

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-307

**RISK ASSESSMENT AND RISK MITIGATION
REVIEW(S)**

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

Eli Lilly and Company
Lilly Corporate Center, Indianapolis, IN 46285
Telephone: 317-276-2000, Fax: 317-433-2255 (US regulatory affairs)

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.

MEDICATION GUIDE

Effient™ (Ef'-fee-ent) (prasugrel) Tablets

Read this Medication Guide before you start taking Effient and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your doctor about your medical condition or your treatment.

What is the most important information I should know about Effient?

- Effient is used to lower your chance of having a heart attack or other serious problems with your heart or blood vessels. But, Effient can cause bleeding, which can be serious, and sometimes lead to death. You should not start to take Effient if it is likely that you will have heart bypass surgery (coronary artery bypass graft surgery or CABG) right away. You have a higher risk of bleeding if you take Effient and then have heart bypass surgery.
- **Do not take Effient if you:**
 - currently have abnormal bleeding, such as stomach or intestinal bleeding, or bleeding in your head
 - have a history of stroke, or “mini-stroke” (transient ischemic attack or TIA)
- You should stop taking Effient if you have a stroke.
- **Whenever possible, you should stop taking Effient at least 7 days before any surgery, as instructed by the doctor who prescribed Effient for you.**

You may also have a higher risk of bleeding if you take Effient and:

- have had trauma, such as an accident or surgery
- have stomach or intestine bleeding that is recent or keeps coming back, or you have a stomach ulcer
- have severe liver problems
- weigh less than 132 pounds
- take other medicines that increase your risk of bleeding, including:
 - warfarin sodium (Coumadin*, Jantoven*)
 - a medicine that contains heparin
 - other medicines to prevent or treat blood clots
 - non-steroidal anti-inflammatory drugs (NSAIDs) for a long time

Tell your doctor if you take any of these medicines. Ask your doctor if you are not sure if your medicine is one listed above.

- Effient increases your risk of bleeding because it lessens the ability of your blood to clot. While you take Effient:
 - you will bruise and bleed more easily
 - you are more likely to have nose bleeds
 - it will take longer for any bleeding to stop
- Call your doctor right away if you have any of these signs or symptoms of bleeding:
 - unexpected bleeding or bleeding that lasts a long time

- bleeding that is severe or you can not control
 - pink or brown urine
 - red or black stools (looks like tar)
 - bruises that happen without a known cause or get larger
 - cough up blood or blood clots
 - vomit blood or your vomit looks like “coffee grounds”
- **Do not stop taking Effient without talking to the doctor who prescribes it for you. People who are treated with angioplasty and have a stent, and stop taking Effient too soon, have a higher risk of a blood clot in the stent, having a heart attack, or dying. If you must stop Effient because of bleeding, your risk of a heart attack may be higher. See “What are the possible side effects of Effient?” for more information about side effects.**

What is Effient?

Effient is a prescription medicine used to treat people who:

- have had a heart attack or severe chest pain that happens when your heart does not get enough oxygen, and
- have been treated with a procedure called “angioplasty” (also called balloon angioplasty).

Effient is used to lower your chance of having another serious problem with your heart or blood vessels, such as another heart attack, a stroke, blood clots in your stent, or death.

Platelets are blood cells that help with normal blood clotting. Effient helps prevent platelets from sticking together and forming a clot that can block an artery or a stent.

It is not known if Effient is safe and works in children.

What should I tell my doctor before taking Effient?

Effient may not be right for you. Tell your doctor about all of your medical conditions, including if you:

- have any bleeding problems
- have a history of stomach ulcers, colon polyps, diverticulosis
- have liver problems
- have had any recent severe injury or surgery
- plan to have surgery or a dental procedure. See “What is the most important information I should know about Effient?”
- pregnant, or are planning to get pregnant. It is not known if Effient will harm your baby.
- if you are breast-feeding. It is not known if Effient passes into your breast-milk. You and your doctor should decide if you will take Effient or breast-feed. You should not do both without talking with your doctor.

Tell all of your doctors and dentists that you are taking Effient. They should talk to the doctor who prescribed Effient for you, before you have **any** surgery or invasive procedure.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Certain medicines may increase your risk of bleeding. See “What is the most important information I should know about Effient?”

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist when you get a new medicine.

How should I take Effient?

- Take Effient exactly as prescribed by your doctor.
- Take Effient one time each day.
- You can take Effient with or without food.
- Take Effient with aspirin as instructed by your doctor.
- Your doctor will decide how long you should take Effient. Do not stop taking Effient without first talking to the doctor who prescribed it for you. See “What is the most important information I should know about Effient?”
- If you miss a dose, take Effient as soon as you remember. If it is almost time for your next dose, skip the missed dose. Just take the next dose at your regular time. Do not take two doses at the same time unless your doctor tells you to.
- If you take too much Effient, call your local emergency room or poison control center right away.

What are the possible side effects of Effient?

Effient can cause serious side effects, including:

- See “What is the most important information I should know about Effient?”
- **A blood clotting problem called Thrombotic Thrombocytopenic Purpura (TTP).** TTP can happen with other medicines that are like Effient, sometimes after a short time (less than 2 weeks). TTP is a blood clotting problem where blood clots form in blood vessels and can happen all over the body. TTP needs to be treated in a hospital right away, because you may die. Get medical help right away if you have any of these symptoms and they can not be explained by another medical condition:
 - purplish spots called purpura on the skin or mucous membranes (such as on the mouth) due to bleeding under the skin
 - paleness or jaundice (a yellowish color of the skin or eyes)
 - feeling tired or weak
 - fever
 - fast heart rate or feeling short of breath
 - headache, speech changes, confusion, coma, stroke, or seizure
 - low amount of urine, or urine that is pink-tinged or has blood in it
 - stomach area (abdominal) pain, nausea, vomiting, or diarrhea
 - visual changes

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all of the possible side effects of Effient. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects.

You may report side effects to FDA at 1-800-FDA-1088.

How should I store Effient?

- Keep Effient at room temperature between 59°F to 86°F (15°C to 30°C).
- Keep Effient in the container it comes in.
- Keep the container closed tightly with the gray cylinder inside.
- Protect Effient from moisture.

Keep Effient and all medicines out of the reach of children.

General Information about Effient

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Effient for a condition for which it was not prescribed. Do not give your Effient to other people, even if they have similar symptoms. It may harm them.

This Medication Guide summarizes the most important information about Effient. If you would like more information about Effient, talk with your doctor or pharmacist. For more information, call 1-800-545-5979 or go to the following website: www.Effient.com

What are the ingredients in Effient?

Active Ingredient: prasugrel

Inactive Ingredients: mannitol, hypromellose, croscarmellose sodium, microcrystalline cellulose, and vegetable magnesium stearate. The color coatings contain lactose, hypromellose, titanium dioxide, triacetin, iron oxide yellow, and iron oxide red (only in Effient 10 mg tablet).

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Issued Month dd, yyyy

Manufactured by Eli Lilly and Company, Indianapolis, IN, 46285
Marketed by Daiichi Sankyo, Inc. and Eli Lilly and Company

This Medication Guide has been approved by the U.S. Food and Drug Administration.



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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