CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-908s005

OTHER REVIEW(S)

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: 4/4/2008

TO: Tom Moreno, M.S., Regulatory Project Manager
Helen Sile, M.D., Medical Officer

FROM: Khairy W. Malek, M.D.
Good Clinical Practice Branch I
Division of Scientific Investigations

THROUGH: Constance Lewin, M.D., Ph.D.
Branch Chief, Good Clinical Practice Branch I
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 21-908/S-005

APPLICANT: Sucampo Pharmaceuticals, Inc.

DRUG: Amitiza (lubiprostone)

NME: No

THERAPEUTIC CLASSIFICATION: Standard

INDICATIONS: 1. Treatment of Constipation-Predominant Irritable Bowel Syndrome

CONSULTATION REQUEST DATE: August 27, 2007

DIVISION ACTION GOAL DATE: April 29, 2008
PDUFA DATE: April 29, 2008

1. BACKGROUND:

Irritable bowel syndrome (IBS) is a functional disorder which can be characterized into three primary types: constipation-predominant, diarrhea-predominant and alternating. Lubiprostone has shown to enhance bowel movements, improve stool consistency and reduce abdominal discomfort.

There are two protocols used in this study, 0431 and 0432. Both protocols are for 12 weeks but in protocol 0431, the 12-week treatment period is followed by a 4-week blinded randomized withdrawal of lubiprostone to examine any lasting or rebound effect related to withdrawal of the drug. In both protocols there is a 4-week open-label study extension.

Protocols SPI/0211SIB-0431 and 0432:

"A 12-Week, Multicenter, Double-Blind, Randomized Efficacy and Safety Study of Lubiprostone for the Treatment of Constipation-Predominant Irritable Bowel Syndrome". Two sites were chosen for each protocol.

II. RESULTS (by Site):

Name of CI, and site #	City and State	Insp. Date	Protocol	Final Classification
Edward Sargent, M.D. Site 151	San Antonio TX	10/30-11/15/97	SPI/0211SIB-0431	OAI
Lawrence Wruble, M.D. Site 164	Germantown TN	12/10-12/11/07	SPI/0211SIB-0431	VAI
Scott Wofford, M.D. Site 205	North Little Rock- AR	11/26-12/05/07	SPI/0211SIB-0432	VAI
Robert Marks, M.D. Site 236	Alabaster, AL	3/11-3/17/08	SPI/0211SIB-0432	VAI
Sucampo Pharmaceuticals	Bethesda, MD	2/27-3/18/08	SPI/0211SIB-0432 and SPI/0211SIB-0431	Pending
(b) (4)				(b) (4)

Key to Classifications
NAI = No deviation from regulations.
VAI-No Response Requested= Deviations(s) from regulations.
VAI-R = Response Requested = Deviation(s) from regulations.
OAI = Significant deviations from regulations.
Pending = Preliminary classification based on information in 483; EIR has not been received from the field and complete review of EIR is pending.

1. Edward Sargent, M.D.-Site # 151
   8042 Wurzbach, San Antonio, TX 78299

   a. What was inspected: The field investigator reviewed the records of 20 subjects out of 33 enrolled. Inspection was limited in that, due to data collection methods, the primary endpoint data could not be verified during this inspection. Follow-up inspections at the sponsor and contract research organization ([(b) (4)] were conducted to evaluate the primary endpoint data.
   b. General observations/commentary:
   The violations revealed during the inspection were:

      - Failure of the clinical investigator to supervise the study.

      - Inadequate and inaccurate records: Signatures entered on physical examinations for subjects 048 and 032 were similar to the signature of the clinical investigator (CI) or sub-investigator; however, the clinical investigator and sub-investigator denied signing the forms. In addition, a signature similar to the clinical investigator's signature was on the informed consent form for subject 059; however, inspection the clinical investigator denied signing the form.

      - Failure of the CI to maintain adequate and accurate case histories as the site did not keep a copy of data uploaded electronically to the sponsor server.

   c. Assessment of data integrity: The integrity of the data from this site cannot be assured at this time. DSI recommends the data obtained from this site not be used in support of the NDA supplement.

2. Lawrence Wruble, M.D. - Site # 164
   8000 Germantown, TN 38138

   a. What was inspected: The field investigator reviewed the records of all 31 subjects in the study. Inspection was limited in that, due to data collection methods, the primary endpoint data could not be verified during this inspection. Follow-up inspections at the sponsor and [(b) (4)] the contract research organization (CRO) responsible for primary endpoint data collection, were conducted to evaluate the primary endpoint data.

   b. General observations/commentary:
   At this site, one violation was revealed in that the CI did not keep a record or a copy of the subject's electronic diary data.

   c. Assessment of data integrity:
   As already noted, the primary endpoint data could not be verified through inspection at this site. Follow-up inspections of the sponsor and CRO responsible for the collection of the primary endpoint data revealed that the computerized systems used were

adequately validated to assure that they met their stated purpose for the collection of this data. Data from this site are considered acceptable in support of the pending application.

3. Scott Wofford, M.D. - Site # 205
   3401 Springhill Drive, North Little Rock, AR 72117

   a. What was inspected: The field investigator reviewed the records of all subjects in the study. At this site, 40 subjects were enrolled, but 27 completed the study. Four subjects withdrew their consent during the study, 1 withdrew due to adverse reaction, rash, 1 placebo subject withdrew because of colon surgery, 1 DC because of ear surgery and 3 were lost to follow-up. Inspection was limited in that, due to data collection methods, the primary endpoint data could not be verified during this inspection. Follow-up inspections at the sponsor and (b) (4) CRO responsible for primary endpoint data collection, were conducted to evaluate the primary endpoint data.

   b. General observations/commentary:
   The CI did not keep a record or a copy of the subjects' electronic diary data.

   c. Assessment of data integrity:
   As already noted, the primary endpoint data could not be verified through inspection at this site. Follow-up inspections of the sponsor and CRO responsible for the collection of the primary endpoint data revealed that the computerized systems used were adequately validated to assure that they met their stated purpose for the collection of this data. Data from this site are considered acceptable in support of the pending application.

4. Robert Marks, M.D.-Site # 236
   1010 First Street North, Suite 112, Alabaster, AL 35007-8617

   a. What was inspected:
   Thirty three subjects enrolled in the study. The field investigator reviewed the records of all subjects in the study. Inspection was limited in that, due to data collection methods, the primary endpoint data could not be verified during this inspection. Follow-up inspections at the sponsor and (b) (4) the CRO responsible for primary endpoint data collection, were conducted to evaluate the primary endpoint data.

   b. General Observation/commentary:
   The violation observed during the inspection was that the CI did not maintain an in-time copy of the subjects' electronic diaries.

   c. Assessment of data integrity:
   As already noted, the primary endpoint data could not be verified through inspection at this site. Follow-up inspections of the sponsor and CRO responsible for the

collection of the primary endpoint data revealed that the computerized systems used were adequately validated to assure that they met their stated purpose for the collection of this data. Data from this site are considered acceptable in support of the pending application.

5. Sucampo Pharmaceuticals
   Bethesda, MD

   a. What was inspected: Clinical study documents for protocols SPI/0211SIB-0432 and SPI/0211SIB-0431.

   b. General observations/commentary:
   Sucampo Pharmaceuticals, Inc contracted the services of (b) (4) to collect ePRO system component electronic information from two sources:
   1) Diary (b) (4) devices taken home by each subject. The electronic information was transferred through the phone lines each night to the (b) (4) server. After the last transfer of information, the device was erased.
   2) Site (b) (4) devices used by site personnel to gather Quality of Life and Bowel Symptom survey. The Site (b) (4) device remained at study site, and subject information was transferred electronically to the server after each visit.
   3) (b) (4) was not listed on the statement of transfer of responsibilities (Form FDA 1571).

   c. Assessment of data integrity: Verification of the validation of the computerized system used to capture data could not be performed during the inspection of the sponsor, as these responsibilities were contracted out to (b) (4) As such, an inspection of (b) (4) was conducted.

Observations noted for Sucampo Pharmaceuticals are based on the Form FDA 483 and communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

6. (b) (4)

   a. What was inspected: Validation documentation pertaining to the computerized system used to capture data for protocols SPI/0211SIB-0432 and SPI/0211SIB-0431 including validation plan, test plan, summary, and testing rescords were inspected.

   b. General Observation/Commentary: No significant regulatory violations were observed. The firm had documentation of validation of the extraction of data from the server to SAS files provided to the sponsor and to .PDF files provided to the sponsor and clinical investigators. The firm has a back-up copy of the data on their server. The firm demonstrated the system by tracing a study subject's data from the server data to the SAS files and .PDF files. Representatives from Sucampo Pharmaceuticals (the

sponsor) demonstrated how they converted the data and averaged the information for the data listings.

c. Assessment of data integrity: Data collected by (b) (4) validated computerized system for protocols SPI/0211SIB-0432 and SPI/0211SIB-0431 may be used in support of the respective indications.

Observations noted for (b) (4) are based on communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Other than the data from site # 151 which is Dr. Sargent's site, the data from the other 3 sites are acceptable and can be used in support of the NDA supplement.

As previously mentioned, observations noted for Sucampo Pharmaceuticals and (b) (4) are based on communications with the field investigators. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIRs.

{See appended electronic signature page}

Khairy Malek, M.D.
Good Clinical Practice Branch I
Division of Scientific Investigations

CONCURRENCE:

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Constance Lewin, M.D., M.P.H
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/s/

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Entered in DFS on behalf of Dr. Malek

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4/8/2008 01:28:47 PM
MEDICAL OFFICER

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	November 14, 2007
To:	Dan Shames, MD Acting Director, Division of Gastroenterology Products
Thru:	Todd Bridges, RPh, Team Leader Denise Toyer, PharmD, Deputy Director Carol Holquist, RPh, Director Division of Medication Errors and Technical Support
From:	Tselaine Jones Smith, PharmD, Safety Evaluator Division of Medication Errors and Technical Support
Subject:	Medication Error Label and Labeling Review
Drug Name(s):	Amitiza (Lubiprostone) Capsules
Application Type/Number:	NDA #21-908
Submission Number:	SE1-005
Applicant/sponsor:	Sucampo Pharmaceuticals, Inc.
OSE RCM #:	2007-1634

1 INTRODUCTION

This memorandum is in response to the July 25, 2007, request from the Division of Gastroenterology Products for a review of the proposed labels and labeling of Amitiza submitted under an efficacy supplement that provides for a new 8 mcg capsule strength of Amitiza for an expanded indication of treatment of irritable bowel syndrome with constipation in adults. Amitiza has been marketed since 2006 as a 24 mcg capsule for the treatment of chronic idiopathic constipation in adults. The recommended dose for the treatment of chronic idiopathic constipation in adults is 24 mcg twice daily orally with food and water. The dosage for the expanded indication of irritable bowel syndrome with constipation in adults is 8 mcg twice daily orally with food and water.

2 METHODS AND MATERIALS

2.1 INTRODUCTION

Since Amitiza is currently marketed, DMETS conducted a search of the Agency's Adverse Event Reporting System (AERS) for medication errors associated with the use of Amitiza.

2.2 AERS SELECTION OF CASES

DMETS searched AERS using the established name "lubiprostone", the trade name "Amitiza" and the verbatim term "Amiti%" as well as the MedDRA high level group term "medication error".

2.3 MATERIAL REVIEWED

Container labels, insert and carton labeling submitted to the Agency on June 29, 2007.

3 RESULTS

The AERS search identified two medication error cases associated with the use of Amitiza. In the first case, the "patient punctured the capsules and took only half the contents". The patient reported that the decreased dose did not relieve her constipation. The reporter in the second case states that the patient took two capsules simultaneously. As a result of the overdose, the patient experience severe diarrhea.

4 DISCUSSION

We note that the frequency and way Amitiza 8 mcg is taken (i.e., with food and water) will be the same as the currently marketed Amitiza 24 mcg which will minimize confusion with dosing and administration errors. However, when changes are made to an existing product line, confusion generally occurs upon introduction of the new strength/product into the marketplace, primarily because of healthcare practitioner's lack of awareness of the availability of the new strength/product. Education may help to decrease the lack of knowledge with respect to the new strength and expanded indication of use.

Our review also noted potential failure modes with the current layout/design of the container labels and carton labeling that may contribute to decreased readability and decreased prominence of key product information. The presentation of the proprietary and established names on the sample carton labeling does not include the strength and finished dosage form. The strength and dosage form are separated by graphics on the principal display panel. Practitioners generally look for this information to be presented together because it identifies the important information

needed to select and dispense a drug. We note that the sponsor has presented this important information together on the side panel; however, it is too small to read. If the drug is packaged with the side panel up, practitioners will be unable to read the name of the drug and strength. Keeping this information together on the principal display panel allows less eye movement and increases recognition of this information. The sponsor also includes a bird graphic over the proprietary name, which may visually distract away from the established name, proprietary name and the strength. These graphics are unnecessary and just add clutter to the labels and labeling. A review of the trade container label notes that the net quantity appears as the same color as the strength and is presented in close proximity to the strength. Postmarketing reporting has shown that confusion may occur between the net quantity and strength when the net quantity is presented in close proximity to the strength.

Since it is important for these capsules to be swallowed whole, we are also concerned that the labels and labeling do not include a warning against chewing or puncturing the capsules.

5 CONCLUSIONS

There likely will be confusion surrounding the introduction of the new strength and expanded indication of use unless the sponsor commits to educating health care practitioners about the new strength and indication of use prior to launch and during the first year of actual marketing. Additionally, the following label and labeling revisions should be implemented in order to minimize the anticipated product selection errors and to increase the readability of critical information on the labels and labeling and to provide sufficient product differentiation.

6 RECOMMENDATIONS

6.1 EDUCATIONAL EFFORTS

6.1.1 DMETS recommends that the sponsor implement an educational campaign that informs practitioners of the introduction of the new 8 mcg strength of Amitiza and its indication for the treatment of irritable bowel syndrome with constipation in adults. This educational campaign should begin before introducing this product into the marketplace and should continue for at least one year following marketing.

6.1.2 To increase the awareness of the new strength and indication of use, DMETS recommends that the sponsor include a 'New Strength and New Indication of Use' banner on the container labels and carton labeling. However, we remind you that the "'New Strength and New Indication of Use' banner is only permitted for a period of time not to exceed six months. Additionally, we recommend that the banner appears prominently next to the new strength.

6.2 CONTAINER LABEL (60 COUNT)

6.2.1 Relocate the net quantity away from the strength (e.g., to the bottom of the principal display panel). Additionally, revise the font color of the net quantity so that it is different than the blue color font color of the product strength.

6.3 CARTON LABELING (SAMPLE CARTON)

6.3.1 Revise the established name to include the finished dosage form and relocate the strength to appear immediately following the established name. For example:

amitiza
(lubiprostone) capsules
8 mcg

6.3.2 Increase the font size of the established name, proprietary name, dosage form and strength on the side panel. Additionally, include this information on the other side panel. This will ensure that this important information is always visible regardless of the position of the carton labeling.

6.3.3 Delete the graphic that appears above the proprietary name as this may be a visual distraction away from the proprietary name, the established name and the strength.

6.4 CARTON LABELING (SAMPLE DISPLAY TRAY)

6.4.1 See Comment 6.3.3.

6.4.2 Include "Rx Only" and 'Professional Sample-Not for Sale" statements on the top panel to help ensure that they are not overlooked.

6.5 INSERT LABELING

6.5.1 Dosage and Administration (Highlights of Prescribing Information and Full Prescribing Information)

Comment on whether or not Amitiza capsules may be broken open and sprinkled or chewed.

We would be willing to meet with the Division for further discussion, if needed. DMETS would appreciate feedback of the final outcome of this memorandum. Please copy DMETS on any communication to the sponsor with regard to this review. If you have further questions or need clarifications, please contact Cherye Milburn, Project Manager, at 301-796-2084.

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/s/

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