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APPLICATION NUMBER:

21-908

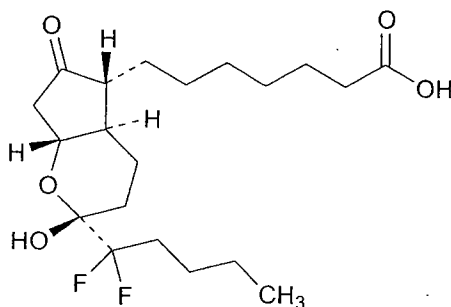
APPROVED LABELING

AMITIZA™
(lubiprostone)
Soft Gelatin Capsules

Rx Only, Prescribing Information

DESCRIPTION

AMITIZA™ (lubiprostone) is chemically designated as (-)-7-[(2*R*,4*aR*,5*R*,7*aR*)-2-(1,1-difluoropentyl)-2-hydroxy-6-oxooctahydrocyclopenta[*b*]pyran-5-yl]heptanoic acid. The molecular formula of lubiprostone is C₂₀H₃₂F₂O₅ with a molecular weight of 390.46 and a chemical structure as follows:



Lubiprostone drug substance occurs as white, odorless crystals or crystalline powder and is very soluble in ether and ethanol, and practically insoluble in hexane and water. AMITIZA™ is available for oral administration in an imprinted, oval, orange, soft gelatin capsule containing 24 mcg lubiprostone and the following inactive ingredients: medium-chain triglycerides, gelatin, sorbitol, FD&C Red #40, D&C Yellow #10, and purified water.

CLINICAL PHARMACOLOGY

Mechanism of Action:

Chronic idiopathic constipation is generally defined by infrequent or difficult passage of stool. The signs and symptoms associated with chronic idiopathic constipation (*i.e.*, abdominal pain or discomfort, bloating, straining, and hard or lumpy stools) may be the result of abnormal colonic motility that can delay the transit of intestinal contents and impede the evacuation of rectal contents. One approach to the treatment of chronic idiopathic constipation is the secretion of fluid into the

abdominal lumen through the activation of chloride channels in the apical membrane of the gastrointestinal epithelium.

Lubiprostone is a locally acting chloride channel activator that enhances a chloride-rich intestinal fluid secretion without altering sodium and potassium concentrations in the serum. Lubiprostone acts by specifically activating ClC-2 , which is a normal constituent of the apical membrane of the human intestine, in a protein kinase A-independent fashion. By increasing intestinal fluid secretion, lubiprostone increases motility in the intestine, thereby increasing the passage of stool and alleviating symptoms associated with chronic idiopathic constipation. Patch clamp cell studies in human cell lines have indicated that the majority of the beneficial biological activity of lubiprostone and its metabolites is observed only on the apical (luminal) portion of the gastrointestinal epithelium.

Pharmacokinetics:

Lubiprostone has low systemic availability following oral administration and concentrations of lubiprostone in plasma are below the level of quantitation (10 pg/mL). Therefore, standard pharmacokinetic parameters such as area under the curve (AUC), C_{max} , and $t_{1/2}$ cannot be reliably calculated. However, the pharmacokinetic parameters of M3 (only measurable active metabolite) have been characterized.

Absorption:

Concentrations of lubiprostone in plasma are below the level of quantitation (10 pg/mL) because lubiprostone has a low systemic availability following oral administration. Peak plasma levels of M3, after a single oral dose of 24 mcg of lubiprostone, occur at approximately 1.14 hours. The C_{max} was 41.9 pg/mL and the mean AUC was 59.1 pg•hr/mL. AUC of M3 increases dose proportionally after single 24-mcg and 144-mcg doses of lubiprostone.

Distribution:

In vitro protein binding studies indicate lubiprostone is approximately 94% bound to human plasma proteins. Studies in rats with radiolabeled lubiprostone indicate minimal distribution beyond the gastrointestinal tissues. Concentrations of radiolabeled compound at 48 hours post-administration were minimal in all tissues.

Metabolism:

The results of both human and animal studies indicate that lubiprostone is rapidly and extensively metabolized by 15-position reduction, α -chain β -oxidation, and ω -chain ω -oxidation. These biotransformations are not mediated by the hepatic cytochrome P450 system but rather appear to be mediated by the ubiquitously expressed carbonyl reductase. M3, a metabolite of lubiprostone in both humans and animals is formed by the reduction of the carbonyl group at the 15-hydroxy moiety that consists of both α -hydroxy and β -hydroxy epimers. M3 makes up less than 10% of the dose of radiolabeled lubiprostone. Animal studies have shown that metabolism of lubiprostone rapidly occurs within the stomach and jejunum, most likely in the absence of any systemic absorption. This is presumed to be the case in humans as well.

Elimination:

Lubiprostone could not be detected in plasma; however, M3 has a $t_{1/2}$ ranging from 0.9 to 1.4 hours. After a single oral dose of 72 mcg of ^3H -labeled lubiprostone, 60% of total administered radioactivity was recovered in the urine within 24 hours and 30% of total administered radioactivity was recovered in the feces by 168 hours. Lubiprostone and M3 are only detected in trace amounts in feces in humans.

Food Effect:

A study was conducted with a single 72-mcg dose of ^3H -labeled lubiprostone to evaluate the potential of a food effect on lubiprostone absorption, metabolism, and excretion (AME). Pharmacokinetic parameters of total radioactivity demonstrated that $C_{\max}$ decreased by 55% while $\text{AUC}_{0-\infty}$ was unchanged when lubiprostone was administered with a high-fat meal. The clinical relevance of the effect of food on the pharmacokinetics of lubiprostone is not clear. However, lubiprostone was administered with food in a majority of clinical trials.

Special Populations:**Gender:**

Gender has no effect on the pharmacokinetics of M3 when lubiprostone is dosed.

Hepatic Impairment:

Lubiprostone has not been studied in hepatically impaired populations.

Renal Impairment:

Lubiprostone has not been studied in renally impaired populations.

CLINICAL STUDIES

A dose-finding, double-blind, parallel-group, placebo-controlled, Phase 2 study was conducted in patients with chronic idiopathic constipation. Following a 2-week baseline/washout period, patients received 3 weeks of double-blind medication. Patients (n = 127) were randomized to receive placebo (n = 33), AMITIZA™ 24 mcg/day (24 mcg QD; n = 29), AMITIZA™ 48 mcg/day (24 mcg BID; n = 32), or AMITIZA™ 72 mcg/day (24 mcg TID; n = 33). Patients were chosen for participation based on their need for relief of constipation, which was defined as < 3 spontaneous bowel movements (SBMs) per week. The primary efficacy variable was the daily average number of SBMs.

The study demonstrated that all patients who took AMITIZA™ experienced a noticeable improvement in clinical response. Based on the efficacy analysis, there was no statistically significant improvement in the clinical response beyond a total daily dose of 24 mcg between treatment weeks 2 and 3 (Figure 1).

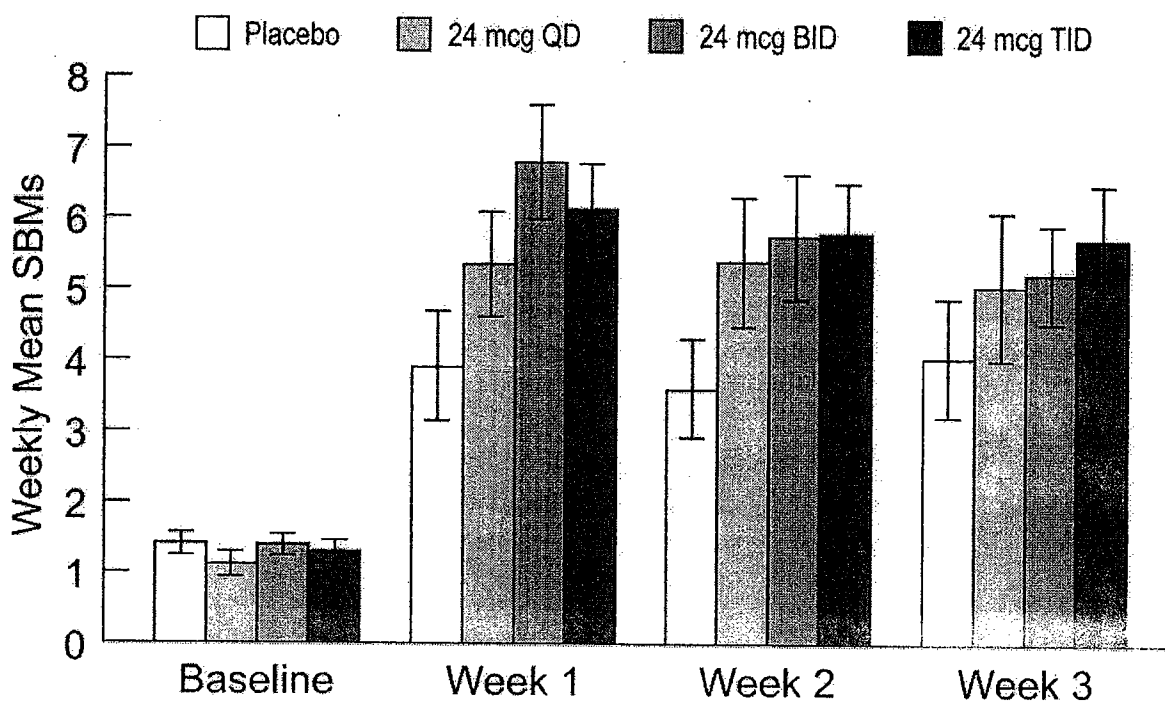


Figure 1: Weekly Mean (± Standard Error) Spontaneous Bowel Movements (Dose-finding Study)

Two double-blind, placebo-controlled studies of identical design were conducted in patients with chronic idiopathic constipation. Chronic idiopathic constipation was defined as, on average, less than 3 SBMs per week with one or more of the following symptoms for constipation for at least 6 months prior to randomization: 1) very hard stools for at least a quarter of all bowel movements; 2) sensation of incomplete evacuation following at least a quarter of all bowel movements; and 3) straining with defecation at least a quarter of the time.

Following a 2-week baseline/washout period, a total of 479 patients (88.9% female, mean age 47.2 [range 20.0–81.0], 80.8% Caucasian, 9.6% African American, 10.9% ≥ 65 years of age) were randomized to receive 4 weeks of double-blind treatment with either AMITIZA™ 24 mcg BID (48 mcg/day) or placebo. The primary endpoint of the studies was SBM frequency following initiation of double-blind treatment. The studies demonstrated that patients treated with AMITIZA™ had a higher frequency of SBMs during Week 1 than the placebo patients. In both studies, results similar to those in Week 1 were also observed in Weeks 2, 3, and 4 of therapy.

Table 1: Spontaneous Bowel Movement Frequency Rates – AMITIZA™ 24 mcg BID vs. Placebo

Trial	Study Arm	Baseline Mean $\pm$ SD Median	Week 1 Mean $\pm$ SD Median	Week 2 Mean $\pm$ SD Median	Week 3 Mean $\pm$ SD Median	Week 4 Mean $\pm$ SD Median	Week 1 Change from Baseline Mean $\pm$ SD Median	Week 4 Change from Baseline Mean $\pm$ SD Median
Study 1	Placebo	1.6 $\pm$ 1.3 1.5	3.5 $\pm$ 2.3 3.0	3.2 $\pm$ 2.5 3.0	2.8 $\pm$ 2.2 2.0	2.9 $\pm$ 2.4 2.3	1.9 $\pm$ 2.2 1.5	1.3 $\pm$ 2.5 1.0
	AMITIZA™	1.4 $\pm$ 0.8 1.5	5.7 $\pm$ 4.4 5.0	5.1 $\pm$ 4.1 4.0	5.3 $\pm$ 4.9 5.0	5.3 $\pm$ 4.7 4.0	4.3 $\pm$ 4.3 3.5	3.9 $\pm$ 4.6 3.0
Study 2	Placebo	1.5 $\pm$ 0.8 1.5	4.0 $\pm$ 2.7 3.5	3.6 $\pm$ 2.7 3.0	3.4 $\pm$ 2.8 3.0	3.5 $\pm$ 2.9 3.0	2.5 $\pm$ 2.6 1.5	1.9 $\pm$ 2.7 1.5
	AMITIZA™	1.3 $\pm$ 0.9 1.5	5.9 $\pm$ 4.0 5.0	5.0 $\pm$ 4.2 4.0	5.6 $\pm$ 4.6 5.0	5.4 $\pm$ 4.8 4.3	4.6 $\pm$ 4.1 3.8	4.1 $\pm$ 4.8 3.0

The above frequency rates are calculated as 7 times (number of SBMs) / (number of days observed for that week).

In both studies, AMITIZA™ demonstrated increases in the percentage of patients who experienced SBMs within the first 24 hours after administration when compared to placebo (56.7% vs. 36.9% in Study 1 and 62.9% vs. 31.9% in Study 2; respectively). Similarly, the time to first SBM was shorter for AMITIZA™ patients than for those receiving placebo.

Signs and symptoms related to constipation, including abdominal bloating, abdominal discomfort, stool consistency, and straining, as well as constipation severity ratings, were also improved in AMITIZA™ patients versus placebo. The results were consistent in subpopulation analysis for gender, race, and elderly patients (≥ 65 years of age).

Following 4 weeks of treatment with AMITIZA™ 24 mcg BID, withdrawal of AMITIZA™ did not result in a rebound effect.

Long-term Clinical Studies:

Three open-label, long-term clinical safety studies were conducted in patients with chronic idiopathic constipation receiving 24 mcg BID. These studies included 871 patients (86.1% female, mean age 51 [range 19–86] years, 87% Caucasian, 7.3% African American, 18.4% ≥ 65 years of age) who were treated for 6–12 months (24–48 weeks). Patients provided regular assessments of abdominal bloating, abdominal discomfort, and constipation severity. The results of these studies demonstrated that AMITIZA™ decreased abdominal bloating, abdominal discomfort, and constipation severity over the 6–12 month treatment periods.

INDICATION AND USAGE

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

CONTRAINDICATION

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.

WARNING

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

Carcinogenesis:

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.

Renal Impaired:

AMITIZA™ has not been studied in patients who have renal impairment.

Hepatic Impaired:

AMITIZA™ has not been studied in patients who have hepatic impairment.

ADVERSE REACTIONS

In clinical trials, 1429 patients received AMITIZA™ 24 mcg BID or placebo. Table 2 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 2: 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 Dose¹ 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

¹Includes 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.

HOW SUPPLIED

AMITIZA™ is available as an oval, orange, soft gelatin capsule with “SPT” printed on one side. Each capsule contains 24 mcg lubiprostone. AMITIZA™ is available as follows:

Bottles of 100.....NDC 64764-240-10

STORAGE

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

MARKETED BY:

Sucampo Pharmaceuticals, Inc.
Bethesda, MD 20814

and

Takeda Pharmaceuticals America, Inc.
Lincolnshire, IL 60069

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/s/

Julie Beitz

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