HeartMate II Outcomes Continue to Improve

BY DOUG BRUNK

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FROM THE ANNUAL MEETING OF THE SOCIETY OF THORACIC SURGEONS

SAN DIEGO - Survival rates of patients implanted with the HeartMate II ventricular assist device have improved significantly, according to a long-term multicenter analysis designed to compare outcomes from the time of the clinical trial to those in the post-Food and Drug Administration approval period. Excellent outcomes have been maintained and the incidence of adverse events has trended downward with the HeartMate II, a continuous-flow left ventricular assist device (LVAD) for bridge to heart transplantation, Dr. Ranjit John said at the meeting.

A multicenter trial of the HeartMate II, manufactured by Thoratec Corp., was conducted from 2005 to 2008 and led to FDA clearance of the device for bridge to transplantation. Since FDA clearance in April 2008, more than 1,400 additional patients implanted with the device for bridge to transplantation have been tracked by the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS), which is funded by the National Institutes of Health.

The HeartMate II, also cleared for destination therapy, has been implanted in more than 6,000 patients worldwide, with more than 5,000 patient years of support, according to Dr. John, of the department of cardiothoracic surgery at the University of Minnesota, Minneapolis.

The original trial of the device enrolled 486 bridge to transplantation patients at 36 centers in North America between March 2005 and April 2008. The post-trial commercial use study enrolled

Effient® (prasugrel) tablets **Brief Summary of Prescribing Information**

BRIEF SUMMARY: Please see Full Prescribing Information for additional information about Effient.

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

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[®] 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

Emerit has been shown to reduce the rate of a combined emploint 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 UANSTEMI patients until coronary anatomy was established. For the small fraction of patients that required urgent CABG after treatment with Efficient, the risk of significant bleeding was substantial Isee 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 Initiate Ement treatment as a single ou ring or a locuing use and then continue at 10 mg or ally once daily. Patients taking Effent should also take aspirin (75 mg to 325 mg) daily [see Drug Interactions (7) and Clinical Pharmacology (12.3)]. Effent may be administered with or without food [see Clinical Pharmacology (12.3)] and Clinical Studies (141) and Clinical Studies (14)].

Dosing in Low Weight Patients: Compared to patients weighing ≥ 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.

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

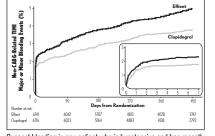
in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel), patients with a history of TIA or ischemic stroke (>3 months prior to enrollment) had a higher rate of stroke on Effient (6.5%; of which 4.2% were thrombotic stroke and 2.3% were intracranial hemorrhage [[CH]] than on clopidogrel (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 humorrhagic stroke at any time were excluded from TRTON-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)1

4.3 Hypersensitivity: Effient is contraindicated in patients with hypersensitivity (e.g., anaphylaxis) to prasugrel or any component of the product *[see Adverse Reactions (6.2)]*.

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 >5 g/dL, is interpreted becardress and TIMI (Mise can be becard as a factor). or intracranial hemoglobin of ≥ 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).

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



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 Contraindication's (4.1 and 4.2)]. Other risk factors for bleeding are:

 Age ≥75 years. Because of the risk of bleeding (including fatal bleeding) and uncertain effectiveness in patients ≥75 years of age, use of Effient is generally not recommended in these patients except in high-risk situations (patients with diabetes or history of myocardial infarction) where its effect appears to be greater and its use may be considered [see Adverse Reactions (6.1), Use in Specific Populations (8.5), Clinical Pharmacology (12.3), and Clinical Trials (14)].

CABG or other surgical procedure [see Warnings and

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

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 prasugrel's active metabolite is short relative to the lifetime of the platelet, it may be possible to restore hemostasis by administering exogenous pla however, platelet transfusions within 6 hours of the loading dose or 4 hours of the maintenance dose may be less effective.

5.2 Coronary Artery Bypass Graft Surgery-Related Bleeding: The risk of bleeding is increased in patients receiving Effient who undergo CABG. If possible. Effient should be discontinued at least 7 days prior to CABG

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 clopidogrel group [see Adverse] Reactions (6.1)]. The higher risk for bleeding events in patients treated

with Effient persisted up to 7 days from the most recent dose of study drug. For patients receiving a thienopyridine within 3 days prior to CABG, the frequencies of TIMI Major or Minor bleeding were 26.7% (12) of 45 patients) in the Effient group, compared with 5.0% (3 of 60 patients) in the clopidogrel group. For patients who received their last dose of thienopyridine within 4 to 7 days prior to CABG, the frequencies decreased to 11.3% (9 of 80 patients) in the prasugrel group and 3.4% (3 of 89 patients) in the clopidogrel group.

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.

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

5.4 Thrombotic Thrombocytopenic Purpura: Thrombotic thrombocytopenic purpura (TTP) has been reported with the use of Effient. TTP can occur after a brief exposure (< 2 weeks). TTP is a serious condition that can be fatal and requires urgent treatment, including plasmapheresis (plasma exchange). TTP is characterized by thrombocytopenia, microangiopathic hemolytic anemia (schistocytes [fragment red blood cells] seen on peripheral smear), neurological findings, renal dysfunction, and fever [see Adverse Reactions (6.2)].

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience: The following serious adverse Bleeding [see Boxed Varning and Varnings and Precautions (5.1, 5.2)]

• Thrombotic thrombocytopenic purpura [see Warnings and

• Informotic functional participation of the par months; 4136 patients were treated for more than 1 year). The population treated with Effient was 27 to 96 years of age, 25% female, and 92% Caucasian. All patients in the TRITON-TIMI 38 study were to receive aspirin. The dose of clopidogrel in this study was a 300 mg loading dose and 75 mg once daily.

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

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

Bleeding: Bleeding Unrelated to CABG Surgery - In TRITON-TIMI 38, overall rates of TIMI Major or Minor bleeding adverse reactions unrelated to coronary artery bypass graft surgery (CABG) were significantly higher on Effient than on clopidogrel, as shown in Table 1. Table 1: Non-CARG-Related Rieeding^a (TRITON-TIMI 38)

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	Effient (%) (N=6741)	Clopidogrel (%) (N=6716)	p-value		
TIMI Major or Minor bleeding	4.5	3.4	p=0.002		
TIMI Major bleeding ^b	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 ^b	2.4	1.9	n=0.022		

Patients may be counted in more than one row. ^b See 5.1 for definition.

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

1,496 patients at 83 centers between April 2008 and September 2010. The study's primary end point was survival. Secondary end points included frequency of adverse events and complications, functional status as assessed by the 6minute walk, and quality of life as assessed by the Kansas City Cardiomyopathy Questionnaire in the original trial and the EuroQol (EQ-5D) instrument in the post trial.

Dr. John reported that the 1-year survival rate improved significantly from 76% in the original trial to 85% in post trial. "With every era of the trial, there

DR. JOHN

lessons learned from the early phases of the original trial," he commented.

Bleeding rates in patients with the risk factors of age ≥75 years and weight <60 kg are shown in Table 2. to reliably estimate their frequency or establish a causal relationship to drug exposure. Table 2: Bleeding Rates for Non-CABG-Related Bleeding by Weight and Age (TRITON-TIMI 38)

• • •				
	Major/Minor		Fatal	
	Effient (%)	Clopidogrel (%)	Effient (%)	Clopidogrel (%)
Weight <60kg (N=308 Effient, N=356 clopidogrel)	10.1	6.5	0.0	0.3
Weight ≥60kg (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

Bleeding Related to CABG - In TRITON-TIMI 38, 437 patients who Executed at hieropyridine underwent CABG during the 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 clopidogrel group (Table 3). The higher risk for bleeding adverse reactions in patients treated with Effient persisted up to 7 days from the most recent dose of study drug. Table 3: CABG-Related Bleeding® (TRITON-TIMI 38)

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

^a Patients may be counted in more than one row

Bleeding Reported as Adverse Reactions - Hemorrhagic events Bleeding Heported as Adverse Heactions - Hemorrhagic events reported as adverse reactions in TRITON-TIMI 38 were, for Effient and clopidogrel, respectively: 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%), pericardial effusion/hemorrhage (1.0%) 0.2%), and retinal hemorrhage (0.0%, 0.1%).

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

Other Adverse Events: In TRITON-TIMI 38. common and other important <u>Oter Average Press</u>, in Hindow Hindo & Common and Oter Hindowan non-hemorrhagic adverse events were, for Effent and clopidogrel, respectively: severe thrombocytopenia (0.06%, 0.04%), anemia (2.2%, 2.0%), abnormal hepatic function (0.22%, 0.27%), allergic reactions (0.36%, 0.36%), and angioedema (0.06%, 0.04%). Table 4 summarizes the adverse events reported by at least 2.5% of patients.

Table 4: Non-Hemorrhagic Treatment Emergent Adverse 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 10º 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

6.2 Postmarketing Experience: The following adverse reactions have been identified during post approval use of Effient. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible

to reliably estimate their frequency or establish a causal relationship to drug exposure. Blood and lymphatic system disorders — Thrombocytopenia, Thrombotic thrombocytopenic purpura (TTP) [see Warnings and Precautions (5.4) and Patient Counseling Information (17.3)] Immune system disorders — Hypersensitivity reactions including anaphylaxis [see Contraindications (4.3)]

7 DRUG INTERACTIONS

7.1 Warfarin: Coadministration of Effient and warfarin increases the risk of bleeding [see Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)].

72 Non-Steroidal Anti-Inflammatory Drugs: Coadministration of Effient and NSAIDs (used chronically) may increase the risk of bleeding [see Warnings and Precautions (5.1)]. 7.3 Other Concomitant Medications: Effient can be administe

with drugs that are inducers or inhibitors of cytochrome P450 enzymes [see Clinical Pharmacology (12.3)].

Effient can be administered with aspirin (75 mg to 325 mg per day), heparin, GPIIb/IIIa inhibitors, statins, digoxin, and drugs that elevate gastric pH, including proton pump inhibitors and H₂ blockers [see Clinical Pharmacology (12.3)].

8 USE IN SPECIFIC POPULATIONS

8 USE IN SPECIFIC POPULATIONS 8.1 Pregnancy: Pregnancy Category B - There are no adequate and well controlled studies of Efficient use in pregnant women. Reproductive and developmental toxicology studies in rats and rabbits at doses of up to 30 times the recommended therapeutic exposures in humans changed an elemen curvement. In the argin critic element human (based on plasma exposures to the major circulating human metabolite) revealed no evidence of fetal harm; however, animal studies are not always predictive of a human response. Effient should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

In embryo fetal developmental toxicology studies, pregnant rats and In other you have been and the second in either species. In prenatal and postnatal rat studies, maternal treatment with prasugrel had no effect on the behavioral or reproductive development of the offspring at doses greater than 150 times the human exposure *[see Nonclinical Toxicology (13.1)]*.

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

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

85 Geriatric Use: In TRITON-TIMI 38, 38.5% of patients were ≥65 years of age and 13.2% were ≥75 years of age. The risk of bleeding increased with advancing age in both treatment groups, although the relative risk of bleeding (Effient compared with clopidogrel) was similar across age groups.

Patients ≥75 years of age who received Effient had an increased risk fatal bleeding events (1.0%) compared to patients who received copidogrel (0.1%). In patients ≥75 years of age, symptomatic intracranial hemorrhage occurred in 7 patients (0.8%) who received Effient and in 3 patients (0.3%) who received clopidogrel. Because of the risk of bleeding, and because effectiveness is uncertain in patients 75 years of a concertain (0.4%) who received patients (0.8%) who received patients (0.4%) who received patients (0.4% ≥75 years of age *[see Clinical Studies (14)*], use of Effient is generally not recommended in these patients, except in high-risk situations (diabetes and past history of myocardial infarction) where its effect appears to be greater and its use may be considered [see Warnings and Precautions (5.1), Clinical Pharmacology (12.3), and Clinical Studies (14)].

8.6 Low Body Weight: In TRITON-TIMI 38, 4.6% of patients treated with Efficient had body weight <60 kg. Individuals with body weight <60 kg had an increased risk of bleeding and an increased exposure to the No ned an increased nost of increasing and an increased exposite to the active metabolite of prasugrel [see Dosage and Administration (2), *Warnings and Precautions* (5.1), and *Clinical Pharmacology* (12.3)]. Consider lowering the maintenance dose to 5 mg in patients <60 kg. The effectiveness and safety of the 5 mg dose have not been argumentificult distribution. prospectively studied.

8.7 Renal Impairment: No dosage adjustment is necessary for patients with renal impairment. There is limited experience in patients with end-stage renal disease [see Clinical Pharmacology (12.3)].

8.8 Hepatic Impairment: No dosage adjustment is necessary in with mild to moderate hepatic impairment (Child-Pugh Class A and B). The pharmacokinetics and pharmacodynamics of prasugre

in patients with severe hepatic disease have not been studied, but such patients are generally at higher risk of bleeding *[see Warnings* and *Precautions (5.1)* and *Clinical Pharmacology (12.3)*].

8.9 Metabolic Status: In healthy subjects, patients with stable atherosclerosis, and patients with ACS receiving prasugrel, there was

References: 1. Effient® (prasugrel) prescribing information. Daiichi Sankyo, Inc. and Eli Lilly and Company. 2. Data on file: #EFF20100129h: DSI/Lilly. 3. Data on file: #EFF20091204b: DSI/Lilly. 4. Data on file: #EFF20100129h: DSI/Lilly.

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The percentage of patients transplanted by 1 year decreased from 48% in the original trial to 39% in the post trial, while the percentage of patients receiving ongoing support increased from 32% in the original trial to 45% in the post trial.

The overall incidences of bleeding and infection in the post trial were 36% and 38%, respectively. Specifically, the incidence of bleeding requiring surgical reexploration was 7%, while the incidence of driveline infections was 13%.

The incidence of adverse events trended downward in the post trial, compared

no relevant effect of genetic variation in CYP2B6, CYP2C9, CYP2C19, or CYP3A5 on the pharmacokinetics of prasugrel's active metabolite or its inhibition of platelet aggregation. 10 OVERDOSAGE

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

10.2 Recommendations about Specific Treatment: Platelet transfusion may restore clotting ability. The prasugrel active metabolite is not likely to be removed by dialysis.

13 NONCLINICAL TOXICOLOGY

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

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

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

· 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).

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minute walk test. At 6 months, the proportion of patients who could complete the test improved to 92% and 94%, respectivelv.

Dr. John also reported that quality of life measures improved in up to 6 months in the original trial and up to 12 months in the post trial.

with the original trial. For example, the

incidence of bleeding requiring reex-

ploration was 21% in the original trial

vs. 7% in the post-trial group. Similar de-

clines were seen in the incidence of per-

cutaneous lead infections (20% vs. 13%,

respectively), right heart failure requir-

ing right ventricular assist device (7% vs.

1%), and the need for device replace-

At baseline, only 13% of patients in

the original trial and 16% of patients in

the post trial could complete the 6-

The invited discussant, Dr. Michael A. Acker, said that the results of the post trial demonstrate "that new VAD technology that utilizes continuous flow - a disruptive concept compared to pulsatile flow – can be taught, along with appro-

Major Finding: The 1-year survival rate improved significantly from 4 76% in the original HeartMate II trial to 85% in a commercial use trial of the device.

Data Source: A study of 1,496 patients at 83 centers who received the device between April 2008 and September 2010 for bridge to transplantation.

Disclosures: Dr. John disclosed that he received a research grant from Thoratec Corp. to conduct the study. One of the study investigators is employed by the company.

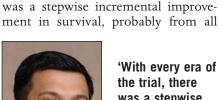
priate patient selection, and can be disseminated to a broad range of clinical centers. If similar successful dissemination occurs after the destination therapy approval, small continuous-flow pumps will constitute a paradigm shift for the treatment of end-stage heart failure."

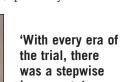
Dr. Acker, who heads the cardiovascular surgery division at the University of Pennsylvania Medical Center, Philadelphia, noted that the trial also demonstrates "that mandatory prospective databases such as INTERMACS are essential for monitoring outcomes and providing feedback needed to improve results.'

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ment (5% vs. 1%).

29

incremental improvement in survival.'