

# Medicare May Cover DNA Stool Screening Test

The Centers for Medicare and Medicaid Services is considering whether to add DNA stool testing as an alternative method of colorectal cancer screening, the agency announced in August.

Exact Sciences holds the patent for the stool DNA analysis technology behind the PreGen-Plus test. The company has requested that the CMS cover a DNA stool test every 5 years as an alternative to a screening colonoscopy, which is covered

every 10 years, or as an alternative to sigmoidoscopy, which is covered every 4 years.

Currently, Medicare covers fecal occult blood testing, sigmoidoscopy, colonoscopy, and barium enema for average-risk beneficiaries aged 50 years and older.

The PreGen-Plus test, marketed by the Laboratory Corporation of America (LabCorp), costs about half as much as colonoscopy and is less invasive and uncomfortable, which might support better patient adherence to screening guidelines,

according to Exact Sciences. The company recommends that a follow-up colonoscopy be done for patients who test positive with PreGen-Plus.

However, an August 2006 BlueCross BlueShield Technology Evaluation Center assessment concluded that "several questions remain before fecal DNA screening can be widely recommended."

PreGen-Plus currently is not approved by the Food and Drug Administration, but is offered as a "home-brew" diagnostic

under the Clinical Laboratory Improvement Amendments.

PreGen-Plus has been on the market since 2003, and more than 300 private payers have paid for the test thus far, according to Exact Sciences president Jeff Luber.

The companies are waiting for the American Cancer Society to formally recommend stool DNA testing in its colorectal cancer guidelines before they "seek an FDA approval on a test kit of some kind," he said.

This step will mandate coverage by private insurers in 19 states, Mr. Luber explained, adding that his company expects revised guidelines soon. "That's when the private payers start to look more closely at coverage."

The CMS expects to propose a decision by Feb. 2, 2008, and complete its analysis by May 1, 2008.

—Ingrid Mezo

Ingrid Mezo is a staff writer for Elsevier's "The Gray Sheet."

## AMITIZA™

(lubiprostone) soft gelatin capsules

**BRIEF SUMMARY OF PRESCRIBING INFORMATION—Please see package insert for complete prescribing information 720-03565**

### AMITIZA™

(lubiprostone)  
Soft Gelatin Capsules

### INDICATIONS AND USAGE

AMITIZA™ is indicated for the treatment of chronic idiopathic constipation in the adult population.

### CONTRAINDICATIONS

AMITIZA™ is contraindicated in those patients with a known hypersensitivity to the drug or any of its excipients, and in patients with a history of mechanical gastrointestinal obstruction.

### WARNINGS

Patients with symptoms suggestive of mechanical gastrointestinal obstruction should be evaluated prior to initiating AMITIZA™ treatment.

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 **Teratogenic Effects: Pregnancy Category C**).

### PRECAUTIONS

#### Patient Information:

AMITIZA™ may cause nausea. If this occurs, concomitant administration of food with AMITIZA™ may reduce symptoms of nausea. AMITIZA™ should not be administered to patients that have severe diarrhea. Patients should be aware of the possible occurrence of diarrhea during treatment. If the diarrhea becomes severe consult your physician.

#### 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 M3. 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 in primary cultures of human hepatocytes show no induction of the cytochrome P450 isoforms 1A2, 2B6, 2C9, and 3A4. 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.

#### Carcinogenesis, Mutagenesis, Impairment of Fertility:

Two 2-year oral (gavage) carcinogenicity studies (one in Crl:BB63F1 mice and one in Sprague-Dawley rats) were conducted with lubiprostone. In the 2-year carcinogenicity study in mice, lubiprostone doses of 25, 75, 200, and 500 mcg/kg/day (approximately 2, 6, 17, and 42 times the recommended human dose, respectively, based on body surface area) were used. In the 2-year rat carcinogenicity study, lubiprostone doses of 20, 100, and 400 mcg/kg/day (approximately 3, 17, and 68 times the recommended human dose, respectively, based on body surface area) were used. In the mouse carcinogenicity study, there was no significant increase in any tumor incidences. There was a significant increase in the incidence of interstitial cell adenoma of the testes in male rats at the 400 mcg/kg/day dose. In female rats, treatment with lubiprostone produced hepatocellular adenoma at the 400 mcg/kg/day dose.

Lubiprostone was not genotoxic in the *in vitro* Ames reverse mutation assay, the *in vitro* mouse lymphoma (L5178Y TK<sub>+</sub>) forward mutation assay, the *in vitro* Chinese hamster lung (CHL/IU) chromosomal aberration assay, and the *in vivo* mouse bone marrow micronucleus assay.

Lubiprostone, at oral doses of up to 1000 mcg/kg/day, had no effect on the fertility and reproductive function of male and female rats. The 1000 mcg/kg/day dose in rats is approximately 166 times the recommended human dose of 48 mcg/kg/day, based on the body surface area.

#### Teratogenic Effects: Pregnancy Category C:

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 and rabbits. In guinea pigs, lubiprostone caused fetal loss at repeated doses of 10 and 25 mcg/kg/day (approximately 2 and 6 times the 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 BID, 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.

#### 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.

#### Pediatric Use:

AMITIZA™ has not been studied in pediatric patients.

### ADVERSE REACTIONS

In clinical trials, 1429 patients received AMITIZA™ 24 mcg BID or placebo. Table 1 presents data for the adverse experiences that were reported in at least 1% of patients who received AMITIZA™ and that occurred more frequently on study drug than placebo. It should be noted that the placebo data presented are from short-term exposure (≤4 weeks) whereas the AMITIZA™ data are cumulative data that were collected over 3- or 4-week, 6-month, and 12-month observational periods and that some conditions are common among otherwise healthy patients over a 6- and 12-month observational period.

Table 1. Adverse Events Reported for Patients Treated with AMITIZA™

System/Adverse Experience	Placebo n = 316 %	AMITIZA™ 24 mcg QD n = 29 %	AMITIZA™ 24 mcg BID n = 1113 %	Any Active Dose* n = 1195 %
<b>Gastrointestinal disorders</b>				
Nausea	5.1	17.2	31.1	30.8
Diarrhea	0.9	10.3	13.2	13.2
Abdominal distension	2.2	0.0	7.1	6.8
Abdominal pain	2.6	3.4	6.7	6.6
Flatulence	1.9	3.4	6.1	5.9
Vomiting	0.9	0.0	4.6	4.4
Loose stools	0.0	0.0	3.4	3.2
Dyspepsia	1.3	0.0	2.9	2.7
Abdominal pain upper	1.9	0.0	2.2	2.1
Abdominal pain lower	0.6	0.0	1.9	1.9
Gastroesophageal reflux disease	0.6	0.0	1.8	1.7
Abdominal discomfort	0.0	3.4	1.5	1.5
Dry mouth	0.3	0.0	1.5	1.4
Constipation	0.9	0.0	1.1	1.0
Stomach discomfort	0.3	0.0	1.1	1.0
<b>Infections and infestations</b>				
Sinusitis	1.6	0.0	4.9	4.8
Upper tract infections	1.9	3.4	4.4	4.3
Upper respiratory tract infection	0.9	0.0	3.7	3.6
Nasopharyngitis	2.2	0.0	2.9	2.7
Influenza	0.6	0.0	2.0	1.9
Bronchitis	0.3	3.4	1.6	1.7
Gastroenteritis viral	0.0	3.4	1.0	1.0
Viral infection	0.3	3.4	0.5	0.6
<b>Nervous system disorders</b>				
Headache	6.6	3.4	13.2	13.0
Dizziness	1.9	3.4	4.1	4.0
Hypoaesthesia	0.0	3.4	0.5	0.6
<b>General disorders and site administration conditions</b>				
Edema peripheral	0.3	0.0	3.8	3.6
Fatigue	1.9	6.9	2.3	2.5
Chest discomfort	0.0	3.4	1.6	1.6
Chest pain	0.0	0.0	1.1	1.0
Fatigue	0.3	0.0	1.1	1.0
<b>Musculoskeletal and connective tissue disorders</b>				
Arthralgia	0.3	0.0	3.1	3.0
Back pain	0.9	3.4	2.3	2.3
Pain in extremity	0.0	3.4	1.9	1.9
Muscle cramp	0.0	0.0	1.0	0.9
<b>Respiratory, thoracic, and mediastinal disorders</b>				
Dyspnea	0.0	3.4	2.4	2.5
Pharyngolaryngeal pain	2.2	0.0	1.7	1.6
Cough	0.6	0.0	1.6	1.5
<b>Investigations</b>				
Weight increased	0.0	0.0	1.0	0.9
<b>Psychiatric disorders</b>				
Depression	0.0	0.0	1.4	1.4
Anxiety	0.3	0.0	1.4	1.4
Insomnia	0.6	0.0	1.4	1.4
<b>Vascular disorders</b>				
Hypertension	0.0	0.0	1.0	0.9

\*Includes patients dosed at 24 mcg QD, 24 mcg BID, and 24 mcg TID

#### AMITIZA™-induced Nausea:

Among constipated patients, 31.1% of those receiving AMITIZA™ 24 mcg BID reported nausea. Of those patients, 3.4% reported severe nausea and 8.7% discontinued treatment due to



nausea. It should be noted that the incidence of nausea increased in a dose-dependent manner with the lowest overall incidence for nausea seen at the 24 mcg QD dose (17.2%). Further analysis of nausea has shown that long-term exposure to AMITIZA™ does not appear to place patients at elevated risk for experiencing nausea. In the open-label, long-term studies, patients were allowed to titrate the dose of AMITIZA™ down to 24 mcg QD from 24 mcg BID if experiencing nausea. It should also be noted that nausea decreased when AMITIZA™ was administered with food and that, across all dose groups, the rate of nausea was substantially lower among constipated men (13.2%) and constipated elderly patients (18.6%) when compared to the overall rate (30.9%). No patients in the trials were hospitalized due to nausea.

#### AMITIZA™-induced Diarrhea:

Among constipated patients, 13.2% of those receiving AMITIZA™ 24 mcg BID reported diarrhea. Of those patients, 3.4% reported severe diarrhea and 2.2% discontinued treatment due to diarrhea. The incidence of diarrhea did not appear to be dose-dependent. No serious adverse events were reported for electrolyte imbalance in the six clinical trials and no clinically significant changes were seen in serum electrolyte levels while patients were receiving AMITIZA™.

#### Other Adverse Events:

The following list of adverse events include those that were considered by the investigator to be possibly related to AMITIZA™ and reported more frequently (>0.2%) on AMITIZA™ than placebo and those that lead to discontinuation more frequently (≥0.2%) on AMITIZA™ than placebo. Although the events reported occurred during treatment with AMITIZA™, they were not necessarily attributed to dosing of AMITIZA™:

- **Gastrointestinal disorders:** watery stools, fecal incontinence, abnormal bowel sounds, frequent bowel movements, retching
- **Nervous system disorders:** syncope, tremor, dysgeusia, paraesthesia
- **General disorders and administration site conditions:** rigors, pain, asthenia, malaise, edema
- **Respiratory, thoracic, and mediastinal disorders:** asthma, painful respiration, throat tightness
- **Skin and subcutaneous tissue disorders:** hyperhidrosis, urticaria, rash
- **Psychiatric disorders:** nervousness
- **Vascular disorders:** flushing, palpitations
- **Metabolism and nutrition disorders:** decreased appetite
- **Ear and labyrinth disorders:** vertigo

#### Overdose:

There have been two confirmed reports of overdose with AMITIZA™. The first report involved a 3-year-old child who accidentally ingested 7 to 8 capsules of 24 mcg of AMITIZA™ and fully recovered. The second report was a study subject who self-administered a total of 96 mcg AMITIZA™ per day for 8 days. The subject experienced no adverse events during this time. Additionally, in a definitive Phase 1 cardiac repolarization study, 51 patients administered a single oral dose of 144 mcg of AMITIZA™, which is 6 times the normal single administration dose. Thirty-nine (39) of the 51 patients experienced an adverse event. The adverse events reported in >1% of this group included the following: nausea (45.1%), vomiting (27.5%), diarrhea (25.5%), dizziness (17.6%), loose or watery stools (13.7%), headache (11.8%), retching (7.8%), abdominal pain (5.9%), flushing or hot flush (5.9%), dyspnea (3.9%), pallor (3.9%), stomach discomfort (3.9%), syncope (3.9%), upper abdominal pain (2.0%), anorexia (2.0%), asthenia (2.0%), chest discomfort (2.0%), dry mouth (2.0%), hyperhidrosis (2.0%), skin irritation (2.0%), and vasovagal episode (2.0%).

#### DOSAGE AND ADMINISTRATION

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

#### MARKETED BY:

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720-03565  
L-LUB-00003

Revised: July 2006

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