Summary Review for Regulatory Action

Date	April 29, 2008
From	Donna Griebel Division Director Division of Gastroenterology Products Office of New Drugs III Center for Drug Evaluation and Research
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	NDA 21-908 S005
Applicant Name	Sucampo Pharmaceuticals
Date of Submission	June 29, 2007
PDUFA Goal Date	April 29, 2008
Proprietary Name / **Established (USAN) Name**	Amitiza (lubiprostone)
Dosage Forms / Strength	Capsules/ 8 micrograms
Proposed Indication(s)	Amitiza is indicated for treatment of irritable bowel syndrome with constipation in women ≥18 years old.
Action	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Helen Sile, MD Ruyi He, MD
Statistical Review	Milton Fan, PhD
Pharmacology Toxicology Review	Sushanta Chakder, Ph.D.
CMC Review/OBP Review	Ray Frankewich, PhD
Microbiology Review	NA
Clinical Pharmacology Review	NA
DDMAC	NA
DSI	Khairy Malek, MD Constance Lewin, MD, MPH
CDTL Review	Ruyi He, MD
OSE/DMETS	Tselaine Jones Smith, PharmD
OSE/DDRE	NA
OSE/DSRCS	NA
Other	NA

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMETS=Division of Medication Errors and Technical Support
DSI=Division of Scientific Investigations

DDRE= Division of Drug Risk Evaluation
DSRCS=Division of Surveillance, Research, and Communication Support
CDTL=Cross-Discipline Team Leader

Division Director Review

1. Introduction

In this efficacy supplement Sucampo Pharmaceuticals, Inc. proposes to add a new indication, treatment of Irritable Bowel Syndrome – Constipation predominant subtype, and new dose level for its product lubiprostone (Amitiza). In this review I will summarize the major review issues that were identified by the review teams and discuss my reasons for supporting their conclusions that this NDA should be approved.

2. Background

Lubiprostone, a prostaglandin E1 analog, is an activator of CIC-2 chloride channels. CIC-2 chloride channels are found throughout the human body, including the apical membrane of intestinal epithelial cells. Activation of these chloride channels increases chloride transport and fluid secretion into the intestinal lumen. In the current application, the applicant seeks approval of lubiprostone 8 microgram (mcg) twice daily for the treatment of Irritable Bowel Syndrome – Constipation predominant subtype (IBS-C). Lubiprostone was approved for treatment of chronic idiopathic constipation in adults on January 31, 2006 at a higher dose of 24 micrograms twice daily. The prior approval was based on two double-blinded, placebo-controlled studies of 4 week duration, identical in design, that enrolled 479 patients, mostly female, who had on average less than 3 spontaneous bowel movements per week with at least one of the additional features associated with at least 25% of bowel movements: very hard stools, sensation of incomplete evacuation or straining with defecation, or straining with defecation. Patients treated with lubiprostone had a higher weekly frequency of spontaneous bowel movements than those treated with placebo during the first week of treatment. The product has been on the market for over two years at a dose higher than that proposed in the current application.

Irritable Bowel Syndrome (IBS) is a chronic condition with clinical manifestations that include recurrent abdominal pain/discomfort and changes in bowel habits. There is no FDA approved treatment for IBS-C. (Zelnorm, a serotonin type 4 agonist, was withdrawn from the market in March 2007 because of cardiovascular adverse events.) The underlying pathophysiology of IBS is not well understood. It has a female predominance and diagnosis peaks in the third and fourth decade of life. The Rome III criteria for diagnosis of IBS include **continuous or intermittent abdominal discomfort** of at least 6 months duration, accompanied for at least 3 months by at least two of the following: 1)**improvement of discomfort with defecation**, 2) onset associated with **change in stool frequency**, and/or 3) onset associated with **change in stool appearance**. Irritable Bowel Syndrome with Constipation (IBS-C) is a sub-type of irritable bowel syndrome that is characterized in the Rome III criteria (which were launched in May 2006) **by hard stools ≥25% of bowel movements and loose stools <25% of time**.

The design of the two major studies that were conducted to support an indication for use of lubiprostone 8 mcg to treat IBS-C were discussed in an End of Phase 2 meeting in March 2005. The DGP in that meeting recommended that the monthly responder definition should be based on a global assessment of symptom relief. DGP also recommended that this global assessment should be collected weekly and that the patient at the time of each assessment should compare her symptoms to her baseline. The eligibility criteria for the studies were based on the Rome II criteria for IBS-C, which predated the Rome III criteria, and combined components of number of spontaneous bowel movements per week (<3), stool consistency (hard) and straining. [**Eligibility criteria for the two major studies included having 2 or more of: (1) <3 spontaneous bowel movements per week at least 25% of the time over a 4 week run-in period, (2) at least 25% of spontaneous bowel movements recorded as having been associated with at least moderate straining and/or (3) at least 25% of spontaneous bowel movements having been associated with stools that were hard or very hard** .] The impact of the change in the Rome criteria on the study analysis was discussed with DGP at the pre-NDA meeting in March 2007, and the DGP recommended adherence to the original analysis plan of the studies. Rome III–defined subgroup analyses would be considered exploratory.

3. CMC

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. The new 8 mcg capsule has the same formulation as the 24 mcg capsule and is produced using the same process. Because the manufacturing facilities for the 8 mcg capsule are the same as for the already approved 24 mcg capsule, an EER was only submitted for the packaging facility, which the Office of Compliance gave an overall recommendation of Acceptable on February 20, 2008. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval. I agree with his recommendations to include the information regarding reduction in implantation sites and live embryos from the Segment I reproductive toxicity study in rats in the label.

5. Clinical Pharmacology/Biopharmaceutics

There were no new pharmacokinetic studies conducted for this new indication. A phase 2 dose response study was conducted in patients with IBS-C. It was reviewed by the primary clinical reviewer, Dr. Helen Sile. The doses evaluated in this 12 week placebo-controlled study were 8 mcg BID, 16 mcg BID and 24 mcg BID (the approved dose for chronic idiopathic constipation). Although the primary efficacy endpoint was change from baseline in mean abdominal discomfort/pain during month 1, multiple secondary evaluations were captured

including daily and monthly ratings of abdominal bloating, constipation, daily counts of spontaneous bowel movements, degree of straining , stool consistency of spontaneous bowel movements, weekly ratings of treatment effectiveness and safety. The dose taken forward into the two major trials of the current application was the lowest dose evaluated in the phase 2 study, 8 mcg BID. The applicant believed the low dose was most appropriate for phase 3 evaluation in a population with IBS-C based on its relative tolerability compared to the higher dose levels. It was associated with the lowest proportion of adverse events that led to study discontinuation and the side effects of the product are primarily gastrointestinal – nausea and diarrhea.

6. Clinical Microbiology

NA

7. Clinical/Statistical-Efficacy

As stated in **Section 2. Background** above, individuals with IBS-C have a constellation of clinical symptoms that includes abdominal pain/discomfort and varying constipation. Abdominal discomfort/pain in IBS is relieved by bowel movements. The eligibility criteria for the trial in this application were based on the Rome II criteria, which delineate number of spontaneous bowel movements per week, hardness of stool and degree of straining. The IBS-C subtype is defined in the revised Rome III on the basis of whether stools are more frequently hard or loose. The Rome criteria indicate that patients with IBS-C are not always constipated and may in fact have an intermittent component of loose stools or urgency.

Given the multiple clinical features of this functional bowel disorder, the DGP stated in the March 2005 end of phase 2 meeting that the primary endpoint of the two major studies conducted to support the IBS-C indication should be a patient's own global assessment of symptom relief, that that assessment should be performed weekly, and that the comparison should be made to baseline symptoms. No validated patient reported outcome instrument exists for evaluating the symptoms and impact of therapy for IBS-C. The weekly response to the single question "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" was the tool utilized for the primary efficacy analysis. This single question is clearly global in scope, and the 7 potential responses are necessarily comparative (significantly relieved, moderately relieved, a little bit relieved, unchanged, a little worse, moderately worse, significantly worse). The patient is asked to assess her own symptoms over a 7 day recall period and to make a comparison to her memory of how she felt at baseline, which at study end would be 3 months in the past. An alternative form of self assessment, asking the patient to assign a current, non-comparative severity score for the prior 7 days at sequential points during her participation in the study, including baseline, was not utilized for the global primary endpoint in these studies. The latter approach could have avoided the reliance on patients' remembering how they felt months in the past for making "real-time" comparative self-assessments.

The primary efficacy analysis in both major trials supporting this application was a comparison of proportion of "overall responders" between the lubiprostone and placebo arms. An overall responder was defined as having been, in at least 2 of 3 months on study, a "monthly responder", which was defined as having reported (in response to the global question described above) that her symptoms were either "moderately relieved" compared to baseline all 4 weeks of the month or "significantly relieved" compared to baseline at least 2 of 4 weeks of the month. A single week reported as worsened symptoms led to that month being designated a non-responder month, as did increase in use of rescue medication or study discontinuation during the month for lack of efficacy**.** If a patient did not answer the question, a response of "unchanged" was assigned to those missing response weeks. A last observation carried forward methodology was not employed for the primary efficacy analysis. In both trials, there was a statistically significantly higher proportion of patients who were classified overall responders on the lubiprostone arm than on placebo. The overall response to lubiprostone in the two studies was similar, 13.8% and 12.1%. The placebo response in both trials was also similar, 7.8% and 5.7%, respectively. Although the results were consistent between trials, and both statistically significant, the observed treatment effect, 6.0% and 6.4% in the respective trials, was not dramatic.

Given this relatively low overall response, the clinical and statistical review teams evaluated the pre-specified major secondary endpoints for further supportive evidence of a clinically meaningful impact of lubiprostone treatment in IBS-C. As stated in the review of Dr. Milton Fan, PhD, the prespecified major secondary endpoints were monthly responder rates. The statistical analysis plan specified a step-wise procedure for comparing lubiprostone and placebo in each of the 3 months in each trial. In one trial, the responder rate on the lubiprostone arm was found to be statistically significantly higher in month 2, but not in month 1 and 3. In the second trial, because step 1 of the testing procedure did not yield a statistically significant result, the comparisons in Month 2 and 3 were not considered statistically significant, though without appropriate adjustment they did appear higher on the lubiprostone arm.

The clinical and statistical teams also examined a number of post hoc exploratory analyses as "sensitivity analyses". These analyses included comparison of the proportion of patients in each study arm that met the criteria of "monthly responder" in all 3 months on study (instead of in 2/3) and an additional analysis that included patients who reported that they felt at least "a little bit relieved" in the definition of responder. In both of these exploratory analyses no significant difference was found between arms in either of the studies.

Based on the mechanism of action of lubiprostone, the major impact on symptoms of IBS-C would be anticipated to be relief of constipation. Given that the discomfort/pain associated with IBS is often relieved by defecation, and that the components of the Rome II criteria for subtyping IBS-C are related to constipation, it is reasonable to believe that lubiprostone could be effective in treating the symptoms of IBS-C. Self assessment data for the specific symptom components of the Rome III criteria for IBS-C, i.e., stool frequency, stool hardness, and degree of straining were in fact collected and evaluated in each of the studies. However, there was not a prespecified plan for adjusting for multiple comparisons in these analyses, and a last observation carried forward (LOCF) approach to missing data was employed. Interestingly,

baseline demographic distribution tables presented in the Appendix of Dr. Milton Fan's Statistical Review indicate that of the 3 bowel movement descriptor eligibility criteria for the two studies (number of spontaneous bowel movements, stool hardness and straining), the two most common descriptors defining eligibility were stool hardness and straining (>90% of patients compared to approximately 75% of patients meeting the <3 spontaneous bowel movement criterion). In one of the studies (Study 0432, Table 14 of Dr. Fan's review Appendix) there was an imbalance between the lubiprostone and placebo arms in the proportion of patients eligible based on straining and on stool consistency. More patients in the lubiprostone arm were eligible based on straining or hard stools than on the placebo arm. I will briefly describe the observed outcomes for the "eligibility symptoms" exploratory analyses below, in the context of examining them to better understand the small but statistically significant treatment effect observed in the primary endpoint.

In this IBS-C application the baseline number of spontaneous bowel movements over a **month** ranged 3.7-4.0 in the two major studies. In the first **month**, the number of spontaneous bowel movements on the lubiprostone arm had increased to 5.3 in one study and 5.6 in the other, while on placebo it also increased to 4.9 and 5.3, respectively. The difference between arms in both studies was not statistically significant. Similarly, throughout the subsequent months on study, spontaneous bowel movements were somewhat higher numerically on the lubiprostone arm than the increase observed on placebo. (In contrast to the impact of the 8 mcg dose in the IBS-C studies, the 24 mcg dose in the chronic constipation studies resulted in an increase in the median number of spontaneous bowel movements **per week** from a baseline of 1.5 to 5 in the first week on study. During week 4 the median number had increased from the 1.5 baseline value to 4.)

Hardness of stool was an eligibility criterion (at least 25% of bowel movements had to be associated with stool that was characterized by the patient as "hard" or "very hard"). This was assessed with a daily diary question of "What was the average stool consistency of your spontaneous bowel movements?" The rating on a scale of 0 (very loose) to 4 (very hard) was averaged for each patient over a month and compared to baseline. The mean score at baseline in the two studies ranged 2.54 – 2.75 among the arms. (A score of 2 = "normal" and a score of 3 = "hard".) In this secondary analysis, the decrement in stool hardness score was consistently numerically greater on the lubiprostone arms than the placebo arms in all 3 months of the study in both major studies. Although the differences in one of the studies were presented as significantly different in months 1 and 2, appropriate adjustment for multiple comparisons was not performed, and the differences were not found to be similarly significant in the second trial.

Straining, another eligibility criterion (associated with at least 25% of spontaneous bowel movements), was assessed with a daily diary question "How would you rate your average straining with your spontaneous bowel movements" and a 5 point scoring system that ranged from 0 (absent) to 4 (very severe). The mean baseline score in the two studies ranged 2.38 – 2.39. (A score of 2= moderate straining and a score of 3 = severe straining.) Again, the decrement in monthly average straining scores was greatest on the lubiprostone arms across all 3 months on study, in both major studies.

Overall, these various pre-specified and post hoc analyses do not strongly corroborate or clarify the meaningfulness of the consistent and statistically significant outcome in the global primary endpoint observed in the two trials, although they numerically favor the lubiprostone arms in the non-post hoc, exploratory analyses.

One of the two major studies incorporated a randomized withdrawal phase to evaluate whether patients would experience a rebound effect. Patients randomized to lubiprostone at study start were also pre-randomized either to remain on lubiprostone or switch to placebo after 3 months on study. Patients who started the study on placebo remained on placebo for the full 4 months. The withdrawal phase analysis focused on the final 4 weeks on study. The rebound analysis was the comparison of the 4 month placebo patients to the lubiprostone patients who were overall responders in the first 3 months on study who switched to placebo during the last 4 weeks. There was no adjustment for multiple comparisons for this analysis, and this analysis compared the "monthly response" at month 4 of a small lubiprostone subset of 30 responder patients to 139 patients who took placebo all 4 months. There was no evidence of rebound, and the response in the lubiprostone responder subset was higher than in the placebo group. When the monthly response in month 4 within the lubiprostone subset of patients considered "overall responders" in the first 3 months was evaluated comparing those who were randomized between placebo or continuing lubiprostone in month 4, the response was numerically similar – 40% and 38%.

There is no FDA approved product currently on the market for patients with IBS-C. This disorder can have a major impact on patients' quality of life. The two major studies in this application both found that treatment with oral lubiprostone 8 mcg BID resulted in a statistically significant higher proportion of patients who experienced improvement of their overall symptoms of IBS-C compared to placebo, though the proportion who did respond was still quite low, approximately 6%. Although the treatment effect is small, lack of a currently available therapy for this condition makes it important to have a treatment option available to patients with this condition. I concur with the recommendation of the clinical and statistical reviewers that the efficacy demonstrated in the two major clinical trials supports approval of the application and the primary efficacy analysis conducted without last observation carried forward should be presented in the product label. I also concur that given that a very small proportion of the study population was male (<10%) the indication should state that the 8 mcg BID dose is indicated for treatment of women with IBS-C. Although a similarly low proportion of males were enrolled in the major clinical trials that supported approval of the chronic idiopathic constipation indication for both men and women, the clinical review team believes that because chronic idiopathic constipation is a better understood clinical condition than IBS-C, the efficacy data from women with chronic constipation can be more readily extrapolated to males. In light of the lack of pediatric studies, the indication will be further limited to women aged 18 and older.

I also concur with the clinical review team's concerns that the small treatment effect observed with 8 mcg BID in IBS-C, concurrent with the relatively small impact on spontaneous bowel movements relative to the higher dose labeled for treatment for chronic idiopathic, will lead to treatment of IBS-C patients who do not adequately respond to the 8 mcg dose with the higher available dose. The applicant has agreed to a post marketing study commitment to evaluate a

16 mcg BID dose in patients with IBS-C, in an effort to determine whether efficacy can be enhanced with this higher dose while retaining tolerability. They concur that a controlled study to describe the true efficacy and safety of the higher dose in this population is the optimal public health approach to answer this question definitely for physicians and patients.

8. Safety

The data base for this application included 1105 individuals who received lubiprostone and 256 received placebo. One thousand eleven patients were treated with the 8 mcg BID dose. The application included data from an open-label long term safety study (520 patients treated for 9 months in addition to their exposure while participating in the two major efficacy studies), so there were data available from 179 individuals who were treated with lubiprostone for 9 months, 80 for 12 months, and 261 for 13 months. The duration of the placebo controlled portion was 3 months in one of the major trials and 4 months in the other. The proportion that withdrew from study because of an adverse event was similar between lubiprostone and placebo arms. The most common adverse event was nausea, followed by diarrhea, and both occurred more frequently in the lubiprostone arm. Both nausea and diarrhea are recognized adverse events associated with lubiprostone and are currently in the label for the 24 mcg BID dose level, although at a higher frequency than observed at the lower 8 mcg BID dose. Abdominal pain was reported as an adverse event in the IBS-C data, but the rate was similar between lubiprostone and placebo. Abdominal pain was also observed at the higher dose studied for chronic idiopathic constipation indication.

Dr. Helen Sile noted in her safety review that across the clinical trials that were submitted in support of this application, there were reports of dyspnea that ranged from 0.3% to 2.7%. Only a small proportion of these events, 0.2% were considered severe, but most patients who experienced a dyspneic event withdrew from the study. Higher dose levels seemed more likely to be associated with dyspnea. In the dose response study, 2.1% of the 32 mcg dose patients and 4.4% of the 48 mcg patients experienced dyspnea. In the 8 mcg BID studies the frequency was 0.3%. Dyspnea is mentioned in the product labeling for the idiopathic constipation indication under the adverse events subsection “Less common adverse reactions”. In the medical officer review of the chronic constipation application dypnea is reported in 1.8% of patients treated at 24 mcg BID compared to 0% on placebo.

Dr. Sile reviewed the post marketing safety reports for dyspnea for lubiprostone for each quarter after the product’s approval in January 2006 to January 2008. She found 3 SAEs for dyspnea in that period, all occurring before August 2007. There have been multiple and increasing numbers of reports on non-serious dyspnea beginning in the second quarter after approval. The number peaked at 33 and 35 per quarter in May 2007 to July 2007 and August 2007 to October 2007, but dropped to 9 in the final quarter evaluated – November 2007- end of January 2008. The narratives of these events were reviewed and although many were incomplete reports and essentially nonevaluable, the majority provided enough detail to delineate a common presentation. These reports describe acute onset after the first dose of treatment, usually 30 minutes to 1 hour post taking the dose. The symptoms are described as difficulty taking a breath, usually associated with a sensation of chest tightness or tightness in

the throat. They resolve within 3 hours after taking the dose. Symptoms suggestive of allergic reaction such as rash, itching or wheezing were rare. Most patients did not seek immediate medical attention and many rechallenged themselves with at least one additional dose. Nearly all had recurrence of the symptoms. Most stopped treatment because of the symptoms. Only one of the events coded as a serious event, evaluated in an emergency room, was considered an anaphylactic reaction by the hospital staff. She was treated with epinephrine and monitored overnight. One woman who had a history of CHF and COPD was admitted to the ICU and intubated. Only one chest X-ray report was provided, and it was only a follow-up film. It was reportedly read as showing improved CHF, but it is not clear whether CHF was the cause of admission. The few individuals who were reported to have had an ECG were not found to have evidence of acute ischemia.

The applicant agreed to add information describing the postmarketing events of dyspnea in the Warning section of the label, i.e. describing the temporal nature and record of positive rechallenge, and DGP will ask that they provide future reports of dyspnea as expedited 15-day reports to the FDA, not merely waiting to submit them in summary format in quarterly reports. This will enable the FDA to more closely monitor these events for severity, trends in frequency, and to further qualitatively evaluate them to determine whether studies are indicated to delineate the underlying pathophysiology.

9. Advisory Committee Meeting

There was no Advisory Committee meeting for this application. The product has been previously approved at a higher dose for another indication. There is no FDA approved therapy for IBS-C currently on the market, and both major studies that support the IBS-C indication consistently found a statistically significant improvement in the primary endpoint associated with lubiprostone 8 mcg BID relative to placebo.

10. Pediatrics

Based on discussion with the PeRC, pediatric studies will be waived in children less than 6 years of age because IBS-C does not occur in this age group, or the population is too small for study, and deferred for the children aged 6 -17 because the product is ready for approval for use in adults. PeRC strongly supported the DGP's recommendation that the applicant conduct a randomized, controlled efficacy study in the pediatric group aged 6-17. They concurred with a recommendation that this should be a study of 12 month duration, given the potential for long term treatment in this population. Long term efficacy data will help guide management decisions and a 12 month trial will permit evaluation of the drug’s impact on growth and bone mineralization. Prostaglandin treatment has been reported to be associated with hyperostosis.

The applicant has agreed to work with the DGP to design a randomized, placebo controlled study to evaluate efficacy and specific safety parameters. The study will be of 12 month duration, enrolling approximately 300 children. The applicant has expressed concerns that IRBs may not consider a placebo controlled trial ethical in a population of children with IBS-

C, but has committed to exploring that possibility or alternative designs for the long term extension phase. They agreed to work with the DGP in designing the trial.

11. Other Relevant Regulatory Issues

The DSI audit determined that the data from one site, site #151 Dr. Sargent, was not acceptable because the Investigator's signature was not the signature on the physical examination records or on one of the consent forms. Exploratory analyses of the efficacy data were conducted excluding the data from that site, and the primary outcome favoring lubiprostone was not affected.

On her review of the Financial Disclosure information provided in the NDA, Dr. Helen Sile did not detect a financial conflict that caused the review team to question the efficacy and safety data and outcomes presented in this NDA.

12. Labeling

As described in Sections **7. Clinical/Statistical- Efficacy** and **8. Safety** above, the clinical review team recommended limiting the indication to women with IBS-C. The applicant concurred, based on the small number of men in the database. The applicant also agreed to add a warning to both in the Highlights of Prescribing Information section and in Section 5 Warnings and Precautions of the label regarding dyspnea observed in the clinical trials datasets and in postmarketing reports. At the request of the DGP they agreed to provide a description of the events observed in the postmarketing reports – including a description of pattern of onset, resolution and positive rechallenge.

The applicant agreed to update **Section 13 Nonclinical Toxicology subsection Impairment of Fertility** with the information regarding reduction in implantation sites and live embryos from the Segment I reproductive toxicity study in rats.

13. Decision/Action/Risk Benefit Assessment

- I recommend approval of lubiprostone 8 mcg PO twice daily for treatment of women with IBS-C.

- Risk Benefit Assessment

  I concur with the risk benefit assessment of the clinical reviewers, Dr. Helen Sile and Dr. Ruyi He, and their conclusion that the data presented in this NDA

support approval of lubiprostone 8 mcg BID for treatment of women ≥18 years of age with IBS-C. The two major studies in this application both found that treatment with oral lubiprostone 8 mcg BID resulted in a statistically significant higher proportion of patients who experienced improvement of their overall symptoms of IBS-C compared to baseline. The proportion of overall responders in both studies was consistent, however, the treatment effect was quite low, approximately 6%.

Given the low treatment effect, it is particularly important to critically evaluate the safety profile of this product. Lubiprostone has been on the market in the U.S. for approximately 2 years, at a substantially higher dose than the dose that will be approved for this indication. The safety database for the current application identified no new safety signals, and the major side effects are those that were also observed at the higher approved dose, nausea and diarrhea. Availability of two years of post marketing data for the higher dose allowed the review team to further define the dyspnea adverse events that were observed in the safety datasets for the IBS-C application and the idiopathic chronic constipation application. The dyspnea events are rarely serious, and have a relatively consistent pattern of presentation, duration and positive rechallenge. It appears to be more likely to occur with higher doses of the drug. The applicant has agreed to add a Warning section to the label to describe these events.

There is no FDA approved product currently on the market for patients with IBS-C, a disorder that can have a major impact on patients' quality of life. Although the treatment effect of lubiprostone 8 mcg observed in the two major trials that support this application is small, it is consistent, and lack of a currently available therapy for this condition makes it important to have a treatment option available to patients with this condition. The risks associated with lubiprostone are manageable and adverse events associated with its use have rarely been serious.

- Recommendation for Postmarketing Risk Management Activities

  We will request that the applicant provide post marketing safety reports of dyspnea and chest discomfort as expedited 15-day reports to enhance the FDA's ability to assess trends in frequency and severity of these events, which will allow the FDA to determine whether more aggressive risk management activities are indicated in the future to address this safety adverse event.

- Recommendation for other Postmarketing Study Commitments

  We have requested that the applicant design a randomized controlled study of a higher dose of lubiprostone for the treatment of IBS-C. As discussed in my review, the DGP is concerned that given the prior approval of a higher dose of lubiprostone and the relatively low treatment effect of lubiprostone 8 mcg for

this condition, off label use of higher doses will occur in this population . We believe that a controlled clinical trial will provide valid efficacy and safety data to physicians and patients so that they can make evidence-based treatment decisions. In addition, we hope that the applicant will be able to enroll more men into this study so that we will be better able to assess whether lubiprostone is an effective therapy for men with IBS-C.

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/s/

Donna Griebel
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DIRECTOR