CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-908s005

CROSS DISCIPLINE TEAM LEADER REVIEW

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 4/22/2008

FROM: Ruyi He, MD
Medical Team Leader
Division of Gastroenterology Products/ODE III

TO: Donna Griebel, MD,
Director
Division of Gastroenterology Products/ODE III

SUBJECT: GI Team Leader AP Comments
NDA 21-908/S005

APPLICANT: Sucampo Pharmaceuticals, Inc.

DRUG: Amitiza (Lubiprostone) Oral capsule

THERAPEUTIC CLASS: Prostaglandin metabolite analogue

INDICATION: Treatment of irritable bowel syndrome with constipation in women

RECOMMENDATION:

I concur with Dr. Helen Sile's recommendations that NDA 21-908/S005, Amitiza (Lubiprostone) Oral capsule, be approved for the treatment of irritable bowel syndrome with constipation in women ≥ 18 years old. The recommended dose is 16 mcg/day (8 mcg capsules b.i.d). To get approval, the sponsor should incorporate the Division's labeling recommendations and phase 4 commitments.

The sponsor has requested a waiver for the pediatric studies involving ages birth to 5 years old and a deferral for ages 6 and above. I recommend that the requests be granted. The sponsor submitted a pediatric study plan to conduct "multi-center, open-labeled, safety and efficacy study of oral Lubiprostone in pediatric patients with irritable bowel

syndrome with constipation (IBS-C)". The waiver/deferral requests and the pediatric study plan will be presented to Pediatric Review Committee (PeRC) on April 23, 2008.

Standard post-marketing surveillance is recommended to further monitor the efficacy and safety of Amitiza. In addition, I recommend that the sponsor conduct further study to establish efficacy and safety of Lubiprostone at the 16 mcg bid dose in both male and female patients with IBS-C.

There is no risk management steps recommended at this time.

BACKGROUND:

Irritable Bowel Syndrome (IBS) is a chronic medical condition that is characterized by recurrent abdominal pain and discomfort and altered bowel habits. The diagnosis is based on the Rome criteria and the exclusion of physical, laboratory and structural abnormalities. IBS has a prevalence of approximately 12% in the United States and worldwide. Age of onset of IBS varies, but the incidence appears to increase in adolescents and peaks in the third and fourth decade of life. It has a Female predominance.

The cause of IBS is not known at this time. It is believed that IBS patients have altered motility, visceral hypersensitivity and altered visceral sensation of pain. Psychosocial stressors have been proposed to exacerbate symptoms of irritable bowel syndrome. There is also evidence that reveals infection and inflammation may contribute to the symptoms associated with IBS.

IBS is further sub-typed into four groups based on stool form: IBS with constipation (IBS-C), IBS with diarrhea (IBS-D), Mixed IBS (IBS-M), and Un-sub-typed IBS. The goal of therapy is to provide treatment that alleviates the symptoms. There is no FDA approved product for the treatment of IBS-C at this time.

Lubiprostone was approved on January 31, 2006 for the treatment of chronic idiopathic constipation at 24 mcg bid dose, three times higher than current proposed dose for IBS-C.

For this NDA, the sponsor provided two randomized double-blinded multi-centered placebo controlled trials (Studies SIB-0431 and SIB-0432) in patients with IBS-C.

DISCIPLINE REVIEW SUMMARY AND COMMENTARY:

DSI:

Four clinical sites were inspected by the Division of Scientific Investigations (DSI). Three clinical sites were found to be acceptable by DSI. Dr. Edward Sargent (the 4th

inspected site) participated in studies SIB-0431 and SIB-05S1. During a DSI investigation, it was revealed that his clinical site (Site # 151) did not keep adequate and accurate records. The investigator and sub-investigator signatures entered on subjects' physical exam forms, laboratory and ECG report forms were that of the study coordinator rather than the responsible/examining clinicians. The signature irregularities made it difficult to ensure the accuracy of the physical exams and verification of the laboratory and ECG data. Therefore, DSI concluded that data generated at site # 151 for study SIB-0431 are considered unacceptable in support of the efficacy and safety application for this NDA. However, I believe that this violation does not affect the totality of the NDA efficacy conclusion because efficacy data were provided by the patients directly to a 3rd party through an electronic device which did not go through Dr. Edward Sargent's clinical site. Furthermore, this violation would not affect the totality of the NDA safety conclusion because safety profile of Lubiprostone was established with higher doses (24mcg bid) in the original NDA submission for chronic idiopathic constipation. There is no safety signal identified in this NDA and previous studies with higher dose (24 mcg bid) that did include the evaluation of physical exams results, laboratory values and ECG results. In addition, efficacy evaluation was done after excluding data from Dr. Sargent's site and indicated no change in the efficacy conclusion. Thus, this violation will not affect the totality of efficacy and safety evidence for this NDA.

Chemistry and Manufacturing:

From the CMC perspective, this NDA is recommended for approval.

Pre-Clinical Pharmacology/Toxicology:

No new animal data were included with this supplemental application.

Biopharmaceutics:

There was no new pharmacokinetics study conducted for this supplemental indication. All the pharmacokinetics studies were conducted with the original submission, and they were reviewed and evaluated thoroughly as part of the original NDA.

Clinical/Statistical:

This application includes two phase 3 studies; SIB-0431 and SIB-0432. They were multi-center, parallel group, double-blind, placebo-controlled, Phase III studies of 12 weeks duration. These two studies assessed the efficacy and safety of oral 16 mcg Lubiprostone compared to placebo for the treatment of IBS-C. SIB-0431 Treatment Phase I was followed by a 4 week randomized withdrawal study, SIB-0431 Treatment Phase II, which was designed to assess the rebound phenomenon and lasting efficacy of Lubiprostone 16 mcg.

In addition, this application also includes one long-term safety study, SIB-05S1. This study was multi-center, open label study which assessed the safety of 16 mcg of Lubiprostone as the primary endpoint when administered for 36 weeks. The long term study enrolled a total of 522 subjects in 104 centers across the United States.

Efficacy

A total of 1366 subjects with IBS-C were randomized in the clinical development program of Lubiprostone. The primary efficacy analysis was based on the overall responder rate during the 12 week treatment period. An overall responder was defined as a subject that was a monthly responder for at least 2 out of the 3 months during the 12 week treatment period.

Overall and Monthly responder definitions were based on the weekly assessments of global symptom relief obtained as part of the subject's electronic diary responses. Global symptom relief was assessed with the following weekly diary 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? The rating was based on 7 point balanced scale: 3 = significantly relieved, 2 = moderately relieved, 1 = A little bit relieved, 0 = Unchanged, -1 = A little bit worse, and -2 = Moderately Worse. A Monthly responder was defined as a subject whose symptoms were rated as "Moderately relieved" for all 4 weeks within a month or "Significantly relieved" for at least 2 weeks within a month provided three conditions were met: 1. the percent of days of rescue medication use did not increase during the month as compared to baseline, 2. the subject did not discontinue the study during the month due to lack of efficacy, 3. the subject had no ratings of "Moderately worse" or "Significantly worse" during the month.

The overall responder rate data from the Intent-to-Treat (ITT) population without Last-Observation-Carried-Forward (LOCF) are summarized in Table 1.

Table 1: Summary of Responder Rate in the ITT Population without LOCF: Lubiprostone 16 mcg

Study	Study Arm	Responder n (%)	Difference %	p-value
SIB-0431	Placebo N=193	15 (7.8)	6	0.029
	Lubiprostone N=390	54 (13.8)		
SIB-0432	Placebo N=192	11 (5.7)	6.4	0.023
	Lubiprostone N=379	46 (12.1)		
Pooled	Placebo N=385	26 (6.8)	6.2	0.001
	Lubiprostone N=769	100 (13.0)		

As noted above in Table 1, in both pivotal studies, the overall responder rates in the Lubiprostone group were higher (range: 12.1%-13.8%) than that in the placebo group (range: 5.7% - 7.8%). In the pooled group, the overall responder rate was 13.0% for Lubiprostone 16 mcg subjects and 6.8% for placebo subjects and the difference was statistically significant, p=0.001. In both studies, the difference in overall responder rates between treatment groups was similar. In the pooled group, the difference in overall responder rate between subjects that received placebo and active treatment was 6.2%. Lubiprostone demonstrated a marginal clinically meaningful difference (6%) in overall responder rate during the 12 week treatment period (the primary efficacy endpoint) in both studies.

Efficacy results in women are basically the same as ITT population listed above. The percentage of women in Study 1 qualifying as an overall responder was 14% in the group receiving Amitiza 8 mcg twice daily compared to 8% of women receiving placebo twice daily for 12 weeks. In Study 2, 12% of women in the Amitiza 8 mcg group were overall responders versus 6% of women in the placebo group. In both studies, the treatment differences in women between the placebo and Amitiza groups were statistically significant.

A total of 97 (8%) males were enrolled in these two randomized, placebo-controlled, double-blind studies which is insufficient to determine whether they respond differently from women. The treatment differences in males between the placebo and Amitiza groups were not statistically significant.

The secondary efficacy endpoints included Daily abdominal discomfort/pain; Daily abdominal bloating; Frequency rates of spontaneous bowel movements (SBMs); Frequency rates of bowel movements (BMs); Daily stool consistency associated with SBMs; Daily degree of straining associated with SBMs; Daily severity of constipation associated with SBMs; Irritable bowel syndrome quality of life (IBS-QOL) assessment; Weekly symptom relief; and Weekly treatment effectiveness.

Lubiprostone was slightly better than placebo in most of the secondary endpoints. For daily abdominal discomfort/pain, Lubiprostone subjects had an average mean reduction of 0.35 units on the 5 point scoring scale at month 1, 0.46 units at month 2, and 0.48 units at month 3 when compared to baseline. Placebo subjects on the other hand, revealed an average mean reduction of 0.26 units on the 5 point scoring scale at month 1, 0.32 units at month 2 and 0.35 units at month 3 compared to baseline. Both Lubiprostone and placebo did reduce abdominal pain from a rating range of moderate-severe (2-3) to mild-moderate (1-2); however, the decrease was slightly larger in the Lubiprostone treated group which resulted in more ratings closer to the mild range.

Treatment with Lubiprostone 16 mcg did slightly increase the frequency of spontaneous bowel movements more than treatment with placebo in the range of 0.12-0.33. In both pivotal studies, the mean change in spontaneous bowel movement (SBM) frequency rates in the Lubiprostone group was higher for all monthly time points (range: 1.51-1.59) than

that in the placebo group (range: 1.21-1.41) except in Month 3 of SIB-0432 where it was similar to placebo (1.42 Lubiprostone vs. 1.43 Placebo). The difference between placebo and the Lubiprostone treatment groups was not statistically significant at all time points.

There were a total of 1253 ITT subjects in the pooled group and 520 safety evaluable subjects in the Long-term Safety group (LTS). The overall subject population was predominantly female (92%) and mostly Caucasian (78% - 80%). The average proportion of subjects > 65 years old in the pooled population was only 8.1%. Having noted the limitations in the application's patient population, Lubiprostone was analyzed by the primary efficacy variable in three subpopulations; gender (female, male), race (white, non-white), and age [(18 < Age < 65), (65 < Age)]. Females, whites and subjects 18 < Age < 65 revealed statistically significant results for the primary efficacy endpoint favoring Lubiprostone 8 mcg bid over placebo. In the age group > 65, Lubiprostone 8 mcg bid did not show any difference from placebo (10.5% Placebo, 10.3% Lubiprostone) in the overall responder rate which was the primary efficacy variable.

Safety

There were a total of 1361 subjects treated in the safety population, of which 1105 subjects received active drug and 256 received only placebo. Of the 1105 subjects that received all doses of Lubiprostone, 779 subjects received only Lubiprostone and 326 subjects received both placebo and Lubiprostone 16 mcg. One thousand and eleven subjects received Lubiprostone 16 mcg/day (8 mcg bid). In the long term safety study (SIB-05S1), 520 subjects were treated with Lubiprostone 8 mcg bid 9 months or more: 179 subjects received Lubiprostone for 9 months, 80 subjects received Lubiprostone for 12 months, and 261 subjects received Lubiprostone for 13 months.

One subject died in the entire clinical development program. The subject was a 71 year old male in the Lubiprostone/placebo group whose past medical history was significant for Dysphagia, Abdominal hernia, Hepatic Steatosis, Diabetes Mellitus, Hyperlipidemia, Obesity (300 lb), Asthma and Cholecystectomy. Concomitant medications were fluticasone propionate, Fluvastatin, Glibenclamide, metformin, and Salbutamol. On study day 74, the subject experienced cardiac arrest and expired. The last dose of study medication was taken on Study day 72. No autopsy report was provided.

The occurrence of serious adverse events in the studied population was relatively low. Four placebo subjects (0.9%) reported 7 serious adverse events (SAEs) with no preferred term SAE being reported by more than one subject. Seven subjects taking Lubiprostone 16 mcg (0.8%) reported 9 treatment emergent SAEs. Two Lubiprostone subjects reported 4 SAEs (cardiac arrest, atrial fibrillation, coronary artery disease and mitral valve incompetence) in the cardiac disorders system organ class. One SAE of chest pain that was reported as non-cardiac in nature was considered treatment related. In the open label treatment period, 10 subjects reported 11 treatment emergent SAEs. Syncope was the only SAE preferred term reported by more than 1 subject.

Across all active doses of Lubiprostone (N=926) in the safety evaluable population from the well-controlled studies, the most commonly reported adverse event preferred terms were nausea (12.3%), diarrhea (8.2%), headache (4.3%), upper respiratory tract infection (4.1%), abdominal pain (4.0%), and urinary tract infection (4.0%). Comparatively for placebo (N=435), the corresponding reports of adverse events in the above preferred terms were: nausea (6.4%), diarrhea (5.3%), headache (4.4%), upper respiratory tract infection (2.3%), abdominal pain (5.3%), and urinary tract infection (3.4%). In the open label treatment period, the most commonly reported adverse events were similar to the ones reported in the well-controlled trials: diarrhea (8.8%), nausea (6.5%), urinary tract infection (6.5%), headache (4.0%), abdominal pain (3.5%) and upper respiratory tract infection (2.9%).

Overall 2.3% of placebo subjects and 1.9% of Lubiprostone 16 mcg subjects withdrew because of gastrointestinal adverse events. The breakdown of gastrointestinal adverse events in the well-controlled safety population that led to withdrawal for at least 1% of subjects was nausea (1.2%) for the Lubiprostone 16 mcg group and abdominal pain (1.4%) for the placebo group.

The clinical and laboratory data presented in this application including biochemistry, hematology, urinalysis, vital signs and physical examination data appeared clinically acceptable for a population of subjects with constipation predominant irritable bowel syndrome who are otherwise considered generally healthy. ECG and bilateral hand X-rays were evaluated in the dose response study SIB-0221 at baseline and at final assessment. Lubiprostone at doses of 16 mcg, 32 mcg, and 48 mcg per day for 12 weeks showed no evidence of effect on heart rate, cardiac conduction, cardiac repolarization or morphological changes.

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 events that were identified in this study were similar to the events in the two double blind controlled studies.

Pediatric Use:

The sponsor has requested a waiver for the pediatric studies involving ages birth to 5 years old and a deferral for ages 6 and above. I recommend that the requests be granted. The sponsor submitted a pediatric study plan to conduct “multi-center, open-labeled, safety and efficacy study of oral Lubiprostone in pediatric patients with irritable bowel syndrome with constipation (IBS-C)”. The waiver/deferral requests and the pediatric study plan will be presented to Pediatric Review Committee (PeRC) on April 23, 2008.

Labeling Recommendations:

There is limited number of male patients treated in the clinical trials (97, 8%); therefore, it is difficult to assess the benefits and risks of Amitiza use in men with IBS-C. I recommend that the indication be limited to women with IBS-C which is consistent with the labeling of Zelnorm.

I concur with Dr. Helen Sile and review team's labeling recommendations.

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/s/

Ruyi He
4/25/2008 03:04:47 PM
MEDICAL OFFICER