

# Triple-Drug Pill Shows Promise to Reduce BP

VITALS

**Major Finding:** After 12 weeks, 66% of blacks and 72% of nonblacks reached a target BP goal of less than 140/90 mm Hg and 23% of blacks and 29% of nonblacks reached a target of less than 120/80 mm Hg by taking a pill combining three different medications, compared with those who took dual-combination therapies for 12 weeks.

**Data Source:** A phase III, randomized, parallel-group study of 2,492 adults with moderate to severe hypertension.

**Disclosures:** The study was funded by Daiichi Sankyo Inc. Dr. Oparil has received research grants from, and served as a speaker or consultant for, multiple pharmaceutical companies, including Daiichi Sankyo.

BY HEIDI SPLETE

FROM THE ANNUAL MEETING OF THE  
INTERNATIONAL SOCIETY ON  
HYPERTENSION IN BLACKS

WASHINGTON — A triple-combination pill including 40 mg olmesartan, 10 mg amlodipine, and 25 mg hydrochlorothiazide significantly improved diastolic and systolic blood pressure in black and nonblack adults with moderate

to severe hypertension, based on an investigational study.

Dr. Suzanne Oparil of the University of Alabama at Birmingham and her colleagues reviewed data from 2,492 patients in TRINITY, a randomized, phase III, parallel-group study conducted at 317 U.S. and Puerto Rico clinical sites.

The primary measure of effectiveness was a significant reduction in seated diastolic BP after 12 weeks of daily treatment; the secondary measure was a significant reduction in systolic BP over the same period, Dr. Oparil said at the meeting.

Patients were randomized to receive one of four treatment protocols: 40 mg olmesartan, 10 mg amlodipine, and 25 mg hydrochlorothiazide (HCTZ); 40 mg olmesartan and 10 mg amlodipine; 40 mg olmesartan and 25 mg HCTZ; and 10 mg amlodipine and 25 mg HCTZ.

All treatment regimens yielded significant improvements in both systolic and diastolic BP compared with baseline measures. But the triple-drug combination reduced seated diastolic BP by an average of 20.8 mm Hg in black patients and 21.8 mm Hg in nonblack patients, which was significantly greater than the reductions in the three dual-therapy combinations.

The triple-drug combination also significantly reduced systolic BP in blacks and nonblacks, with average reductions of 37.1 mm Hg and 38.9 mm Hg, respectively, both of which were significantly greater than the reductions in each of the three dual-therapy combinations.

In addition, 66% of blacks and 72% of nonblacks with a target BP goal of less than 140/90 mm Hg were able to reach their goal on the triple-combination regimen, as were 23% of blacks and 29% of nonblacks with a target BP goal of less than 120/80 mm Hg. The percentages in the triple-combination group were significantly higher than those in any of the dual-therapy groups.

The researchers excluded pregnant or lactating women and individuals with severe renal insufficiency, uncontrolled diabetes, uncontrolled hypertension, and a history of significant cardiac disease. The baseline demographics were similar across all groups, and the mean age of the patients was 54 years. About 15% of the study population had controlled diabetes, and about 63% were obese.

The incidence of adverse events was similar in all four treatment groups. Adverse events that emerged during treatment in at least 3% of any group included dizziness, headache, peripheral edema, fatigue, and nausea.

**Disclosures:** The study was funded by Daiichi Sankyo Inc. Dr. Oparil has received research grants from, and been a speaker or consultant for, multiple pharmaceutical companies, including Daiichi Sankyo.

**Editor's note:** At press time, Daiichi Sankyo announced that the drug combination had received Food and Drug Administration approval for the treatment of uncontrolled hypertension, and that it would be marketed as Tribenzor.

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 received a thienopyridine 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)

	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

\*Patients may be counted in more than one row.

**Bleeding Reported as Adverse Reactions** - 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%), and retinal hemorrhage (0.0%, 0.1%).

**Malignancies:** 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 non-hemorrhagic adverse events were, for Effient 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 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

## 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)].

**7.2 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 administered 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 H<sub>2</sub> blockers [see Clinical Pharmacology (12.3)].

## 8 USE IN SPECIFIC POPULATIONS

**8.1 Pregnancy:** Pregnancy Category B - There are no adequate and well controlled studies of Effient 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 (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 rabbits received prasugrel at maternally toxic oral doses equivalent to more than 40 times the human exposure. A slight decrease in pup body weight was observed; but, there were no structural malformations 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 human milk; however, metabolites of Effient 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)].

**8.5 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 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 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 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 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 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 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 patients with mild to moderate hepatic impairment (Child-Pugh Class A and B). The pharmacokinetics and pharmacodynamics of prasugrel in patients with severe hepatic disease have not been studied, 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 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 dogs included emesis, increased serum alkaline phosphatase, and hepatocellular atrophy. Symptoms of acute toxicity in rats included mydriasis, irregular respiration, decreased locomotor activity, ptosis, staggering gait, and lacrimation.

**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-year 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 intraperitoneal 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 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).

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