

Esophagectomy Deaths Not Tied to Case Volume

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Mid-Atlantic Bureau

Mortality after esophagectomy is related more to patient factors than to the volume of procedures performed annually at any given hospital, or even by an individual surgeon, according to an analysis of data extracted from the Nationwide Inpatient Sample.

The study, conducted by Dr. Michael

Rodgers and his colleagues at the Oregon Health and Science University in Portland, points up the difficulty of using volume thresholds to choose the best facility or surgeon to perform an esophagectomy.

The average adjusted mortality rate difference between the high- and low-volume hospitals was less than 1%, and the difference between the high- and low-volume surgeons was 3.5% (Arch. Surg. 2007;142:829-38).

Their study group comprised 3,243 esophagectomies performed from 1988 through 2000. The average national inpatient mortality rate was 11%, with a high of 14% in 1988 and low of 8.4% by 1999.

Although there was no significant trend over time, the mortality rate averaged 10% in the last 5 years of the study.

Mortality was significantly associated with gender, age, and race. Women were 1.5 times more likely to die, while blacks

and patients older than 65 years faced a doubling of the risk.

Peripheral vascular disease significantly increased the risk of death.

Other comorbidities, including obesity, valvular heart disease, diabetes, and chronic pulmonary disease, were not significantly associated with an increased risk.

Hypertension appeared to be protective, but the authors believed that could be caused by coding issues, and therefore might not be not a real effect.

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 ¹	Placebo	Amitiza 24 mcg Once Daily	Amitiza 24 mcg Twice Daily	Amitiza Any Dosage ²
	N = 316 %	N = 29 %	N = 1113 %	N = 1175 %
Gastrointestinal disorders				
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 ³	–	3	2	2
Dyspepsia	<1	–	2	2
Dry mouth	<1	–	1	1
Stomach discomfort	<1	–	1	1
Nervous system disorders				
Headache	5	3	11	11
Dizziness	<1	3	3	3
General disorders and site administration conditions				
Edema	<1	–	3	3
Fatigue	<1	–	2	2
Chest discomfort/pain	–	3	2	2
Respiratory, thoracic, and mediastinal disorders				
Dyspnea	–	3	2	2

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

² Includes patients dosed at 24 mcg once daily, 24 mcg twice daily, and 24 mcg three times daily.

³ 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

Mortality rates were similar at urban and rural hospitals and, in the multivariate analysis, teaching hospitals held no mortality advantage over nonteaching facilities.

Hospital volume was initially highly significantly associated with mortality, but that association disappeared when surgeon volume was factored into the analysis.

Surgeons who performed the most procedures had significantly lower patient mortality rates than did surgeons with lower volume; that difference remained significant even after overall hospital volume was factored in to the analysis.

However, the authors noted, the difference in mortality rates between surgeon groups was not great: Average inpatient mortality was 9.25% for high-volume surgeons (six or more cases per year), 7.5% for medium-volume surgeons (two to six cases per year), and 12.75% for low-volume surgeons (fewer than two cases per year).

Because of the wide scatter in each category, picking the best surgeon or hospital based on volume wouldn't work, the authors said.

"This is highlighted by the fact that one hospital with a caseload of more than 13 per year had a mortality rate of

25%, and one surgeon with caseload of more than 6 per year had a mortality rate of 40%. Choosing those particular providers on the basis of volume might well be a mistake," they noted.

A better alternative, they suggested, would be a national system of outcome benchmarks. "A benchmark-based system simply sets clear guidelines and allows institutions and surgeons to find their own means to achieve them," the investigators wrote. "In the medium term, it would also reassure patients that the institution they were going to had satisfactory and verified outcomes for that procedure." ■

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 (≥ 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 ≥ 65 years of age, and 4.2% were ≥ 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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Western Diet Linked to Colon Cancer Return

BY MARY ANN MOON

Contributing Writer

Colon cancer patients who eat a typical Western diet appear to have triple the risk of recurrence, compared with those who do not follow a Western diet.

After a potentially curative resection of stage III colon cancer and adjuvant chemotherapy, a diet replete with sweets, french fries, refined grains, and red and processed meats "may facilitate a milieu that allows residual microscopic disease to proliferate and spread," Dr. Jeffrey A. Meyerhardt of the Dana-Farber Cancer Institute, Boston, and his associates said.

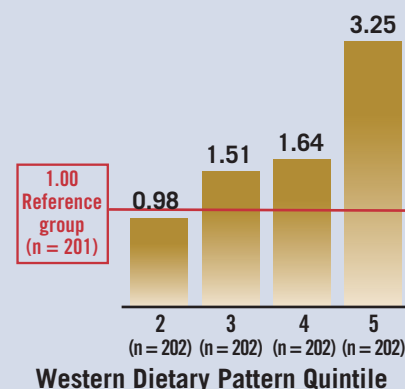
Numerous studies have examined the influence of diet and other lifestyle factors on the development of colon cancer, but few have addressed diet's influence in patients with established colon cancer. Dr. Meyerhardt and his associates assessed the effect of two distinct dietary patterns—a typical Western diet versus what the investigators termed a "prudent" diet that included greater intakes of fruits, vegetables, legumes, fish, poultry, and whole grains—in 1,009 adult subjects who were already participating in a National Cancer Institute trial comparing different chemotherapy regimens.

The subjects had undergone complete surgical resection of the primary tumor in 1999-2001, and were found to have regional lymph node metastases but no distant metastases. Their diets were assessed midway through the course of adjuvant chemotherapy. The patients were followed for a median of 5 years; a total of 324 developed a recurrence during follow-up.

Greater intake of a Western diet was associated with recurrence and with cancer mortality. Patients in the highest quintile of the Western dietary pattern were three times more likely to develop recurrence and to die from cancer than were those in the lowest quintile of the Western dietary pattern, Dr. Meyerhardt and his associates said (JAMA 2007;298:754-64).

In contrast, there was no association between the prudent diet and risk of cancer recurrence or cancer mortality. ■

Hazard Ratios of Cancer Recurrence or Death In Patients With Colon Cancer



Source: JAMA