

Risk Evaluation and Mitigation Strategy

NDA 22-307

**Proposed Trade Name: EFFIENT
(prasugrel)**

United States Food and Drug Administration
Division of Cardiovascular and Renal Products

Eli Lilly and Company

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NDA 22-307 EFFIENT™ (prasugrel)
Thienopyridine platelet inhibitor

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PROPOSED RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. Goal:

To mitigate the serious risk of bleeding associated with the use of EFFIENT by:

1. Informing patients of the serious risks associated with EFFIENT, particularly the increased risk of bleeding.
2. Communicating to prescribers about the increased risk of bleeding associated with EFFIENT and the need for appropriate patient selection.

II. REMS ELEMENTS:

A. Medication Guide

A Medication Guide will be available for distribution with each EFFIENT prescription in accordance with 21 CFR 208.24. For outpatient pharmacy dispensing, each commercial retail bottle will have the Medication Guide affixed and pharmacists will be instructed to dispense EFFIENT in the original container. Hospital blister packs, which are intended to support initial dosing and use during the patient's stay in the hospital, will contain sufficient copies of the Medication Guide in the carton so that one can be given to each patient.

B. Communication Plan

Lilly will implement a communication plan to healthcare providers including in particular interventional cardiologists, clinical cardiologists, emergency medicine physicians, internal medicine physicians, and primary care physicians that will convey the following information:

- The serious risk of bleeding associated with EFFIENT.
- Appropriate patient selection (emphasizing patients in whom EFFIENT should not be used).

The communication plan includes a Dear Healthcare Provider Letter and a Prescriber Brochure. This element of the REMS is not intended to continue over the lifetime of the product; it will function only to inform prescribers of the serious risk of bleeding associated with EFFIENT therapy for a period of 2 years.

1. Introductory Letter

Lilly will issue a Dear Healthcare Provider Letter to targeted healthcare providers within 45 days of approval. The purpose of this letter is to inform healthcare providers of the serious risk of bleeding associated with EFFIENT and the importance of appropriate use and proper patient selection.

2. Prescriber Brochure

The prescriber brochure will emphasize the key safety messages related to risk of bleeding and its management, including risk management by providing guidance on proper patient selection. In addition, the prescriber brochure provides healthcare providers with information to discuss with their patients. Lilly will disseminate the prescriber brochure after the completion of the initial presentation to the prescribers of the product during the first two years after launch.

C. Elements to Assure Safe Use

The REMS for EFFIENT does not include Elements to Assure Safe Use.

D. Implementation System

Because this REMS for EFFIENT does not include elements to assure safe use, an implementation system is not required.

E. Timetable for Submission of Assessments

The timetable for submission of assessment of the REMS is as follows:

	Month/Year Due
1 st REMS assessment (18 months from approval of the REMS)	Jan 31, 2011
2 nd REMS assessment (3 years from approval of the REMS)	July 31, 2012
3 rd REMS assessment (7 years from approval of the REMS)	July 31, 2016

The assessment interval period will close no earlier than 60 days prior to the date the respective assessment is due. The assessment is to be received by the FDA on the due date.

Dear Health Care Professional

We would like to inform you of the FDA approval of a new thienopyridine, Effient™ (prasugrel), which 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-segment elevation myocardial infarction (NSTEMI)
- Patients with ST-segment elevation myocardial (STEMI) when managed with primary or delayed PCI

Based on the 13,608 patient TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel) study, Effient has been shown to reduce the rate of a combined composite endpoint of cardiovascular death, nonfatal myocardial infarction (MI) or nonfatal stroke compared to clopidogrel. The difference between treatments was derived predominantly by MI, with no difference on strokes and little difference on CV death. The efficacy benefits of Effient were accompanied by a significantly higher risk of serious bleeding, including life-threatening and fatal bleeding.

This letter describes those patient populations identified as having the highest risk of bleeding associated with Effient. With this awareness, appropriate patient selection is important to help reduce the risk of serious bleeding. Please see accompanying Full Prescribing Information, including Boxed Warning regarding Bleeding Risks, and the accompanying Medication Guide for more information about Effient.

- ***Patients with a History of Transient Ischemic Attack (TIA) or Stroke:***

Effient is contraindicated in patients with a history of TIA or stroke.

In TRITON-TIMI 38, there was a lack of treatment benefit on the primary endpoint for Effient compared to clopidogrel for this subgroup. This lack of benefit was primarily due to a statistically significant increase in nonfatal and fatal stroke. Specifically, these patients had a higher rate of ischemic or hemorrhagic stroke on Effient (6.5% total stroke, 2.3% intracranial hemorrhage [ICH]) than those treated with clopidogrel (1.2% total stroke, 0% ICH). 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.

In addition, patients who experience a stroke or TIA while on Effient generally should have therapy discontinued.

- **Patients 75 Years of Age and Older:**

In TRITON-TIMI 38, patients ≥ 75 years of age who received Effient had an increased risk of fatal bleeding events (1.0%) compared to patients who received clopidogrel (0.1%). In patients ≥ 75 years of age, symptomatic intracranial hemorrhage occurred in 0.8% of patients who received Effient and in 0.3% of patients who received clopidogrel. Because of the risk of bleeding (including fatal bleeding), and because efficacy is less certain in patients ≥ 75 years of age, the use of *Effient is generally not recommended in these patients, except in high-risk situations (patients with diabetes or past history of myocardial infarction), where its effect appears to be greater and its use may be considered.*

Physicians must carefully consider the risks and benefits in these patients on an individual basis prior to recommending Effient and should counsel these patients about the increased risk of serious bleeding.

- **Patients Weighing less than 60 kg (132 lbs):**

In TRITON-TIMI 38, individuals with a body weight of less than 60 kg had an increased risk of bleeding and had higher blood concentrations of the active metabolite of Effient. For these patients, *consider lowering the maintenance dose to 5 mg.* The efficacy and safety of the 5 mg dose have not been prospectively studied in clinical trials.

- **Patients undergoing CABG:**

In TRITON-TIMI 38, patients undergoing Coronary Artery Bypass Graft Surgery (CABG) had an increased risk of bleeding if the surgery was performed within 7 days after the last dose of Effient. Of the 437 patients who underwent CABG during TRITON-TIMI 38, the rates of CABG-related TIMI Major or Minor bleeding were 14.1% for the Effient group and 4.5% in the clopidogrel group. Because of these findings, *do not start Effient in patients likely to undergo urgent coronary bypass graft surgery (CABG). When possible, discontinue Effient at least 7 days prior to any surgery. Surgery related bleeding may be treated with transfusion of blood products, including packed red blood cells and platelets; however, platelet transfusions within 6 hours of the loading dose or 4 hours of the maintenance dose may be less effective.*

- **Other Risk Factors for Bleeding:**

Effient is contraindicated in patients with active, pathological bleeding such as peptic ulcer or intracranial hemorrhage.

Additional risk factors for bleeding include:

- propensity to bleed

- concomitant use of medications that increase the risk of bleeding (e.g., warfarin, heparin, fibrinolytic therapy, chronic use of nonsteroidal anti-inflammatory drugs [NSAIDs])

Dosage and Administration

Initiate Effient treatment as a single 60 mg oral loading dose (LD) and then continue at 10 mg orally once daily. Patients taking Effient should also take aspirin (75 mg to 325 mg) daily. Effient may be administered with or without food and is available in 5 mg and 10 mg tablets. Consider lowering the maintenance dose to 5 mg in patients <60 kg. The efficacy and safety of the 5 mg dose have not been prospectively studied.

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. For the small fraction of patients that required urgent CABG after treatment with Effient, the risk of significant bleeding was substantial. Therefore, 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.

Summary

Effient is a new thienopyridine which, when taken with aspirin, reduces the risk of thrombotic cardiovascular events, including stent thrombosis, in patients with ACS managed with PCI. The reductions in cardiovascular events with Effient treatment were accompanied by a higher risk of serious bleeding, including life-threatening and fatal bleeding. Understanding the risks and the benefits described above should help you to identify appropriate patients for Effient.

If you would like additional information about Effient, please contact us at 1-877-4DS-PROD (1-877-437-7763) or 1-800-LILLYRX (1-800-545-5979).

Sincerely yours,

DSI and Lilly

EFFIENT™

PRESCRIBER'S OVERVIEW



EFFIENT™ (prasugrel) PRESCRIBER'S OVERVIEW

This brochure has been developed as part of a plan to help reduce the risk of serious adverse reactions and maximize the benefit-risk profile of Effient. ***For more detailed safety information, refer to the Full Prescribing Information, including Boxed Warning.***

The safety profile of Effient is derived from the TRITON-TIMI 38 (TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel) study, a 13,608-patient, multicenter, international, randomized, double-blind, parallel-group study comparing Effient with Plavix® (clopidogrel bisulfate), each added to aspirin and other standard therapy, in patients with acute coronary syndrome (ACS) who were managed with percutaneous coronary intervention (PCI). The key safety endpoints in TRITON-TIMI 38 were non-CABG TIMI major and/or minor bleeding rates. Since non-CABG TIMI major bleeding events, including life-threatening and fatal bleeding, were significantly higher in patients treated with Effient compared with Plavix, the purpose of this brochure is to ensure that healthcare professionals treating patients with Effient:

- Use Effient safely and effectively
- Identify patients in whom Effient use should be avoided or is generally not recommended, as well as those likely to achieve an appropriate balance of benefit and risk
- To weigh the potential benefits associated with Effient against the risks to assist in determining appropriate patients

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I. INDICATIONS AND USAGE

Indications and Usage¹

Effient 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-segment elevation myocardial infarction (NSTEMI)
- Patients with ST-segment elevation myocardial infarction (STEMI) when managed with primary or delayed PCI

Effient has been shown to reduce the rate of a combined endpoint of CV death, nonfatal myocardial infarction (MI), or nonfatal stroke compared to Plavix. The difference between treatments was driven predominantly by MI, with no difference on strokes and little difference on CV death.

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 who required urgent CABG after treatment with Effient, the risk of significant bleeding was substantial. 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.

II. WARNING: BLEEDING RISK

WARNING: BLEEDING RISK¹

Effient can cause significant, sometimes fatal, bleeding. Do not use Effient in patients with active pathological bleeding or a history of transient ischemic attack or stroke. In patients ≥ 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. 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 (eg, warfarin, heparin, fibrinolytic therapy, chronic use of nonsteroidal 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.

Please see provided Full Prescribing Information for details.

Contraindications¹

Active Bleeding

Effient is contraindicated in patients with active pathological bleeding such as peptic ulcer or intracranial hemorrhage.

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, patients with a history of TIA or ischemic stroke (> 3 months prior to enrollment) had a higher rate of ischemic or hemorrhagic stroke on Effient (6.5%, of which 2.3% were intracranial hemorrhage [ICH]) than on Plavix (1.2% total stroke, 0% ICH)
- 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 Plavix, 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

Instruct patients to report signs and symptoms of bleeding to physicians immediately.

III. INCREASED RISK OF BLEEDING

This section focuses on the increased risk of bleeding associated with Effient compared with Plavix and the patient populations at greatest risk for bleeding.

Non-CABG bleeding risk¹

- With the dosing regimens used in TRITON-TIMI 38, the rates of non-CABG-related TIMI major or minor bleeding were significantly higher with Effient compared with Plavix
- In the TRITON-TIMI 38 clinical trial, non-CABG-related TIMI major or minor bleeding was highest initially

Non-CABG-related bleeding (TRITON-TIMI 38)*			
Adverse reactions	All patients		P value
	Effient [†] + ASA (%) (n=6741)	Plavix [†] + ASA (%) (n=6716)	
TIMI major or minor bleeding	4.5	3.4	0.002
TIMI major bleeding [‡]	2.2	1.7	0.029
Life threatening	1.3	0.8	0.015
Fatal	0.3	0.1	–
Symptomatic 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	2.4	1.9	0.022

*Patients may be counted in more than one row. [†]Observed event rates. [‡]Intracranial hemorrhage or clinically overt bleeding associated with a fall in hemoglobin ≥5 g/dL. [§]ICH=intracranial hemorrhage. ^{||}Clinically overt bleeding associated with a fall in hemoglobin of ≥3 g/dL but <5 g/dL.

Bleeding reported as adverse reactions¹

Hemorrhagic events reported as adverse reactions in TRITON-TIMI 38 for Effient and Plavix, respectively, were:

- Epistaxis (6.2%, 3.3%)
- Gastrointestinal hemorrhage (1.5%, 1.0%)
- Hemoptysis (0.6%, 0.5%)
- Subcutaneous hematoma (0.5%, 0.2%)
- Post-procedural hemorrhage (0.5%, 0.2%)
- Retroperitoneal hemorrhage (0.3%, 0.2%)
- Retinal hemorrhage (0.0%, 0.1%)

III. INCREASED RISK OF BLEEDING

High-risk patient populations¹

A post hoc analysis of non-CABG bleeding risk identified three patient groups with a higher risk of bleeding when compared with the overall population: patients with prior TIA/stroke, patients weighing <60 kg, and patients age ≥75 years.

Patients ≥75 years of age¹

- Patients ≥75 years of age who received Effient had an increased risk of fatal bleeding events (1.0%) compared with patients who received Plavix (0.1%)
- In patients ≥75 years of age, symptomatic ICH occurred in 7 patients (0.8%) who received Effient and in 3 patients (0.3%) who received Plavix

Patients with body weight <60 kg (132 lb)¹

- In the TRITON-TIMI 38 clinical trial, 4.6% of patients treated with Effient had body weight <60 kg. Individuals with body weight <60 kg had an increased risk of bleeding and an increased exposure to the active metabolite of Effient
- Consider lowering the maintenance dose to 5 mg in patients <60 kg. The efficacy and safety of the 5-mg dose have not been prospectively studied

Bleeding rates for non-CABG-related bleeding by weight and age (TRITON-TIMI 38)

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

III. INCREASED RISK OF BLEEDING

Patients undergoing CABG¹

Of the 437 patients who underwent CABG during TRITON-TIMI 38, the rates of CABG-related TIMI major or minor bleeding were 14.1% in the Effient group and 4.5% in the Plavix group.

- The higher risk for bleeding events in patients treated with Effient persisted up to 7 days from the most recent dose of study drug
- Do not start Effient in patients likely to undergo urgent CABG
- CABG-related bleeding may be treated with transfusion of blood products, including packed red blood cells and platelets; however, platelet transfusions within 6 hours of the loading dose or 4 hours of the maintenance dose may be less effective

IV. OTHER RISK FACTORS FOR BLEEDING

Propensity to bleed

- Eg. recent trauma, recent surgery, recent or recurrent gastrointestinal (GI) bleeding, active peptic ulcer disease, or severe hepatic impairment

Medications that increase the risk of bleeding

- Eg. oral anticoagulants, chronic use of nonsteroidal anti-inflammatory drugs (NSAIDs), and fibrinolytic agents
- Aspirin and heparin were commonly used in TRITON-TIMI 38

V. MANAGEMENT OF BLEEDING

- Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, PCI, CABG, or other surgical procedures in the setting of Effient
- Thienopyridines inhibit platelet aggregation for the lifetime of the platelet (7–10 days), so withholding a dose will not be useful in managing a bleeding event or the risk of bleeding associated with an invasive procedure. Because the half-life of the active metabolite of Effient is short relative to the lifetime of the platelet, it may be possible to restore hemostasis by administering exogenous platelets; however, platelet transfusions within 6 hours of the loading dose or 4 hours of the maintenance dose may be less effective
- 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

VI. DOSAGE AND ADMINISTRATION

For detailed information about dosage and administration, refer to the provide Full Prescribing Information.

Loading and maintenance dosing¹

Initiate Effient 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.

Effient may be administered with or without food.

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. For the small fraction of patients who required urgent CABG after treatment with Effient, the risk of significant bleeding was substantial. Therefore, 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.

Dosing in low-weight patients¹

Compared with patients weighing ≥ 60 kg, patients weighing < 60 kg have an increased exposure to the active metabolite of Effient 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.

VII. PATIENT COUNSELING AND INFORMATION

Benefits and risks¹

- Summarize the efficacy 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

Bleeding¹

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

Other signs and symptoms requiring medical attention¹

- Inform patients that thrombotic thrombocytopenic purpura (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

Invasive procedures¹

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 healthcare professional before stopping Effient

Concomitant medications¹

- 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

References:

1. Effient™ (prasugrel) prescribing information. Daiichi Sankyo, Inc. and Lilly USA, LLC.
2. Sponsor Briefing Document, FDA Advisory Committee, Pg. 94, Table 6.26.



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The logo for Effient (prasugrel) tablets. It features a stylized green leaf-like graphic on the left, followed by the word "Effient" in a bold, green, sans-serif font with a trademark symbol. Below "Effient" is the text "(prasugrel) tablets" in a smaller, black, sans-serif font.

**This is a representation of an electronic record that was signed electronically and
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/s/

Robert Temple
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