



Symptom Tracker

Created For:
Created Date:

Thank you for downloading your Symptom Tracker!

You have taken an important step. By monitoring your symptoms and becoming more aware of your daily routines and patterns, you will be prepared to have a more thorough discussion with your healthcare provider.

Using Your Tracker:

On page two of this printout, you will find a tracking table that allows you to record detailed information about your experiences every day. The tracking table allows you to record seven days (one week) of symptoms.

Using the tracking table, you will record each of the following daily:

- Whether you have had a bowel movement and the type (using the Bristol Stool Form Scale)
- How many glasses of water you drank
- Your stress and your exercise levels
- What treatments you used (if any)
- Work or social functions missed
- Any other symptoms you feel

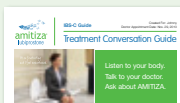
Tracking Tips

- ✓ Develop a routine – track your symptoms at the same time every evening so that you don't forget
- ✓ Be thorough – the more information you can provide to your healthcare provider, the more helpful your discussion will be

Bristol Stool Form Scale

The Bristol Stool Form Scale was developed at the University of Bristol, UK to help measure stool consistency or form. Using this scale to record stool type can be helpful for you and your healthcare provider to measure patterns or changes.

Type 1	Type 2	Type 3	Type 4	Type 5	Type 6	Type 7
Separate hard lumps, like nuts (hard to pass)	Sausage-shaped but lumpy	Like a sausage but with cracks on its surface	Like a sausage or snake, smooth and soft	Soft blobs with clear-cut edges (passed easily)	Fluffy pieces with ragged edges, a mushy stool	Watery, no solid pieces, entirely liquid



Ready to talk to your Healthcare Provider?

Once you have tracked your symptoms and you are ready to see your healthcare provider, you can also download and bring a copy of the **Treatment Conversation Guide**. The guide provides helpful questions and points to consider to ensure you have a thorough conversation with your physician. Visit www.amitiza.com/tcg to get your Treatment Conversation Guide.

Please see Important Safety Information on page

For more information about AMITIZA, call 1-888-5-AMITIZA or visit AMITIZA.com
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Week

Day	Did you have a bowel movement today?	Bristol Stool Form Scale Type	How many glasses of water did you drink?	Rate your stress level Place an "x" on the scale	Rate your exercise level Place an "x" on the scale	What treatment did you use, if any? See bottom of page for key	Indicate any social functions that you missed e.g., work, school	Describe other symptoms e.g., pain, bloating, gas, etc.
Day 1	<input type="checkbox"/> Yes <input type="checkbox"/> No					<input type="checkbox"/> S <input type="checkbox"/> F <input type="checkbox"/> O <input type="checkbox"/> P Other _____		
Day 2	<input type="checkbox"/> Yes <input type="checkbox"/> No					<input type="checkbox"/> S <input type="checkbox"/> F <input type="checkbox"/> O <input type="checkbox"/> P Other _____		
Day 3	<input type="checkbox"/> Yes <input type="checkbox"/> No					<input type="checkbox"/> S <input type="checkbox"/> F <input type="checkbox"/> O <input type="checkbox"/> P Other _____		
Day 4	<input type="checkbox"/> Yes <input type="checkbox"/> No					<input type="checkbox"/> S <input type="checkbox"/> F <input type="checkbox"/> O <input type="checkbox"/> P Other _____		
Day 5	<input type="checkbox"/> Yes <input type="checkbox"/> No					<input type="checkbox"/> S <input type="checkbox"/> F <input type="checkbox"/> O <input type="checkbox"/> P Other _____		
Day 6	<input type="checkbox"/> Yes <input type="checkbox"/> No					<input type="checkbox"/> S <input type="checkbox"/> F <input type="checkbox"/> O <input type="checkbox"/> P Other _____		
Day 7	<input type="checkbox"/> Yes <input type="checkbox"/> No					<input type="checkbox"/> S <input type="checkbox"/> F <input type="checkbox"/> O <input type="checkbox"/> P Other _____		

Treatment Key:

S = Stimulant laxatives, such as ex-Lax, Senokot

F = Fiber supplements, such as Metamucil Powder, Benefiber, etc.

O = Osmotic laxatives, such as MiraLAX, Dulcolax, etc.

P = Probiotics, such as Acidophilus Pearls

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Please see Important Safety Information on page

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Indication

AMITIZA (24 mcg) twice daily is approved to treat Chronic Idiopathic Constipation in adults. "Idiopathic" means the cause of the constipation is unknown and not due to an underlying illness or medication. AMITIZA (8 mcg) twice daily is approved to treat Irritable Bowel Syndrome with Constipation (IBS-C) in women 18 years of age and older.

Important Safety Information

AMITIZA is not for everyone. If you know or suspect you have a bowel blockage, do not take AMITIZA. If you are unsure, your healthcare provider should evaluate your condition before starting AMITIZA. You should not take AMITIZA if you have severe diarrhea.

AMITIZA has not been studied in pregnant women and should only be used during a pregnancy if the potential benefits justify the potential risk to the fetus. Women should have a negative pregnancy test before beginning treatment with AMITIZA and need to practice effective birth control measures. If you are pregnant or become pregnant while being treated with AMITIZA, talk to your healthcare provider to evaluate the risks to the fetus.

Some patients taking AMITIZA may experience nausea or diarrhea. If nausea occurs, take AMITIZA with food. If your nausea or diarrhea becomes severe, tell your healthcare provider.

Within an hour of taking AMITIZA, a sensation of chest tightness and shortness of breath may occur. These symptoms usually go away within three hours, but may recur with repeated use. Tell your healthcare provider if you experience these symptoms.

The most common side effects of taking AMITIZA (24 mcg) twice daily, orange capsules for Chronic Idiopathic Constipation are nausea, diarrhea, and headache. The most common side effects of taking AMITIZA (8 mcg) twice daily, pink capsules for IBS-C are nausea, diarrhea, and abdominal pain. These are not all the side effects associated with AMITIZA.

Tell your doctor if you have liver problems.

Please see complete Prescribing Information on the next page.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

For more information about AMITIZA, call 1-888-5-AMITIZA or visit AMITIZA.com

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HIGHLIGHTS OF PRESCRIBING INFORMATION

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

RECENT MAJOR CHANGES

Dosage and Administration (2) 2/2011

INDICATIONS AND USAGE

Amitiza is a chloride channel activator indicated for:

- Treatment of chronic idiopathic constipation in adults (1.1)
- Treatment of irritable bowel syndrome with constipation in women \geq 18 years old (1.2)

DOSAGE AND ADMINISTRATION

Chronic idiopathic constipation

- 24 mcg taken twice daily orally with food and water (2.1)

Reduce the dosage in patients with moderate and severe hepatic impairment (2.1)

Irritable bowel syndrome with constipation

- 8 mcg taken twice daily orally with food and water (2.2)

Reduce the dosage in patients with severe hepatic impairment (2.2)

DOSAGE FORMS AND STRENGTHS

- Gelatin capsules: 8 mcg and 24 mcg (3)

CONTRAINDICATIONS

- Patients with known or suspected 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)
- Patients taking Amitiza may experience dyspnea within an hour of first dose. This symptom generally resolves within 3 hours, but may recur with repeat dosing (5.4)
- Evaluate patients with symptoms suggestive of mechanical gastrointestinal obstruction prior to initiating treatment with Amitiza (5.5)

ADVERSE REACTIONS

- Most common adverse reactions (incidence $>$ 4%) in chronic idiopathic constipation are nausea, diarrhea, headache, abdominal pain, abdominal distension, and flatulence (6.1)
- Most common adverse reactions (incidence $>$ 4%) in irritable bowel syndrome with constipation are nausea, diarrhea, and abdominal pain (6.1)

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

See 17 for PATIENT COUNSELING INFORMATION

Revised: February 2011

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Chronic Idiopathic Constipation

Amitiza® is indicated for the treatment of chronic idiopathic constipation in adults.

1.2 Irritable Bowel Syndrome with Constipation

Amitiza is indicated for the treatment of irritable bowel syndrome with constipation (IBS-C) in women \geq 18 years old.

2 DOSAGE AND ADMINISTRATION

Amitiza should be taken orally with food and water. Physicians and patients should periodically assess the need for continued therapy.

2.1 Chronic Idiopathic Constipation

The recommended dose is 24 mcg twice daily orally with food and water.

Reduced dosage in patients with hepatic impairment

For patients with moderately impaired hepatic function (Child-Pugh Class B), the recommended dose is 16 mcg twice daily. For patients with severely impaired hepatic function (Child-Pugh Class C), the recommended dose is 8 mcg twice daily. If this dose is tolerated and an adequate response has not been obtained after an appropriate interval, doses can then be escalated to full dosing with appropriate monitoring of patient response.

2.2 Irritable Bowel Syndrome with Constipation

The recommended dose is 8 mcg twice daily orally with food and water.

Reduced dosage in patients with severe hepatic impairment

For patients with severely impaired hepatic function (Child-Pugh Class C), the recommended dose is 8 mcg once daily. If this dose is tolerated and an adequate response has not been obtained after an appropriate interval, doses can then be escalated to full dosing with appropriate monitoring of patient response. Dosage adjustment is not required for patients with moderately impaired hepatic function (Child-Pugh Class B).

3 DOSAGE FORMS AND STRENGTHS

Amitiza is available as an oval, gelatin capsule containing 8 mcg or 24 mcg of lubiprostone.

- 8-mcg capsules are pink and are printed with "SPI" on one side
- 24-mcg capsules are orange and are printed with "SPI" on one side

4 CONTRAINDICATIONS

Amitiza is contraindicated in patients with known or suspected 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 Dyspnea

In clinical trials conducted to study Amitiza in treatment of chronic idiopathic constipation and IBS-C there were reports of dyspnea. This was reported at 2.5% of the treated chronic idiopathic constipation population and at 0.4% in the treated IBS-C population. Although not classified as serious adverse events, some patients discontinued treatment on study because of this event. There have been postmarketing reports of dyspnea when using Amitiza 24 mcg. Most have not been characterized as serious adverse events, but some patients have discontinued therapy because of dyspnea. These events have usually been described as a sensation of chest tightness and difficulty taking in a breath, and generally have an acute onset within 30–60 minutes after taking the first dose. They generally resolve within a few hours after taking the dose, but recurrence has been frequently reported with subsequent doses.

5.5 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.

Chronic Idiopathic Constipation

Adverse reactions in dose-finding, efficacy, and long-term clinical studies:

The data described below reflect exposure to Amitiza in 1175 patients with chronic idiopathic constipation (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 (\leq 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 (\geq 65 years of age). Table 1 presents data for the adverse reactions that occurred in at least 1% of patients who received Amitiza 24 mcg twice daily and that occurred more frequently with study drug than placebo. In addition, corresponding adverse reaction incidences in patients receiving Amitiza 24 mcg once daily is shown.

Table 1: Percent of Patients with Adverse Reactions (Chronic Idiopathic Constipation)

System/Adverse Reaction ¹	Placebo	Amitiza 24 mcg Once Daily	Amitiza 24 mcg Twice Daily
	N = 316 %	N = 29 %	N = 1113 %
Gastrointestinal disorders			
Nausea	3	17	29
Diarrhea	< 1	7	12
Abdominal pain	3	3	8
Abdominal distension	2	-	6
Flatulence	2	3	6
Vomiting	-	-	3
Loose stools	-	-	3
Abdominal discomfort ²	< 1	3	2
Dyspepsia	< 1	-	2
Dry mouth	< 1	-	1
Stomach discomfort	< 1	-	1
Nervous system disorders			
Headache	5	3	11
Dizziness	< 1	3	3
General disorders and site administration conditions			
Edema	< 1	-	3
Fatigue	< 1	-	2
Chest discomfort/pain	-	3	2
Respiratory, thoracic, and mediastinal disorders			
Dyspnea	-	3	2

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

²This term combines “abdominal tenderness,” “abdominal rigidity,” “gastrointestinal discomfort,” and “abdominal discomfort.”

Nausea: Approximately 29% of patients who received Amitiza 24 mcg twice daily experienced an adverse reaction of nausea; 4% of patients had severe nausea while 9% 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 24 mcg twice daily experienced an adverse reaction of diarrhea; 2% 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 adverse reactions (assessed by investigator as probably or definitely related to treatment) occurred in less than 1% of patients receiving Amitiza 24 mcg twice daily in clinical studies, occurred in at least two patients, and occurred more frequently in patients receiving study drug than those receiving placebo: fecal incontinence, muscle cramp, defecation urgency, frequent bowel movements, hyperhidrosis, pharyngolaryngeal pain, intestinal functional disorder, anxiety, cold sweat, constipation, cough, dysgeusia, eructation, influenza, joint swelling, myalgia, pain, syncope, tremor, decreased appetite.

Irritable Bowel Syndrome with Constipation

Adverse reactions in dose-finding, efficacy, and long-term clinical studies: The data described below reflect exposure to Amitiza 8 mcg twice daily in 1011 patients with IBS-C for up to 12 months and from 435 patients receiving placebo twice daily for up to 16 weeks. The total population (N = 1267) had a mean age of 46.5 (range 18–85) years; was 91.6% female; 77.5% Caucasian, 12.9% African American, 8.6% Hispanic, 0.4% Asian; and 8.0% elderly (≥ 65 years of age). Table 2 presents data for the adverse reactions that occurred in at least 1% of patients who received Amitiza 8 mcg twice daily and that occurred more frequently with study drug than placebo.

Table 2: Percent of Patients with Adverse Reactions (IBS-C Studies)

System/Adverse Reaction ¹	Placebo	Amitiza 8 mcg Twice Daily
	N = 435 %	N = 1011 %
Gastrointestinal disorders		
Nausea	4	8
Diarrhea	4	7
Abdominal pain	5	5
Abdominal distension	2	3

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

Less common adverse reactions: The following adverse reactions (assessed by investigator as probably related to treatment) occurred in less than 1% of patients receiving Amitiza 8 mcg twice daily in clinical studies, occurred

in at least two patients, and occurred more frequently in patients receiving study drug than those receiving placebo: dyspepsia, loose stools, vomiting, fatigue, dry mouth, edema, increased alanine aminotransferase, increased aspartate aminotransferase, constipation, eructation, gastroesophageal reflux disease, dyspnea, erythema, gastritis, increased weight, palpitations, urinary tract infection, anorexia, anxiety, depression, fecal incontinence, fibromyalgia, hard feces, lethargy, rectal hemorrhage, pollakiuria.

One open-labeled, long-term clinical study was conducted in patients with IBS-C receiving Amitiza 8 mcg twice daily. This study comprised 476 intent-to-treat patients (mean age 47.5 [range 21–82] years; 93.5% female; 79.2% Caucasian, 11.6% African American, 8.6% Hispanic, 0.2% Asian; 7.8% ≥ 65 years of age) who were treated for an additional 36 weeks following an initial 12–16-week, double-blinded treatment period. The adverse reactions that were reported during this study were similar to those observed in the two double-blinded, controlled studies.

6.2 Postmarketing Experience

The following additional adverse reactions have been identified during post-approval use of Amitiza 24 mcg for the treatment of chronic idiopathic constipation. 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, allergic-type reactions (including rash, swelling, and throat tightness), malaise, increased heart rate, muscle cramps or muscle spasms, 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 *Clinical Pharmacology* (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 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 highest 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, six women became pregnant. Per protocol, Amitiza was discontinued upon pregnancy detection. Four of the six women delivered healthy babies. The fifth 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. The sixth pregnancy was electively terminated.

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

Chronic Idiopathic Constipation

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).

Irritable Bowel Syndrome with Constipation

The safety profile of Amitiza in the elderly (≥ 65 years of age) subpopulation (8.0% were ≥ 65 years of age and 1.8% were ≥ 75 years of age) was consistent with the safety profile in the overall study population. Clinical studies of Amitiza did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently from younger patients.

8.6 Renal Impairment

No dosage adjustment is required in patients with renal impairment [see *Clinical Pharmacology* (12.3)].

8.7 Hepatic Impairment

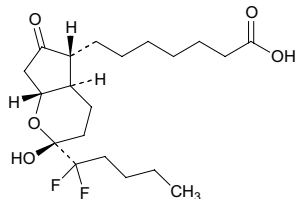
Patients with moderate hepatic impairment (Child-Pugh Class B) and severe hepatic impairment (Child-Pugh Class C) experienced markedly higher systemic drug exposure; therefore, dosing with Amitiza should be modified in these patients [see *Dosage and Administration* (2.1, 2.2) and *Clinical Pharmacology* (12.3)]. No dosage adjustment is required in patients with mild hepatic impairment (Child-Pugh Class A).

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 healthy volunteers given a single oral dose of 144 mcg of Amitiza (6 times the highest 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 volunteers 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*,4*aR*,5*R*,7*aR*)-2-(1,1-difluoropentyl)-2-hydroxy-6-oxooctahydrocyclopent[*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, is very soluble in ether and ethanol, and is practically insoluble in hexane and water. Amitiza is available as an imprinted, oval, soft gelatin capsule in two strengths. Pink capsules contain 8 mcg of lubiprostone and the following inactive ingredients: medium-chain triglycerides, gelatin, sorbitol, ferric oxide, titanium dioxide, and purified water. Orange capsules contain 24 mcg of 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. Additionally, activation of ClC-2 by lubiprostone has been shown to stimulate recovery of mucosal barrier function via the restoration of tight junction protein complexes in *ex vivo* studies of ischemic porcine intestine.

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_{1/2}) 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_{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 human feces.

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. Pharmacokinetic parameters of total radioactivity demonstrated that C_{max} decreased by 55% while AUC_{0-∞} 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 and water in a majority of clinical trials.

Special Populations

Renal Impairment

Sixteen subjects, 34–47 years old (8 severe renally impaired subjects [creatinine clearance (CrCl) < 20 mL/min] who required hemodialysis and 8 control subjects with normal renal function [CrCl > 80 mL/min]), received a single oral 24-mcg dose of Amitiza. Following administration, lubiprostone plasma concentrations were below the limit of quantitation (10 pg/mL). Plasma concentrations of M3 were within the range of exposure from previous clinical experience with Amitiza. Thus there is no need for Amitiza dosage adjustment in patients with impaired renal function.

Hepatic Impairment

Twenty-five subjects, 38–78 years old (9 with severe hepatic impairment [Child-Pugh Class C], 8 with moderate impairment [Child-Pugh Class B], and 8 with normal liver function), received either 12 mcg or 24 mcg of Amitiza under fasting conditions. Following administration, lubiprostone plasma concentrations were below the limit of quantitation (10 pg/mL) except for two subjects. In moderately and severely impaired subjects, the C_{max} and AUC_{0-t} of M3 were increased, as shown in Table 3.

Table 3: Pharmacokinetic Parameters of M3 for Subjects with Normal or Impaired Liver Function following Dosing with Amitiza

Liver Function Status	Mean (SD) AUC _{0-t} (pg-hr/mL)	% Change vs. Normal	Mean (SD) C _{max} (pg/mL)	% Change vs. Normal
Normal (n=8)	39.6 (18.7)	n.a.	37.5 (15.9)	n.a.
Child-Pugh Class B (n=8)	119 (104)	+119	70.9 (43.5)	+66
Child-Pugh Class C (n=8)	234 (61.6)	+521	114 (59.4)	+183

These results demonstrate that there is a correlation between increased exposure of M3 and severity of hepatic impairment. In conjunction with the clinical safety results, which demonstrate an increased incidence and severity of adverse events in subjects with greater severity of hepatic impairment, the starting dosage should be reduced in patients with hepatic impairment receiving Amitiza [see *Dosage and Administration* (2.1, 2.2)]. No dosing adjustment is required in patients with mild hepatic impairment (Child-Pugh Class A).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Two 2-year oral (gavage) carcinogenicity studies (one in CrI: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 highest 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 highest 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.

Mutagenesis

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.

Impairment of Fertility

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. However, the number of implantation sites and live embryos were significantly reduced in rats at the 1000 mcg/kg/day dose as compared to control. The number

of dead or resorbed embryos in the 1000 mcg/kg/day group was higher compared to the control group, but was not statistically significant. The 1000 mcg/kg/day dose in rats is approximately 166 times the highest recommended human dose of 48 mcg/day, based on body surface area.

14 CLINICAL STUDIES

14.1 Chronic Idiopathic Constipation

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).

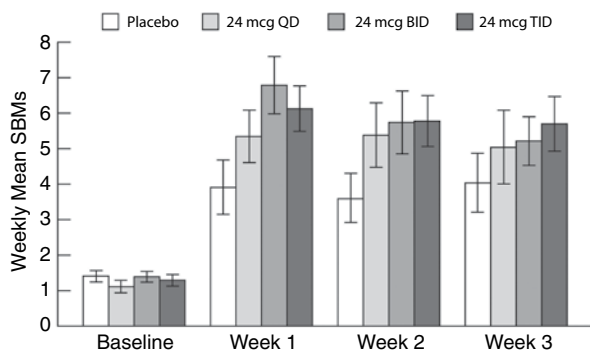


Figure 1: Weekly Mean (± Standard Error) Spontaneous Bowel Movements (Dose-finding Study)

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 4).

Table 4: Spontaneous Bowel Movement Frequency Rates¹ (Efficacy Studies)

Trial	Study Arm	Baseline	Week 1	Week 2	Week 3	Week 4	Week 1	Week 4
		Mean ± SD Median	Mean ± SD Median	Mean ± SD Median	Mean ± SD Median	Mean ± SD Median	Change from Baseline Mean ± SD Median	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
	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
Study 2	Amitiza 24 mcg Twice 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

¹Frequency 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.

Long-term 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.

14.2 Irritable Bowel Syndrome with Constipation

Efficacy Studies

Two double-blinded, placebo-controlled studies of similar design were conducted in patients with IBS-C. IBS was defined as abdominal pain or discomfort occurring over at least 6 months with two or more of the following: 1) relieved with defecation; 2) onset associated with a change in stool frequency; and 3) onset associated with a change in stool form. Patients were sub-typed as having IBS-C if they also experienced two of three of the following: 1) < 3 spontaneous bowel movements per week, 2) > 25% hard stools, and 3) > 25% spontaneous bowel movements associated with straining.

Following a 4-week baseline/washout period, a total of 1154 patients (mean age 46.6 [range 18–85] years; 91.6% female; 77.4% Caucasian, 13.2% African American, 8.5% Hispanic, 0.4% Asian; 8.3% ≥ 65 years of age) were randomized and received Amitiza 8 mcg twice daily (16 mcg/day) or placebo twice daily for 12 weeks. The primary efficacy endpoint was assessed weekly utilizing the patient's response to a global symptom relief question based on a 7-point, balanced scale ("significantly worse" to "significantly relieved"): "How would you rate your relief of IBS symptoms (abdominal discomfort/pain, bowel habits, and other IBS symptoms) over the past week compared to how you felt before you entered the study?"

The primary efficacy analysis was a comparison of the proportion of "overall responders" in each arm. A patient was considered an "overall responder" if the criteria for being designated a "monthly responder" were met in at least 2 of the 3 months on study. A "monthly responder" was defined as a patient who had reported "significantly relieved" for at least 2 weeks of the month or at least "moderately relieved" in all 4 weeks of that month. During each monthly evaluation period, patients reporting "moderately worse" or "significantly worse" relief, an increase in rescue medication use, or those who discontinued due to lack of efficacy, were deemed non-responders.

The percentage of patients in Study 1 qualifying as an "overall responder" was 13.8% in the group receiving Amitiza 8 mcg twice daily compared to 7.8% of patients receiving placebo twice daily. In Study 2, 12.1% of patients in the Amitiza 8 mcg group were "overall responders" versus 5.7% of patients in the placebo group. In both studies, the treatment differences between the placebo and Amitiza groups were statistically significant.

Results in men: The two randomized, placebo-controlled, double-blinded studies comprised 97 (8.4%) male patients, which is insufficient to determine whether men with IBS-C respond differently to Amitiza from women.

Study 1 also assessed the rebound effect from the withdrawal of Amitiza. Following 12 weeks of treatment with Amitiza 8 mcg twice daily, withdrawal of Amitiza did not result in a rebound effect.

16 HOW SUPPLIED/STORAGE AND HANDLING

Amitiza is available as an oval, soft gelatin capsule containing 8 mcg or 24 mcg of lubiprostone with "SPI" printed on one side. Amitiza is available as follows:

- 8-mcg pink capsule
 - Bottles of 60 (NDC 64764-080-60)
- 24-mcg orange capsule
 - Bottles of 60 (NDC 64764-240-60)
 - Bottles of 100 (NDC 64764-240-10)

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

PROTECT FROM EXTREME TEMPERATURES.

17 PATIENT COUNSELING INFORMATION

17.1 Dosing Instructions

Amitiza should be taken twice daily with food and water to reduce potential symptoms of nausea. The capsule should be taken once in the morning and once in the evening daily as prescribed. The capsule should be swallowed whole and should not be broken apart or chewed. Physicians and patients should periodically assess the need for continued therapy.

Patients on treatment who experience severe nausea, diarrhea, or dyspnea should inform their physician. Patients taking Amitiza may experience dyspnea within an hour of the first dose. This symptom generally resolves within 3 hours, but may recur with repeat dosing.

Chronic Idiopathic Constipation

Patients should take a single 24 mcg capsule of Amitiza twice daily with food and water.

Irritable Bowel Syndrome with Constipation

Patients should take a single 8 mcg capsule of Amitiza twice daily with food and water.

Marketed by:



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and
Takeda Pharmaceuticals America, Inc.
Deerfield, IL 60015

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