AMITIZA®

(Lubiprostone)

1. Name of the Medical Product

1.1 Product Name: AMITIZA®

1.2 Strength: 8 mcg and 24 mcg

1.3 Pharmaceutical Dosage Form: soft gelatin capsule

2. Qualitative and Quantitative Composition

2.1 Qualitative Declaration

24 mcg: each capsule contains 24 mcg lubiprostone.
8 mcg: each capsule contains 8 mcg lubiprostone.

2.2 Quantitative Declaration

For a full list of the excipients, see section 6.1, List of Excipients.

3. Pharmaceutical Form

AMITIZA® 8 mcg: oval, pink, soft gelatin capsule with "SPI" printed on one side.

AMITIZA® 24 mcg: oval, orange, soft gelatin capsule with "SPI" printed on one side.

4. Clinical Particulars

4.1 Therapeutic Indications

AMITIZA® is indicated for treatment of:

1.Chronic Idiopathic Constipation

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

2.Opioid-Induced Constipation in Adult Patients with Chronic Non-Cancer Pain

Amitiza is indicated for the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain, including patients with chronic pain related to prior cancer or its treatment who do not require frequent (e.g., weekly) opioid dosage escalation.

Limitation of Use :
Effectiveness of Amitiza in the treatment of opioid-induced constipation in patients taking diphenylheptane opioids (e.g., methadone) has not been established.

3. Irritable bowel syndrome with constipation (IBS-C)

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

4.2 Posology and Method of Administration

Administration Instruction

- Take Amitiza orally with food and water.
- Swallow capsules whole and do not break apart or chew.
- Physicians and patients should periodically assess the need for continued therapy.

The recommended dose is 24 mcg twice daily.

Dosage in patients with hepatic impairment

For patients with moderately impaired hepatic function (Child-Pugh Class B), the recommended starting dose is 16 mcg twice daily. For patients with severely impaired hepatic function (Child-Pugh Class C), the recommended starting 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.

Irritable Bowel Syndrome with Constipation

The recommended dose is 8 mcg twice daily.

Dosage in patients with hepatic impairment

For patients with severely impaired hepatic function (Child-Pugh Class C), the recommended starting 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)

Children

Safety and effectiveness in pediatric (<18 years) patients has not been established.

Elderly

Chronic Idiopathic Constipation

The efficacy of Amitiza in the elderly (≥ 65 years of age) subpopulation was consistent with 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 24 mcg twice daily experienced a lower rate of associated nausea compared to the overall study population taking Amitiza (19%vs. 29%, respectively).

Opioid-Induced Constipation

The safety profile of Amitiza in the elderly (≥ 65 years of age) subpopulation (8.8% were ≥ 65 years of age and 1.6% 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.

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.

Renal Impairment

No dosage adjustment is required in patients with renal impairment.

Hepatic Impairment

Patients with moderate hepatic impairment (Child-Pugh Class B) and severe hepatic impairment (Child-Pugh Class C) experienced markedly higher systemic exposure of lubiprostone active metabolite M3, when compared to normal subjects. Clinical safety results demonstrated an increased incidence and severity of adverse events in subjects with greater severity of hepatic impairment.

In case of chronic idiopathic constipation or opioid-induced constipation indications, the starting dosage of Amitiza should be reduced in patients with moderate hepatic impairment. The starting dose of Amitiza should be reduced in all patients with severe hepatic impairment, regardless of the indication. No dosing adjustment is required in patients with mild hepatic impairment (Child-Pugh Class A).

4.3 Contraindications

AMITIZA® is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction.

4.4 Special warnings and precautions for use

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

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.

Syncope and Hypotension : Syncope and hypotension have been reported with Amitiza in the postmarketing setting and a few of these adverse reactions resulted in hospitalization. Most cases occurred in patients taking 24 mcg twice daily and some occurred within an hour after taking the first dose or subsequent doses of Amitiza. Some patients had concomitant diarrhea or vomiting prior to developing the adverse reaction. Syncope and hypotension generally resolved following Amitiza discontinuation or prior to next dose, but recurrence has been reported with subsequent doses. Several cases reported concomitant use of medications known to lower blood pressure, which may increase the risk for the development of syncope or hypotension.

Patients should be aware of the risk of syncope and hypotension during treatment and that other adverse reactions may increase this risk, such as diarrhea or vomiting.

Dyspnea:

In clinical trials, dyspnea was reported by 3%, 1%, and < 1% of the treated CIC, OIC, and IBS-C populations receiving Amitiza, respectively, compared to 0%, 1%, and < 1% of placebo-treated patients. There have been postmarketing reports of dyspnea when using Amitiza 24 mcg twice daily. Some patients have discontinued treatment 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. Instruct patients to contact their healthcare provider if dyspnea occurs.

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®.

4.5 Interactions with Other Medications and Other Forms of Interaction
No *in vivo* drug–drug interaction studies have been performed with Amitiza.

Based upon the results of *in vitro* human microsome studies, there is low likelihood of pharmacokinetic 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 extensivebiotransformation of lubiprostone to the metabolite M3*)*.

Additionally, *in vitro* studies in human liver microsomes demonstrate that lubiprostone does not inhibit cytochrome P450 isoforms 3A4, 2D6, 1A2, 2A6, 2B6, 2C9, 2C19, or 2E1, and *in vitro* studies of primary cultures of human hepatocytes show no induction of cytochrome P450 isoforms 1A2, 2B6, 2C9, and 3A4 by lubiprostone. Based on the available information, no protein binding–mediated drug interactions of clinical significance are anticipated.

Interaction potential with diphenylheptane opioids (e.g. methadone): Non-clinical studies have shown opioids of the diphenylheptane chemical class (e.g., methadone) to dose-dependently reduce the activation of ClC-2 by lubiprostone in the gastrointestinal tract. There is a possibility of a dose-dependent decrease in the efficacy of Amitiza in patients using diphenylheptane opioids.

4.6 Pregnancy and Lactation

Pregnancy:
Pregnancy Category C.

Risk Summary

There are no adequate and well-controlled studies with Amitiza in pregnant women. A dose dependent increase in fetal loss was observed in pregnant guinea pigs that received lubiprostone doses equivalent to 0.2 to 6 times the maximum recommended human dose (MRHD) based on body surface area (mg/m2). Animal studies did not show an increase in structural malformations.

Amitiza should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations

Current available data suggest that miscarriage occurs in 15-18% of clinically recognized pregnancies, regardless of any drug exposure. Consider the risks and benefits of available therapies when treating a pregnant woman for chronic idiopathic constipation, opioid-induced constipation or irritable bowel syndrome with constipation.

Animal Data

In developmental toxicity studies, pregnant rats and rabbits received oral lubiprostone during organogenesis at doses up to approximately 338 times (rats) and approximately 34 times (rabbits) the maximum recommended human dose (MRHD) based on body surface area (mg/m^2).

Maximal animal doses were 2000 mcg/kg/day (rats) and 100 mcg/kg/day (rabbits). In rats, there were increased incidences of early resorptions and soft tissue malformations (*situs inversus*, cleft palate) at the 2000 mcg/kg/day dose; however, these effects were probably secondary to maternal toxicity. A dose-dependent increase in fetal loss occurred when guinea pigs received lubiprostone after the period of organogenesis, on days 40 to 53 of gestation, at daily oral doses of 1, 10, and 25 mcg/kg/day (approximately 0.2, 2 and 6 times the MRHD based on body surface area (mg/m^2)). The potential of lubiprostone to cause fetal loss was also examined in pregnant Rhesus monkeys. Monkeys received lubiprostone post-organogenesis on gestation days 110 through 130 at daily oral doses of 10 and 30 mcg/kg/day (approximately 3 and 10 times the MRHD based on body surface area (mg/m2)). Fetal loss was noted in one monkey from the 10 mcg/kg dose group, which is within normal historical rates for this species. There was no drug related adverse effect seen in monkeys.

Lactation:
It is not known whether lubiprostone is excreted in human milk. In rats, neither lubiprostone nor its active metabolites were detectable in breast milk following oral administration of lubiprostone. Because lubiprostone increases fluid secretion in the intestine and intestinal motility, human milk-fed infants should be monitored for diarrhea. Caution should be exercised when Amitiza is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

4.7 Effects on Ability to Drive and Use Machine
Not Applicable.

4.8 Undesirable Effects
The following adverse reactions are described below and elsewhere in labeling:

- Nausea *[see 4.4 Special warnings and precautions for use]*
- Diarrhea *[see 4.4 Special warnings and precautions for use]*
- Syncope and Hypotension *[see 4.4 Special warnings and precautions for use]*
- Dyspnea *[see 4.4 Special warnings and precautions for use]*

Clinical Trials 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.

During clinical development of Amitiza for CIC, OIC, and IBS-C, 1234 patients were treated with Amitiza® for 6 months and 524 patients were treated for 1 year (not mutually exclusive).

Chronic Idiopathic Constipation

Adverse reactions in dose-finding, efficacy, and long-term clinical studies: The data described below reflect exposure to Amitiza 24 mcg twice daily in 1113 patients with chronic idiopathic constipation 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 placebo population (N = 316) had a mean age of 47.8 (range 21–81) years; was 87.3% female; 80.7% Caucasian, 10.1% African American, 7.3% Hispanic, 0.9% Asian; and 11.7% elderly (≥ 65 years of age). Of those patients treated with Amitiza 24 mcg twice daily (N=1113), the mean age was 50.3 (range 19-86) years; 86.9% were female; 86.1% Caucasian, 7.6% African American, 4.7% Hispanic, 1.0% Asian; and 16.7% elderly (≥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.

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

System/Adverse Reaction[1]	Placebo N = 316 %	Amitiza 24 mcg Twice Daily N = 1113 %
Gastrointestinal disorders		
Nausea	3	29
Diarrhea	1	12
Abdominal pain	3	8
Abdominal distension	2	6
Flatulence	2	6
Vomiting	0	3
Loose stools	0	3
Abdominal discomfort[2]	1	3
Dyspepsia	< 1	2
Dry mouth	< 1	1
Nervous system disorders		
Headache	5	11
Dizziness	1	3
General disorders and site administration conditions		
Edema	< 1	3
Fatigue	1	2
Chest discomfort/pain	0	2
Respiratory, thoracic, and mediastinal disorders		
Dyspnea	0	2

[1]Includes only those events associated with treatment (possibly, probably, or definitely related, as assessed by the investigator).
[2]This term combines "abdominal tenderness," "abdominal rigidity," "gastrointestinal discomfort," "stomach discomfort", and "abdominal discomfort."

The most common adverse reactions (incidence > 4%) in CIC were nausea, diarrhea, headache, abdominal pain, abdominal distension, and flatulence.

Nausea: Approximately 29% of patients who received Amitiza 24 mcg twice daily experienced nausea; 4% of patients had severe nausea and 9% of patients discontinued treatment due to nausea. The rate of nausea associated with Amitiza 24 mcg twice daily was lower among male (8%) and elderly (19%) patients. No patients in the clinical studies were hospitalized due to nausea.

Diarrhea: Approximately 12% of patients who received Amitiza 24 mcg twice daily experienced diarrhea; 2% of patients had severe diarrhea and 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.

Opioid-Induced Constipation

Adverse reactions in efficacy and long-term clinical studies: The data described below reflect exposure to Amitiza 24 mcg twice daily in 860 patients with OIC for up to 12 months and from 632 patients receiving placebo twice daily for up to 12 weeks. The total population (N = 1492) had a mean age of 50.4 (range 20–89) years; was 62.7% female; 82.7% Caucasian, 14.2% African American, 0.8% American Indian/Alaska Native, 0.8% Asian; 5.2% were of Hispanic ethnicity; and 8.8% were elderly (≥ 65 years of age). Table 2 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.

Table 2: Percent of Patients with Adverse Reactions (OIC Studies)

System/Adverse Reaction[1]	Placebo N = 632 %	Amitiza 24 mcg Twice Daily N = 860 %
Gastrointestinal disorders		
Nausea	5	11
Diarrhea	2	8
Abdominal pain	1	4
Flatulence	3	4
Abdominal distension	2	3
Vomiting	2	3
Abdominal discomfort[2]	1	1
Nervous system disorders		
Headache	1	2
General disorders and site administration conditions		
Peripheral edema	< 1	1

[1]Includes only those events associated with treatment (possibly, probably, or definitely related, as assessed by the investigator).
[2]This term combines "abdominal tenderness," "abdominal rigidity," "gastrointestinal discomfort," "stomach discomfort", and "abdominal discomfort."

The most common adverse reactions (incidence > 4%) in OIC were nausea and diarrhea.

Nausea: Approximately 11% of patients who received Amitiza 24 mcg twice daily experienced nausea; 1% of patients had severe nausea and 2% of patients discontinued treatment due to nausea.

Diarrhea: Approximately 8% of patients who received Amitiza 24 mcg twice daily experienced diarrhea; 2% of patients had severe diarrhea and 1% of patients discontinued treatment due to diarrhea.

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, blood potassium decreased.

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 3 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 3: Percent of Patients with Adverse Reactions (IBS-C Studies)

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

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

The most common adverse reactions (incidence > 4%) in IBS-C were nausea, diarrhea, and abdominal pain.

Nausea: Approximately 8% of patients who received Amitiza 8 mcg twice daily experienced nausea; 1% of patients had severe nausea and 1% of patients discontinued treatment due to nausea.

Diarrhea: Approximately 7% of patients who received Amitiza 8 mcg twice daily experienced diarrhea; <1% of patients had severe diarrhea and <1% of patients discontinued treatment due to diarrhea.

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.

Post-marketing Experience

The following additional 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 and/or hypotension *[see 4.4 Special warnings and precautions for use]*, ischemic colitis,

hypersensitivity/allergic-type reactions (including rash, swelling, and throat tightness), malaise, tachycardia, muscle cramps or muscle spasms, and asthenia.

4.9 Overdosage

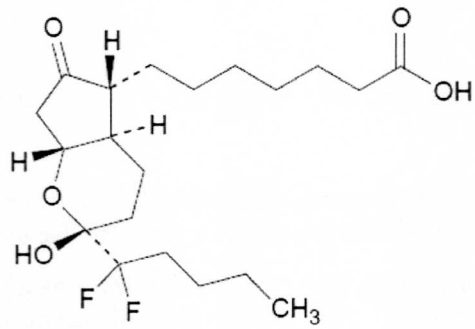
There have been two confirmed reports of overdosage with Amitiza. The first report involved a 3-year-old child who accidentally ingested 7 or 8 capsules of 24 mcg of Amitiza and fully recovered. The second report was a study patient who self-administered a total of 96 mcg of Amitiza per day for 8 days. 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%).

5. Pharmacological Properties

Amitiza (lubiprostone) is a chloride channel activator for oral use.

The chemical name for lubiprostone is (–)-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 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.

Mechanism of Action: Lubiprostone is a locally acting chloride channel activator that enhances a chloride-rich intestinal fluid secretion without altering electrolyte concentrations in the serum. Lubiprostone acts by specifically activating ClC-2, which is a normal constituent of the apical membrane of human intestinal epithelial cells, in a protein kinase A–independent fashion.

By increasing intestinal fluid secretion, lubiprostone facilitates the passage of stool and alleviates 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.

Lubiprostone, via activation of apical ClC-2 channels in intestinal epithelial cells, bypasses the antisecretory action of opiates that results from suppression of secretomotor neuron excitability.

Activation of ClC-2 by lubiprostone has also been shown to stimulate recovery of mucosal barrier function and reduce intestinal permeability via the restoration of tight junction protein complexes in ex vivo studies of ischemic porcine intestine.

5.1 Pharmacodynamic Properties

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.

Clinical Efficacy

Chronic Idiopathic Constipation:

In clinical trials, AMITIZA® has been shown to be effective in patients with chronic idiopathic constipation or chronic constipation (excluding constipation caused by organic diseases). Patients treated with AMITIZA® 24 mcg twice daily had a higher frequency of spontaneous bowel movements during Week 1 and all other study weeks than the patients taking placebo. AMITIZA® demonstrated increases in the percentage of patients who experienced spontaneous bowel movements within the first 24 hours after administration when compared to placebo. Similarly, the time to first spontaneous bowel movements 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 ratings of constipation severity and treatment effectiveness, 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 treatment with AMITIZA®, withdrawal of AMITIZA® did not result in a rebound effect.

Opioid-induced Constipation:

In clinical trials, AMITIZA® has been shown to be effective in patients with opioid-induced constipation who have non-cancer pain. The proportion of AMITIZA®-treated patients who were considered "overall responders" (defined as having ≥1 SBM improvement over baseline for all treatment weeks for which data were available and ≥3 SBMs/week for at least 9 of 12 treatment weeks) were statistically significantly higher than the proportion of patients treated with placebo. Patients treated with AMITIZA® 24 mcg twice daily for 12 weeks had a higher frequency of spontaneous bowel movements at Week 8 or a higher overall frequency of spontaneous bowel movements throughout the entire treatment period than the patients taking placebo. AMITIZA® demonstrated increases in the percentage of patients who experienced spontaneous bowel movements within the first 4, 8, 12, 24 and 48 hours after administration when compared to placebo. Similarly, the time to first spontaneous bowel movements was shorter for patients receiving AMITIZA® than for those receiving placebo. Signs and symptoms related to constipation, including abdominal bloating, stool consistency, abdominal pain 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).

Irritable Bowel Syndrome with Constipation:
In clinical trials AMITIZA® has been shown to be effective in patients with irritable bowel syndrome with constipation. After 12 weeks of treatment the proportion of patients qualifying as an overall responder was greater in those receiving AMITIZA® 8 mcg twice daily than those taking placebo. 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. During a 4-week randomized withdrawal period following one of the pivotal studies, patients who received AMITIZA® during the 12-week treatment period were re-randomized to receive either placebo or to continue treatment with AMITIZA®. In AMITIZA®-treated patients who were "overall responders" and who were re-randomized to placebo, SBM frequency rates did not result in worsening compared to baseline.

5.2 Pharmacokinetic Properties

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 Cmax was 41.5 pg/mL and the mean AUC0–t was 57.1 pg·hr/mL. The AUC0–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.

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 ^{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 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.

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 Cmax and AUC0–t of the active lubiprostone metabolite M3 were increased, as shown in Table 4.

Table 4: Pharmacokinetic Parameters of the Metabolite M3 for Subjects with Normal or Impaired Liver Function following Dosing with Amitiza

Liver Function Status	Mean (SD) AUC0–t (pg·hr/mL)	% Change vs. Normal	Mean (SD) Cmax (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

5.3 Preclinical Safety Data

Carcinogenicity: 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 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. 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 benign 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.

Mutagenicity: 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.

Reproductive and Developmental Toxicity: 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 169 times the highest recommended human dose of 48 mcg/day based on body surface area.

CLINICAL STUDIES

Chronic Idiopathic Constipation

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 spontaneous bowel movements (SBMs) per week (a SBM is a bowel movement occurring in the absence of laxative use) 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 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 alsoobserved in Weeks 2, 3, and 4 of therapy (Table 5).

Table 5: Spontaneous Bowel Movement Frequency Rates1 (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 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

[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).

During a 7-week randomized withdrawal study, patients who received Amitiza during a 4-week treatment period were then randomized to receive either placebo or to continue treatment with Amitiza. In Amitiza-

treated patients randomized to placebo, SBM frequency rates returned toward baseline within 1 week and did not result in worsening compared to baseline. Patients who continued on Amitiza maintained their response to therapy over the additional 3 weeks of treatment.

Opioid-Induced Constipation in Adult Patients with Chronic Non-Cancer Pain

The efficacy of Amitiza in the treatment of opioid-induced constipation in patients receiving opioid therapy for chronic, non-cancer-related pain was assessed in three randomized, doubleblinded, placebo-controlled studies. In Study 1, the median age was 52 years (range 20–82) and 63.1% were female. In Study 2, the median age was 50 years (range 21–77) and 64.4% were female. In Study 3, the median age was 50 years (range 21–89) and 60.1% were female. Patients had been receiving stable opioid therapy for at least 30 days prior to screening, which was to continue throughout the 12-week treatment period. At baseline, mean oral morphine equivalent daily doses (MEDDs) were 99 mg and 130 mg for placebo-treated and Amitiza-treated patients, respectively, in Study 1. Baseline mean MEDDs were 237 mg and 265 mg for placebo-treated and Amitiza-treated patients, respectively, in Study 2. In Study 3, baseline mean MEDDs were 330 mg and 373 mg for placebo-treated and Amitiza-treated patients, respectively. The Brief Pain Inventory-Short Form (BPI-SF) questionnaire was administered to patients at baseline and monthly during the treatment period to assess pain control. Patients had documented opioidinduced constipation at baseline, defined as having less than 3 spontaneous bowel movements (SBMs) per week, with at least 25% of SBMs associated with one or more of the following conditions: (1) hard to very hard stool consistency; (2) moderate to very severe straining; and/or (3) having a sensation of incomplete evacuation. Laxative use was discontinued at the beginning of the screening period and throughout the study. With the exception of the 48-hour period prior to first dose and for at least 72 hours (Study 1) or 1 week (Study 2 and Study 3) following first dose, use of rescue medication was allowed in cases where no bowel movement had occurred in a 3-day period. Median weekly SBM frequencies at baseline were 1.5 for placebo patients and 1.0 for Amitiza patients in Study 1 and, for both Study 2 and Study 3, median weekly SBM frequencies at baseline were 1.5 for both treatment groups.

In Study 1, patients receiving non-diphenylheptane (e.g., non-methadone) opioids (n = 431) were randomized to receive placebo (n = 217) or Amitiza 24 mcg twice daily (n = 214) for 12 weeks. The primary efficacy analysis was a comparison of the proportion of "overall responders" in each treatment arm. A patient was considered an "overall responder" if ≥1 SBM improvement over baseline were reported for all treatment weeks for which data were available *and* ≥3 SBMs/week were reported for at least 9 of 12 treatment weeks. The proportion of patients in Study 1 qualifying as an "overall responder" was 27.1% in the group receiving Amitiza 24 mcg twice daily compared to 18.9% of patients receiving placebo twice daily (treatment difference = 8.2%; p-value = 0.03). Examination of gender and race subgroups did not identify differences in response to Amitiza among these subgroups. There were too few elderly patients (≥ 65 years of age) to adequately assess differences in effects in that population.

In Study 2, patients receiving opioids (N = 418) were randomized to receive placebo (n = 208) or Amitiza 24 mcg twice daily (n = 210) for 12 weeks. Study 2 did not exclude patients receiving diphenylheptane opioids (e.g., methadone). The primary efficacy endpoint was the mean change from baseline in SBM frequency at Week 8; 3.3 vs. 2.4 for Amitiza and placebo-treated patients, respectively; treatment difference = 0.9; p-value = 0.004. The proportion of patients in Study 2 qualifying as an "overall responder," as prespecified in Study 1, was 24.3% in the group receiving Amitiza compared to 15.4% of patients receiving placebo. In the subgroup of patients in Study 2 taking diphenylheptane opioids (baseline mean [median] MEDDs of 691 [403] mg and 672 [450] mg for placebo and Amitiza patients, respectively), the proportion of patients qualifying as an "overall responder" was 20.5% (8/39) in the group receiving Amitiza compared to 6.3% (2/32) of patients receiving placebo. Examination of gender and race subgroups did not identify differences in response to Amitiza among these subgroups. There were too few elderly patients (≥ 65 years of age) to adequately assess differences in effects in that population.

In Study 3, patients receiving opioids (N = 451) were randomized to placebo (n = 216) or Amitiza 24 mcg twice daily (n = 235) for 12 weeks. Study 3 did not exclude patients receiving diphenylheptane opioids (e.g., methadone). The primary efficacy endpoint was the change from baseline in SBM frequency at Week 8. The study did not demonstrate a statistically significant improvement in SBM frequency rates at Week 8 (mean change from baseline of 2.7 vs. 2.5 for Amitiza and placebo-treated patients, respectively; treatment difference = 0.2; p-value = 0.76). The proportion of patients in Study 3 qualifying as an "overall responder," as prespecified in Study 1, was 15.3% in the patients receiving Amitiza compared to 13.0% of patients receiving placebo. In the subgroup of patients in Study 3 taking diphenylheptane opioids (baseline mean [median] MEDDs of 730 [518] mg and 992 [480] mg for placebo and Amitiza patients,respectively), the proportion of patients qualifying as an "overall responder" was 2.1% (1/47) in the group receiving Amitiza compared to 12.2% (5/41) of patients receiving placebo.

Irritable Bowel Syndrome with Constipation

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 (SBMs) per week, 2) > 25% hard stools, and 3) > 25% SBMs 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.

During a 4-week randomized withdrawal period following Study 1, patients who received Amitiza during the 12-week treatment period were re-randomized to receive either placebo or to continue treatment with Amitiza. In Amitiza-treated patients who were "overall responders" during Study 1 and who were re-randomized to placebo, SBM frequency rates did not result in worsening compared to baseline.

6. Pharmaceutical Particulars

6.1 List of Excipients

Medium-chain triglycerides, gelatin, sorbitol, purified water, and black ink. In addition, the following coloring agents are included in the gelatin capsule shell:

24 mcg orange capsule: FD&C Red #40, D&C Yellow #10;
8 mcg capsule: Ferric oxide, Titanium dioxide.

6.2 Incompatibilities

None known to date.

6.3 Shelf Life

Do not use the medicine after expiry date stated on packaging.

6.4 Special Precautions for Storage

Store below 30°C. Protect from light and extreme temperatures. Do not freeze.

6.5 Nature and Contents of Container

AMITIZA® is supplied in blisters.

7. Marketing Authorization Holder

Manufactured by: Catalent Pharma Solutions, LLC, Florida, USA.

Primary and secondary packed by: Packaging Coordinators, LLC, Pennsylvania, USA.

Released by: Sucampo Pharma, LLC., Hyogo, Kobe, Japan.

Imported by: Takeda (Thailand) Ltd., Bangkok, Thailand

8. Marketing Authorization Number

9. Date of authorization

10. Date of revision of the text

USPI Date 1 AUG 2017.

(First registration: Jun 2017)