HIGHLIGHTS OF PRESCRIBING INFORMATION
(If possible, don't have the tradename in all capitals throughout the label.)
These highlights do not include all the information needed to use Amitiza safely and effectively. See full prescribing information for Amitiza.

Amitiza (lubiprostone) Capsules
Initial U.S. Approval: 2006

---------- INDICATIONS AND USAGE ----------

Amitiza is a chloride channel activator indicated for:
- Treatment of chronic idiopathic constipation in adults (1)

---------- DOSAGE AND ADMINISTRATION ----------

- 24 mcg taken twice daily orally with food (2)

---------- DOSAGE FORMS AND STRENGTHS ----------

- Soft gelatin capsules: 24 mcg (3)

---------- CONTRAINDICATIONS ----------

- Patients with known mechanical gastrointestinal obstruction should not receive Amitiza. (4)

---------- WARNINGS AND PRECAUTIONS ----------
- Women who could become pregnant should have a negative pregnancy test prior to beginning therapy and should be capable of complying with effective contraceptive measures (8.1).
- Use during pregnancy only if the potential benefit justifies the potential risk to the fetus (5.1)
- Patients may experience nausea; concomitant administration of food may reduce this symptom (5.2)
- Do not prescribe for patients that have severe diarrhea (5.3)
- Evaluate patients with symptoms suggestive of mechanical gastrointestinal obstruction prior to initiating treatment with AMITIZA (5.4)

---------- ADVERSE REACTIONS ----------

Most common adverse reactions (incidence > 4%) are nausea, diarrhea, headache, abdominal pain, abdominal distension, and flatulence (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceuticals North America, Inc., at 1-877-825-3327 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION

Revised: May/2007

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

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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 STRENGTH

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 n = 316 %	AMITIZA 24 mcg ONCE DAILY n = 29 %	AMITIZA 24 mcg tTWICE DAILY n = 1113	AMITIZA Any Dosage[2] 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

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

(NOTE: Delete this heading because this is a general paragraph about drug-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 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 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

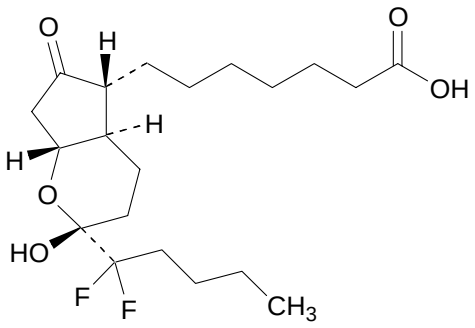
AMITIZA has not been studied in patients who have hepatic impairment.

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%).

11 DESCRIPTION

AMITIZA (lubiprostone) is chemically designated as (–)-7-[(2*R*,4a*R*,5*R*,7a*R*)-2-(1,1-difluoropentyl)-2-hydroxy-6-oxooctahydrocyclopenta[*b*]pyran-5-yl]heptanoic acid. The molecular formula of lubiprostone is $C_{20}H_{32}F_2O_5$ with a molecular weight of 390.46 and a chemical structure as follows:



Lubiprostone drug substance occurs as white, odorless crystals or crystalline powder, is very soluble in ether and ethanol, and is 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.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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 facilitating 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.

12.2 Pharmacodynamics

Although the pharmacologic effects of lubiprostone in humans have not been fully evaluated, animal studies have shown that oral administration of lubiprostone increases chloride ion transport into the intestinal lumen, enhances fluid secretion into the bowels, and improves fecal transit.

12.3 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), maximum concentration (C_{max}), and half-life ($t_{½}$) cannot be reliably calculated. However, the pharmacokinetic parameters of M3 (only measurable active metabolite of lubiprostone) have been characterized. Gender has no effect on the pharmacokinetics of M3 following the oral administration of lubiprostone.

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 with 24 mcg of lubiprostone, occurred at approximately 1.10 hours. The C_{max} was 41.5 pg/mL and the mean AUC_{0-t} was 57.1 pg·hr/mL. The AUC_{0-t} 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 given radiolabeled lubiprostone indicate minimal distribution beyond the gastrointestinal tissues. Concentrations of radiolabeled lubiprostone at 48 hours post-administration were minimal in all tissues of the rats.

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 found 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 $t_{½}$ ranging from 0.9 to 1.4 hours. After a single oral dose of 72 mcg of ^{3}H-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 human feces.

Food Effect

A study was conducted with a single 72-mcg dose of ^{3}H-labeled lubiprostone to evaluate the potential of a food effect on lubiprostone absorption, metabolism, and excretion. Pharmacokinetic parameters of total radioactivity demonstrated that C_{max} decreased by 55% while $AUC_{0-\infty}$ 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.

13 NONCLINICAL TOXICOLOGY

13.1 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 body surface area.

14 CLINICAL STUDIES

14.1 Dose-finding Study

A dose-finding, double-blinded, parallel-group, placebo-controlled, Phase 2 study was conducted in patients with chronic idiopathic constipation. Following a 2-week baseline/washout period, patients (n = 127) were randomized to receive placebo (n = 33), AMITIZA 24 mcg/day (24 mcg once daily; n = 29), AMITIZA 48 mcg/day (24 mcg twice daily; n = 32), or AMITIZA 72 mcg/day (24 mcg three times daily; n = 33) for 3 weeks. Patients were chosen for participation based on their need for relief of constipation, which was defined as less than 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 during treatment weeks 2 and 3 (Figure 1).

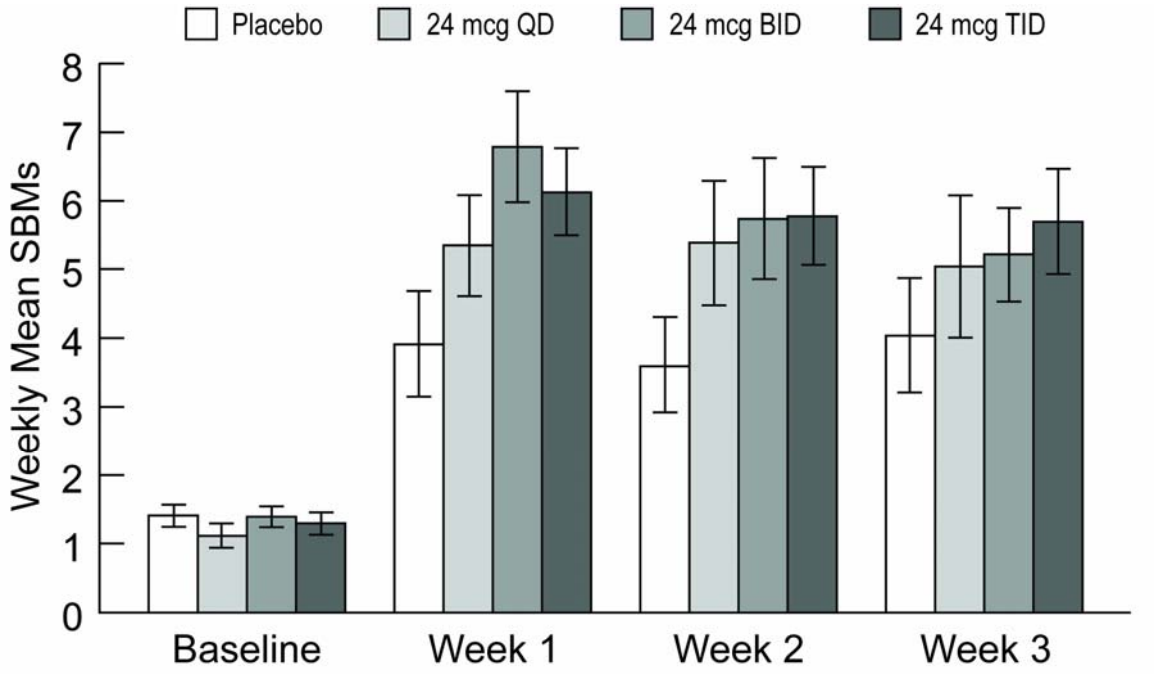


Figure 1: Weekly Mean (± Standard Error) Spontaneous Bowel Movements (Dose-finding Study)

14.2 Efficacy Studies

Two double-blinded, 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 along with one or more of the following symptoms of 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 (mean age 47.2 [range 20–81] years; 88.9% female; 80.8% Caucasian, 9.6% African American, 7.3% Hispanic; 1.5% Asian; 10.9% ≥ 65 years of age) were randomized and received AMITIZA 24 mcg twice daily (48 mcg/day) or placebo twice daily for 4 weeks. The primary endpoint of the studies was SBM frequency. 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 2).

Table 2: Spontaneous Bowel Movement Frequency Rates[1] (Efficacy Studies)

Trial	Study Arm	**Baseline** *Mean ± SD* *Median*	**Week 1** *Mean ± SD* *Median*	**Week 2** *Mean ± SD* *Median*	**Week 3** *Mean ± SD* *Median*	**Week 4** *Mean ± SD* *Median*	**Week 1 Change from Baseline** *Mean ± SD* *Median*	**Week 4 Change from Baseline** *Mean ± SD* *Median*
Study 1	**Placebo**	1.6 ± 1.3 1.5	3.5 ± 2.3 3.0	3.2 ± 2.5 3.0	2.8 ± 2.2 2.0	2.9 ± 2.4 2.3	1.9 ± 2.2 1.5	1.3 ± 2.5 1.0
	AMITIZA 24 mcg twice daily	1.4 ± 0.8 1.5	5.7 ± 4.4 5.0	5.1 ± 4.1 4.0	5.3 ± 4.9 5.0	5.3 ± 4.7 4.0	4.3 ± 4.3 3.5	3.9 ± 4.6 3.0

Study 2	Placebo	1.5 ± 0.8 1.5	4.0 ± 2.7 3.5	3.6 ± 2.7 3.0	3.4 ± 2.8 3.0	3.5 ± 2.9 3.0	2.5 ± 2.6 1.5	1.9 ± 2.7 1.5
	AMITIZA 24 mcgtwice daily	1.3 ± 0.9 1.5	5.9 ± 4.0 5.0	5.0 ± 4.2 4.0	5.6 ± 4.6 5.0	5.4 ± 4.8 4.3	4.6 ± 4.1 3.8	4.1 ± 4.8 3.0

[1]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 patients receiving AMITIZA 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 with AMITIZA versus placebo. The results were consistent in subpopulation analyses for gender, race, and elderly patients (≥ 65 years of age).

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

14.3 Long-term Clinical Studies

Three open-labeled, long-term clinical safety and efficacy studies were conducted in patients with chronic idiopathic constipation receiving AMITIZA 24 mcg twice daily. These studies comprised 871 patients (mean age 51.0 [range 19–86] years; 86.1% female; 86.9% Caucasian, 7.3% African American, 4.5% Hispanic, 0.7% Asian; 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. These studies demonstrated that AMITIZA decreased abdominal bloating, abdominal discomfort, and constipation severity over the 6–12-month treatment periods.

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)

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 24mcg 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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