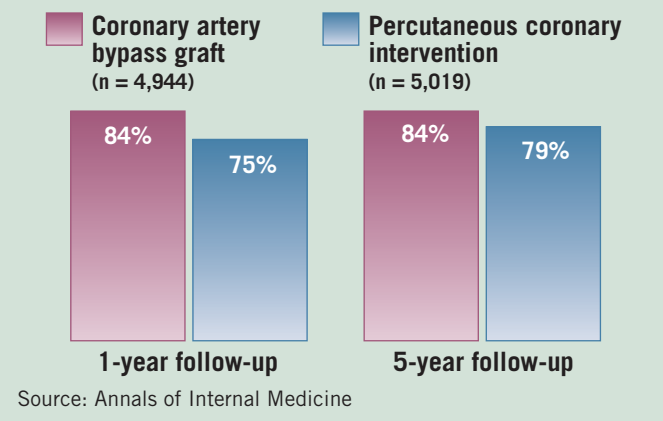


## Percentage of Patients Experiencing Angina Relief



## CABG Relieves Angina Better Than PCI

BY MARY ANN MOON  
Contributing Writer

Coronary artery bypass grafting was more effective at relieving angina, and required fewer repeat revascularization procedures, than did percutaneous coronary interventions, according to investigators who conducted a review of randomized clinical trials reported in the literature.

Neither procedural survival nor

long-term survival differed significantly between CABG and PCI, but the short-term risk for stroke was significantly higher for CABG, the researchers said.

Dr. Dena M. Bravata and her associates at Stanford (Calif.) University's center for primary care and outcomes research reviewed 23 randomized trials that directly compared the effectiveness of the two approaches to revascularization. The trials included nearly

10,000 subjects in whom both procedures were technically feasible (5,019 randomly assigned to undergo PCI and 4,944 assigned to CABG). Most of the studies took place in Europe.

The rate of procedure-related stroke, reported in 15 of the trials, was higher for CABG (1.2%) than for PCI (0.6%).

Follow-up in the clinical trials ranged from 6 months to 13 years. Long-term survival was not signifi-

**Amitiza®**  
(lubiprostone) Capsules

Initial U.S. Approval: 2006

**BRIEF SUMMARY OF PRESCRIBING INFORMATION-** Please see package insert for complete prescribing information.

### 1 INDICATIONS AND USAGE

Amitiza® is indicated for the treatment of chronic idiopathic constipation in adults.

### 2 DOSAGE AND ADMINISTRATION

The recommended dosage for Amitiza is 24 mcg taken twice daily orally with food. Physicians and patients should periodically assess the need for continued therapy.

### 3 DOSAGE FORMS AND STRENGTHS

Amitiza is available as an oval, orange, soft gelatin capsule with "SPI" printed on one side. Each capsule contains 24 mcg of lubiprostone.

### 4 CONTRAINDICATIONS

Amitiza is contraindicated in patients with known mechanical gastrointestinal obstruction.

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Pregnancy

The safety of Amitiza in pregnancy has not been evaluated in humans. In guinea pigs, lubiprostone has been shown to have the potential to cause fetal loss. Amitiza should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Women who could become pregnant should have a negative pregnancy test prior to beginning therapy with Amitiza and should be capable of complying with effective contraceptive measures. See *Use in Specific Populations* (8.1).

#### 5.2 Nausea

Patients taking Amitiza may experience nausea. If this occurs, concomitant administration of food with Amitiza may reduce symptoms of nausea. See *Adverse Reactions* (6.1).

#### 5.3 Diarrhea

Amitiza should not be prescribed to patients that have severe diarrhea. Patients should be aware of the possible occurrence of diarrhea during treatment. Patients should be instructed to inform their physician if severe diarrhea occurs. See *Adverse Reactions* (6.1).

#### 5.4 Bowel Obstruction

In patients with symptoms suggestive of mechanical gastrointestinal obstruction, the treating physician should perform a thorough evaluation to confirm the absence of such an obstruction prior to initiating therapy with Amitiza.

### 6 ADVERSE REACTIONS

#### 6.1 Clinical Studies Experience

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

*Adverse reactions in dose-finding, efficacy, and long-term clinical studies:*

The data described below reflect exposure to Amitiza in 1175 patients (29 at 24 mcg once daily, 1113 at 24 mcg twice daily, and 33 at 24 mcg three times daily) over 3- or 4-week, 6-month, and 12-month treatment periods; and from 316 patients receiving placebo over short-term exposure (≤ 4 weeks). The total population (N = 1491) had a mean age of 49.7 (range 19–86) years; was 87.1% female; 84.8% Caucasian, 8.5% African American, 5.0% Hispanic, 0.9% Asian; and 15.5% elderly (≥ 65 years of age). Table 1 presents data for the adverse reactions that occurred in at least 1% of patients who received Amitiza (any dosage) and that occurred more frequently with study drug than placebo. In addition, corresponding adverse reaction incidence rates in patients receiving Amitiza 24 mcg once daily and in patients receiving Amitiza 24 mcg twice daily are shown.

**Table 1: Percent of Patients with Adverse Reactions in Clinical Studies of Amitiza**

System/Adverse Reaction <sup>1</sup>	Placebo	Amitiza 24 mcg	Amitiza 24 mcg	Amitiza
	N = 316 %	Once Daily N = 29 %	Twice Daily N = 1113 %	Any Dosage <sup>2</sup> N = 1175 %
<b>Gastrointestinal disorders</b>				
Nausea	3	17	29	29
Diarrhea	<1	7	12	12
Abdominal pain	3	3	8	8
Abdominal distension	2	–	6	6
Flatulence	2	3	6	5
Vomiting	–	–	3	3
Loose stools	–	–	3	3
Abdominal discomfort <sup>3</sup>	–	3	2	2
Dyspepsia	<1	–	2	2
Dry mouth	<1	–	1	1
Stomach discomfort	<1	–	1	1
<b>Nervous system disorders</b>				
Headache	5	3	11	11
Dizziness	<1	3	3	3
<b>General disorders and site administration conditions</b>				
Edema	<1	–	3	3
Fatigue	<1	–	2	2
Chest discomfort/pain	–	3	2	2
<b>Respiratory, thoracic, and mediastinal disorders</b>				
Dyspnea	–	3	2	2

<sup>1</sup> Includes only those events associated with treatment (possibly, probably, or definitely related, as assessed by the investigator).

<sup>2</sup> Includes patients dosed at 24 mcg once daily, 24 mcg twice daily, and 24 mcg three times daily.

<sup>3</sup> This term combines "abdominal tenderness," "abdominal rigidity," "gastrointestinal discomfort," and "abdominal discomfort."

**Nausea:** Approximately 29% of patients who received Amitiza (any dosage) experienced an adverse reaction of nausea; 3% of patients had severe nausea while 8% of patients discontinued treatment due to nausea. The rate of nausea associated with Amitiza (any dosage) was substantially lower among male (7%) and elderly patients (18%). Further analysis of the safety data revealed that long-term exposure to Amitiza does not appear to place patients at an elevated risk for experiencing nausea. The incidence of nausea increased in a dose-dependent manner with the lowest overall incidence for nausea reported at the 24 mcg once daily dosage (17%). In open-labeled, long-term studies, patients were allowed to adjust the dosage of Amitiza down to 24 mcg once daily from 24 mcg twice daily if experiencing nausea. Nausea decreased when Amitiza was administered with food. No patients in the clinical studies were hospitalized due to nausea.

**Diarrhea:** Approximately 12% of patients who received Amitiza (any dosage) experienced an adverse reaction of diarrhea; 3% of patients had severe diarrhea while 2% of patients discontinued treatment due to diarrhea.

**Electrolytes:** No serious adverse reactions of electrolyte imbalance were reported in clinical studies, and no clinically significant changes were seen in serum electrolyte levels in patients receiving Amitiza.

**Less common adverse reactions:** The following list of adverse reactions includes those that occurred in less than 1% of patients receiving Amitiza (any dosage) in dose-finding, efficacy, and long-term clinical studies and that were considered by the investigator to be probably or definitely related to treatment with study drug. Moreover, the list includes only those events that occurred in at least two patients and more frequently in patients receiving Amitiza than those receiving placebo.

**Gastrointestinal disorders:** fecal incontinence, defecation urgency, frequent bowel movements, intestinal functional disorder, constipation, eructation  
**Musculoskeletal and connective tissue disorders:** muscle cramp, joint swelling, myalgia

**Nervous system disorders:** dysgeusia, syncope, tremor

**Respiratory, thoracic, and mediastinal disorders:** pharyngolaryngeal pain, cough

**Skin and subcutaneous tissue disorders:** hyperhidrosis, cold sweat  
**General disorders and administration site conditions:** influenza, pain

**Metabolism and nutrition disorders:** decreased appetite

**Psychiatric disorders:** anxiety

icantly different at any time point: 96.4% for CABG and 96.5% for PCI at 1 year; 90.7% and 89.7%, respectively, at 5 years.

Angina relief was superior for CABG. At 1 year, 84% of CABG patients, compared with 75% of PCI patients, were free of angina. At 5 years, the proportions were 84% and 79%, respectively.

PCI patients were 24% more likely to require repeat revascularization (26% at 1 year and 40% at 5 years), compared with CABG patients (4% at 1 year and 10% at 5 years).

The review's finding of similar long-term survival for CABG and PCI differ from reports based on clinical registries,

which show improved survival after CABG, the investigators noted. "These observations suggest that the seemingly disparate results of randomized trials and clinical registries can be reconciled by taking into account that the overall outcomes in clinical registries are heavily weighted by the large number of events in the higher-risk patients with the most extensive disease, who appear to have better outcomes after CABG than after PCI." By contrast, overall outcomes in the randomized trials "were assessed in intermediate-risk patients, in whom CABG and PCI outcomes were also similar in clinical registries," they explained. ■

## Anemia Tied to Worse Acute Coronary Syndrome Outcomes

BY MITCHEL L. ZOLER  
Philadelphia Bureau

VIENNA — Anemia was a significant risk factor for worse outcomes in patients with acute coronary syndrome in a post hoc analysis of almost 14,000 patients enrolled in a recent trial.

Despite this evidence of anemia's risk, it's premature to conclude that treating

anemia—either with blood transfusions or with erythropoietin—is the best way to reduce the risk, Dr. Roxana Mehran said at the annual congress of the European Society of Cardiology.

"We believe that anemia is another risk factor, like age or diabetes, but there may be confounders when you find anemia in ACS [acute coronary syndrome] patients, so it's hard to tease out," said Dr. Mehran, director of outcomes research at the center for interventional vascular therapy at Columbia University, New York.

The effects of anemia in ACS were studied using data collected on 13,819 patients with either unstable angina or non-ST elevation myocardial infarction enrolled in the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial. The primary end point of the study showed that benefit and risk from treatment with the antithrombotic drug bivalirudin (Angiomax) alone was similar to standard treatment with a heparin (either unfractionated heparin or low-molecular-weight heparin) plus a glycoprotein IIb/IIIa inhibitor, or to treatment with bivalirudin plus a GP IIb/IIIa inhibitor (N. Engl. J. Med. 2006;355:2203-16).

The trial was sponsored by the Medicines Co., which markets Angiomax. Dr. Mehran is a speaker for and had received honoraria from the Medicines Co.

Anemia information at baseline was available for about 94% of patients, including 10,839 without anemia and 2,200 with anemia. The primary end point in the ACUITY trial was a composite risk and benefit measure for the first 30 days after treatment that added the total number of deaths, myocardial infarctions, unplanned revascularization procedures, and major bleeding events. For the patients with anemia, the rate was 16.2%, compared with a 10.2% rate in the nonanemic patients, a statistically significant difference, said Dr. Mehran. Anemia was linked with significantly worse outcomes for each of these outcome measures, except for the rate of unplanned revascularization. (See box.) The worse outcomes of patients with anemia were also seen uniformly regardless of how the ACS patients were managed. ■

### 6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Amitiza. 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.

Voluntary reports of adverse reactions occurring with the use of Amitiza include the following: syncope, malaise, increased heart rate, muscle cramps or muscle spasms, rash, and asthenia.

### 7 DRUG INTERACTIONS

Based upon the results of *in vitro* human microsome studies, there is low likelihood of drug-drug interactions. *In vitro* studies using human liver microsomes indicate that cytochrome P450 isoenzymes are not involved in the metabolism of lubiprostone. Further *in vitro* studies indicate microsomal carbonyl reductase may be involved in the extensive biotransformation of lubiprostone to the metabolite M3 (See *Pharmacokinetics, Metabolism* [12.3]). Additionally, *in vitro* studies in human liver microsomes demonstrate that lubiprostone does not inhibit cytochrome P450 isoforms 3A4, 2D6, 1A2, 2A6, 2B6, 2C9, 2C19, or 2E1, and *in vitro* studies of primary cultures of human hepatocytes show no induction of cytochrome P450 isoforms 1A2, 2B6, 2C9, and 3A4 by lubiprostone. No additional drug-drug interaction studies have been performed. Based on the available information, no protein binding-mediated drug interactions of clinical significance are anticipated.

### 8 USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy

*Teratogenic effects:* Pregnancy Category C. [See *Warnings and Precautions* (5.1).]

Teratology studies with lubiprostone have been conducted in rats at oral doses up to 2000 mcg/kg/day (approximately 332 times the recommended human dose, based on body surface area), and in rabbits at oral doses of up to 100 mcg/kg/day (approximately 33 times the recommended human dose, based on body surface area). Lubiprostone was not teratogenic in rats or rabbits. In guinea pigs, lubiprostone caused fetal loss at repeated doses of 10 and 25 mcg/kg/day (approximately 2 and 6 times the recommended human dose, respectively, based on body surface area) administered on days 40 to 53 of gestation.

There are no adequate and well-controlled studies in pregnant women. However, during clinical testing of Amitiza at 24 mcg twice daily, four women became pregnant. Per protocol, Amitiza was discontinued upon pregnancy detection. Three of the four women delivered healthy babies. The fourth woman was monitored for 1 month following discontinuation of study drug, at which time the pregnancy was progressing as expected; the patient was subsequently lost to follow-up.

Amitiza should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. If a woman is or becomes pregnant while taking the drug, the patient should be apprised of the potential hazard to the fetus.

#### 8.3 Nursing Mothers

It is not known whether lubiprostone is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from lubiprostone, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

#### 8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been studied.

#### 8.5 Geriatric Use

The efficacy of Amitiza in the elderly ( $\geq 65$  years of age) subpopulation was consistent with the efficacy in the overall study population. Of the total number of constipated patients treated in the dose-finding, efficacy, and long-term studies of Amitiza, 15.5% were  $\geq 65$  years of age, and 4.2% were  $\geq 75$  years of age. Elderly patients taking Amitiza (any dosage) experienced a lower incidence rate of associated nausea compared to the overall study population taking Amitiza (18% vs. 29%, respectively).

#### 8.6 Renal Impairment

Amitiza has not been studied in patients who have renal impairment.

#### 8.7 Hepatic Impairment

Amitiza has not been studied in patients who have hepatic impairment.

### 10 OVERDOSAGE

There have been two confirmed reports of overdosage with Amitiza. The first report involved a 3-year-old child who accidentally ingested 7 or 8 capsules of 24 mcg of Amitiza and fully recovered. The second report was a study patient who self-administered a total of 96 mcg of Amitiza per day for 8 days. The patient experienced no adverse reactions during this time. Additionally, in a Phase 1 cardiac repolarization study, 38 of 51

patients given a single oral dose of 144 mcg of Amitiza (6 times the recommended dose) experienced an adverse event that was at least possibly related to the study drug. Adverse reactions that occurred in at least 1% of these patients included the following: nausea (45%), diarrhea (35%), vomiting (27%), dizziness (14%), headache (12%), abdominal pain (8%), flushing/hot flash (8%), retching (8%), dyspnea (4%), pallor (4%), stomach discomfort (4%), anorexia (2%), asthenia (2%), chest discomfort (2%), dry mouth (2%), hyperhidrosis (2%), and syncope (2%).

### 16 HOW SUPPLIED/STORAGE AND HANDLING

Amitiza is available as an oval, orange, soft gelatin capsule with "SPI" printed on one side. Each capsule contains 24 mcg of lubiprostone. Amitiza is available as follows:

- Bottles of 100 (NDC 64764-240-10)
- Bottles of 60 (NDC 64764-240-60)

Store at 25°C (77°F); excursions permitted to 15°–30°C (59°–86°F).

PROTECT FROM EXTREME TEMPERATURES.

### 17 PATIENT COUNSELING INFORMATION

#### 17.1 Dosing Instructions

Patients should take a single 24 mcg capsule of Amitiza twice daily with food or a meal. The capsule should be taken once in the morning and once in the evening daily as prescribed. Physicians and patients should periodically assess the need for continued treatment with Amitiza.

#### 17.2 Nausea and Diarrhea

Patients should take Amitiza with food or a meal to reduce symptoms of nausea. Patients on treatment who experience severe nausea or diarrhea should inform their physician.

#### Marketed by:

Sucampo Pharmaceuticals, Inc., Bethesda, MD 20814  
and

Takeda Pharmaceuticals America, Inc., Deerfield, IL 60015

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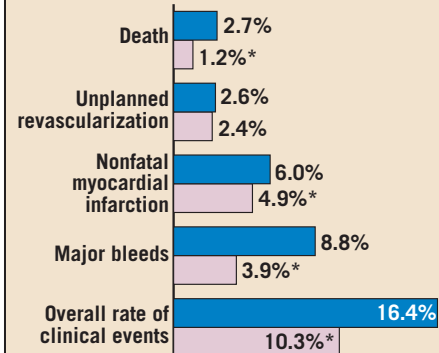
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### 30-Day Outcomes in Acute Coronary Syndrome

■ Anemia at baseline (n = 2,200) ■ No anemia at baseline (n = 10,839)



\*Statistically significant.

Source: Dr. Mehran