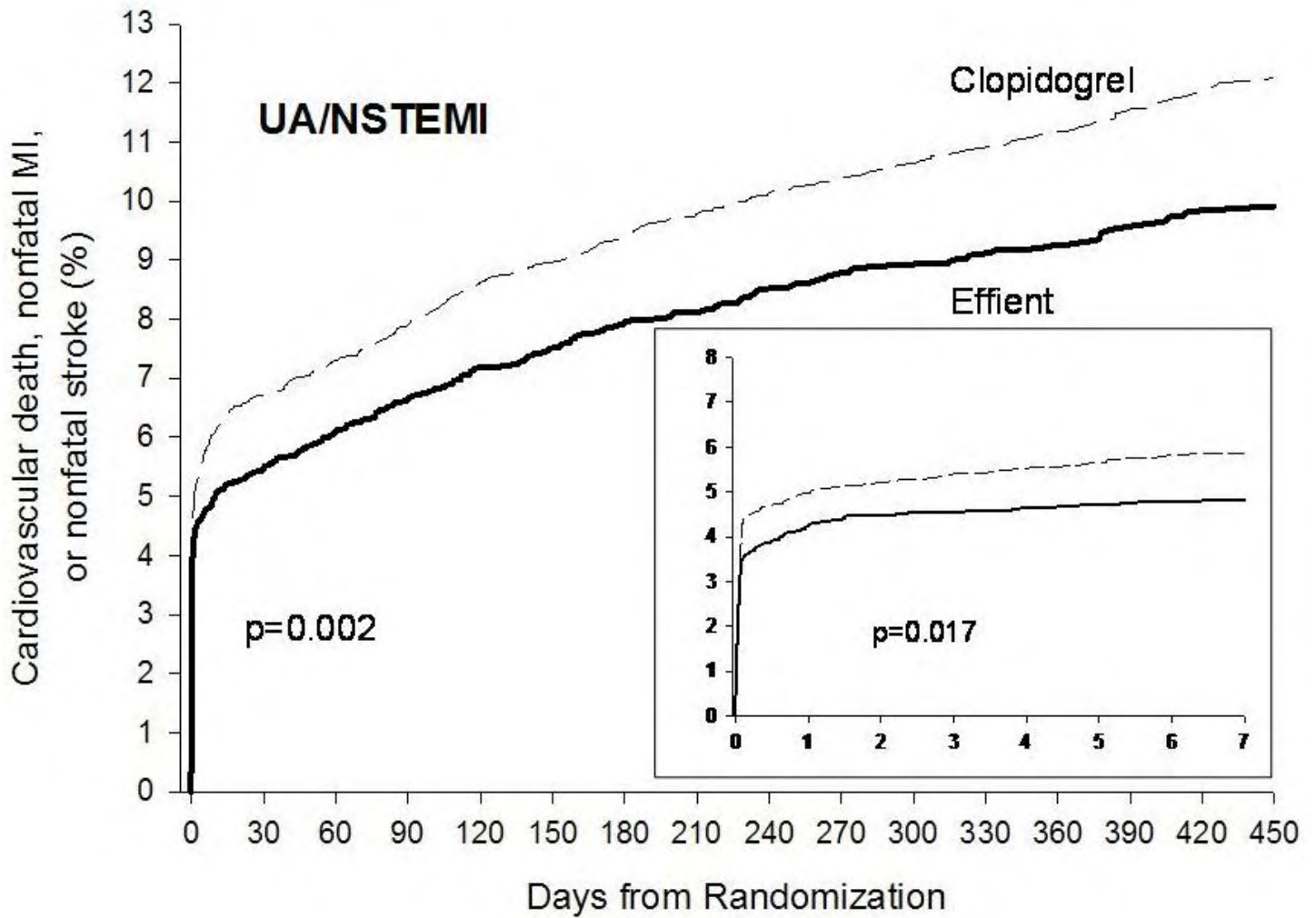
372 Patients were randomized to receive Effient (60-mg loading dose followed by 10 mg once daily) or clopidogrel (300-mg  
373 loading dose followed by 75 mg once daily), with administration and follow-up for a minimum of 6 months (actual median  
374 14.5 months). Patients also received aspirin (75 mg to 325 mg once daily). Other therapies, such as heparin and intravenous  
375 glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors, were administered at the discretion of the treating physician. Oral anticoagulants, other  
376 platelet inhibitors, and chronic NSAIDs were not allowed.

377 The primary outcome measure was the composite of cardiovascular death, nonfatal MI, or nonfatal stroke in the UA/NSTEMI  
378 population. Success in this group allowed analysis of the same endpoint in the overall ACS and STEMI populations. Nonfatal MIs  
379 included both MIs detected solely through analysis of creatine kinase muscle-brain (CK-MB) changes and clinically apparent  
380 (investigator-reported) MIs.

381 The patient population was 92% Caucasian, 26% female, and 39%  $\geq 65$  years of age. The median time from symptom onset to  
382 study drug administration was 7 hours for patients with STEMI and 30 hours for patients with UA/NSTEMI. Approximately 99% of  
383 patients underwent PCI. The study drug was administered after the first coronary guidewire was placed in approximately 75% of  
384 patients.

385 Effient significantly reduced total endpoint events compared to clopidogrel (*see* Table 5 and Figure 3). The reduction of total  
386 endpoint events was driven primarily by a decrease in nonfatal MIs, both those occurring early (through 3 days) and later (after 3  
387 days). Approximately 40% of MIs occurred peri-procedurally and were detected solely by changes in CK-MB. Administration of the  
388 clopidogrel loading dose in TRITON-TIMI 38 was delayed relative to the placebo-controlled trials that supported its approval for  
389 ACS. Effient produced higher rates of clinically significant bleeding than clopidogrel in TRITON-TIMI 38 [*see Adverse Reactions*  
390 (6.1)]. Choice of therapy requires balancing these differences in outcome.

391 The treatment effect of Effient was apparent within the first few days, and persisted to the end of the study (*see* Figure 3). The  
392 inset shows results over the first 7 days.  
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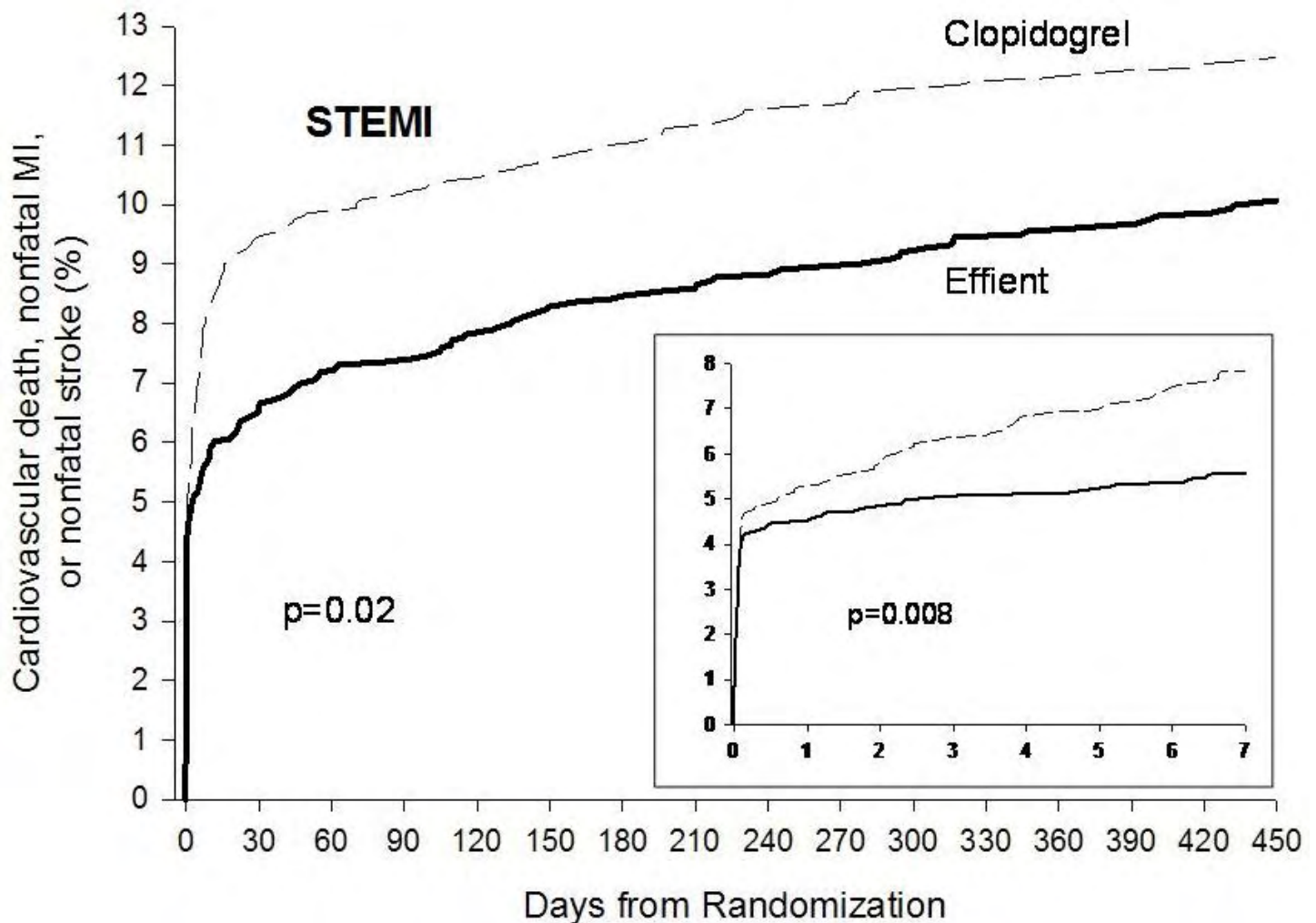


Figure 3: Time to first event of CV death, MI, or stroke (TRITON-TIMI 38).

The Kaplan-Meier curves (Figure 3) show the primary composite endpoint of CV death, nonfatal MI, or nonfatal stroke over time in the UA/NSTEMI and STEMI populations. In both populations, the curves separate within the first few hours. In the UA/NSTEMI population, the curves continue to diverge throughout the 15 month follow-up period. In the STEMI population, the early separation was maintained throughout the 15 month follow-up period, but there was no progressive divergence after the first few weeks.

Effient reduced the occurrence of the primary composite endpoint compared to clopidogrel in both the UA/NSTEMI and STEMI populations (*see* Table 5). In patients who survived an on-study myocardial infarction, the incidence of subsequent events was also lower in the Effient group.

Table 5: Patients with Outcome Events (CV Death, MI, Stroke) in TRITON-TIMI 38

	Patients with events		From Kaplan-Meier analysis	
	Effient (%) N=5044	Clopidogrel (%) N=5030	Relative Risk Reduction (%) <sup>a</sup> (95% CI)	p-value
<b>UA/NSTEMI</b>				
CV death, nonfatal MI, or nonfatal stroke	9.3	11.2	18.0 (7.3, 27.4)	0.002
CV death	1.8	1.8	2.1 (-30.9, 26.8)	0.885
Nonfatal MI	7.1	9.2	23.9 (12.7, 33.7)	<0.001
Nonfatal Stroke	0.8	0.8	2.1 (-51.3, 36.7)	0.922
<b>STEMI</b>				
CV death, nonfatal MI, or nonfatal stroke	9.8	12.2	20.7 (3.2, 35.1)	0.019
CV death	2.4	3.3	26.2 (-9.4, 50.3)	0.129
Nonfatal MI	6.7	8.8	25.4 (5.2, 41.2)	0.016
Nonfatal Stroke	1.2	1.1	-9.7 (-104.0, 41.0)	0.77

<sup>a</sup> RRR = (1-Hazard Ratio) x 100%. Values with a negative relative risk reduction indicate a relative risk increase.

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The effect of Effient in various subgroups is shown in Figures 4 and 5. Results are generally consistent across pre-specified subgroups, with the exception of patients with a history of TIA or stroke [see *Contraindications (4.2)*]. The treatment effect was driven primarily by a reduction in nonfatal MI. The effect in patients  $\geq 75$  years of age was also somewhat smaller, and bleeding risk is higher in these individuals [see *Adverse Reactions (6.1)*]. See below for analyses of patients  $\geq 75$  years of age with risk factors.

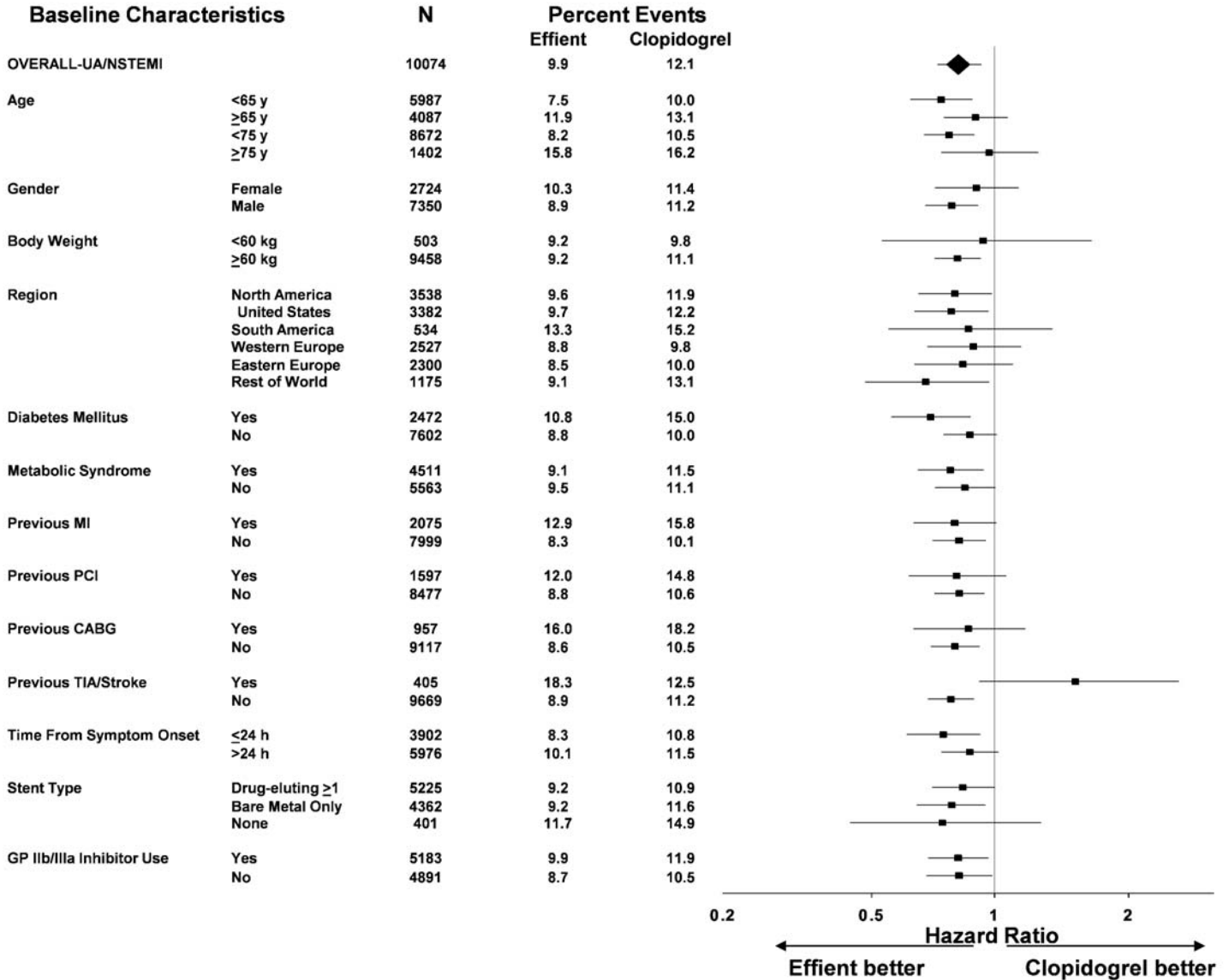


Figure 4: Subgroup analyses for time to first event of CV death, MI, or stroke (HR and 95% CI; TRITON-TIMI 38) – UA/NSTEMI Patients.

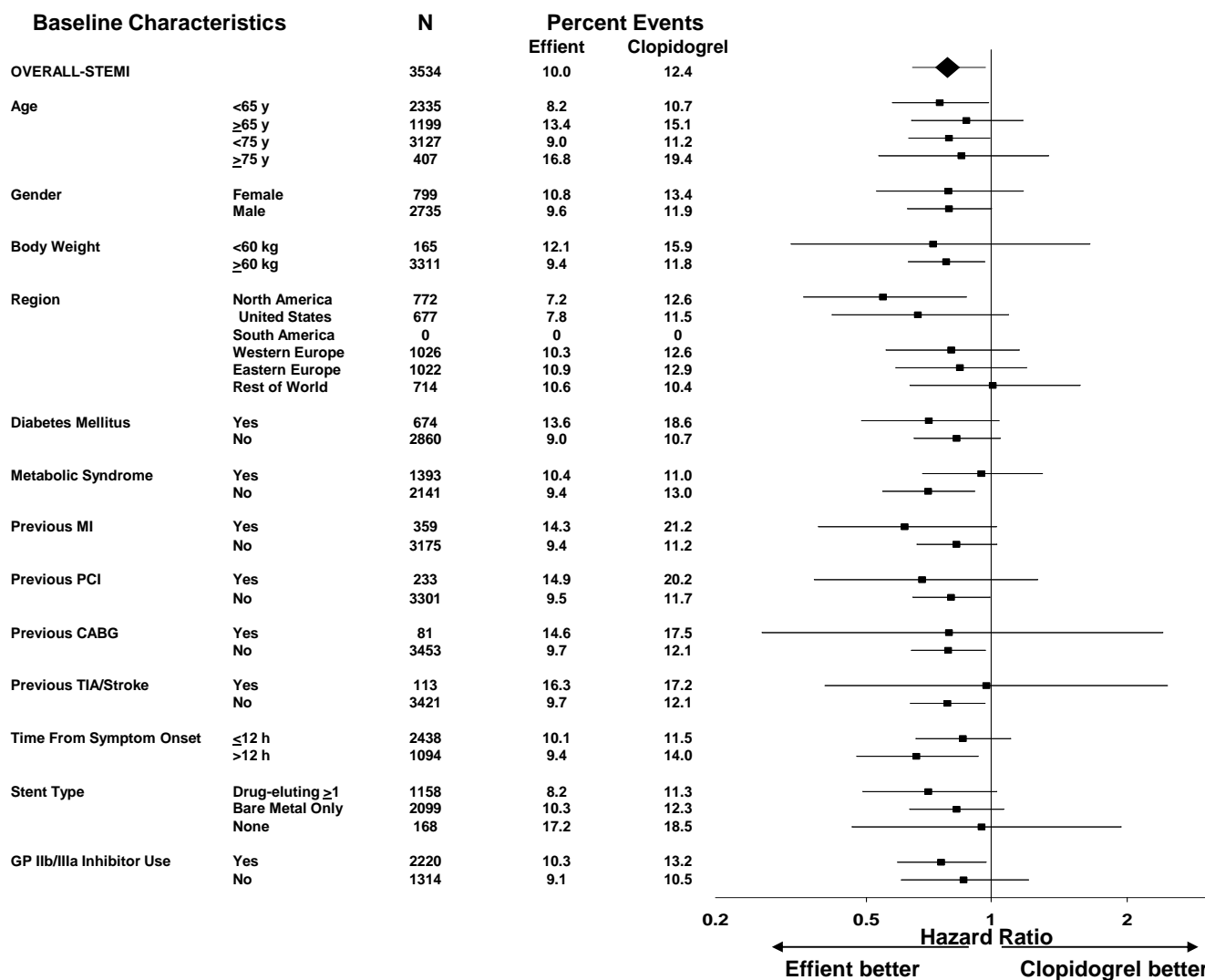


Figure 5: Subgroup analyses for time to first event of CV death, MI, or stroke (HR and 95% CI; TRITON-TIMI 38) – STEMI Patients.

Effient is generally not recommended in patients  $\geq 75$  years of age, except in high-risk situations (diabetes mellitus or prior MI) where its effect appears to be greater and its use may be considered. These recommendations are based on subgroup analyses (Table 6) and must be interpreted with caution, but the data suggest that Effient reduces ischemic events in such patients.

Table 6: Subgroup Analyses for Time to First Event of CV Death, MI, or Stroke: Patients  $<$  or  $\geq 75$  Years of Age,  $\pm$  Diabetes,  $\pm$  Prior History of MI, All ACS Patient Population

	Effient		Clopidogrel		Hazard Ratio (95% CI)	p-value
	N	% with events	N	% with events		
<b>Age <math>\geq 75</math></b>						
Diabetes - yes	249	14.9	234	21.8	0.64 (0.42, 0.97)	0.034
Diabetes - no	652	16.4	674	15.3	1.1 (0.83, 1.43)	NS
<b>Age <math>&lt; 75</math></b>						
Diabetes - yes	1327	10.8	1336	14.8	0.72 (0.58, 0.89)	0.002
Diabetes - no	4585	7.8	4551	9.5	0.82 (0.71, 0.94)	0.004
<b>Age <math>\geq 75</math></b>						
Prior MI - yes	220	17.3	212	22.6	0.72 (0.47, 1.09)	0.12
Prior MI - no	681	15.6	696	15.2	1.05 (0.80, 1.37)	NS
<b>Age <math>&lt; 75</math></b>						

Prior MI - yes	1006	12.2	996	15.4	0.78 (0.62, 0.99)	0.04
Prior MI - no	4906	7.7	4891	9.7	0.78 (0.68, 0.90)	<0.001

There were 50% fewer stent thromboses (95% C.I. 32% - 64%;  $p < 0.001$ ) reported among patients randomized to Effient (0.9%) than among patients randomized to clopidogrel (1.8%). The difference manifested early and was maintained through one year of follow-up. Findings were similar with bare metal and drug-eluting stents.

In TRITON-TIMI 38, prasugrel reduced ischemic events (mainly nonfatal MIs) and increased bleeding events [see *Adverse Reactions (6.1)*] relative to clopidogrel. The findings are consistent with the intended greater inhibition of platelet aggregation by prasugrel at the doses used in the study [see *Clinical Pharmacology (12.2)*]. There is, however, an alternative explanation: both prasugrel and clopidogrel are pro-drugs that must be metabolized to their active moieties. Whereas the pharmacokinetics of prasugrel's active metabolite are not known to be affected by genetic variations in CYP2B6, CYP2C9, CYP2C19, or CYP3A5, the pharmacokinetics of clopidogrel's active metabolite are affected by CYP2C19 genotype, and approximately 30% of Caucasians are reduced-metabolizers. Moreover, certain proton pump inhibitors, widely used in the ACS patient population and used in TRITON-TIMI 38, inhibit CYP2C19, thereby decreasing formation of clopidogrel's active metabolite. Thus, reduced-metabolizer status and use of proton pump inhibitors may diminish clopidogrel's activity in a fraction of the population, and may have contributed to prasugrel's greater treatment effect and greater bleeding rate in TRITON-TIMI 38. The extent to which these factors were operational, however, is unknown.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

Effient (prasugrel) 5 mg is supplied as a yellow, elongated hexagonal, film-coated, non-scored tablet debossed with "5121" on one side and 3 parallel arched lines followed by a "5" on the other.

5 mg tablets are supplied as follows:

Bottles of 30 - NDC 0002-5121-30

Blisters ID 24\* - NDC 0002-5121-52

Effient (prasugrel) 10 mg is supplied as a beige, elongated hexagonal, film-coated, non-scored tablet debossed with "5123" on one side and 3 parallel arched lines followed by a "10" on the other.

10 mg tablets are supplied as follows:

Bottles of 30 - NDC 0002-5123-30

Blisters ID 90\* - NDC 0002-5123-77

(\*Identi Dose<sup>®</sup>, unit dose medication, Lilly)

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP controlled room temperature].

Dispense and keep product in original container. Keep container closed and do not remove desiccant from bottle. Do not break the tablet.

## 17 PATIENT COUNSELING INFORMATION

See Medication Guide

### 17.1 Benefits and Risks

- Summarize the effectiveness features and potential side effects of Effient.
- Tell patients to take Effient exactly as prescribed.
- Remind patients not to discontinue Effient without first discussing it with the physician who prescribed Effient.
- Recommend that patients read the Medication Guide.

### 17.2 Bleeding

Inform patients that they:

- will bruise and bleed more easily.
- will take longer than usual to stop bleeding.
- should report any unanticipated, prolonged, or excessive bleeding, or blood in their stool or urine.

### 17.3 Other Signs and Symptoms Requiring Medical Attention

- Inform patients that TTP is a rare but serious condition that has been reported with medications in this class of drugs.
- Instruct patients to get prompt medical attention if they experience any of the following symptoms that cannot otherwise be explained: fever, weakness, extreme skin paleness, purple skin patches, yellowing of the skin or eyes, or neurological changes.

### 17.4 Invasive Procedures

Instruct patients to:

- inform physicians and dentists that they are taking Effient before any invasive procedure is scheduled.
- tell the doctor performing the invasive procedure to talk to the prescribing health care professional before stopping Effient.

### 17.5 Concomitant Medications

Ask patients to list all prescription medications, over-the-counter medications, or dietary supplements they are taking or plan to take so the physician knows about other treatments that may affect bleeding risk (e.g., warfarin and NSAIDs).

Literature Revised: month dd, yyyy

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487 **Manufactured by Eli Lilly and Company, Indianapolis, IN, 46285**

488 **Marketed by Daiichi Sankyo, Inc. and Eli Lilly and Company**

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