Options May Lead Patients to Put Off Screening

BY SHERRY BOSCHERT
San Francisco Bureau

LAKE TAHOE, CALIF. — Patients may be more likely to be screened for colon cancer if physicians schedule colonoscopies and tell the patients to show up rather than giving them a choice of screening options, Dr. John M. Inadomi said at a meeting on gastroenterology and hepatology sponsored by the University of California, Davis.

That's what he and associates at the University of California, San Francisco, found in a small pilot study, and they plan to study this further in a much larger trial, he said.

In the pilot study, they randomized 41 subjects and followed them for 6 months to see how many completed the colon cancer screening tests. None of the patients who either chose or were told to get three fecal occult blood tests (FOBTs) plus flexible sigmoidoscopy completed both. "So first of all, if you're trying to get people to do both FOBT and flex sig, forget it," said Dr. Inadomi, chief of clinical gastroenterology at San Francisco General Hospital and director of GI Outcomes and Health Services Research at the university.

Patients who were told to get a colonoscopy were twice as likely to get one as patients who were counseled about screening options and who chose to get a colonoscopy, he added.

Fifteen patients in the "choice" arm of the study were counseled by a nurse-specialist who recited a scripted message designed to help patients choose between getting a colonoscopy or getting three FOBTs plus a flexible sigmoidoscopy. If the FOBTs or the flexible sigmoidoscopy was positive, the patient was to get a colonoscopy.

Nine patients chose colonoscopy, and three of them (33%) got the test. Of the six patients who chose FOBTs plus flexible sigmoidoscopy, two completed the FOBTs and two underwent flexible sigmoidoscopy but none completed both tests.

Among 26 patients in the "no choice" arm, 13 were told to show up for a colonoscopy and 9 patients (69%) did so. Of the 13 patients who were told to get FOBTs plus flexible sigmoidoscopy, 1 patient completed the FOBTs and 4 patients underwent the sigmoidoscopy, but none got both tests.

Newer screening options have joined these mainstays and further confuse patients when given a choice, Dr. Inadomi noted. The lack of a clearly defined preference leads people to defer a decision when given a choice. "The main thing to improve adherence with screening guidelines is to schedule patients for the test that they will complete," he said. ■

AMITIZA™
(lubiprostone) soft gelatin capsules

SUCAMPO PHARMACEUTICALS, INC. Takeda

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:B6C3F1 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+/–) 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/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 %	AMITIZA™ Any Active Dose† n = 1175 %
Gastrointestinal disorders				
Nausea	5.1	17.2	31.1	30.9
Diarrhea	0.9	10.3	13.2	13.2
Abdominal distension	2.2	0.0	7.1	6.8
Abdominal pain	2.8	3.4	6.7	6.8
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	1.8
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
Infections and infestations				
Sinusitis	1.6	0.0	4.9	4.8
Urinary 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
Nervous system disorders				
Headache	6.6	3.4	13.2	13.0
Dizziness	1.3	3.4	4.1	4.0
Hypoesthesia	0.0	3.4	0.5	0.6
General disorders and site administration conditions				
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
Pyrexia	0.3	0.0	1.1	1.0
Musculoskeletal and connective tissue disorders				
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
Respiratory, thoracic, and mediastinal disorders				
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
Investigations				
Weight increased	0.0	0.0	1.0	0.9
Psychiatric disorders				
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
Vascular disorders				
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

Overdosage:
There have been two confirmed reports of overdosage 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:
Sucampo Pharmaceuticals, Inc.
Bethesda, MD 20814
and
Takeda Pharmaceuticals America, Inc.
Deerfield, IL 60015

AMITIZA™ is a trademark of Sucampo Pharmaceuticals, Inc.
© 2006 Sucampo Pharmaceuticals, Inc.

720-03565 Revised: July 2006
L-LUB-00003

Screening Interval Should Reflect Duration of IBD

LAKE TAHOE, CALIF. — The frequency of colonoscopies to screen for cancer in patients with Crohn's disease colitis or ulcerative colitis should be based on how long they've had colitis, Dr. Joshua R. Korzenik said at a meeting on gastroenterology and hepatology sponsored by the University of California, Davis.

But if a colonoscopy can answer an important clinical question facing the patient today, it should be done now regardless of the colitis duration, said Dr. Korzenik, codirector of the Crohn's and Colitis Center at Massachusetts General Hospital, Boston.

Without that pressing motivation, a screening colonoscopy typically would be appropriate every 3-4 years during the first decade of a patient's Crohn's or ulcerative colitis. Because these patients can develop cancer not only from polyps but from flat, normal-appearing mucosa, multiple biopsies are needed. A minimum of 33 biopsies should be taken, spaced about every 4-10 cm throughout the colon.

"That has about a 90% likelihood of picking up dysplasia," he said.

For patients with a disease duration of 10-20 years, colonoscopy should be performed every other year. For those with a disease duration longer than 20 years, annual colonoscopy is preferred.

"We're beginning to move toward chromoendoscopy, where we spray the colon with a contrast material that picks up dysplasia a little bit better," he added.

If the colonoscopy detects high-grade dysplasia, the patient should undergo a colectomy, Dr. Korzenik advised.

—Sherry Boschert