DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NOV 26 2012

Sidney M. Wolfe, M.D.
Elizabeth Barbehenn, Ph.D.
Public Citizen
1600 20th Street, NW
Washington, DC 20009

Re: Docket No. FDA-2009-P-0208

Dear Dr. Wolfe and Ms. Barbehenn:

This responds to your citizen petition (Petition) received on May 6, 2009. In the Petition, you state that Amitiza (lubiprostone) is a potential abortifacient and that the warnings in the current labeling are inadequate for safe use in women of child-bearing potential. You request that the Food and Drug Administration (FDA or Agency) take the following actions:

- Add a black box warning regarding the risk of abortion to the product label
- Change the pregnancy category from C to X
- Contraindicate nursing while taking the drug
- Require the distribution of an FDA-approved Medication Guide for all patients; and
- Mandate a "Dear Doctor" letter

We have carefully considered your Petition. For the reasons described in detail below, your Petition is denied. We have determined, however, that the labeling should be clarified in certain respects and should provide additional data from nonclinical studies. The labeling has been updated as described in greater detail below.

I. BACKGROUND

A. Amitiza

FDA approved Amitiza (lubiprostone) for the treatment of idiopathic constipation in adults (24 microgram (mcg) oral capsule taken twice daily) on January 31, 2006 (new drug application (NDA) 021908), and for the treatment of irritable bowel syndrome with constipation (IBS-C) in women 18 years of age and older (8 mcg oral capsule taken twice daily) on April 29, 2008 (NDA 21-908/S-005). Sucampo Pharma Americas, Inc. (Sucampo) holds the NDA for Amitiza.

Lubiprostone is a locally acting prostaglandin E_1 (PGE_1) metabolite analog and is a specific activator of CIC-2 chloride channels that are involved in the secretion of fluids into the gastrointestinal tract. Following oral administration, lubiprostone and its active metabolite have low systemic availability.

Today, FDA approved a new labeling supplement for Amitiza that reflects revised pregnancy and warning information. Sections of the recently approved Amitiza labeling related to your requests are discussed in this response.

B. Warnings in Prescription Drug Labeling and Pregnancy Categories

1. Contraindications, Warnings and Precautions, and Boxed Warnings

FDA regulations state that the WARNINGS AND PRECAUTIONS section of prescription drug and biological product labeling (including the product's package insert) must describe clinically significant adverse reactions, other potential safety hazards, limitations in use imposed by them, and steps that should be taken if these situations occur (21 CFR 201.57(c)(6)(i); see also 21 CFR 201.80(e) and (f)). Labeling must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of an association of the hazard with the product (201.80(e) and (f)). For products described in 21 CFR 201.56, a summary of the most clinically significant warnings and precautions information must be included in the HIGHLIGHTS OF PRESCRIBING INFORMATION (HIGHLIGHTS) for the product (§201.57(a)(10)).

Under § 201.57(c)(1), a boxed warning (which your Petition refers to as a "black box warning") may be required for certain contraindications or serious warnings, particularly those that may lead to death or serious injury (see also § 201.80(e)). A boxed warning must contain, in uppercase letters, a heading that includes the word "WARNING" and other words that convey the general focus of information in the box. A boxed warning briefly explains the risk and refers to more detailed information in the CONTRAINDICATIONS or WARNINGS AND PRECAUTIONS section (§ 201.57(c)(1)). A summary of a boxed warning (with the heading WARNING and other words identifying the subject of the warning) must be included in the HIGHLIGHTS section in a box and in bold type (§§ 201.56(d)(1) and 201.57(a)(4)).

FDA's guidance for industry *Warnings and Precautions, Contraindications, and Boxed Warnings Sections of Labeling for Human Prescription Drug and Biological Products—Content and Format* (Warnings Guidance)[1] states on page 11 that a boxed warning ordinarily is used to highlight one of the following situations:

- There is an adverse reaction so serious in proportion to the potential benefit from the drug (e.g., a fatal, life-threatening or permanently disabling adverse reaction) that it is essential that it be considered in assessing the risks and benefits of using a drug, or

[1] Available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075096.pdf.

- There is a serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of the drug (e.g., patient selection, careful monitoring, avoiding certain concomitant therapy, addition of another drug or managing patients in a specific manner, avoiding use in a specific clinical situation), or

- FDA approved the drug with restrictions to ensure safe use because FDA concluded that the drug can be safely used only if its distribution or use is restricted (e.g., under 21 CFR 314.520 and 601.42 "Approval with restrictions to assure safe use" or under 505-1(f)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) "Risk Evaluation and Mitigation Strategies" Elements to assure safe use).

The Warnings Guidance (at 11-12) also states that there may be other situations in which a boxed warning may be appropriate to highlight information that is especially important to a prescriber.

2. Pregnancy Categories

FDA regulations state that if a drug is absorbed systemically, the *Pregnancy* subsection of drug product labeling must address the teratogenic effects of the drug by inclusion of the appropriate pregnancy category, as well as the relevant required statements for that category (§§ 201.57(c)(9)(i) and 201.80(f)(6)(i)). The regulations specify the following criteria used to designate the appropriate category:[2]

- Pregnancy Category A: "adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters)" (21 CFR 201.57(c)(9)(i)(A)(*1*) and 201.80(f)(6)(i)(*a*)).

- Pregnancy Category B: "animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women" or "animal reproduction studies have shown an adverse effect (other than decrease in fertility), but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence of a risk in later trimesters)" (21 CFR 201.57(c)(9)(i)(A)(*2*) and 201.80(f)(6)(i)(*b*)).

- Pregnancy Category C: "animal reproduction studies have shown an adverse effect on the fetus, if there are no adequate and well-controlled studies in humans, and if the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks" or "there are no animal reproduction studies and no adequate and well-controlled studies in humans" (21 CFR 201.57(c)(9)(i)(A)(*3*) and 201.80(f)(6)(i)(*c*)).

[2] FDA has issued a proposed rule to amend its regulations concerning the requirements for pregnancy and lactation information in prescription drug and biological product labeling. See 73 FR 30831 (May 29, 2008). The proposed rule, if finalized, would remove the pregnancy categories from prescription drug and biological product labeling.

- Pregnancy Category D: "there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks (for example, if the drug is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective)" (21 CFR 201.57(c)(9)(i)(A)(*4*) and 201.80(f)(6)(i)(*d*)).

- Pregnancy Category X: "studies in animals or humans have demonstrated fetal abnormalities or if there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both, and the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit (for example, safer drugs or other forms of therapy are available)" (21 CFR 201.57(c)(9)(i)(A)(*5*) and 201.80(f)(6)(i)(*e*)).

II. DISCUSSION

In the Petition, you state that Amitiza (lubiprostone) is a potential abortifacient and that the warnings in the current labeling are inadequate for safe use in women of child-bearing potential. You request that the Agency add a boxed warning regarding the risk of abortion to the product label, change the pregnancy category from C to X, contraindicate nursing while taking the drug, require the distribution of an FDA-approved Medication Guide for all patients, and mandate a "Dear Doctor" letter. For the reasons described below, these requests are denied. Although we deny your specific requests, we agree that the labeling should be clarified in certain respects and should provide additional information from certain nonclinical studies. Along with discussing your requests, we discuss today's newly approved Amitiza labeling changes in further detail below.

A. Request to Add a Boxed Warning

You request that FDA require a boxed warning for lubiprostone similar to that for misoprostol, which states that women should have had a negative pregnancy test, be capable of complying with contraceptive measures, and have received both oral and written warnings about the risks in pregnancy (Petition at 6). Your request for a labeling change is based on lubiprostone's structural and functional similarity to misoprostol, another PGE_1 analog, and a known abortifacient (Petition at 2). You also discuss in vitro data, in vivo data, and the medical reviews of the NDA (Petition at 2-5).

As described in greater detail below, we do not believe that a boxed warning similar to that for misoprostol is warranted at this time.

1. Misoprostol and In Vitro Data

In the Petition, you state that lubiprostone is a PGE_1 analog in the same drug family as misoprostol (Petition at 1). You state that misoprostol is used off-label in medical abortions to induce uterine contractions after an initial treatment with mifepristone (Petition at 2), and you ask that the Amitiza labeling be changed to include warnings similar to those in the misoprostol

labeling (Petition at 6). You claim that the sponsor's awareness of the similarities between lubiprostone and misoprostol was presumably the reason for doing abortion studies and comparing misoprostol and lubiprostone binding (Petition at 2). You state that these studies are not typically performed as part of an NDA (Petition at 2).

Further, you point to *in vitro* studies submitted in the original Amitiza NDA. In the Petition, you state these studies show that lubiprostone and misoprostol have almost identical potencies in causing contractions in isolated guinea pig ileum (longitudinal) muscle (Petition at 2). According to the Petition, Amitiza's sponsor did not compare Amitiza with misoprostol in isolated guinea pig uterine muscle, and such a study could have explored their comparable abilities to cause abortions (Petition at 2). The Petition also states that *in vivo* studies in pregnant guinea pigs clearly show that Amitiza causes dose-dependent abortions, beginning at two times the human exposure at the maximum recommended human doses, and that a study in pregnant monkeys is also suggestive of Amitiza's abortifacient effects (Petition at 3).

We agree that nonclinical studies evaluating a drug's potential to cause spontaneous abortion (frequently referred to as a "miscarriage") are not typically performed to support an NDA. Because of structural and pharmacological similarities between lubiprostone and misoprostol (both are a class of prostaglandin analogs), the applicant assessed the potential of lubiprostone to cause fetal loss in guinea pigs and rhesus monkeys.

The applicant, Sucampo, conducted *in vitro* studies comparing the potency of lubiprostone to other prostaglandin agonists (including misoprostol, other PGE_1 analogs, PGE_2, and $PGF_{2\alpha}$) with respect to smooth muscle contractility. In that study, guinea pig ileum longitudinal smooth muscle, circular smooth muscle, guinea pig vas deferens, and dog iris sphincter muscles were used to assess effects on prostaglandin receptors EP_1, EP_2, EP_3 and FP respectively.

Based on study findings, we agree that lubiprostone and misoprostol exhibited similar potencies in causing contractions in isolated guinea pig ileum longitudinal smooth muscle. The findings suggest that both lubiprostone and misoprostol may have similar, albeit weak affinities for prostaglandin EP_1 receptors. In contrast, in vitro studies on guinea pig ileum circular smooth muscle, guinea pig vas deferens and dog iris sphincter showed that lubiprostone had significantly lower (>1000-fold) affinities than misoprostol for prostaglandin EP_2, EP_3 and FP receptors, respectively. (In addition to the involvement of EP_1 receptors, uterine contractile responses are also mediated by prostaglandin EP_2, EP_3 and FP receptors).

Although lubiprostone caused dose-dependent fetal loss in guinea pigs, the findings may not be a true reflection of the activity of lubiprostone in humans. Thus, these results do not provide sufficient information regarding any risks of lubiprostone in humans.

In the monkey study there was fetal loss in one monkey, which is within normal historical rates for this species. As such, we do not agree that the single fetal loss and early delivery in the monkey study provides sufficient information regarding fetal risks from Amitiza in humans. Also, the effects were not dose-dependent, and no remarkable toxicities were observed in monkeys at any dose of Amitiza used in the study. Although the applicant could have used higher doses in the monkey study, it was considered acceptable based on the multiples of human

dose evaluated in the monkey (doses of up to 10 times the human dose based on body surface area).

Sucampo later funded an *in vitro* study that examined the effects of lubiprostone and prostaglandins PGE_1 and PGE_2 on cultured human uterine smooth muscle cells.[3] The authors of the study concluded that the mechanisms via which lubiprostone acts are fundamentally different from those of PGE_1 and PGE_2. In this study, PGE_1 and PGE_2 caused an increase in the intracellular calcium and cyclic adenosine monophosphate (cyclic AMP) levels in cultured uterine smooth muscle cells, but lubiprostone had no effect. In addition, lubiprostone had opposite effects on the membrane potential when compared to the effects of PGE_1 and PGE_2. However, misoprostol was not used as a comparator in this study. Subsequently, Sucampo submitted *in vitro* study reports in which the effects of lubiprostone, its major metabolite (M3) and misoprostol were assessed in cultured human uterine smooth muscle cells. In this study, the cellular effects of lubiprostone on human uterine cells appeared to be different from misoprostol. Misoprostol, PGE_1, and PGE_2 had similar effects on the intracellular calcium, cyclic AMP and membrane potential, but lubiprostone had either no effect or an opposite effect.

2. Human Data

In the Petition, you state that six women became pregnant during the placebo-controlled clinical trials and one of the babies had bilateral club feet (Petition at 4). You also state that in the clinical controlled trials for chronic constipation, four women became pregnant even though women agreed to use at least two methods of contraception (Petition at 4). You then go on to say that since completion of the clinical trials, eight additional pregnancies were reported to the FDA and one of these babies was born with an unspecified congenital anomaly (Petition at 4). The Petition states that when pregnancies occur even under the stringent requirements of a clinical trial, it is clear that the warnings and other systems to prevent pregnancy are inadequate (Petition at 4).

Thus, you argue that adequate safeguards to protect the health of women of reproductive potential who were enrolled in clinical trials of Amitiza were lacking. We disagree. We find that the safeguards implemented in the clinical trials of Amitiza were appropriate for the level of risk. Nor do we agree that the occurrence of pregnancies after the product was approved for marketing leads to a conclusion that the information in the drug's labeling is insufficient.[4]

During the clinical studies, patients were instructed to use birth control and were excluded from participation if they were pregnant or planning to become pregnant. The study drug was immediately discontinued as soon as pregnancy was discovered. Nearly 2,000 patients were involved in the Amitiza clinical studies submitted for approval. Of these patients, the overwhelming majority were female. Informed consent documents warned of the unknown fetal

[3] Cuppoletti J, Malinowska D, Chakrabarti J, Ueno R. Effects of lubiprostone on uterine smooth muscle cells. Prostaglandins & other Lipid Mediators, 86 (2008) 56–60.

[4] The Office of Safety and Epidemiology reviewed postmarketing exposures to lubiprostone from 2006 to September 2009 from the FDA Adverse Event Reporting System (AERS) and found that of the limited exposures, in the vast majority lubiprostone was discontinued upon positive pregnancy test. We also note that there are no AERS reports of fetal losses among women exposed to Amitiza during pregnancy (from initial US marketing approval through 8/23/12).

risks and advised on the methods of birth control that should be used during the study. Despite these warnings, pregnancies occurred in Amitiza clinical studies. The occurrence of pregnancies in Amitiza clinical trials is fairly low (on the order of 0.4% based on our calculation), and could have resulted despite contraceptive use.

Further, unintended pregnancy can occur with typical use of any contraceptive method. Pregnancies occur even in the most stringent pregnancy prevention programs despite warnings and contraceptive requirements because of human behavior. For example, Tsur and Berkovitch in 2006[5] and Boucher and Beaulac-Baillargeon in 2008,[6] looked at contraceptive compliance in women of childbearing age using isotretinoin and found that:

- Although most women understood the pregnancy prevention recommendations when provided, most women did not comply with the recommendations.

- Very few women used two forms of contraception simultaneously.

We also note that clubfoot is a congenital anomaly that is a common birth defect, and the etiology remains largely unknown.[7]

In summary, even in the most stringent of drug pregnancy prevention programs, pregnancies still occur during treatment. Therefore, the occurrence of pregnancies during the clinical trials for Amitiza does not lead to the conclusion that the warnings against pregnancy are inadequate, but rather reflects the limits of current contraceptive methods and the potential for non-compliance with their use.

3. *Amitiza Labeling In Comparison to Misoprostol Labeling and "Fetal Loss"*

The Petition also states that the results of *in vivo* and *in vitro* studies caused the reviewing division, DGIEP, to ask for a formal consult from the Division of Reproductive and Urologic Products (DRUP) (Petition at 5). The Petition goes on to state that the medical reviewer concluded that, "labeling for lubiprostone should include many of the recommendations presently found in the boxed warnings for misoprostol" (Petition at 5). With respect to the WARNINGS AND PRECAUTIONS section, according to the Petition, misoprostol labeling contains boxed warnings concerning abortion and premature birth, and current Amitiza labeling warns that women should have a negative pregnancy test prior to beginning therapy and should use effective contraception (Petition at 5). With respect to PATIENT COUNSELING INFORMATION section, the Petition states that the misoprostol labeling contains a warning to not take the drug if pregnant, warns against becoming pregnant, and cautions that it is possible to become pregnant even if on birth control (Petition at 6). In addition, this section of the

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[5] Tsur K, Berkovitch M. The effect of drug consultation center guidance on contraceptive use among women using isotretinoin: a randomized controlled study. Womens Health, 2008 May;17(4):579-84.

[6] Boucher N, Beaulac-Baillargeon L. Pregnancy prevention among women taking isotretinoin: failure to comply with the recommendations. Can Fam Physician, 2006 Mar;52:338-9.

[7] Parker S, Mai C, Strickland M, Olney R, Rickard R, Marengo L, Wang Y. Hashmi S, Meyer R, National Birth Defects Prevention Network. Multistate study of the epidemiology of clubfoot. Birth Def Res, 2009 Aug; 85(11):897-904.

misoprostol labeling explains what a patient should do if she does become pregnant. According to the Petition, the PATIENT COUNSELING INFORMATION section of the Amitiza labeling contains no information about pregnancy and should be changed to include information similar to what is included in the misoprostol labeling (Petition at 6). The Petition also states that the *Pregnancy* subsection of the Amitiza label mentions "fetal loss" but, unlike the misoprostol label, does not explain that this term means "abortion" (Petition at 5).

We have reviewed the differences in the labeling for misoprostol and Amitiza, which you outlined in your Petition, and we have re-evaluated the labeling for Amitiza and the information in the medical reviews that you cite in the Petition. Based on the circumstances relevant to each drug, we disagree that the Amitiza labeling should be similar to the misoprostol labeling in the ways you describe for a number of reasons.

First, there are differences in the approved indications for misoprostol and Amitiza and the manner in which these drugs are used. Misoprostol is indicated for reducing the risk of NSAID (nonsteroidal anti-inflammatory drugs, including aspirin) – induced gastric ulcers in patients at high risk of complications from gastric ulcer, e.g. the elderly and patients with concomitant debilitating disease, as well as patients at high risk of developing gastric ulceration, such as patients with a history of ulcer. Misoprostol is available as 100 microgram (mcg) and 200 mcg oral tablets. Amitiza, on the other hand, is indicated for the treatment of chronic idiopathic constipation in adults, and the treatment of irritable bowel syndrome with constipation in women $\geq$ 18 years old. Amitiza is available as an oval, gelatin capsule containing 8 mcg or 24 mcg of lubiprostone. As we also noted, the *in vitro* studies, some of which were performed after the cited medical reviews were finalized, also suggested differences in the activity of the receptors of lubiprostone and misoprostol. To date, we are not aware of any reports of fetal loss or uterine rupture with Amitiza. Thus, based on the available data we find that the differences in the labeling between misoprostol and Amitiza are appropriate.

We also disagree that the labeling should be revised to explain that "fetal loss" means "spontaneous abortion." In the labeling, fetal loss is used to describe animal data to describe the results of the studies. It may be appropriate to use the term "spontaneous abortion" in describing human data, but fetal loss is a more general term and appropriately used in the labeling, because there are no data in humans for Amitiza.

Furthermore, as explained in the next section, based on our review of the labeling and the totality of available data, FDA has decided that Amitiza should retain Pregnancy Category C and that the labeling should include only language that is typically used for drugs classified as Pregnancy Category C. This is reflected in the labeling approved today for Amitiza.

B. Amitiza Labeling Pregnancy Category C

In the Petition, you state that "the risk to the fetus (abortion) with lubiprostone does not justify the small benefit provided to the mother for which other, safer drugs could be used temporarily," mandating that Amitiza be placed in Pregnancy Category X (Petition at 6).

Amitiza labeling designates the drug as Pregnancy Category C. As stated above, the regulations specify that Pregnancy Category C be designated when "animal reproduction studies have shown an adverse effect on the fetus, ... there are no adequate and well-controlled studies in humans, and ... the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks" or "there are no animal reproduction studies and no adequate and well-controlled studies in humans" (§§ 201.57(c)(9)(i)(A)(3) and 201.80(f)(6)(i)(c)). Pregnancy Category X is appropriate when studies in animals or humans have demonstrated fetal abnormalities or positive evidence of fetal risk, and the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit (for example, safer drugs or other forms of therapy are available) (§§ 201.57(c)(9)(i)(A)(5) and 201.80(f)(6)(i)(e)).

Amitiza was approved in 2006 with a Pregnancy Category C, based on the review of the data and consideration of applicable regulations. However, because of concerns with potential fetal loss in one of two species evaluated, language was added to the WARNINGS AND PRECAUTIONS section of labeling to inform prescribers that women of childbearing potential should have a negative pregnancy test before initiating therapy and should comply with effective contraceptive measures during therapy. Upon review of other drugs classified as Pregnancy Category C, we noted that a WARNING AND PRECAUTION for use in pregnancy or for females of childbearing potential is rarely associated with labeling that is designated with Pregnancy Category C. A warning is included for Pregnancy Category D drugs, and a contraindication is included for Category X drugs (21 CFR 201.57(c)(9)(i)(A) and 201.80(f)(6)(i)).

After reviewing the available data, we continue to believe that it is appropriate for Amitiza to be labeled as Pregnancy Category C. In reaching this conclusion, we reviewed the available data on Amitiza, including the clinical and nonclinical data submitted with the NDA and postmarketing adverse event reports from the Adverse Event Reporting System (AERS) database through August 2012.

As noted in your Petition, six pregnancies occurred during the Amitiza clinical development program. Four pregnancies occurred during the chronic constipation trials. Of these, two women had healthy babies, one woman was lost to follow-up (result of pregnancy unknown), and the fourth woman had a baby born with bilateral club feet. Two pregnancies occurred during the clinical trials for irritable bowel syndrome with predominant chronic constipation. One woman had a healthy baby and the other woman had an ectopic pregnancy.

The review of adverse event reports identified nine total pregnancy exposure cases involving Amitiza. All but two cases state that Amitiza was discontinued upon a positive pregnancy test. Of the nine cases of exposure during pregnancy, one newborn was reported to have been born with a "birth defect,"[8] and one woman experienced an ectopic pregnancy. For the remaining seven cases, there was no adverse outcome (n=3) or the outcome was not reported (n=4). There were no AERS reports of fetal losses among women exposed to Amitiza during pregnancy.

In general, all pregnancies have a background risk of birth defects (about 3%), ectopic pregnancies (about 2%), pregnancy loss (about 12% to 26%),[9] or other adverse outcomes

[8] At 14 weeks of pregnancy, it was determined that the fetus did not have a fibula.
[9] Williams Obstetrics - 23rd Ed. (2010).

regardless of drug exposure. Clubfoot is a spontaneous congenital anomaly that occurs with a prevalence of approximately 1 per 1000 live births, and the etiology remains largely unknown.[10] A single report of clubfoot, two reports of ectopic pregnancies, and a single report of a missing fetal fibula, cannot be attributed to the drug without more data. The totality of the data for Amitiza indicates that the benefits from the use of the drug in pregnant women may be acceptable despite the drug's potential risks, and thus, it remains appropriate for Amitiza to remain as Pregnancy Category C.

Based on our evaluation of the information currently available to the Agency, we have since reconsidered our labeling recommendation for Amitiza, and now recommend that only Pregnancy Category C regulatory language be used in Amitiza labeling. We have concluded that currently available data for Amitiza do not indicate an increased risk of spontaneous abortion or an increased teratogenic risk in humans that warrants additional warnings in the label. Upon reconsideration of the issues and review of the available data, the Agency decided that the Pregnancy Category C classification is appropriate for the Amitiza labeling and there is no justification for including additional language beyond what is used for other drugs classified as Pregnancy Category C. In light of our most recent evaluation, the *Fetal Risk Potential* subsection (5.1) was deleted from WARNINGS AND PRECAUTIONS. More generally, language typical of Pregnancy Category D or X in the Amitiza label was deleted. This includes the following phrases not typical of Pregnancy Category C that were previously in the Amitiza label:

- WARNINGS AND PRECAUTIONS Subsection 5.1 (*Pregnancy*): "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."
- USE IN SPECIFIC POPULATIONS Subsection 8.1 (*Pregnancy*): "If a woman is or becomes pregnant while taking the drug, the patient should be apprised of the potential hazard to the fetus."

Other appropriate Pregnancy Category C language in subsection 5.1 (*Pregnancy*) ("use in pregnancy only if the potential benefit justifies the potential risk to the fetus") was also moved to subsection 8.1 (*Pregnancy*) in USE IN SPECIFIC POPULATIONS. Further, data from the monkey study, considered relevant for inclusion in labeling based on FDA's re-evaluation, were added to subsection 8.1, for the reasons described in the Discussion in Section C.

In sum, current data support the Pregnancy Category C designation of Amitiza. Given the data we have for Amitiza including six years of postmarketing experience, the Pregnancy Category C language specified by regulation is appropriate. We continue to monitor these reports associated with lubiprostone in pregnant women. FDA has requested that the applicant expeditiously submit reports of all spontaneous reports of pregnancy exposure, regardless of outcome.

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[10] Parker S, Mai C, Strickland M, Olney R, Rickard R, Marengo L, Wang Y, Hashmi S, Meyer R, National Birth Defects Prevention Network. Multistate study of the epidemiology of clubfoot. Birth Def Res, 2009 Aug; 85(11):987-904.

Our approach to the Amitiza labeling changes that we approved today are consistent with our approach to the labeling for Vibativ (telavancin) Injection (NDA 22-110). Major malformations were noted at clinically relevant doses of telavancin in animal reproduction studies involving three different species, indicating a high risk for potential human embryofetal toxicity. The televancin labeling has a Pregnancy Category C classification with additional wording to convey the increased fetal risk. This approach was used to balance the potential benefit of use in a pregnant woman with a complicated skin and skin structure infection against the risk for major malformations. Telavancin also has a Medication Guide and Communication Plan Risk Evaluation and Mitigation Strategy. When we compared the labeling approach taken for Amitiza to the labeling approach for telavancin, we concluded, given the relatively low level of concern raised by the available data for Amitiza, that Amitiza labeling should not include additional language beyond what is typically included for a drug classified as Pregnancy Category C.

Finally, we considered the factor of whether other safer therapies are available as it relates to a Pregnancy Category X classification (§§ 201.57(c)(9)(i)(A)(*5*) and 201.80(f)(6)(i)(*e*)). Although you state that other safer drugs could be used temporarily, there are no other approved medications for the indication of treatment of irritable bowel-constipation predominant (IBS-C). There is one other approved prescription medication for chronic idiopathic constipation (CIC), lactulose (classified as Pregnancy Category B). Miralax (classified as Pregnancy Category C) is available as an over-the-counter treatment option for pregnant women with occasional constipation. Miralax is not approved for chronic use, and is labeled for seven day courses only.[11]

C. Nonclinical Animal Study Data Labeling

Beyond your specific recommendations, the Petition suggests that the Amitiza label should explain the results of the guinea pig and monkey abortion studies (Petition at 5).

The original labeling included all nonclinical reproductive data generated from rat, rabbit and guinea pig studies, but not reproductive data from the monkey study in the USE IN SPECIFIC POPULATIONS subsection 8.1 (*Pregnancy*). We agree that the labeling should include outcomes data from the monkey study in subsection 8.1, and the labeling now includes that information.

At the time of Amitiza's approval, we concluded that data from the monkey study would not be useful to prescribing physicians because the female monkeys could have tolerated higher doses. The information was not included in the original labeling. Upon re-evaluation, while the doses tested did not reach the highest possible levels, they did test doses up to 10 times the human dose based upon body surface area and the results are informative. Thus, it is appropriate for the labeling to include additional information regarding the findings in monkeys.

In addition, in connection with our consideration of this petition, we evaluated whether additional in vitro studies would be useful. We determined that additional in vitro studies, especially utilizing human uterine tissue, would not be definitive and further in vitro testing

[11] Miralax was originally approved for chronic constipation as a prescription product, but underwent an OTC switch that involved a change in indication to occasional use.

would not be useful in distinguishing the comparative effects of misoprostol and lubiprostone beyond the information already available to us.

Section 8.1 of the Amitiza labeling has been revised to the following (information on the monkey study is noted in italics):

> **8.1 Pregnancy**
>
> Pregnancy Category C.
>
> Risk Summary
> There are no adequate and well-controlled studies with Amitiza in pregnant women. A dose dependent increase in fetal loss was observed in pregnant guinea pigs that received lubiprostone doses equivalent to 0.2 to 6 times the maximum recommended human dose (MRHD) based on body surface area (mg/m^2). Animal studies did not show an increase in structural malformations. Amitiza should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
>
> Clinical Considerations
> Current available data suggest that miscarriage occurs in 15-18% of clinically recognized pregnancies, regardless of any drug exposure. Consider the risks and benefits of available therapies when treating a pregnant woman for chronic idiopathic constipation or irritable bowel syndrome with constipation.
>
> Animal Data
> In developmental toxicity studies, pregnant rats and rabbits received oral lubiprostone during organogenesis at doses up to approximately 338 times (rats) and approximately 34 times (rabbits) the maximum recommended human dose (MRHD) based on body surface area (mg/m^2). Maximal animal doses were 2000 mcg/kg/day (rats) and 100 mcg/kg/day (rabbits). In rats, there were increased incidences of early resorptions and soft tissue malformations (*situs inversus*, cleft palate) at the 2000 mcg/kg/day dose; however, these effects were probably secondary to maternal toxicity. A dose-dependent increase in fetal loss occurred when guinea pigs received lubiprostone after the period of organogenesis, on days 40 to 53 of gestation, at daily oral doses of 1, 10 and 25 mcg/kg/day (approximately 0.2, 2 and 6 times the MRHD based on body surface area (mg/m^2)). *The potential of lubiprostone to cause fetal loss was also examined in pregnant Rhesus monkeys. Monkeys received lubiprostone post-organogenesis on gestation days 110 through 130 at daily oral doses of 10 and 30 mcg/kg/day (approximately 3 and 10 times the MRHD based on body surface area (mg/m^2)). Fetal loss was noted in one monkey from the 10-mcg/kg dose group, which is within normal historical rates for this species. There was no drug-related adverse effect seen in monkeys.*

D. Human Milkfeeding When a Woman Is Taking Amitiza

In the Petition, you state that the information in the labeling that provides "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...," is not helpful (Petition at 6). You also state that although the sponsors did not perform the usual animal study to test for drug secretion in milk, many drugs are secreted in milk, and the potential for serious adverse reactions

in infants would appear to outweigh the benefits (Petition at 6). You specifically refer to nausea as a common adverse event in patients taking lubiprostone and diarrhea seen in nursing infants on a similar drug, and state that unless the sponsors can demonstrate that lubiprostone is not secreted in milk nursing should be contraindicated, as it is in misoprostol (Petition at 6-7).

We disagree that the labeling should contraindicate breastfeeding while taking Amitiza. FDA does not generally recommend a contraindication for breastfeeding unless there is a known serious adverse effect that can cause serious harm to a human milk-fed infant or the mother has a medical condition (e.g., HIV) that carries a contraindication for breastfeeding (See 21 CFR 201.57(c)(9)(iii)). PGE_1 and other prostaglandins appear normally in colostrum and human milk.[12] Lubiprostone has low systemic bioavailability following oral administration, and therefore, levels in human milk also are expected to be low.

We do agree, however, that additional information would be appropriate in the labeling. Because lubiprostone has a known local effect on the GI tract, infants could be monitored for adverse reactions, mainly the occurrence of diarrhea. Subsection 8.3 (*Nursing Mothers*) of USE IN SPECIAL POPULATIONS has been revised to balance the benefits of human milk feeding against the potential risks of the drug to a human milk-fed child and to advise that because lubiprostone has a known local effect on the GI tract, infants could be monitored for adverse reactions, mainly the occurrence of diarrhea:

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

E. Request for a Medication Guide

You request that FDA require the distribution of an FDA-approved Medication Guide for all patients (Petition at 1). You also request that FDA write a Medication Guide that includes information about the risk of abortion and premature labor during treatment with Amitiza and suggestions for preventing pregnancy (Petition at 7).

We deny your request. Given the level of potential risk, we have determined that the standard for requiring a Medication Guide has not been met. Part 208 of the Code of Federal Regulations (21 CFR 208.1–208.26) sets forth requirements for Medication Guides for human prescription drug products, including biological products, that the Agency determines pose a serious and significant public health concern requiring distribution of FDA-approved patient information. The purpose of Medication Guides, as specified by regulation, "is to provide information when the FDA determines in writing that it is necessary to patients' safe and effective use of drug products" (§ 208.1(b)).

Under section 208.1(c), Medication Guides will be required if FDA determines that at least one of three circumstances described in the regulation has been met. We summarize below the

[12] See Lactmed (The drugs and Lactation Database).

applicability of each circumstance described in the regulation to your request for a Medication Guide.

> Circumstance (1): The drug product is one for which patient labeling could help prevent serious adverse effects.[13]

As discussed above, there are no data indicating that there are serious adverse effects associated with the risk of spontaneous abortion or premature labor during treatment with Amitiza. We are not aware of any new safety data that suggest the risks and benefits of this drug have changed since the original approval.

> Circumstance (2): The drug product is one that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decision to use, or to continue to use, the product.[14]

Based on the totality of available data, the Agency has adequately and appropriately communicated the risks associated with the use of Amitiza during pregnancy. The available *in vivo* and *in vitro* studies discussed above do not suggest that Amitiza raises serious safety risks that would warrant a Medication Guide.

> Circumstance (3): The drug product is important to health and patient adherence to directions for use is crucial to the drug's effectiveness.[15]

As previously noted, there are no data demonstrating that there are serious adverse effects associated with the risk of spontaneous abortion or premature labor during treatment with Amitiza. As a result, we do not find that the risk of spontaneous abortion or premature labor during treatment with Amitiza meets this criterion. The Agency has no unusual concerns about the ability of patients to adequately adhere to use of this oral medication.

The Agency has determined that none of the three circumstances described in federal regulations that require a Medication Guide are met here. A Medication Guide on the risk of spontaneous abortion or premature labor during treatment with Amitiza and suggestions for preventing pregnancy is not necessary to patients' safe and effective use of the drug product. We therefore deny your request for a Medication Guide. Based on our review of the available data, FDA continues to find that Amitiza is adequately labeled without a Medication Guide.

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[13] The Agency stated in the preamble to the final rule "Prescription Drug Labeling Medication Guide Requirements" (63 FR 66378, December 1, 1998) (Medication Guide Final Rule) that drugs potentially falling into this category are those "cases in which there is a known 'risk control strategy'" or "where easily taken preventative measures can prevent harm" (Medication Guide Final Rule at 66388).

[14] The Agency stated that drugs potentially meeting this criterion would be those in which "the risk of a drug is relatively great, greater than a patient would anticipate given the relatively benign condition being treated . . . [or] where understanding the adverse effects is a critical choice among alternative treatments with different safety and effectiveness profiles . . ." (Id. at 66388).

[15] The Agency stated that drugs potentially falling into this category are those for which "nonadherence could compromise patients' health by interfering with effectiveness" (Id. at 66388).

F. Request for a "Dear Doctor" Letter

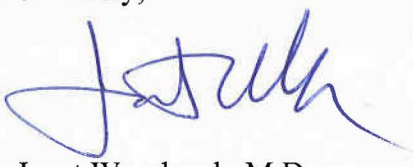
In the Petition, you request that FDA mandate that manufacturers send a letter to Health Care Professionals regarding Amitiza that encourages Health Care Professionals to report adverse events during pregnancy and that also includes information about the risk of abortion and premature labor and the necessity of using contraception while taking the drug (Petition at 7).

We deny your request that we mandate that manufacturers send a letter to healthcare professionals as you request. As we have discussed, we disagree with your assessment of the risks of Amitiza for women of child-bearing potential. Mandating a Dear Doctor letter would not be appropriate based on our evaluation of the data.

III. CONCLUSION

Based on the reasons described in this response, we deny your Petition. As with all drug products, we will continue to monitor the safety of Amitiza and take further action if we determine it is appropriate.

Sincerely,



Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research