AMITIZA® (lubiprostone) 8 mcg Twice Daily in the Management of Irritable Bowel Syndrome with Constipation in Women 18 Years of Age and Older

SPECIAL ADVERTISING SECTION
This product information guide is funded by Takeda Pharmaceuticals North America, Inc.

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DEFINITION
Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder, generally defined as a group of symptoms resulting from changes in bowel function without intestinal structural or biochemical abnormalities. IBS has been further classified into subtypes according to stool patterns. IBS with constipation, or IBS-C, is characterized by hard or lumpy stools 25% of the time or more, and loose or watery stools less than 25% of the time. Other subtypes of IBS include IBS with diarrhea (IBS-D) and IBS with alternating diarrhea and constipation. The prevalence of IBS in North America is approximately 10%-15%; of these patients, about 20% suffer from IBS-C. 

DIAGNOSIS
The diagnosis of IBS-C is made after a complete medical history is obtained and physical examination is performed. IBS-C has no biochemical or structural abnormalities associated with it, so there are no specific tests that can confirm the diagnosis. However, it can be easily diagnosed in the
doctor’s office without additional testing. According to the American College of Gastroenterology, there is no need to perform routine sigmoidoscopy; colonoscopy; barium enema; stool tests for occult blood, ova and parasite or culture; or thyroid function tests in patients with IBS-C complaints who have no “alarm symptoms.” Alarm symptoms include items such as blood in the stool, a greater than 10-pound weight loss, family history of colon cancer, recurring fever, anemia, or chronic severe diarrhea.

Several symptom-based criteria have been used to diagnose IBS-C, including the Manning Criteria and the ROME Criteria. These criteria are most useful for standardizing enrollment of patients into clinical trials, and less useful for clinicians in their clinical practice decisions about diagnosis and treatment of IBS-C. Identification of IBS-C can be made if abdominal pain or discomfort is present over at least 6 months and is active within the past 3 months, with 2 or more of the following: 1) relieved with defecation; 2) onset associated with a change in frequency of stool; and 3) onset associated with a change in form (appearance) of stool. Patients can be sub-typed as having IBS-C if they also experience 2 of 3 of the following: 1) <3 spontaneous bowel movements per week, 2) >25% hard stools, and 3) >25% spontaneous bowel movements associated with straining.

**TREATMENT**

The goal of treatment is to improve symptoms of IBS-C such as abdominal discomfort, bloating, and constipation.

The general approach to the treatment of IBS-C depends in large part on the type of symptoms the patient is experiencing and their severity. Some patients with mild symptoms may find a slow increase in dietary fiber, a healthy amount of exercise and restful sleep, and education about IBS-C are adequate to improve their condition. Patients whose lives are significantly affected by symptoms typically require both lifestyle changes and drug therapy to manage their IBS-C.

Several categories of drugs have been used to treat IBS-C symptoms, including bulk-forming, stimulant, and osmotic laxatives as well as stool softeners and lubricants. These drugs are not indicated or proven to be effective in the relief of global symptoms. Agents such as psyllium, methylcellulose, calcium polycarbophil, lactulose, sorbitol, polyethylene glycol, and magnesium hydroxide may be effective for constipation, but treatment of IBS-C should be aimed at relieving global symptoms. Antispasmodics such as hyoscyamine and dicyclomine have been studied in patients with IBS-C, but there are insufficient data to recommend these agents for global symptom control. Even probiotics have been tried in IBS-C patients to decrease abdominal pain and bloating, but none of these agents have been proven effective and safe for chronic use in treating the global symptoms of IBS-C.

**Zelnorm** (tegaserod maleate), a 5-HT<sub>4</sub> (serotonin) receptor agonist used to decrease transit time and increase intestinal secretion in women with IBS-C, was until recently available only under a restricted-access program due to its potential for increasing the chance of heart attack, stroke, and worsening heart chest pain that could lead to a heart attack. This restricted-access program was closed April 2, 2008, making this drug currently unavailable for general use, except for as an emergency investigational new drug (IND) application option available through the FDA.

**FOCUS ON AMITIZA**

AMITIZA 8 mcg twice daily received approval by the FDA for the treatment of IBS-C in women ≥ 18 years old.

**PHARMACOLOGY**

Lubiprostone activates chloride channels (ClC-2) in the apical
Management of IBS-C in Women 18 Years of Age and Older

(luminal) membrane of the gastrointestinal epithelium, thereby enhancing the secretion of a chloride-rich intestinal fluid without altering serum electrolyte levels. This activity results in increased motility in the intestine and facilitates the passage of stool.³

PHARMACOKINETIC PROFILE

Lubiprostone has low systemic availability following oral administration and plasma concentrations are below the level of quantitation (10 pg/mL). Studies in rats given radiolabeled lubiprostone indicate minimal distribution beyond the gastrointestinal tissues. In vitro studies using human liver microsomes indicate that microsomal carbonyl reductase may be involved in the extensive biotransformation of lubiprostone. Further in vitro studies indicate that cytochrome P450 isoenzymes are not involved in the metabolism of lubiprostone. The M3 metabolite, the only measurable active metabolite of lubiprostone, makes up less than 10% of the dose of radiolabeled lubiprostone.³

Peak plasma levels of M3, after a single oral dose of 24 mcg of lubiprostone, occurred at approximately 1.10 hours. In vitro protein binding studies indicate lubiprostone is approximately 94% protein bound.³

The effect of food on the pharmacokinetics of a 72 mcg dose of radiolabeled lubiprostone showed the Cmax decreased by 55% while the AUC0-8 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. Dosage and administration instructions for lubiprostone state that lubiprostone be taken twice daily orally with food and water.³

EFFICACY IN CLINICAL TRIALS

AMITIZA 8 mcg, 16 mcg, and 24 mcg, twice daily, were studied in a dose-finding, double-blinded, randomized, placebo-controlled Phase 2 study of 195 adult patients with IBS-C. The primary endpoint was a change from baseline in abdominal discomfort or pain during the first treatment month.⁹ Given the favorable combination of efficacy and safety profiles seen with the 8 mcg twice daily dose, this dose was chosen for Phase 3 evaluation.

AMITIZA 8 mcg twice daily was studied in 2 double-blinded, placebo-controlled clinical trials of similar design in patients with IBS-C. IBS was defined as having abdominal pain or discomfort occurring over at least 6 months with 2 or more of the following: 1) relieved with defecation; 2) onset associated with a change in frequency of stool; and 3) onset associated with a change in form of stool. Patients were sub-typed as having IBS-C if they also experienced 2 of 3 of the following: 1) <3 spontaneous bowel movements per week; 2) >25% hard stools; and 3) >25% spontaneous bowel movements associated with straining.⁸ In the 2 studies, an intent-to-treat population of 1154 patients were randomized and received AMITIZA 8 mcg twice daily or placebo twice daily for 12 weeks. The primary efficacy endpoint was assessed weekly using the patient’s response to a global symptom relief question based on a 7-point, balanced scale. Patients considered to be “overall responders” (the primary endpoint of the study) were 13.8% (N=390) and 12.1% (N=379), compared to 7.8% (N=193) and 5.7% (N=192), respectively, in the placebo groups. In both studies, the treatment differences between the placebo and AMITIZA groups were statistically significant. Study 1
also assessed the rebound effect from the withdrawal of AMITIZA. Following the 12 weeks of treatment with AMITIZA 8 mcg twice daily, withdrawal of AMITIZA did not result in a rebound effect.\(^8\)

In general, AMITIZA 8 mcg twice daily was well tolerated in clinical trials and has a demonstrated safety and efficacy profile for adult female patients with IBS-C. The most common adverse reactions in 1011 patients through 1 year on AMITIZA 8 mcg twice daily (incidence greater than 1%) were nausea (8%), diarrhea (7%), abdominal pain (5%), and abdominal distension (3%) versus 435 patients up to 16 weeks on placebo (4%, 4%, 5%, and 2%, respectively).\(^8\)

**CONTRAINDICATIONS,WARNINGS, AND PRECAUTIONS**

AMITIZA is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction. In patients with symptoms suggestive of mechanical gastrointestinal obstruction, the treating healthcare provider should perform a thorough evaluation to confirm the absence of such an obstruction prior to initiating therapy with AMITIZA.\(^8\)

The safety of AMITIZA in pregnancy has not been evaluated in humans. 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.\(^8\)

Patients taking AMITIZA may experience nausea. If this occurs, concomitant administration of food with AMITIZA may reduce symptoms of nausea.

AMITIZA should not be prescribed to patients who have severe diarrhea. Patients should be aware of the possibility of diarrhea during treatment, and should be instructed to inform their physician if severe diarrhea and nausea occur.\(^8\)

In post-marketing clinical trials studying AMITIZA 8 mcg twice daily, there were reports of dyspnea at 0.4% in the treated IBS-C population. 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 to 60 minutes after taking the first dose. These symptoms generally resolve within a few hours after taking the dose, but recurrence has been frequently reported with subsequent doses.\(^8\)

**DRUG INTERACTIONS**

Based upon the results of in vitro human microsome studies, there is low likelihood of drug-drug interactions with lubiprostone. In vitro studies using human liver microsomes indicate that cytochrome P450 isoenzymes are not involved in the metabolism of 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.\(^8\)

**CONCLUSION**

Although the underlying pathophysiology is not completely understood and there is no specific test or cure for IBS-C, patients can learn to manage their symptoms with diet, lifestyle changes, and drug therapy. Pharmacists have the opportunity to refer patients who suffer from the symptoms of IBS-C to their physicians, who now have a demonstrated, well-tolerated, and efficacious therapy available to treat this condition. AMITIZA 8 mcg gelcaps taken twice daily is an approved treatment for adult women who suffer from IBS-C.\(\ast\)

See Important Safety Information on next page.
Indication

AMITIZA® (lubiprostone) is indicated for the treatment of Irritable Bowel Syndrome with Constipation (8 mcg twice daily) in women ≥ 18 years old.

Important Safety Information

• AMITIZA is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction. Patients with symptoms suggestive of mechanical gastrointestinal obstruction should be thoroughly evaluated by the treating healthcare provider to confirm the absence of such an obstruction prior to initiating AMITIZA treatment.

• The safety of AMITIZA in pregnancy has not been evaluated in humans. AMITIZA should be used during pregnancy only if the 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.

• Patients taking AMITIZA may experience nausea. If this occurs, concomitant administration of food with AMITIZA may reduce symptoms of nausea. Patients who experience severe nausea should inform their healthcare provider.

• AMITIZA should not be prescribed to patients that have severe diarrhea. Patients should be aware of the possible occurrence of diarrhea during treatment and inform their healthcare provider if the diarrhea becomes severe.

• Patients taking AMITIZA may experience dyspnea within an hour of first dose. This symptom generally resolves within three hours, but may recur with repeat dosing. Patients who experience dyspnea should inform their healthcare provider. Some patients have discontinued therapy because of dyspnea.

• In clinical trials of AMITIZA (8 mcg twice daily vs placebo; N=1011 vs N=435) in patients with Irritable Bowel Syndrome with Constipation, the most common adverse reactions (incidence > 4%) were nausea (8% vs 4%), diarrhea (7% vs 4%), and abdominal pain (5% vs 5%).

Please see the accompanying complete prescribing information for AMITIZA. 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.
Management of IBS-C in Women 18 Years of Age and Older

REFERENCES


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Resources on Irritable Bowel Syndrome with Constipation

**National Digestive Diseases Information Clearinghouse**

2 Information Way

Bethesda, MD 20892-3570

Phone: 1-800-891-5389

[www.digestive.niddk.nih.gov](http://www.digestive.niddk.nih.gov)

**American Gastroenterological Association**

4930 Del Ray Avenue

Bethesda, MD 20814

Phone: 301-654-2055

[www.gastro.org](http://www.gastro.org)

**American College of Gastroenterology**

P.O. Box 342260

Bethesda, MD 20827-2260

Phone: 301-263-9000

[www.acg.gi.org](http://www.acg.gi.org)

**International Foundation for Functional Gastrointestinal Disorders (IFFGD), Inc.**

P.O. Box 170864

Milwaukee, WI 53217-8076

Phone: 1-888-964-2001

[www.iffgd.org or www.aboutibs.org](http://www.iffgd.org or www.aboutibs.org)
Amitiza® (lubiprostone) capsules

FULL PRESCRIBING INFORMATION

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

Amitiza is indicated for the treatment of irritable bowel syndrome with constipation in women ≥18 years old.

2.1 Chronic Idiopathic Constipation

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

2.2 Irritable Bowel Syndrome

To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceuticals at 1-877-825-3237 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

2.3 Irritable Bowel Syndrome with Constipation

Evaluate 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.

3 DOSAGE FORMS AND STRENGTHS

Gelatin capsules: 8 mcg and 24 mcg (3)

4 CONTRAINDICATIONS

• Patients with known or suspected mechanical gastrointestinal obstruction should not receive Amitiza (4)

5 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)

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

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 3-4 week, 6-month, and 12-month treatment periods; and from 316 patients receiving placebo over short-term experience (<4 weeks).

6.2 Postmarketing Experience

In clinical trials conducted to study Amitiza in treatment of chronic idiopathic constipation and IBS-C there were reports of dyspepsia. This was reported at 23% of the treated chronic idiopathic constipation population and at 6.5% 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 dyspepsia when using Amitiza 24 mcg. Most have not been characterized as serious adverse events, but some patients have discontinued therapy because of dyspepsia. 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.

6.3 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.

6.4 General Disorders and Site Effects

• Edema < 1 - 3
• Stomach discomfort < 1 - 1
• Headache 5 3 11
• Dry mouth < 1 - 1
• Flatulence 2 3 6

7 CLINICAL STUDIES

7.1 Phase 2 Clinical Studies

7.2 Phase 3 Clinical Studies

7.3 Phase 4 Clinical Studies

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation

8.3 Nursing Mothers

8.4 Pediatric Use

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17 PATIENT COUNSELING INFORMATION

Seventeen patients who received Amitiza 24 mcg (7.0% of the 1113 treated patients) reported abdominal pain as an adverse reaction. One patient had an increase in cholesterol and 2 treated patients reported increased blood pressure. None of these patients had a history of cardiovascular disease, and no relationship to therapy could be established.

17 PATIENT COUNSELING INFORMATION

Revised: Ap/2008

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

<table>
<thead>
<tr>
<th>System/Adverse Reaction</th>
<th>Placebo</th>
<th>Amitiza 24 mcg</th>
<th>Amitiza 24 mcg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 316</td>
<td>Once Daily N = 29</td>
<td>Twice Daily N = 1133</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>3</td>
<td>17</td>
<td>29</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>3</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>2</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Flatulence</td>
<td>2</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Loss of stool</td>
<td>1</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>1</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>1</td>
<td>3</td>
<td>3</td>
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<tr>
<td>Nervous system disorders</td>
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<td>Headache</td>
<td>5</td>
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<td>11</td>
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<tr>
<td>Dizziness</td>
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<tr>
<td>General disorders and site administration conditions</td>
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<tr>
<td>Edema</td>
<td>3</td>
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<tr>
<td>Fatigue</td>
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<tr>
<td>Chest discomfort/pain</td>
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<td>Respiratory, thoracic, and mediastinal disorders</td>
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</tr>
<tr>
<td>Dyspnea</td>
<td>3</td>
<td>2</td>
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</tr>
</tbody>
</table>

INCLUDES ONLY THOSE ADVERSE REACTIONS THAT ARE ADEQUATELY ASSESSED, AS ASSESSED BY THE INVESTIGATOR.

ADVERSE REACTIONS

• 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 (1%). 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.

SIDE EFFECTS OBSTRUCTIVE INTESTINAL DYSFUNCTION

• Electrolyte: 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.

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 2 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.

8.1 Pregnancy

Teratogenic effects: Pregnancy Category C. [See Warnings and Precautions (5.1)].

In rats and rabbits, lubiprostone and its metabolites (C4 and M3) have been detected in fetal plasma and tissues. In pregnant rats, lubiprostone produces increases in fetal weight, length, and body weight. In rabbits, lubiprostone produces increases in fetal weight, length, and crown-rump (C-R) length. In rabbits, lubiprostone causes a dose-related increase in the incidence of cleft palate. In rats, lubiprostone causes a dose-related increase in the incidence of cleft palate and cleft lip. In rabbits, lubiprostone causes a dose-related increase in the incidence of cleft palate and cleft lip. In rats, lubiprostone causes a dose-related increase in the incidence of cleft palate and cleft lip. In rabbits, lubiprostone causes a dose-related increase in the incidence of cleft palate and cleft lip. In rabbits, lubiprostone causes a dose-related increase in the incidence of cleft palate and cleft lip. 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Frequency rates are calculated as 7 times (number of SBMs) / (number of days observed for that week).

Study 1: Amitiza

<table>
<thead>
<tr>
<th>Trial Arm</th>
<th>Baseline Mean ± SD</th>
<th>Week 1 Mean ± SD</th>
<th>Week 2 Mean ± SD</th>
<th>Week 3 Mean ± SD</th>
<th>Week 4 Mean ± SD</th>
<th>Change from Baseline Mean ± SD</th>
<th>Change from Baseline Mean ± SD</th>
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<td>Placebo</td>
<td>1.8 ± 1.3</td>
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<td>3.2 ± 2.5</td>
<td>2.8 ± 2.2</td>
<td>2.9 ± 2.4</td>
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<td>1.3 ± 2.5</td>
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<tr>
<td>Amitiza</td>
<td>1.4 ± 0.8</td>
<td>5.7 ± 4.4</td>
<td>5.1 ± 4.1</td>
<td>5.3 ± 4.9</td>
<td>5.3 ± 4.7</td>
<td>4.3 ± 4.3</td>
<td>3.9 ± 4.6</td>
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</tbody>
</table>

Study 2: Amitiza

<table>
<thead>
<tr>
<th>Trial Arm</th>
<th>Baseline Mean ± SD</th>
<th>Week 1 Mean ± SD</th>
<th>Week 2 Mean ± SD</th>
<th>Week 3 Mean ± SD</th>
<th>Week 4 Mean ± SD</th>
<th>Change from Baseline Mean ± SD</th>
<th>Change from Baseline Mean ± SD</th>
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<td>Placebo</td>
<td>1.5 ± 0.8</td>
<td>4.0 ± 2.7</td>
<td>3.6 ± 2.7</td>
<td>3.4 ± 2.8</td>
<td>3.5 ± 2.9</td>
<td>2.5 ± 2.6</td>
<td>1.9 ± 2.7</td>
</tr>
<tr>
<td>Amitiza</td>
<td>1.3 ± 0.9</td>
<td>5.9 ± 4.0</td>
<td>5.0 ± 4.2</td>
<td>5.6 ± 4.6</td>
<td>5.4 ± 4.8</td>
<td>4.6 ± 4.1</td>
<td>4.1 ± 4.8</td>
</tr>
</tbody>
</table>

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. 38.9% 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 subgroup analyses for gender, race, and ethnicity. Patients ≥ 65 years of age had a median age of 51.0 [range 19–85] 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 over the 6–12-month treatment periods.

14 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 at least 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 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, 12.3% African American, 8.5% Hispanic, 0.4% Asian; 82.3% ≤ 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 per study who met the "overall responder" criteria was 13.8% in the group receiving Amitiza 8 mcg twice daily compared to 7.8% of patients receiving placebo twice daily. At 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 87 (9.4%) 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 oral, 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°C–30°C (59°F–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 as prescribed. The capsules are available in 8-mcgcapsules, each should 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 dyspepsia should inform their physician. Patients taking Amitiza may experience dyspepsia within an hour of the first dose. This symptom generally resolves within 3 hours, but may recur with repeat dosing.

Chronic Constipation with Bowel Dysfunction

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.