

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 21-908/S-008

Trade Name: **AMITIZA**

Generic Name: Lubiprostone

Sponsor: Sucampo Pharma Americas, Inc.

Approval Date: 02/24/2011

Indications:

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 21-908/S-008

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	X
Other Action Letters	
Labeling	X
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Medical Review(s)	X
Chemistry Review(s)	
Environmental Assessment	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	X
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Other Review(s)	X
Administrative/Correspondence Document(s)	X

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 21-908/S-008

APPROVAL LETTER



NDA 21-908/S-008

SUPPLEMENT APPROVAL

Sucampo Pharma Americas, Inc.
Attention: Robert S. Cormack, Ph.D., RAC
Director, Regulatory Affairs
4520 East-West Highway, Suite 300
Bethesda, MD 20814

Dear Dr. Cormack:

Please refer to your Supplemental New Drug Application (sNDA) dated and received May 29, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Amitiza® (lubiprostone) Capsules.

This “Prior Approval” supplemental new drug application provides for the addition of information regarding dose reduction in patients with hepatic impairment. The effected sections in the package insert include: 2 (Dosage and Administration), 8 (Use in Specific Populations), and 12 (Clinical Pharmacology).

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling with the addition of any labeling changes in pending “Changes Being Effected” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number and annual report date.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at <http://www.fda.gov/opacom/morechoices/fdaforms/cder.html>; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Heather Buck, Regulatory Project Manager, at (301) 796-1413.

Sincerely,

{See appended electronic signature page}

Joyce Korvick, M.D., M.P.H
Deputy, Safety
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE: Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOYCE A KORVICK
02/24/2011

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 21-908/S-008

LABELING

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

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

- 1.1 Chronic Idiopathic Constipation
- 1.2 Irritable Bowel Syndrome with Constipation

2 DOSAGE AND ADMINISTRATION

- 2.1 Chronic Idiopathic Constipation
- 2.2 Irritable Bowel Syndrome with Constipation

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Pregnancy
- 5.2 Nausea
- 5.3 Diarrhea
- 5.4 Dyspnea
- 5.5 Bowel Obstruction

6 ADVERSE REACTIONS

- 6.1 Clinical Studies Experience
- 6.2 Postmarketing Experience

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use

- 8.5 Geriatric Use
- 8.6 Renal Impairment
- 8.7 Hepatic Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

- 14.1 Chronic Idiopathic Constipation
- 14.2 Irritable Bowel Syndrome with Constipation

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

- 17.1 Dosing Instructions

*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 (≤ 4 weeks). The total population (N = 1491) had a mean age of 49.7 (range 19–86) years; was 87.1% female; 84.8% Caucasian, 8.5% African American, 5.0% Hispanic, 0.9% Asian; and 15.5% elderly (≥ 65 years of age). Table 1 presents data for the adverse reactions that occurred in at least 1% of patients who received Amitiza 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

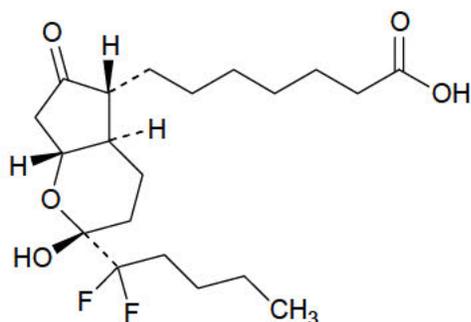
Patients with moderate hepatic impairment (Child-Pugh Class B) and severe hepatic impairment (Child-Pugh Class C) experienced markedly higher systemic drug exposure; therefore, dosing with Amitiza should be modified in these patients [see *Dosage and Administration (2.1, 2.2)* and *Clinical Pharmacology (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-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.

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 $AUC_{0-\infty}$ 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. 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 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 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).

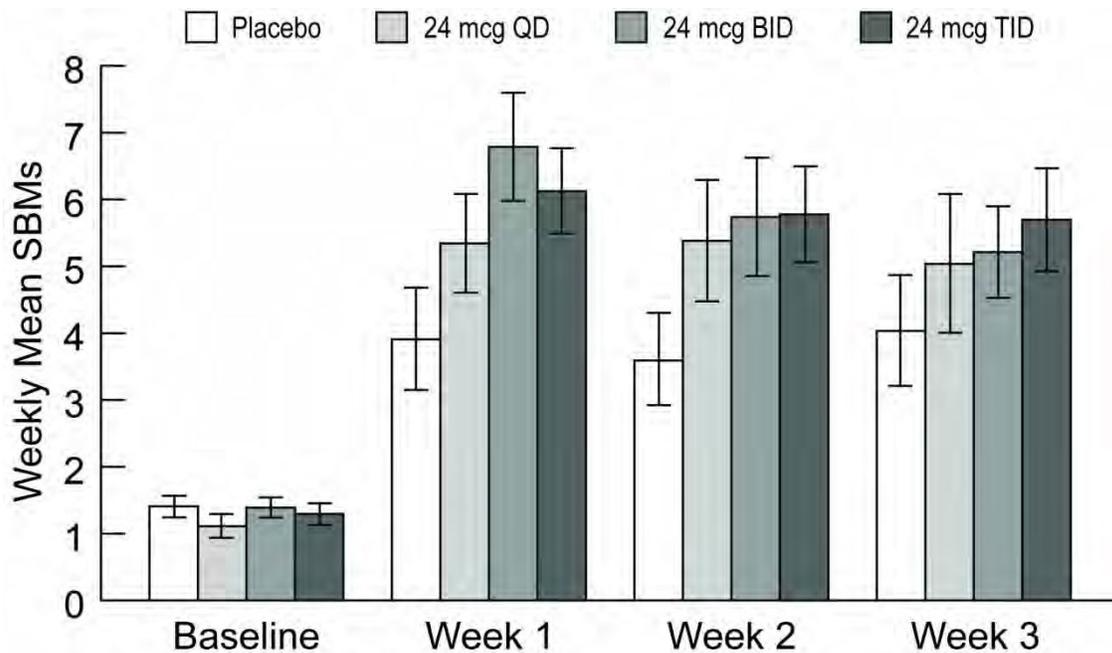


Figure 1: Weekly Mean (\pm Standard Error) Spontaneous Bowel Movements (Dose-finding Study)

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% \geq 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 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

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:

Sucampo Pharma Americas, Inc.
Bethesda, MD 20814

and

Takeda Pharmaceuticals America, Inc.
Deerfield, IL 60015

Amitiza[®] is a registered trademark of Sucampo Pharmaceuticals, Inc.

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 21-908/S-008

MEDICAL REVIEW(S)

DIVISION OF GASTROENTEROLOGY PRODUCTS

MEDICAL OFFICER'S LABELING REVIEW

Application Type NDA
Submission Number 21-908
Submission Code S008

Date: February 11, 2011

To: Joyce Korvick, MD, MPH
Deputy Director for Safety
Division of Gastroenterology Products

From: Aisha Peterson Johnson, MD, MPH, MBA
Medical Reviewer
Division of Gastroenterology Products

Through: Robert Fiorentino, MD, MPH
Acting Medical Team Leader
Division of Gastroenterology Products

Subject: Review of proposed labeling changes for
Amitiza

I. Recommendation on Regulatory Action

It is the recommendation of this reviewer that current Amitiza labeling be revised to include information regarding dosing adjustments in patients with renal and hepatic impairment based on the results of Phase 4 pharmacokinetic and safety studies submitted by the sponsor. It is also the recommendation of this reviewer that the results of the open-label pediatric study submitted by the sponsor not be included in current labeling as it does not provide enough information to make pediatric dosing recommendations.

See, Amitiza label, updated February 2011, for finalized label revisions.

II. Product Background

Amitiza[®] (lubiprostone) was approved on January 31, 2006 (NDA 021-908) for the treatment of chronic idiopathic constipation in the adult population at a dose

of 24 mcg twice daily. An efficacy supplement was approved on March 29, 2008, for the treatment of irritable bowel syndrome with constipation (IBS-C) in women 18 years old and older at a dose of 8 mcg twice daily.

Lubiprostone is a “locally acting” prostaglandin E₁ (PGE₁) metabolite analogue and is a specific activator of ClC-2 chloride channels that are involved in the secretion of fluids into the gastrointestinal tract. The plasma concentration of lubiprostone is below the level of quantitation (10pg/mL). Therefore, during studies following oral administration, the bioavailability of Amitiza is studied using M3, a metabolite of lubiprostone.

With the current submission, labeling supplement (S008) to NDA 21-908, the Sponsor seeks to amend the label to add new uses in special populations (renal and hepatic impairment) and new pharmacokinetic data (renal and hepatic impairment, pediatric constipation).

III. Relevant Prior Regulatory History

The current labeling supplement seeks to include information from postmarketing study commitment final study reports (see Table 1. below).

The renal impairment, hepatic impairment, and pediatric pharmacokinetic studies have been reviewed by Dr. Christian Grimstein (see full review dated 11/09/2009).

Table 1. Postmarketing Study Commitments

Commitment	Study Title	Date Submitted
“Perform a Phase IV Study to assess the need for potential dose adjustment in patients with renal impairment”	“A Multi-Center, Open-Labeled Study of the Safety and Pharmacokinetics of Oral Lubiprostone in Subjects with Renal Impairment”	04/07/2008
“Perform a Phase IV Study to assess the need for potential dose adjustment in patients with hepatic impairment”	“A Multi-Center, Open-Labeled Study of the Safety and Pharmacokinetics of Oral Lubiprostone in Subjects with Hepatic Impairment”	05/29/2009
Treatment of Chronic Idiopathic Constipation in pediatric patients ages 0 to 17 years*	“A Multi-Center, Open-Labeled Study of the Safety, Efficacy, and Pharmacokinetics of Lubiprostone in Pediatric Patients with Constipation”	05/29/2009

*Pediatric Research Equity Act (PREA) requirement triggered by the January 2006 approval of Amitiza for ClC in adults.

IV. **Proposed Labeling Changes**

A. USE IN SPECIFIC POPULATIONS, 8.6 Renal Impairment

Current labeling:

Amitiza has not been studied in patients who have renal impairment.

Sponsor-Proposed labeling:

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

Clinical Reviewer Comment:

The Sponsor's proposed labeling appears adequate. In patients with renal impairment, the bioavailability of M3 was similar to that seen in patients without renal impairment.

B. USE IN SPECIFIC POPULATIONS, 8.7 Hepatic Impairment

Current labeling:

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

(b) (4)



DGP Proposed labeling:

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).

Clinical Reviewer Comment:

Patients with mild (Child-Pugh Class A), moderate (Child-Pugh Class B), and severe (Child-Pugh Class C) hepatic impairment along with patients with normal renal function were enrolled in the study. Patients were given a single oral dose of lubiprostone (12 or 24 mcg). For subjects with severe hepatic impairment, the exposure to M3 was 521% higher than was observed in patients with normal hepatic function. For subjects with moderate hepatic impairment, the exposure (AUC_{0-t}) to M3 was 119% higher than was observed in patients with normal hepatic function.

None of the subjects with normal hepatic function reported adverse events (AEs) during the study. There were a total of 15 AEs reported with 13 of these reported by patients with severely impaired hepatic function. There were no deaths during the study.

The study showed that both exposure and occurrence of AEs were increased in patients with moderate and severe hepatic impairment. This, in addition to the PK data, suggests that the recommended dose of Amitiza should be reduced in the population of patients with severe hepatic impairment. Dose reduction is not necessary in patients with mild or moderate hepatic impairment.

(b) (4) *The DGP proposed labeling follows clinical pharmacology recommendations and should be adopted.*

C. CLINICAL PHARMACOLOGY, 12.3 Pharmacokinetics, Special Populations, Pediatrics

Current Labeling:

No pediatric pharmacokinetic labeling is currently provided.

(b) (4)

DGP Proposed labeling:

No pediatric pharmacokinetic labeling is currently recommended

Clinical Reviewer Comment:

The submitted pediatric study was a 4-week, open-label study in 109 patients. Dosing was stratified by age and weight to receive 12 mcg once daily, 12 mcg twice daily, or 24 mcg twice daily. The primary efficacy endpoint was the frequency of spontaneous bowel movements during Week 1. The mean SBM frequency was higher at Week 1 than at baseline (3.11 vs 1.48; $p < 0.0001$).

The primary safety endpoint was the incidence of AEs. During the study, 57.3% of patients reported at least one TEAE. A total of 8 patients withdrew from the study. The highest incidence of treatment-related AEs occurred in the 24 mcg

BID group. No patients died during the study and there were two serious adverse events reported—sickle cell crisis and abdominal pain secondary to fecal mass.

The study was reviewed by the Pediatric and Health Staff (see full Review by Dr. Felicia Collins, 11/18/2009). Dr. Collins concluded that the study does not satisfy PREA requirements due to the (b) (4)

Dr. Collins recommends that current labeling not be changed to include any of the results of the pediatric study.

I agree with the PMHS pediatric labeling recommendations.

D. CLINICAL PHARMACOLOGY, 12.3 Pharmacokinetics, Special Populations, Renal Impairment

(b) (4)

(b) (4)

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.

Clinical Review Comment:

The labeling proposed by DGP follows clinical pharmacology recommendations and should be accepted.

E. CLINICAL PHARMACOLOGY, 12.3 Pharmacokinetics, Special Populations,
Hepatic Impairment

(b) (4)



(b) (4)



Table 3: Pharmacokinetic Parameters of M3 for Patients with Normal or Impaired Liver Function Following 24 mcg of 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

1 (b) (4)



(b) (4)



Clinical Review Comment:
The labeling proposed by DGP follows clinical pharmacology recommendations and should be accepted.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AISHA E Peterson Johnson
02/17/2011

ROBERT FIORENTINO
02/18/2011

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 21-908/S-008

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Addendum 2 to Clinical Pharmacology review (PMR/PMC) of NDA 21908

This addendum summarizes updated labeling recommendations for NDA 21908 (AMITIZA) based on labeling negotiations with the sponsor following submission of the labeling supplement on 05/29/09 (PMR/PMC hepatic impairment study). Reference is made to the original PMC/PMR Clinical Pharmacology review (dated 11/09/2009) and Addendum 1 to that review (dated 11/13/09) as well as a teleconference with the sponsor held on 12/14/10.

In the original PMC/PMR Clinical Pharmacology review for NDA 21908 [DARRTS date: 11/9/2009], dose reduction is recommended in IBS-C and CIC patients with severe hepatic impairment. (b) (4) the recommendation to reduce the dose of lubiprostone was extended to CIC patients with moderate hepatic impairment (see below: Labeling recommendations).

As discussed in the original Clinical Pharmacology review (DARRTS date: 11/9/2009; "Review of Hepatic Impairment Study (CSR0211-09-002-01") moderate hepatic impaired subjects had increased exposure of metabolite M3 compared to normal subjects. With respect to metabolite M3, in subjects with moderate hepatic impairment (N=8), C_{max} was increased by 66% (90% CI: 99.33, 277.13) and AUC_{0-t} was increased by 119% [90% CI: 105.97, 454.08] when compared to subjects with normal liver function. Clinical studies in CIC patients (Table 1 and 2) showed an increase of AEs with increasing exposure of lubiprostone. Therefore a reduced starting dose of lubiprostone is recommended in CIC patients with moderate impaired hepatic function as described in the updated recommended labeling and discussed with the sponsor during a teleconference on 12/14/2010.

Table 1 (Reference: AMITIZA label):

(b) (4)

System/Adverse Reaction	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

Table 2: Overall Summary of Adverse Events in Well-Controlled Safety Group with CIC patients.

Category	Placebo	Lubiprostone 16 mcg	Lubiprostone 32 mcg	Lubiprostone 48 mcg
Subjects N(%)	435 (100%)	832(100%)	49(100%)	(45%)
≥ 1 AE	225 (51.7)	426 (51.2)	30 (61.2)	32 (71.1)
≥ 1 TRAE	91 (20.9)	186 (22.4)	21 (42.9)	19 (42.2)
≥ 1 SAE	4 (0.9)	7 (0.8)	1 (2.0)	2 (4.4)
≥ 1 TRSAE	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
Discontinued due to AE	26 (6.0)	39 (4.7)	8 (16.3)	6 (13.3)

AE: Adverse Events; TRAE: Treatment-related Adverse Events; SAE: Severe Adverse Events; TRSAE: Treatment-related Severe Adverse Events.

Reviewer's table modified from Table 2.7.4.2.1, page 27 of 126, Summary of Clinical Safety for RU-0211

(b) (4)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTIAN GRIMSTEIN
02/15/2011

EDWARD D BASHAW
02/16/2011

Addendum to Clinical Pharmacology review (PMR/PMC) of NDA 21908

On January 31, 2006, the following postmarketing commitments were requested by the Agency:

1. *“Perform a Phase IV study to assess the need for potential dose adjustment in patients with hepatic impairment.”*
2. *“Perform a Phase IV study to assess the need for potential dose adjustment in patients with renal impairment.”*

To address dose adjustment in patients with hepatic impairment, the sponsor conducted a study entitled *“A Multi-Center, Open-Labeled Study of the Safety and Pharmacokinetics of Oral Lubiprostone in Subjects with Hepatic Impairment.”*

To address dose adjustment in patients with renal impairment, the sponsor conducted a study entitled *“A Multicenter, Open-labeled Study of the Safety and Pharmacokinetics of Oral Lubiprostone in Subjects with Renal Impairment.”*

The sponsor submitted the study report for the hepatic impairment study on 5/29/09 and the study report for the renal impairment study on 04/07/08. Both study reports were reviewed by the clinical pharmacology reviewer and appropriate labeling was developed along with successful closure of the review on 11/09/09. From a clinical pharmacology point of view, PMCs regarding dose adjustment in hepatic impaired and renal impaired patients are fulfilled.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-21908

SUPPL-8

SUCAMPO
PHARMACEUTICA
LS INC

AMITIZA 24 MCG CAPSULES

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTIAN GRIMSTEIN
11/13/2009

EDWARD D BASHAW
11/13/2009

CLINICAL PHARMACOLOGY REVIEW

PRODUCT (Generic Name)	Lubiprostone
PRODUCT (Proposed Brand Name)	Amitiza
NDA:	021908 SDN 83 (hepatic, pediatric) SDN 62 (renal)
TYPE OF SUBMISSION	Labeling Supplement
PROPOSED INDICATIONS	Chronic idiopathic constipation, irritable bowel syndrome with constipation
SUBMISSION DATE	05/29/09 (hepatic, pediatric) 4/07/08 (renal)
PRIMARY REVIEWER	Christian Grimstein, Ph.D.
SECONDARY REVIEWER	CAPT E. Dennis Bashaw, Pharm.D.
OCP DIVISION	DCP 3
SPONSOR	Sucampo Pharma Americas, Inc.

BACKGROUND

Lubiprostone is a functional fatty acid and member of a class of compounds called prostones. Under the trade name Amitiza[®], lubiprostone has been approved in the United States for the treatment of chronic idiopathic constipation as well as irritable bowel syndrome with constipation. 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 (CIC). Lubiprostone is rapidly and extensively metabolized in the liver. From 11 different metabolites which could be detected in human plasma, metabolite M3 is the major active one.

Fourteen studies have been conducted during the clinical development of lubiprostone including 5 Phase 1 studies and 6 Phase 2 and 3 studies for the treatment of chronic idiopathic constipation and irritable bowel syndrome with constipation. These studies supported the U.S. Food and Drug Administration (FDA) approval of lubiprostone for the treatment of CIC in adults. Lubiprostone 48 mcg/day (24 mcg twice daily [BID]) has been shown to increase the overall frequency of spontaneous bowel movements (SBMs) and to improve the signs and symptoms related to constipation, including abdominal bloating, abdominal discomfort, stool consistency, straining, and constipation severity. In addition, 3 post-approval Phase 4 studies were completed in subjects with renal impairment, hepatic impairment and in pediatric patients with functional constipation.

The sponsor submitted a labeling supplement to Amitiza (lubiprostone) that revises the labeling text to add new uses to special populations (renal and hepatic impairment) and new pharmacokinetic data (renal and hepatic impairment, pediatric constipation) obtained from the completed post marketing commitments. In addition the sponsor submitted an amendment to the

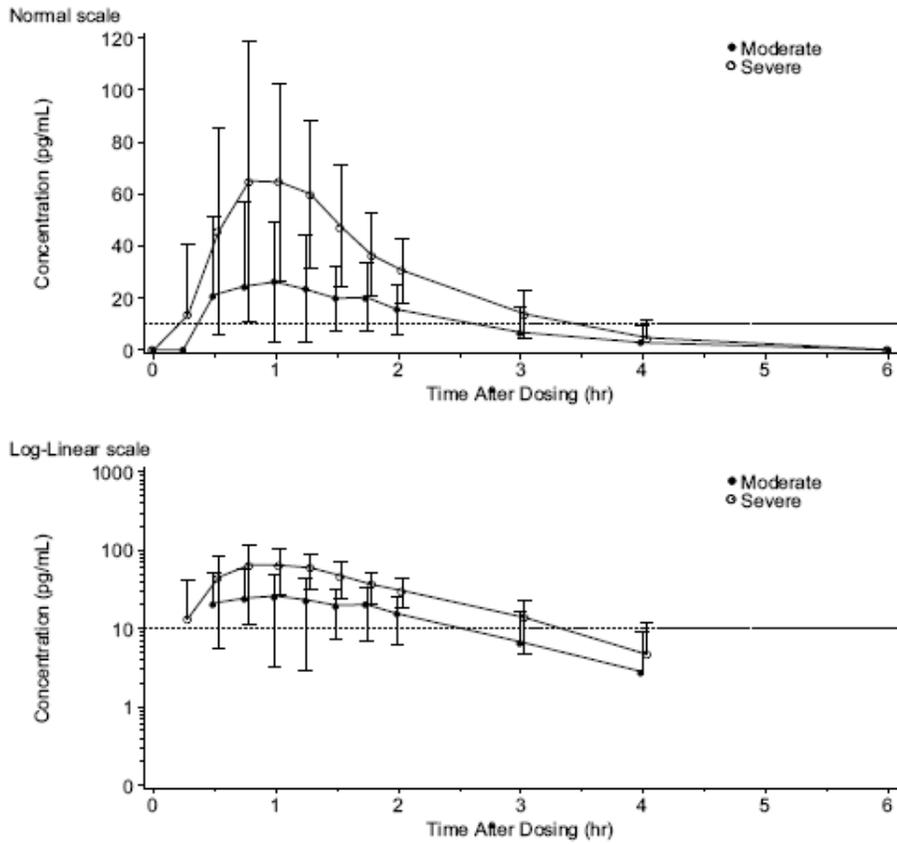
final analytical report (No.2) PBC104-003 which include a response to the FDA request on the linearity, precision and accuracy of the assay methodology during sample analysis for the lubiprostone renal impairment study (Study report CSR0211-08-001-01).

Review of Hepatic Impairment Study (CSR0211-09-002-01)

As a post marketing commitment to the FDA, lubiprostone (12 mcg and 24 mcg) was studied in adults with hepatic impairment to assess pharmacokinetics (PK), safety and the potential need for dose adjustment in this population. On January 31, 2006, a postmarketing commitment was requested by the Agency entitled: *“Perform a Phase IV study to assess the need for potential dose adjustment in patients with hepatic impairment.”*

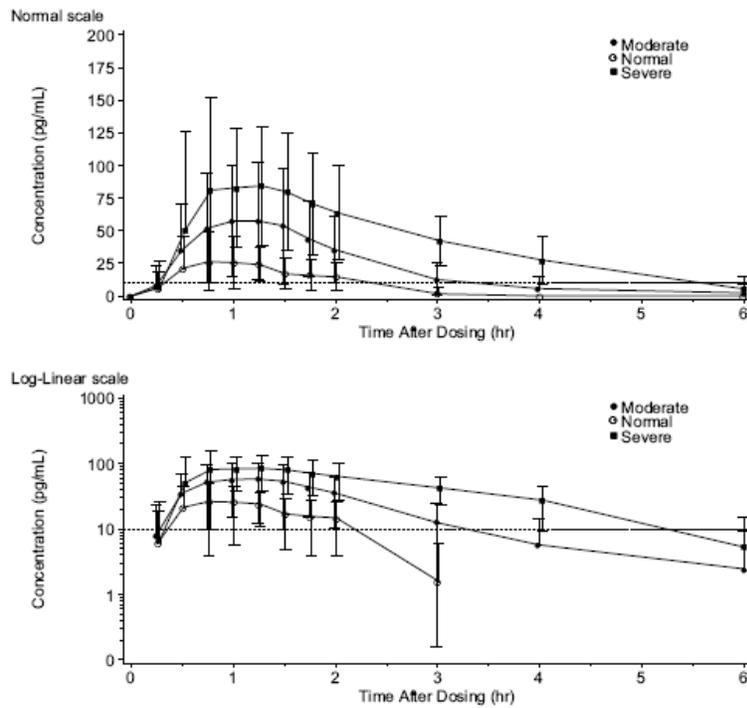
The sponsor conducted a study entitled *“A Multi-Center, Open-Labeled Study of the Safety and Pharmacokinetics of Oral Lubiprostone in Subjects with Hepatic Impairment”* over a period of 14 days. The primary objective was to determine the need, if any, for dose adjustment in subjects with hepatic impairment who may be treated with lubiprostone. The secondary objective was to evaluate the safety and tolerability of lubiprostone in subjects with impaired hepatic function by monitoring severity and duration of spontaneously reported adverse events (AEs); clinical laboratory analyses; vital signs and body weight; electrocardiograms (ECGs); and physical examination (newly occurring abnormalities).

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) were enrolled in the study. Subjects with normal hepatic function and moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment received a single oral administration of lubiprostone 12 mcg or 24 mcg under fasting conditions (6 hours). In 23 of 25 subjects, all analyzed plasma concentrations of lubiprostone were below the limit of quantification (10 pg/mL). This is consistent with the previous finding that lubiprostone is extensively and rapidly converted to its active metabolite M3. Plasma concentrations of lubiprostone were detected in two subjects. As a result of this limited data, no statistical PK analysis was performed for lubiprostone. Instead, plasma concentrations of the active metabolite M3 were determined by a validated LC/MS/MS method and concentration-time profiles established (Figure 1 and 2). A summary of the mean PK parameter data for M3 is presented in Table 11-1.



NOTE: Error bars represent +/-1 standard deviation.
 --- Lower limit of quantification (10 pg/mL)

Figure 1: Mean Concentration-Time Profiles for Analyte M3, Treatment: 12mcg lubiprostone



NOTE: Error bars represent +/-1 standard deviation.
 --- Lower limit of quantification (10 pg/mL)

Figure 2: Mean Concentration-Time Profiles for Analyte M3, Treatment: 24 mcg lubiprostone

Table 11-1 Summary of Mean (SD) Plasma PK Parameter Data for M3 Metabolite

PK Parameter	Units	12 mcg lubiprostone		24 mcg lubiprostone		
		Moderate Hepatic Impairment	Severe Hepatic Impairment	Normal Hepatic Function	Moderate Hepatic Impairment	Severe Hepatic Impairment
C_{max}	(pg/mL)	40.1 (26.3)	79.5 (43.8)	37.5 (15.9)	70.9 (43.5)	114 (59.4)
T_{max}^a	(hr)	1.00 (0.783, 1.75)	1.00 (0.500, 2.00)	1.00 (0.250, 1.75)	1.13 (0.750, 2.00)	1.51 (0.500, 3.00)
AUC_{0-24}	(pg*hr/mL)	NC	148 (53.5)	69.2 (31.1)	184 (136)	292 (47.2)
AUC_{0-t}	(pg*hr/mL)	58.0 (28.1)	113 (52.3)	39.6 (18.7)	119 (104)	234 (61.6)
$AUC_{0-\infty}$	(pg*hr/mL)	NC	148 (53.5)	69.3 (31.1)	186 (140)	292 (47.7)
$t_{1/2}$	(hr)	NC	0.904 (0.398)	0.777 (0.249)	1.56 (1.61)	1.26 (0.828)
λ_z	(1/hr)	NC	0.893 (0.355)	0.973 (0.331)	0.753 (0.439)	0.689 (0.274)

Source: Table 14.2.2-2.

^a Median (min, max) presented for T_{max} .

NC: Not calculated.

Hepatic Data Analysis

The statistical analysis (ANOVA) to compare the PK of M3 in subjects with moderate or severe hepatic impairment to subjects with normal hepatic function for the 24 mcg dose of lubiprostone indicated that the least squares (LS) mean C_{max} for subjects with moderate and severe hepatic impairment were 66% and 183% higher, respectively, than subjects with normal hepatic function, as shown in Table 11-2 (below).

Table 11-2 Statistical Analysis of Pharmacokinetic Data of M3 Metabolite (Hepatic Impaired Relative to Normal)

Parameter (Units)	Comparison	LS Means ^a				Test/ Reference ^b	90% Confidence	
		N	(Test)	N	(Reference)		Interval ^c	P-value
C_{max} (pg/mL)	Moderate vs. Normal	8	58.1	8	35.0	166	(99.33 , 277.13)	0.1041
	Severe vs. Normal	8	99.2	8	35.0	283	(181.84 , 441.95)	0.0010
AUC_{0-t} (pg*hr/mL)	Moderate vs. Normal	8	79.4	8	36.2	219	(105.97 , 454.08)	0.0780
	Severe vs. Normal	8	225	8	36.2	621	(438.61 , 878.19)	<0.0001
AUC_{0-24} (pg*hr/mL)	Moderate vs. Normal	5	156	3	63.3	246	(107.25 , 565.28)	
	Severe vs. Normal	6	288	3	63.3	455	(294.78 , 703.39)	

Note: For M3, the area of extrapolation for $AUC_{0-\infty}$ was greater than 30% for Subject Nos. 01-009 (Period 2), 01-015 (Period 1), 01-019 (Period 1), and 01-022 (Period 1). As a result, $AUC_{0-\infty}$ and AUC_{0-24} were not analyzed for these subjects. Due to the small sample size, the 90% CIs for $AUC_{(0-24)}$ and $AUC_{(0-\infty)}$ are presented for informational purposes only.

^a Least squares means from ANOVA. Natural log (ln) parameter means calculated by transforming the natural log means back to the linear scale (ie, geometric means).

^b Ratio of parameter means for natural log transformed parameter (expressed as a percent). Natural log transformed ratios transformed back to the linear scale.

^c 90% confidence interval for ratio of parameter means of natural log transformed parameter (expressed as a percent). Natural log transformed confidence limits transformed back to the linear scale.

^d P-value for group difference from the Wilcoxon Rank-Sum test for T_{max} .

Reference: [Table 14.2.3-1](#).

Drug exposure was also increased in hepatic impaired patients receiving 24 mcg lubiprostone compared to subjects with normal renal function. For subjects with severe hepatic impairment, LS mean AUC_{0-t} for M3 was 521% higher, than those observed for subjects with normal hepatic function.

The 90% CIs for M3 C_{max} and AUC_{0-t} values for subjects with either moderate or severe hepatic impairment did not demonstrate equivalence to subjects with normal hepatic function. Moderate and severe hepatic impairment resulted in elevated plasma levels of increased exposure of lubiprostone in these patients.

Hepatic Data (dose normalized analysis)

The sponsor performed a dose-normalized analysis to obtain information whether PK parameters are different comparing administration of 12 mcg and 24 mcg dose. M3 dose normalized (DN) - C_{max} and DN- AUC_{0-t} values for subjects with moderate hepatic impairment were 14.4%, and 17.1% lower, respectively, in subjects dosed with 12 mcg lubiprostone than in subjects dosed with 24 mcg lubiprostone, and M3 DN- C_{max} , DN- AUC_{0-t} , and DN- AUC_{0-24} values for subjects with severe hepatic impairment were 34% greater, 8.5% lower, and 3% lower, respectively, in

subjects dosed with 12 mcg lubiprostone than in subjects dosed with 24 mcg lubiprostone (Table 11-3).

The 90% CI for the LS mean ratios of DN- C_{max} , DN-AUC_{0-t} and DN-AUC₀₋₂₄ for severe hepatic impaired patients) indicated a statistically significant difference in the intra-subject bioavailability of M3 between the 12 mcg and 24 mcg dose levels in subjects with moderate and severe hepatic impairment.

Table 11-3 Statistical Analysis of Intra-Subject Bioavailability of M3 Metabolite (12 mcg Relative to 24 mcg Lubiprostone)

Analyte	Group	Parameter (Units)	LS Means ^a				Test/Reference ^b	90% Confidence Interval ^c
			N	(Test - 12 mcg)	N	(Reference - 24 mcg)		
M3	Moderate Hepatic Impairment	DN- C_{max} (pg/mL/mcg)	4	2.07	8	2.42	85.6	(70.88 , 103.47)
		DN-AUC _{0-t} (pg*hr/mL/mcg)	4	2.74	8	3.31	82.9	(43.47 , 157.93)
	Severe Hepatic Impairment	DN- C_{max} (pg/mL/mcg)	9	5.69	8	4.25	134	(108.71 , 164.70)
		DN-AUC _{0-t} (pg*hr/mL/mcg)	9	8.60	8	9.40	91.5	(70.06 , 119.49)
		DN-AUC ₀₋₂₄ (pg*hr/mL/mcg)	7	11.7	6	12.0	97.0	(72.95 , 128.93)

Note: DN= Dose normalized to the lubiprostone dose.

Dose-normalized AUC₀₋₂₄ of the moderate hepatic impairment cohort was not compared between dose levels due to limited data.

^a Least squares means from ANOVA. Natural log (ln) parameter means calculated by transforming the natural log means back to the linear scale (ie, geometric means).

^b Ratio of parameter means for natural log transformed parameter (expressed as a percent). Natural log transformed ratios transformed back to the linear scale.

^c 90% confidence interval for ratio of parameter means of natural log transformed parameter (expressed as a percent). Natural log transformed confidence limits transformed back to the linear scale.

Source: Table 14.2.2-1.

Conclusion (hepatic impairment study)

The PK results from this study demonstrate that there is a correlation between increased exposure to M3 and the severity of hepatic impairment. In conjunction with the clinical safety results, which demonstrate an increased incidence and severity of AEs in patients with greater severity of hepatic impairment, the starting dosage should be reduced in patients with severe hepatic impairment (Child-Pugh C) receiving lubiprostone. No dosing adjustment is required in patients with mild and moderate hepatic impairment.

Review of Renal Impairment Study (CSR0211-08-001-01)

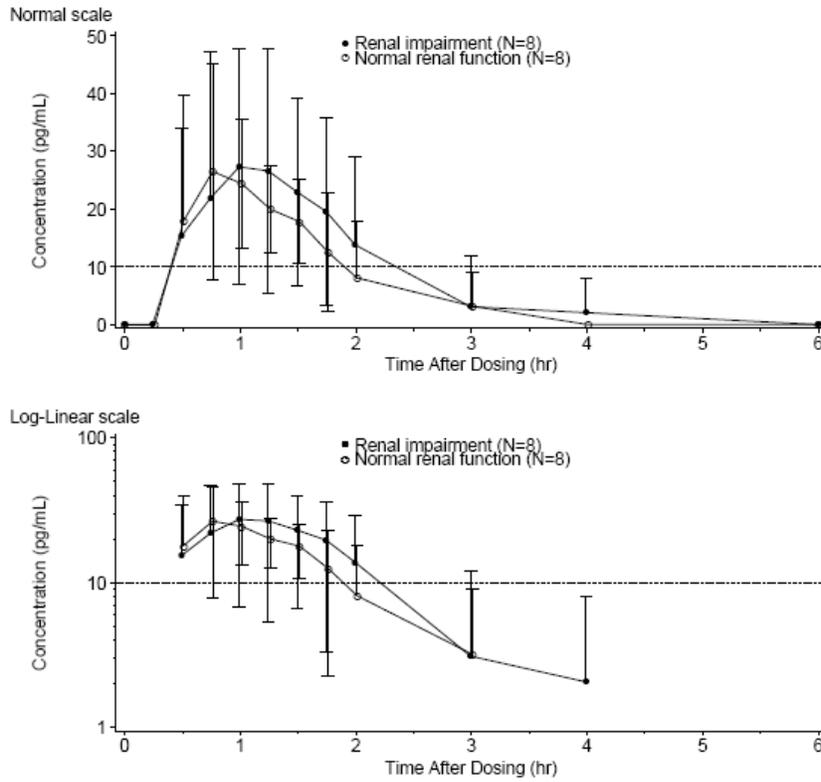
As a post marketing commitment to the FDA, lubiprostone (24 mcg, single dose) was studied in adults with severe renal impairment requiring hemodialysis to assess pharmacokinetics (PK), safety and the potential need for dose adjustment in this population. On January 31, 2006, the agency requested a postmarketing commitment entitled: “Perform a Phase IV study to assess the need for potential dose adjustment in patients with renal impairment.”

Following this request, the sponsor conducted a study entitled "*A Multicenter, Open-labeled Study of the Safety and Pharmacokinetics of Oral Lubiprostone in Subjects with Renal Impairment.*"

The primary objective was to determine the need for dose adjustment in subjects with renal impairment who may be treated with lubiprostone. The secondary objective was to evaluate the safety and tolerability of lubiprostone in subjects with impaired renal function by monitoring the following parameters: severity and duration of spontaneously reported adverse events (AEs); clinical laboratory analyses; vital signs and body weight; electrocardiograms (ECGs); and physical examination (newly occurring abnormalities only).

The study was conducted over a period of 14 days to evaluate the PK profile and safety of Amitiza in subjects with renal impairment. 16 subjects (8 severe renally impaired subjects [creatinine clearance (CrCl) < 20 mL/min], 35 to 45 years old, who required hemodialysis and 8 control subjects with normal renal function [CrCl >80 mL/min], 34 to 47 years old, were enrolled in the study. All subjects received a single oral 24 mcg dose of Amitiza. Plasma samples were analyzed by a validated LC/MS/MS method. Results showed that Amitiza plasma concentration were below the limit of quantification (10 pg/mL). However, the main active metabolite M3 could be detected. The mean concentration-time profiles for M3 are shown in Figure 14.2.1-1 and pharmacokinetic parameters from both groups are summarized in Table 11-1.

Figure 14.2.1-1 Mean Concentration-Time Profiles for M3



NOTE: Error bars represent +/-1 standard deviation.
- - - Lower limit of quantification (10 pg/mL)
Study Population: Full Analysis
Reference: Listing 16.2.8-1

Table 11-1 Summary Mean (SD) Pharmacokinetic Parameters for M3

PK Parameter	Unit	Lubiprostone 24 mcg	
		Renal Impairment Undergoing Dialysis (Test)	Lubiprostone 24 mcg Normal Renal Function (Reference)
AUC _{0-t}	(pg.hr/mL)	46.7 (41.9)	33.1 (12.9)
AUC ₀₋₂₄	(pg.hr/mL)	54.7 (45.6)	37.9 (14.3)
AUC _{0-∞}	(pg.hr/mL)	104 (53.2)	50.3 (5.87)
C _{max}	(pg/mL)	39.4 (15.9)	31.8 (15.6)
T _{max} ^a	(hr)	1.13 (0.750, 1.75)	0.875 (0.750, 1.50)
λ _z	(1/hr)	0.950 (0.421)	0.818 (0.724)
t _{1/2}	(hr)	0.877 (0.499)	2.48 (2.28)

Source: Table 14.2.2-1.

^a Median (min, max) shown for T_{max}.

C_{max} and AUC_{0-t} of M3 following a single, oral dose of 24 mcg of Amitiza were increased by 25% and 12%, respectively, over normal subjects with a high degree of variability (Table 11-2).

Table 11-2 Statistical Analysis of Pharmacokinetic Parameters for M3 (Renal Impaired Relative to Normal)

Parameter (Units)	Comparison	N	LS Means ^a			Test/Reference ^b	90% Confidence Interval ^c	P-value ^d
			(Test)	N	(Reference)			
C _{max} (pg/mL)	Dialysis vs. Normal	8	35.5	8	28.4	125	(78.40 , 198.33)	0.4162
AUC _{0-t} (pg.hr/mL)	Dialysis vs. Normal	7	33.6	8	30.2	112	(58.63 , 212.15)	0.7685
AUC ₀₋₂₄ (pg.hr/mL)	Dialysis vs. Normal	7	42.0	8	34.7	121	(67.59 , 216.50)	0.5725
T _{max} (hr)	Dialysis vs. Normal	8	1.13	8	0.875			0.2238

Source: Table 14.2.2-1.

Note: All concentrations for lubiprostone were below the limit of quantitation, so neither PK nor statistical analysis was performed for this analyte.

AUC_{0-∞} was not statistically analyzed due to the limited amount of data available.

^a Least squares means from ANOVA, calculated by transforming the natural log means back to the linear scale (i.e., geometric mean). Medians are reported for T_{max}.

^b Ratio of parameter means (expressed as a percent), transformed back to the linear scale.

^c 90% confidence interval for ratio of parameter means (expressed as a percent), transformed back to the linear scale.

^d P-value testing group difference from the ANOVA (for C_{max}, AUC_{0-t}, and AUC₀₋₂₄) or the Wilcoxon Rank-Sum test (for T_{max}).

The observed bioavailability of M3 in patients with renal impairment was within the range of exposure from previous clinical experience with lubiprostone, therefore there is no need for lubiprostone dose adjustment in patients with impaired renal function.

Review of Analytical PMC

The sponsor also submitted an amendment to the final analytical report (No.2) from a study entitled: *Determination of lubiprostone (RU-0211) and M3 (U-E232) concentrations in human plasma obtained from “A Multi-center, Open-labeled Study of the Safety and Pharmacokinetics of Oral Lubiprostone in Subjects with Renal Impairment (Clinical Protocol No.:SPI/0211SPK-0641)”*. This amendment includes a response to the FDA request on the linearity, precision and accuracy of the assay methodology during sample analysis for the lubiprostone renal impairment study (Study report CSR0211-08-001-01). Calibration samples, blank samples and QC samples were analyzed by the sponsor. Precision (correlation variant: CV) and accuracy (relative error: RE) were calculated. The results of the suitability check are shown in Appendix 2.

Appendix 2 Results of system suitability check

Analyte	Concentration (pg/mL)						
	20.0		200		800		
	Value	RE (%)	Value	RE (%)	Value	RE (%)	
RU-0211		19.1	-4.5	209	4.5	686	-14.3
		19.9	-0.5	218	9.0	770	-3.8
		19.7	-1.5	235	17.5	711	-11.1
		19.8	-1.0	207	3.5	810	1.3
		21.1	5.5	204	2.0	737	-7.9
	Mean	19.9	-0.5	215	7.5	743	-7.1
	SD	0.729	-	12.5	-	48.8	-
CV	3.7	-	5.8	-	6.6	-	
U-E232		22.5	12.5	184	-8.0	762	-4.8
		22.3	11.5	171	-14.5	907	13.4
		22.3	11.5	198	-1.0	776	-3.0
		20.6	3.0	199	-0.5	885	10.6
		20.2	1.0	205	2.5	826	3.3
	Mean	21.6	8.0	191	-4.5	831	3.9
	SD	1.09	-	13.8	-	64.2	-
CV	5.0	-	7.2	-	7.7	-	

-: Not calculated

Based on the precision (correlation variant: CV) and accuracy (relative error: RE) performance of the assay, the analytical procedure performed by the sponsor to determine concentration of lubiprostone (RU-0211) and M3 (U-E232) in plasma is acceptable.

Review of Pediatric Study (CSR0211-09-001-01)

A required postmarketing study commitment (PMC) under section 2 of the Pediatric Research Equity Act (PREA) was requested by the agency on January 31, 2009. The PMC was entitled “*Deferred pediatric studies under PREA for the treatment of chronic idiopathic constipation in pediatric patients ages 0 to 17 years.*” Following this request, the sponsor submitted a study

entitled “*A Multi-center, Open-labeled Study of the Safety, Efficacy and Pharmacokinetics of lubiprostone in Pediatric Patients with Constipation*”.

On April 29, 2009 the pediatric study requirement for ages 0 to 5 years was waived by the Agency because necessary studies are impossible or highly impracticable. This is because Irritable Bowel Syndrome with constipation does not occur in this age group or the population is too small.

The objectives of this study were to assess the safety and efficacy of lubiprostone in a pediatric population in relation to the safety and efficacy data available for adults with chronic idiopathic constipation. Further, the pharmacokinetics (PK) profile of lubiprostone and its major active metabolite, M3, were evaluated following administration of a single lubiprostone dose in a subset of children and adolescents (n=24). Lubiprostone was administered to pediatric patients at doses of 12 mcg/day (12 mcg QD), 24 mcg/day (12 mcg BID), or 48 mcg/day (24 mcg BID) over a 4-week period.

Plasma concentrations of lubiprostone were below the limit of quantification (BLQ) in all samples obtained from the study patients excluding a single sample. As shown in Figure 1, mean C_{max} plasma concentrations of U-E232 (metabolite M3) are similar among different dosing and weight groups except for patients with at least 12 kg but less than 24 kg body weight group receiving 12 mcg QD. However it should be mentioned that this group only consisted of n=3 patients and the data has high variability.

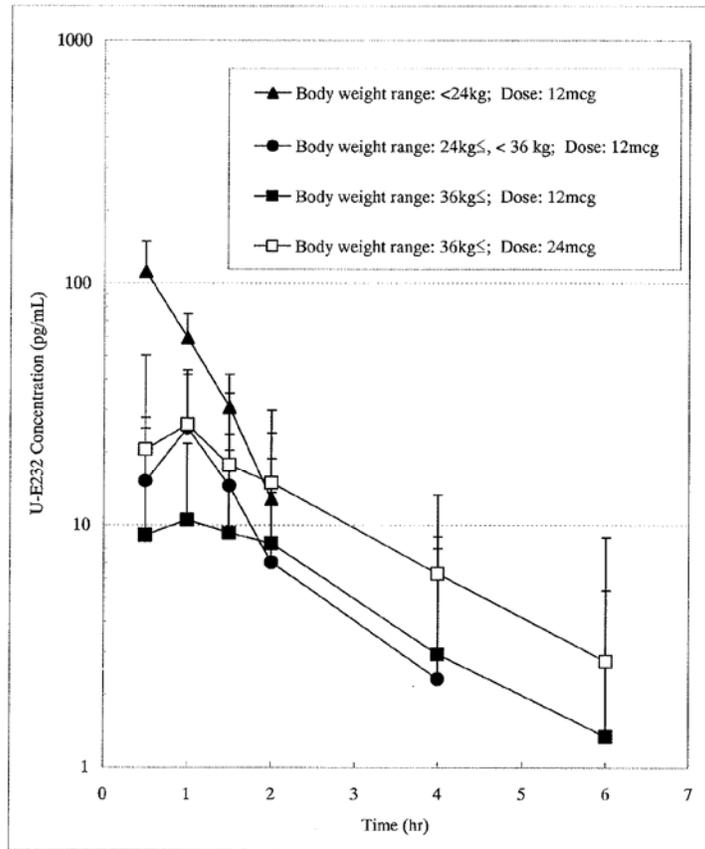


Figure 1. Mean U-E232 Concentrations in Human Plasma After Oral Administration of RU-0211 in Pediatric Patients with Constipation (log-linear plot)

Tables 6-1, 6-2, 6-3, and Table 6-4 show individual PK parameters from each patient in respective dosing and weight groups. Although mean $AUC_{0-\infty}$ values were generally similar among groups (range 82 to 121 $\text{pg}\cdot\text{hr}/\text{mL}$), mean AUC_{0-t} values were substantially higher for the patients with body weights less than 24 kg treated with lubiprostone 12 mcg QD (103 $\text{pg}\cdot\text{hr}/\text{mL}$) as compared to patients with body weights of at least 24 kg but less than 36 kg treated with lubiprostone 12 mcg BID, and those with body weights ≥ 36 kg treated with lubiprostone 12 mcg BID or 24 mcg BID (32.6, 23.0, and 58.5 $\text{pg}\cdot\text{hr}/\text{mL}$, respectively). It should be noted that for subjects with body weights ≥ 36 kg receiving 12 mcg BID, the $AUC_{0-\infty}$ was only calculated for 2/9 subjects.

In pediatric patients with chronic constipation, mean pharmacokinetic parameters of M3 appeared to follow dose-dependent trends that correlated to patient body weights, with lower systemic bioavailability observed for patients with greater body weights treated with equivalent doses of lubiprostone. The highest observed concentrations of M3 were reported for the patients with body weights less than 24 kg treated with lubiprostone 12 mcg QD. Systemic bioavailability of lubiprostone in pediatric patients aged 7–16 years and more than 36 kg body weight treated with lubiprostone 24 mcg (n=6) is comparable to that of their adult counterparts treated with the same dose of lubiprostone, with mean C_{max} and AUC_{0-t} of M3 values of 41.8 pg/mL and 58.5

pg×hr/mL vs. 41.5 pg/mL and 57.1 pg×hr/mL (Sucampo Pharmaceuticals Inc. Amitiza[®] Prescribing Information. 2008. Bethesda, Maryland, USA.), respectively.

No reliable conclusions regarding safety and drug exposure in pediatric patients can be drawn from this study due to the small sample size and variability in drug exposure due to different ages of the pediatric patients.

(b) (4)

3 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21908	SUPPL-8	SUCAMPO PHARMACEUTICA LS INC	AMITIZA 24 MCG CAPSULES

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTIAN GRIMSTEIN
11/09/2009

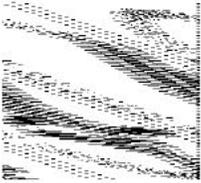
EDWARD D BASHAW
11/09/2009

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 21-908/S-008

OTHER REVIEW(S)

Amitiza[®] (lubiprostone)



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs - Immediate Office
Pediatric and Maternal Health Staff
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9858

M E M O R A N D U M

DATE: November 18, 2009

FROM: Felicia Collins, MD, MPH, Medical Officer
Pediatric and Maternal Health Staff, Office of New Drugs

THROUGH: Lisa Mathis, MD, OND Associate Director
Pediatric and Maternal Health Staff, Office of New Drugs

TO: Donna Griebel, MD, Director
Division of Gastroenterology Products, Office of New Drugs

RE: Adequacy of a submitted pediatric study for PREA

Background

Drug: Amitiza[®] (lubiprostone)
Dosage Form: (b) (4)
Administration Route: Oral
Sponsor: Sucampo Pharmaceuticals
Indications: (approved) Treatment of chronic constipation in adults and treatment of irritable bowel syndrome with constipation in women \geq 18 years old
Application: NDA 21-908
Document Date: May 29, 2009

Division's Consult Comments

On May 29, 2009, Sucampo Pharmaceuticals (Sponsor) submitted a final pediatric study report. Although the study provided efficacy results, the Sponsor submitted the study report as part of a labeling supplement (and not as an efficacy supplement) that included new proposed pediatric pharmacokinetic labeling information. The Division of Gastroenterology Products (Division) requests help from the Pediatric and Maternal Health Staff (PMHS) in the determination of whether the Sponsor's pediatric study report should have been submitted as an efficacy supplement by the Sponsor. If it is determined that this study should be submitted as an efficacy supplement, we also request your help in negotiating with the Sponsor to have this study submitted as such.

Materials Reviewed

- Sponsor's submission, May 29, 2009
- Prior PMHS review regarding the Sponsor's proposed lubiprostone study to address PREA requirements, November 4, 2008
- Meeting minutes from a November 13, 2008 Sponsor Meeting
- Amitiza[®] drug labeling, Drugs@FDA website, April 29, 2008

Product Description

According to the Pharmacokinetics (PK) Section of the drug labeling, Amitiza[®] (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. 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. The drug labeling also notes that lubiprostone has low systemic availability following oral administration and concentrations of lubiprostone in plasma are below the level of quantification. Therefore, standard PK parameters such as area under the curve (AUC), maximum concentration (C_{max}), and half-life ($t_{1/2}$) cannot be reliably calculated. However, the PK parameters of M3 (the only measurable active metabolite of lubiprostone) have been characterized.

Reviewer Comment: PMHS believes that pediatric effectiveness data (not PK data) will be needed to determine pediatric lubiprostone dosing since lubiprostone is a locally acting drug with low systemic availability. However, the Clinical Pharmacology Reviewer's input is needed in this area.

Completed Pediatric Study

The Sponsor's May 29, 2009 submission included the final report for the study titled *A Multi-center, Open-labeled Study of the Safety, Efficacy, and Pharmacokinetics of Lubiprostone in Pediatric Patients with Constipation* (Protocol SPI/0211SC-0641). Per the study synopsis, the study was a 4-week, open-label study in which 109 pediatric patients received lubiprostone capsules based on age-weight cohorts.

The Sponsor's report states that three dosages of lubiprostone were tested in pediatric patients (i.e., 12 mcg QD, 12 mcg BID, and 24 mcg BID). According to the Sponsor, the pediatric lubiprostone dosages were selected to reflect the safe and efficacious mcg/kg adult drug dosage (the daily adult lubiprostone dosage for constipation, 24 mcg BID, ranges from 0.5–0.6 mcg/kg to 0.9–1.1 mcg/kg based on Centers for Disease Control and Prevention growth chart data). Additionally, twice daily dosing of lubiprostone was maintained for pediatric patients as much as possible since the Sponsor believes this dosing schedule may contribute to lubiprostone's safety and effectiveness. The specific dosing regimen used for each pediatric age-weight cohort was as follows.

Younger Children < 6 years old	Children 6 to 11 years old			Adolescents 12 to 17 years old	
	≥ 12 kg	12 to < 24 kg	24 to < 36 kg	≥ 36 kg	[no weight given]
12 mcg QD	12 mcg QD	12 mcg BID	24 mcg BID	12 mcg BID (included up to 24 patients)	24 mcg BID

Reviewer Comment: PMHS understands that the < 6 year old cohort included patients down to 3 years old per a table in the Sponsor's final report.

PMHS presumes that the adolescent cohort receiving 12 mcg BID weighed < 36 kg, but we did not find the weight for this cohort listed in the Sponsor's report (an adolescent cohort weighing < 36 kg seems reasonable as 36 kg is the 25th percentile for a 12 year old boy).

(b) (4)

In summary,

(b) (4)

(b) (4)

Please see the Regulatory History Section and Pediatric Research Equity Act Section below for additional details.

Regulatory History

In brief, Amitiza® was approved in January 2006 for the treatment of chronic idiopathic constipation (CIC) in adults and was approved in 2008 for the treatment of irritable bowel syndrome with constipation (IBS-C) in adult women. The January 2006 approval letter noted the following postmarketing study commitment under the Pediatric Research Equity Act (PREA).

Deferred pediatric studies for the treatment of chronic idiopathic constipation in pediatric patients ages 0 to 17 years.

- Protocol Submission: by July 31, 2006
- Study Start: by January 31, 2007
- Final Report Submission: by January 31, 2008

On November 13, 2008, the Division met with the Sponsor to discuss the acceptability of the Sponsor's pediatric constipation study for meeting PREA requirements. Selected excerpts from the meeting minutes are noted below.

Background

On July 31, 2006, the Sponsor submitted a protocol for an open-label clinical study (SPI/0211SC-0641) to investigate the safety and efficacy of lubiprostone in pediatric patients.

(b) (4)

Response to the Sponsor

Pediatric Questions for the Chronic Constipation Study

3) Does the Division agree the Sponsor's pediatric constipation study has fulfilled the postmarketing commitment and PREA requirements with respect to lubiprostone and pediatric constipation?

FDA Response: No, an open-label trial (b) (4) does not fulfill PREA requirements.

(b) (4)



(b) (4)

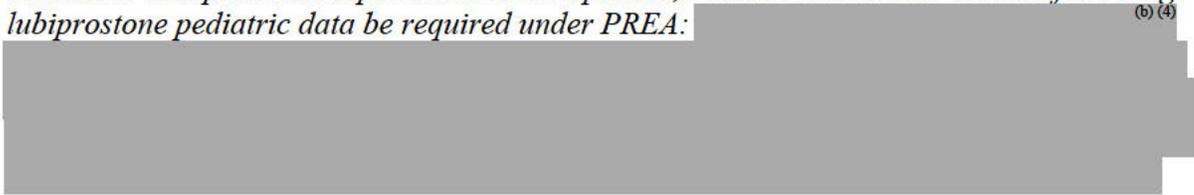


The Sponsor has not proposed any new labeling language for the Pediatric Use Section (8.4).

Pediatric Research Equity Act Requirements

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients 0 to < 17 years old unless this requirement is waived, deferred, or inapplicable. In addition, PREA of 2007 requires the labeling of the Agency's determination that a pediatric assessment does or does not demonstrate that a drug is safe and effective in pediatric populations and the labeling of the assessment results.

Reviewer Comment: As noted earlier, PREA was triggered when lubiprostone was approved for the new indication of adult CIC. PMHS defers to the Division to assess if the pathophysiology of CIC is the same in adults and children and if lubiprostone is expected to have the same mechanism of action in adults and children. If the Division determines that CIC pathophysiology and lubiprostone's drug effects are the same in adults and children, extrapolating efficacy from adults to pediatric patients may be reasonable. In that case, consistent with prior correspondence to the Sponsor, PMHS recommends that the following lubiprostone pediatric data be required under PREA:



Since the Sponsor's submitted pediatric study is inadequate for making pediatric efficacy, safety, and dosing determinations, PMHS does not recommend any labeling changes related to the submitted pediatric study. However, once the Sponsor submits a full pediatric assessment (i.e., data that are sufficient to support safety, efficacy, and dosing determinations in the relevant pediatric populations), lubiprostone's labeling must include the assessment results and the Division's determination that the assessment does or does not demonstrate the drug's safety and effectiveness in the pediatric population.

Conclusions and Recommendations

PMHS believes that the Sponsor's pediatric study titled *A Multi-center, Open-labeled Study of the Safety, Efficacy, and Pharmacokinetics of Lubiprostone [capsules] in Pediatric Patients with Constipation* (Protocol SPI/0211SC-0641) does not satisfy PREA requirements due to the lack of the following.

- [REDACTED] (b) (4)
- [REDACTED] (b) (4)
- [REDACTED] (b) (4)

PMHS notes that the Agency has provided the Sponsor with appropriate guidance regarding the types of studies required to satisfy lubiprostone's PREA requirement. Consequently, the Sponsor should not be released from its PREA postmarketing requirement.

Since the Sponsor's submitted pediatric study is inadequate for making efficacy, safety, and dosing determinations, PMHS does not recommend any labeling changes related to the submitted pediatric study. However, once the Sponsor submits a full pediatric assessment (i.e., data that are sufficient to support safety, efficacy, and dosing determinations in the relevant pediatric populations), lubiprostone's labeling must include the assessment results and the Division's determination that the assessment does or does not demonstrate the drug's safety and effectiveness in the pediatric population.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21908	SUPPL-8	SUCAMPO PHARMACEUTICA LS INC	AMITIZA 24 MCG CAPSULES

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

FELICIA L COLLINS
11/21/2009

LISA L MATHIS
11/24/2009
Concur

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Gastroenterology Products

Application Number: 21-908 / S-008

Name of Drug: Amitiza® (lubiprostone) Capsules

Applicant: Sucampo Pharma Americas, Inc.

Material Reviewed:

Submission Dates: May 29, 2009

Receipt Date: May 29, 2009

Submission Date of Structure Product Labeling (SPL): May 29, 2009

Type of Labeling Reviewed: Word & SPL

Background and Summary

The present labeling supplement received May 29, 2009, was accompanied by postmarketing study commitment final reports for protocols SPI/0211SC-0641 and [REDACTED] (b)(4), as well as by a response to an FDA information request sent April 30, 2009. This review is limited to the labeling portion of this submission. The Amitiza label was last approved with S-005 on April 29, 2008.

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

Review

The label last approved on April 29, 2008, was compared to the package insert and SPL proposed on May 29, 2009. No differences were found except for those proposed and annotated. There were no formatting issues found.

Recommendations

This labeling supplement is recommended for approval, pending review by the medical officer.

Heather Buck, MS, MBA
Regulatory Project Manager

Supervisory Comment/Concurrence:

Cristi Stark, MS
Acting Chief, Project Management Staff

Drafted: HB 8/12/09

Revised/Initialed:

Finalized:

Filename: CSO Labeling Review Template (updated 1-16-07).doc

CSO LABELING REVIEW OF PLR FORMAT

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HEATHER G BUCK
08/12/2009

CRISTI L STARK
09/02/2009

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 21-908/S-008

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

Buck, Heather

From: Cormack, Robert [rcormack@sucampo.com]
Sent: Monday, February 07, 2011 10:22 AM
To: Buck, Heather
Subject: RE: Amitiza - FDA-Revisions

Heather,

Thanks. We will go with (b) (4) i.e., February 2011, as you updated.

Robert

From: Buck, Heather [mailto:Heather.Buck@fda.hhs.gov]
Sent: Monday, February 07, 2011 10:07 AM
To: Cormack, Robert
Subject: RE: Amitiza - FDA-Revisions

Revised date can either be Revised: Month Year or (b) (4). Which do you prefer? No problem on the AR reporting statement - I'll make the change. Thanks.
-Heather

From: Cormack, Robert [mailto:rcormack@sucampo.com]
Sent: Monday, February 07, 2011 9:32 AM
To: Buck, Heather
Subject: RE: Amitiza - FDA-Revisions

Heather,

Thank you for the update and the catch.

Sucampo's marketing partner wishes to use the name "Takeda Pharmaceuticals" in the Highlights sections (toll-free number) instead of Takeda Pharmaceuticals North America, Inc," as is written in the current Word version. For the approval can you please make this changes? That is:

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.

(b) (4)

Robert

From: Buck, Heather [mailto:Heather.Buck@fda.hhs.gov]
Sent: Monday, February 07, 2011 8:33 AM
To: Cormack, Robert
Subject: RE: Amitiza - FDA-Revisions

I updated the revised and recent major changes date with the month of approval. (b) (4) Otherwise, the label is ready for approval. I will append the final version (see attached) to the approval letter, and will keep you posted on its progress through the sign-off process.
Thanks again for all your help,
Heather

Reference ID: 2902560

From: Cormack, Robert [mailto:rcormack@sucampo.com]
Sent: Thursday, February 03, 2011 9:23 AM
To: Buck, Heather
Subject: RE: Amitiza - FDA-Revisions

Heather,

I have a quick question. Since the official FDA approval of the revised Amitiza labeling text will occur this month should the Revised date in the Highlights of Prescribing Information be [REDACTED] (b) (4)

Thank you,
 Robert

From: Buck, Heather [mailto:Heather.Buck@fda.hhs.gov]
Sent: Monday, January 31, 2011 9:01 AM
To: Cormack, Robert
Subject: RE: Amitiza - FDA-Revisions

Thank you. I'll let you know if we have any issue with the latest version. Otherwise, I will append the final, clean version to the approval letter. You don't have to submit SPL until we send the approval letter (within 14 days of receipt). Thanks,
 Heather

From: Cormack, Robert [mailto:rcormack@sucampo.com]
Sent: Friday, January 28, 2011 11:47 AM
To: Buck, Heather
Subject: RE: Amitiza - FDA-Revisions

Heather,

Thank you very much for the response. Sucampo agrees with the FDA's recommended changes to the labeling text for Amitiza. Upon review of the document we identified a few minor errors and inconsistencies. Attached is the FINAL labeling text (MS Word) with corrections (see PDF/Track Changes). Let me know if the final labeling text is acceptable to the Division.

Should Sucampo wait for an official letter from FDA approving of the supplement before submitting the final labeling text and accompanying SPL?

Warm regards,
 Robert

From: Buck, Heather [mailto:Heather.Buck@fda.hhs.gov]
Sent: Wednesday, January 26, 2011 1:26 PM
To: Cormack, Robert
Subject: Amitiza - FDA-Revisions

Hello Robert,
 My apologies again for the delay. We have further revisions. [REDACTED] (b) (4)

[REDACTED] We propose 8mcg QD in this patient population with the option of dose escalation to full dosing with appropriate monitoring of patient response. Please see attached revisions, and let me know if you have questions.

Regards,
 Heather
 Heather Buck, MS, MBA
 Regulatory Project Manager

2/8/2011

Division of Gastroenterology Products
CDER/OND/ODEIII
(301) 796-1413
fax (301) 796-9904
Heather.Buck@fda.hhs.gov

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HEATHER G BUCK
02/08/2011

Buck, Heather

From: Buck, Heather
Sent: Wednesday, January 26, 2011 1:26 PM
To: 'Cormack, Robert'
Subject: Amitiza - FDA-Revisions

Attachments: Amitiza_FDA-Revised 1-26-11.docx

Hello Robert,

My apologies again for the delay. We have further revisions.

(b) (4)

We propose 8mcg QD in this patient population with the option of dose escalation to full dosing with appropriate monitoring of patient response. Please see attached revisions, and let me know if you have questions.

Regards,
Heather



Amitiza_FDA-Revised
1-26-11.docx

Heather Buck, MS, MBA
Regulatory Project Manager
Division of Gastroenterology Products
CDER/OND/ODEIII
(301) 796-1413
fax (301) 796-9904
Heather.Buck@fda.hhs.gov

17 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HEATHER G BUCK
02/08/2011

Buck, Heather

From: Cormack, Robert [rcormack@sucampo.com]
Sent: Friday, December 17, 2010 11:57 AM
To: Buck, Heather
Subject: RE: Amitiza 21-908/S-008
Importance: High
Attachments: sucampo-amitiza-markup.docx; sucampo-amitiza-clean.docx; emfalert.txt

Heather,

Based on Tuesday's teleconference, attached is an update to the labeling text for Amitiza (lubiprostone). Both a tracked changes and "clean" version of the text are provided.

Please note the following:

- (1)  (b) (4)
- (2) The text for section 12.3 regarding renal and hepatic impairment were edited for clarity and consistency without altering the content or intent of the sections.
- (3)  (b) (4)
- (4) Minor editorial changes, corrections, and style/format revisions.

Sucampo looks forward to a response from the Agency. If possible, we would like the process finalized next week.

Warm regards,
Robert

From: Buck, Heather [mailto:Heather.Buck@fda.hhs.gov]
Sent: Tuesday, December 14, 2010 3:26 PM
To: Cormack, Robert
Subject: RE: Amitiza 21-908/S-008

Hello Dr. Cormack,
Thank you for your time today. I have summarized action items below in red. We look forward to your response. Regards,
Heather

From: Cormack, Robert [mailto:rcormack@sucampo.com]
Sent: Wednesday, December 08, 2010 3:56 PM
To: Buck, Heather
Subject: RE: Amitiza 21-908/S-008
Importance: High

Dear Heather,

For next Tuesday's teleconference with the Division regarding renal and hepatic impairment labeling for Amitiza (lubiprostone) capsules, Sucampo has identified the following unresolved issues which we

2/8/2011

would like to discuss:

- The FDA recommends differential dose reduction regimens for patients with severe hepatic insufficiency based on disease state, i.e., those with chronic idiopathic constipation (8 mcg BID) versus those with IBS-C (8 mcg QD). Does the Agency have a reason to believe that hepatically impaired patients diagnosed with IBS-C are more susceptible to potential undesirable effects due to exposure levels than those diagnosed with chronic idiopathic constipation?

The FDA notices an increase in exposure in those with severe hepatic impairment at a dose of 8 mcg BID. Sucampo pointed out that there is no increase in exposure when going from 8 mcg QD to BID; both show complete elimination. The FDA will consider the discussion and may respond with an additional information request.

- The FDA recommends dosing moderate hepatic impairment patients with 16 mcg of Amitiza twice daily notwithstanding that capsules of this strength are not commercially available. Sucampo is concerned that prescribers and pharmacists may be confused by the suggested dosage and this could possibly lead to medication errors. Does the Agency agree an alternate approach for dosing be adopted such as 8 mcg BID for patients with moderately impaired hepatic function?

Sucampo agreed that dosing with 16 mcg BID is acceptable.

- In Section 12.3 (Pharmacokinetics/Special Populations/Hepatic Impairment), the FDA recommends the inclusion of Table 3, Pharmacokinetic Parameters of M3 for patients with Normal or Impaired Liver Function Following 24 mcg of Amitiza. Sucampo is concerned that prescribers may not fully understand the purpose or meaning of the data presented in such tabular form, especially for a study with a small sample size. Can the Agency please provide a justification for inclusion of the table? Alternatively, could the relevant findings from the study be presented in a brief narrative?

The FDA feels that Table 3 is necessary to summarize important data that does not lend itself to narrative. However, Sucampo is welcome to submit a simplified table for FDA's review. Sucampo also points out that the first sentence under *Renal Impairment* is necessary.

Sucampo will submit a revised label that takes the above points into consideration.

Warm regards,

Robert S. Cormack, Ph.D., RAC
 Director, Regulatory Affairs
 Sucampo Pharma Americas, Inc.
 4520 East-West Highway, Suite 300, Bethesda, MD 20814
 Telephone: 240-223-3605

From: Buck, Heather [mailto:Heather.Buck@fda.hhs.gov]
Sent: Friday, December 03, 2010 2:03 PM
To: Cormack, Robert
Subject: RE: Amitiza 21-908/S-008

Robert,
 Can you tell us more specifically what you have issues with in preparation for our t-con?
 Thanks,
 Heather

From: Cormack, Robert [mailto:rcormack@sucampo.com]
Sent: Tuesday, November 23, 2010 10:16 AM
To: Reference ID: 2902556
Subject: RE: Amitiza 21-908/S-008

2/8/2011

Heather,

Sucampo evaluated the review division's markup to our counterproposal for Amitiza regarding renal and hepatic impairment labeling and determined that there are still issues that need to be resolved. Sucampo would like to request a teleconference with DGP to help us understand the rationale for the labeling decisions and to reach a consensus on the final prescribing information. Can you please schedule a meeting in the near future to accomplish these goals?

I look forward to you're the division's response.

Warm regards,
Robert

From: Buck, Heather [mailto:Heather.Buck@fda.hhs.gov]
Sent: Tuesday, November 16, 2010 10:15 AM
To: Cormack, Robert
Subject: RE: Amitiza 21-908/S-008

Hello Robert,
Thank you for your patience. Our revised label is attached for your review. Please confirm receipt, and let me know if you have any questions. Hopefully we can close this out before the holidays.
Regards,
Heather

From: Cormack, Robert [mailto:rcormack@sucampo.com]
Sent: Friday, November 05, 2010 4:07 PM
To: Buck, Heather
Subject: RE: Amitiza 21-908/S-008

Hello Heather,

Sucampo is still expecting a response from the Division. Are you able to commit to a date when we will receive the response?

Warm regards,
Robert

From: Buck, Heather [mailto:Heather.Buck@fda.hhs.gov]
Sent: Tuesday, September 28, 2010 7:42 AM
To: Cormack, Robert
Subject: RE: Amitiza 21-908/S-008

Hello Robert,
My apologies for not getting back to you. I have been waiting for the team to discuss and finalize something. I should have information for you this week. Feel free to contact me with any questions in the meantime. Thanks,
Heather

From: Cormack, Robert [mailto:rcormack@sucampo.com]
Sent: Monday, September 13, 2010 12:22 PM
To: Buck, Heather
Subject: RE: Amitiza 21-908/S-008

Heather,

Sucampo is still waiting for a response from the Division to the labeling counterproposal for Amitiza. Can you please update me on the status of the supplement?
Reference ID: 2902556

2/8/2011

Warm regards,
Robert

From: Buck, Heather [mailto:Heather.Buck@fda.hhs.gov]
Sent: Monday, July 19, 2010 12:18 PM
To: Cormack, Robert
Subject: RE: Amitiza 21-908/S-008

Hello Robert,
The reviewers are actually planning to discuss this label today. I should have more information for you in the next couple of days.
Thanks for checking in,
Heather

From: Cormack, Robert [mailto:rcormack@sucampo.com]
Sent: Monday, July 19, 2010 10:45 AM
To: Buck, Heather
Subject: RE: Amitiza 21-908/S-008

Heather,

Sucampo is still waiting for a response from the Division in regards to our counter-markup of the Amitiza labeling regarding renal/hepatic impairment. When can we expect a formal response?

Regards,
Robert

From: Buck, Heather [mailto:Heather.Buck@fda.hhs.gov]
Sent: Monday, June 21, 2010 1:35 PM
To: Cormack, Robert
Subject: RE: Amitiza 21-908/S-008

Robert,
Please send the revisions via email using track-changes in Word. You may also submit it to the NDA as well, but it is not required.
-Heather

From: Cormack, Robert [mailto:rcormack@sucampo.com]
Sent: Monday, June 21, 2010 12:05 PM
To: Buck, Heather
Subject: RE: Amitiza 21-908/S-008

Heather,

Sucampo has prepared a response to the FDA's markup. What would be the best method to communicate this? Can this be mediated via e-mail or should it be filed to the NDA?

Regards,
Robert

From: Buck, Heather [mailto:Heather.Buck@fda.hhs.gov]
Sent: Monday, June 21, 2010 12:02 PM
To: Cormack, Robert
Subject: RE: Amitiza 21-908/S-008
Reference ID: 2902556

Hello Robert,
I am following up on this supplement. Update me whenever you can.
-Heather

From: Buck, Heather
Sent: Monday, May 17, 2010 9:05 AM
To: 'rcormack@sucampo.com'
Subject: Amitiza 21-908/S-008

Dear Dr. Cormack,
I have attached our revised label for Amitiza 21-908/S-008. Please reply with any additional revisions or comments you may have, or let me know if you agree. I am also happy to answer any specific question about the changes. Thank you for your patience.

Regards,
<< File: Amitiza_FDA-Revised 5-17-10.doc >> Heather

Heather Buck, MS, MBA
Regulatory Project Manager
Division of Gastroenterology Products
CDER/OND/ODEIII
(301) 796-1413
fax (301) 796-9905
Heather.Buck@fda.hhs.gov

16 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

Reference ID: 2902556

2/8/2011

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HEATHER G BUCK
02/08/2011

Buck, Heather

From: Buck, Heather
Sent: Tuesday, November 16, 2010 10:15 AM
To: 'Cormack, Robert'
Subject: RE: Amitiza 21-908/S-008
Attachments: Amitiza_FDA-Revisions 11-16-10.doc

Hello Robert,
Thank you for your patience. Our revised label is attached for your review. Please confirm receipt, and let me know if you have any questions. Hopefully we can close this out before the holidays.
Regards,
Heather

From: Cormack, Robert [mailto:rcormack@sucampo.com]
Sent: Friday, November 05, 2010 4:07 PM
To: Buck, Heather
Subject: RE: Amitiza 21-908/S-008

Hello Heather,

Sucampo is still expecting a response from the Division. Are you able to commit to a date when we will receive the response?

Warm regards,
Robert

From: Buck, Heather [mailto:Heather.Buck@fda.hhs.gov]
Sent: Tuesday, September 28, 2010 7:42 AM
To: Cormack, Robert
Subject: RE: Amitiza 21-908/S-008

Hello Robert,
My apologies for not getting back to you. I have been waiting for the team to discuss and finalize something. I should have information for you this week. Feel free to contact me with any questions in the meantime. Thanks,
Heather

From: Cormack, Robert [mailto:rcormack@sucampo.com]
Sent: Monday, September 13, 2010 12:22 PM
To: Buck, Heather
Subject: RE: Amitiza 21-908/S-008

Heather,

Sucampo is still waiting for a response from the Division to the labeling counterproposal for Amitiza. Can you please update me on the status of the supplement?

Warm regards,
Robert

From: Buck, Heather [mailto:Heather.Buck@fda.hhs.gov]
Sent: Monday, July 19, 2010 12:18 PM
To: Cormack, Robert
Subject: RE: Amitiza 21-908/S-008

Reference ID: 2902552

Hello Robert,

The reviewers are actually planning to discuss this label today. I should have more information for you in the next couple of days.

Thanks for checking in,
Heather

From: Cormack, Robert [mailto:rcormack@sucampo.com]
Sent: Monday, July 19, 2010 10:45 AM
To: Buck, Heather
Subject: RE: Amitiza 21-908/S-008

Heather,

Sucampo is still waiting for a response from the Division in regards to our counter-markup of the Amitiza labeling regarding renal/hepatic impairment. When can we expect a formal response?

Regards,
Robert

From: Buck, Heather [mailto:Heather.Buck@fda.hhs.gov]
Sent: Monday, June 21, 2010 1:35 PM
To: Cormack, Robert
Subject: RE: Amitiza 21-908/S-008

Robert,
Please send the revisions via email using track-changes in Word. You may also submit it to the NDA as well, but it is not required.
-Heather

From: Cormack, Robert [mailto:rcormack@sucampo.com]
Sent: Monday, June 21, 2010 12:05 PM
To: Buck, Heather
Subject: RE: Amitiza 21-908/S-008

Heather,

Sucampo has prepared a response to the FDA's markup. What would be the best method to communicate this? Can this be mediated via e-mail or should it be filed to the NDA?

Regards,
Robert

From: Buck, Heather [mailto:Heather.Buck@fda.hhs.gov]
Sent: Monday, June 21, 2010 12:02 PM
To: Cormack, Robert
Subject: RE: Amitiza 21-908/S-008

Hello Robert,
I am following up on this supplement. Update me whenever you can.
-Heather

From: Buck, Heather
Sent: Monday, May 17, 2010 9:05 AM

2/8/2011

Reference ID: 2902552

To: 'rcormack@sucampo.com'

Subject: Amitiza 21-908/S-008

Dear Dr. Cormack,

I have attached our revised label for Amitiza 21-908/S-008. Please reply with any additional revisions or comments you may have, or let me know if you agree. I am also happy to answer any specific question about the changes. Thank you for your patience.

Regards,

<< File: Amitiza_FDA-Revised 5-17-10.doc >> Heather

Heather Buck, MS, MBA
Regulatory Project Manager
Division of Gastroenterology Products
CDER/OND/ODEIII
(301) 796-1413
fax (301) 796-9905
Heather.Buck@fda.hhs.gov

17 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

Reference ID: 2902552

2/8/2011

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HEATHER G BUCK
02/08/2011

Buck, Heather

From: Cormack, Robert [rcormack@sucampo.com]
Sent: Tuesday, June 22, 2010 1:39 PM
To: Buck, Heather
Subject: RE: Amitiza 21-908/S-008
Attachments: sucampo-amitiza-rationale.pdf; sucampo-amitiza-counter-markup.docx; sucampo-amitiza-counter-markup-finalview.pdf; emfalert.txt

Heather,

Please find attached the following for FDA review:

1. Counter markup to the FDA's revision of the labeling text for Amitiza (lubiprostone) capsules regarding pediatrics and renal and hepatic impairment. Please note all FDA changes were accepted then new proposals were added using Tracked Changes (Word).
2. Counter markup to the FDA's revision of the labeling text for Amitiza (lubiprostone) capsules (Final View; PDF)
3. Rationale for each counter markup to the labeling text presented in a matrix fashion.

Let me know if you need additional information.

Regards,
Robert

From: Buck, Heather [mailto:Heather.Buck@fda.hhs.gov]
Sent: Monday, June 21, 2010 1:35 PM
To: Cormack, Robert
Subject: RE: Amitiza 21-908/S-008

Robert,
Please send the revisions via email using track-changes in Word. You may also submit it to the NDA as well, but it is not required.
-Heather

From: Cormack, Robert [mailto:rcormack@sucampo.com]
Sent: Monday, June 21, 2010 12:05 PM
To: Buck, Heather
Subject: RE: Amitiza 21-908/S-008

Heather,

Sucampo has prepared a response to the FDA's markup. What would be the best method to communicate this? Can this be mediated via e-mail or should it be filed to the NDA?

Regards,
Robert

From: Buck, Heather [mailto:Heather.Buck@fda.hhs.gov]
Sent: Monday, June 21, 2010 12:02 PM
To: Cormack, Robert
Subject: RE: Amitiza 21-908/S-008
Reference ID: 2902551

6/23/2010

Hello Robert,

I am following up on this supplement. Update me whenever you can.

-Heather

From: Buck, Heather
Sent: Monday, May 17, 2010 9:05 AM
To: 'rcormack@sucampo.com'
Subject: Amitiza 21-908/S-008

Dear Dr. Cormack,

I have attached our revised label for Amitiza 21-908/S-008. Please reply with any additional revisions or comments you may have, or let me know if you agree. I am also happy to answer any specific question about the changes. Thank you for your patience.

Regards,

<< File: Amitiza_FDA-Revised 5-17-10.doc >> Heather

Heather Buck, MS, MBA
Regulatory Project Manager
Division of Gastroenterology Products
CDER/OND/ODEIII
(301) 796-1413
fax (301) 796-9905
Heather.Buck@fda.hhs.gov

20 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

Reference ID: 2902551

6/23/2010

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HEATHER G BUCK
02/08/2011

Buck, Heather

From: Buck, Heather
Sent: Monday, May 17, 2010 9:05 AM
To: 'rcormack@sucampo.com'
Subject: Amitiza 21-908/S-008

Attachments: Amitiza_FDA-Revised 5-17-10.doc

Dear Dr. Cormack,
I have attached our revised label for Amitiza 21-908/S-008. Please reply with any additional revisions or comments you may have, or let me know if you agree. I am also happy to answer any specific question about the changes. Thank you for your patience.

Regards,



Amitiza_FDA-Revised
5-17-10.doc...

Heather

Heather Buck, MS, MBA
Regulatory Project Manager
Division of Gastroenterology Products
CDER/OND/ODEIII
(301) 796-1413
fax (301) 796-9905
Heather.Buck@fda.hhs.gov

19 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HEATHER G BUCK
02/08/2011

Buck, Heather

From: Buck, Heather
Sent: Tuesday, December 14, 2010 3:26 PM
To: 'Cormack, Robert'
Subject: RE: Amitiza 21-908/S-008

Hello Dr. Cormack,

Thank you for your time today. I have summarized action items below in red. We look forward to your response. Regards,
Heather

From: Cormack, Robert [mailto:rcormack@sucampo.com]
Sent: Wednesday, December 08, 2010 3:56 PM
To: Buck, Heather
Subject: RE: Amitiza 21-908/S-008
Importance: High

Dear Heather,

For next Tuesday's teleconference with the Division regarding renal and hepatic impairment labeling for Amitiza (lubiprostone) capsules, Sucampo has identified the following unresolved issues which we would like to discuss:

- The FDA recommends differential dose reduction regimens for patients with severe hepatic insufficiency based on disease state, i.e., those with chronic idiopathic constipation (8 mcg BID) versus those with IBS-C (8 mcg QD). Does the Agency have a reason to believe that hepatically impaired patients diagnosed with IBS-C are more susceptible to potential undesirable effects due to exposure levels than those diagnosed with chronic idiopathic constipation?
The FDA notices an increase in exposure in those with severe hepatic impairment at a dose of 8 mcg BID. Sucampo pointed out that there is no increase in exposure when going from 8 mcg QD to BID; both show complete elimination. The FDA will consider the discussion and may respond with an additional information request.
- The FDA recommends dosing moderate hepatic impairment patients with 16 mcg of Amitiza twice daily notwithstanding that capsules of this strength are not commercially available. Sucampo is concerned that prescribers and pharmacists may be confused by the suggested dosage and this could possibly lead to medication errors. Does the Agency agree an alternate approach for dosing be adopted such as 8 mcg BID for patients with moderately impaired hepatic function?
Sucampo agreed that dosing with 16 mcg BID is acceptable.
- In Section 12.3 (Pharmacokinetics/Special Populations/Hepatic Impairment), the FDA recommends the inclusion of Table 3, Pharmacokinetic Parameters of M3 for patients with Normal or Impaired Liver Function Following 24 mcg of Amitiza. Sucampo is concerned that prescribers may not fully understand the purpose or meaning of the data presented in such tabular form, especially for a study with a small sample size. Can the Agency please provide a justification for inclusion of the table? Alternatively, could the relevant findings from the study be presented in a brief narrative?

The FDA feels that Table 3 is necessary to summarize important data that does not lend itself to narrative. However, Sucampo is welcome to submit a simplified table for FDA's review. Sucampo also points out that the first sentence under *Renal Impairment* is necessary.

Sucampo will submit a revised label that takes the above points into consideration.

Reference ID: 2877652
Warm regards,

12/14/2010

Robert S. Cormack, Ph.D., RAC

Director, Regulatory Affairs
Sucampo Pharma Americas, Inc.
4520 East-West Highway, Suite 300, Bethesda, MD 20814
Telephone: 240-223-3605

From: Buck, Heather [mailto:Heather.Buck@fda.hhs.gov]
Sent: Friday, December 03, 2010 2:03 PM
To: Cormack, Robert
Subject: RE: Amitiza 21-908/S-008

Robert,
Can you tell us more specifically what you have issues with in preparation for our t-con?
Thanks,
Heather

From: Cormack, Robert [mailto:rcormack@sucampo.com]
Sent: Tuesday, November 23, 2010 10:16 AM
To: Buck, Heather
Subject: RE: Amitiza 21-908/S-008

Heather,

Sucampo evaluated the review division's markup to our counterproposal for Amitiza regarding renal and hepatic impairment labeling and determined that there are still issues that need to be resolved. Sucampo would like to request a teleconference with DGP to help us understand the rationale for the labeling decisions and to reach a consensus on the final prescribing information. Can you please schedule a meeting in the near future to accomplish these goals?

I look forward to you're the division's response.

Warm regards,
Robert

From: Buck, Heather [mailto:Heather.Buck@fda.hhs.gov]
Sent: Tuesday, November 16, 2010 10:15 AM
To: Cormack, Robert
Subject: RE: Amitiza 21-908/S-008

Hello Robert,
Thank you for your patience. Our revised label is attached for your review. Please confirm receipt, and let me know if you have any questions. Hopefully we can close this out before the holidays.
Regards,
Heather

From: Cormack, Robert [mailto:rcormack@sucampo.com]
Sent: Friday, November 05, 2010 4:07 PM
To: Buck, Heather
Subject: RE: Amitiza 21-908/S-008

Hello Heather,

Sucampo is still awaiting a response from the Division. Are you able to commit to a date when we will receive the response?

12/14/2010

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HEATHER G BUCK
12/14/2010

REQUEST FOR CONSULTATION

TO (Office/Division): **Rosemany Addy, PMHS**

FROM (Name, Office/Division, and Phone Number of Requestor): **Matthew Scherer, Div of Gastroenterology**

DATE
8-21-09

IND NO.

NDA NO.
21-908

TYPE OF DOCUMENT
Final Peds Study
Report

DATE OF DOCUMENT
May 29, 2009

NAME OF DRUG
Amitiza

PRIORITY CONSIDERATION
standard

CLASSIFICATION OF DRUG
laxative

DESIRED COMPLETION DATE
8-28-09

NAME OF FIRM:

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|---|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILTY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS:

Brief Background:

Amitiza (NDA 21-908, lubiprostone) was approved in 2006 for treatment of chronic idiopathic constipation in adults and approved in 2008 for the treatment of IBS with constipation in adult women.

The January 2006 approval letter stated the following:

Deferred pediatric studies under PREA for the treatment of chronic idiopathic constipation in pediatric patients ages 0 to 17 years.

Protocol Submission: by July 31, 2006

Study Start: by January 31, 2007

Final Report Submission: by January 31, 2008

On May 29, 2009, the Sponsor submitted the Final Study Report of Protocol SPI/0211SC-0641 titled "A Multi-center, Open-labeled Study of the Safety, Efficacy, and Pharmacokinetics of Lubiprostone in Pediatric Patients with Constipation." The study report was submitted as part of a labeling supplement that proposed to include pediatric PK information and not as an efficacy supplement although the study provided efficacy results. This submission is

electronic and can be found in the EDR.

PMHS Consult Request:

We request your help in the determination of whether this pediatric study report should have been submitted as an efficacy supplement by the Sponsor. If it is determined that this study should be submitted as an efficacy supplement, we also request your help in negotiating with the Sponsor to have this study submitted as such. Please contact the DGP medical reviewer, Aisha Peterson Johnson, with any questions. Thank you.

SIGNATURE OF REQUESTOR

Matthew Scherer

METHOD OF DELIVERY (Check one)

DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MATTHEW C SCHERER
08/21/2009



NDA 21-908/S-008

PRIOR APPROVAL SUPPLEMENT

Sucampo Pharma Americas, Inc.
Attention: Robert S. Cormack, Ph.D.
4520 East-West Highway, Suite 300
Bethesda, MD 20814

Dear Dr. Cormack:

We have received your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Amitiza® (lubiprostone) Capsules
NDA Number: 21-908
Supplement number: S-008
Date of supplement: May 29, 2009
Date of receipt: May 29, 2009

This supplemental application proposes to add to the package insert, new uses in special populations and new pharmacokinetic data obtained from postmarketing study commitment final reports.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on July 28, 2009, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be November 27, 2009.

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA 21-908/S-008

Page 2

If you have questions, please call me at (301) 796-1413.

Sincerely,

{See appended electronic signature page}

Heather Buck, MS, MBA
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Heather G Buck
6/10/2009 11:20:14 AM