CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-908

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

EXCLUSIVITY SUMMARY FOR NDA # 21-908 SUPPL # N/A

Trade Name: Amitiza™
Generic Name: Lubiprostone Capsules

Applicant Name: Sucampo Pharmaceuticals, Inc. HFD # HFD-180

Approval Date If Known: January 31, 2006

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES / X / NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /X/

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /_X__/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

---

d) Did the applicant request exclusivity?

YES /___/ NO /X/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /___/ NO /_X__/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /X/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /__X_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES / / NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES / / NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES / / NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO / /

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO / /

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO / /

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO / /

Investigation #2 YES /___/ NO / /

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO / /

Investigation #2 YES /___/ NO / /

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

YES / / NO /___/ Explain: _____

YES / / NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1
YES /___/ Explain _____ NO /___/ Explain _____

Investigation #2
YES /___/ Explain _____ NO /___/ Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO / /

If yes, explain: _____

{See appended electronic signature page}

Tanya Clayton
Regulatory Health Project Manager

Brian E. Harvey, M.D., Ph.D.
Division Director
Division of Gastroenterology Products
Office of New Drug Evaluation III
Center for Drug Evaluation and Research

cc: Original NDA-DFS
HFD-93 Mary Ann Holovac

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

/s/

Tanya Clayton
2/1/2006 10:12:36 AM

Brian Harvey
2/1/2006 11:02:15 AM

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

A # : 21-908 **Supplement Type (e.g. SE5):** N/A **Supplement Number:** N/A

Stamp Date: March 31, 2005 **Action Date:** [redacted]

→ waiting for Actual date Like Fix sign off in DFS

Trade and generic names/dosage form: Amitiza (Lubiprostone, Soft Gelatin Capsules)

Applicant: Sucampo Pharmaceuticals, Inc. **Therapeutic Class:** 1S

Indication(s) previously approved: N/A

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: treatment of chronic idiopathic constipation

Is there a full waiver for this indication (check one)?

☐ **Yes: Please proceed to Section A.**

☒ **No: Please check all that apply:** ____Partial Waiver __X__Deferred ____Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____	kg_____	mo._____	yr._____	Tanner Stage_____
Max_____	kg_____	mo._____	yr._____	Tanner Stage_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____	**kg**_____	**mo.**__0__	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**__11__	**yr.**__17__	**Tanner Stage**_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☒ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): __January 31, 2008_____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

ction D: Completed Studies

Age/weight range of completed studies:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____

Regulatory Project Manager

cc: NDA
HFD-950/Grace Carmouze
(revised 9-24-02) FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-950
301-796-7654

SUCAMPO
PHARMACEUTICALS

SUCAMPO PHARMACEUTICALS, INC.

Debarment Certification Statement

Sucampo Pharmaceuticals, Inc., hereby certifies that it did not, and will not, use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Signature:

Sachiko Kuno, PhD
Chief Executive Officer, Sucampo Pharmaceuticals, Inc.

Jan 25, 2005
Date

NDA ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-908		
Drug: Lubiprostone, 24 mcg (Amitiza™)	Applicant: Sucampo Pharmaceuticals, Inc.	
RPM: Tanya Clayton	HFD-180	Phone 301-796-0871
Application Type: (X) 505(b)(1) () 505(b)(2)	Reference Listed Drug (NDA #, Drug name): N/A	

❖ Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	1
• Other (e.g., orphan, OTC)	N/A
❖ User Fee Goal Date	January 31, 2006
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	(X) Paid -User Fee reimbursed
• User Fee waiver	(X) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	N/A
• OC clearance for approval	N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(X) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(X) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) () (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified

❖ Exclusivity (approvals only)	
• Exclusivity summary	X
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!*	( ) Yes, Application #_____ **(X)** No
❖ Administrative Reviews (Project Manager, June 7, 2005)	X
General Information	
❖ Actions	
• Proposed action	**(X)** AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	**(X)** Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	**(X)** Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	( ) None **(X)** Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	X (January 31, 2006 revision date)
• Most recent applicant-proposed labeling *(January 27, 2006)*	X
• Original applicant-proposed labeling *(March 31, 2005)*	X
• Labeling reviews (Office of Drug Safety trade name review) • *ODS DMETS- (November 18, 2005, December 23, 2005)* • *ODS DDMAC – November 15, 2005*	X
• Other relevant labeling (e.g., most recent 3 in class)	N/A
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed (March 31, 2005 and January 27, 2005)	X
• Reviews DMETS (November 18, 2005 and December 23, 2005); DDMAC (November 15, 2005)	X
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	X
• Documentation of discussions and/or agreements relating to post-marketing commitments	X
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• Pre-NDA meeting (May 24, 2004) •	X
• Filing meeting (May 12, 2005)	X
• Pharmacology/Toxicology, Type A meeting (October 5, 2005)	X
• Pre-Approval Safety Conference	X

❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)-Tentative Final Monograph	N/A
Summary Application Review	
❖ Summary Review (e.g., Office Director, Division Director, Medical Team Leader)	Office Director-January 30, 2006 Division Director- January 30, 2006 Medical Team Leader- January 7, 2006
Clinical Information	
❖ Clinical review (December 19, 2005)	X
❖ Microbiology (efficacy) review (October 5, 2005	X
❖ Safety Update review (included in December 19, 2005 Clinical review)	X
❖ Pediatric Page (separate page for each indication addressing status of all age groups)	X
❖ Demographic Worksheet *(NME approvals only)*	X
❖ Statistical review (December 16, 2005)	X
❖ Biopharmaceutical (January 5, 2006)	X
❖ Controlled Substance Staff review and recommendation for scheduling	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies (November 21, 2005)	X
• Bioequivalence studies	N/A
CMC Information	
❖ CMC reviews (December 5, 2005 and January 26, 2006)	X
❖ Environmental Assessment	
• Categorical Exclusion – In Chemistry review (December 5, 2005)	X
• Review & FONSI	N/A
• Review & Environmental Impact Statement	N/A
❖ Micro (validation of sterilization & product sterility	N/A
❖ Facilities inspection (provide EER report)	X
❖ Methods validation	N/A
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review, including referenced IND reviews (December 23, 2005)	X
❖ Nonclinical inspection review summary	N/A
❖ Statistical review of carcinogenicity studies (November 8, 2005)	X
❖ CAC/ECAC report (December 21, 2005)	X

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

/s/

Tanya Clayton
2/6/2006 02:43:40 PM

Demographic Worksheet

ation Information *(Enter all identifying information for the submission pertaining to this summary)*

NDA Number: 21-908 **Submission Type:** NDA **Serial Number:** 000

Populations Included In Application *(Please provide information for each category listed below from the primary safety database excluding PK studies)*

Category		Number Exposed To Study Drug		Number Exposed To Study Drug		Number Exposed To Study Drug
Gender	Males	152	All Females	1023	Females >50	*
Age:	0-≤1 Mo.	0	>1 Mo.- ≤2Year	0	>2-≤12	0
	12-16	0	17-64	981	≥65	194
Race:	White	1010	Black	95	Asian	11
	Other	59				

Gender-Based Analyses *(Please provide information for each category listed below.)*

Category	Was Analysis Performed?		If no is checked, indicate which applies or provide comment below	
Efficacy	☒ Yes	☐ No	☐ Inadequate #'s	☐ Disease Absent
Safety	☒ Yes	☐ No	☐ Inadequate #'s	☐ Disease Absent

Was gender-based analysis included in labeling?	
Yes	No
☐	☒
☐	☒

Is a dosing modification based on gender recommended in the label? ☐ Yes ☒ No

If the analysis was completed, who performed the analysis ☐ Sponsor ☐ FDA

Age-Based Analyses *(Please provide information for each category listed below)*

ıtegory	Was Analysis Performed?		If no is checked, indicate which applies or provide comment below	
Efficacy	☒ Yes	☐ No	☐ Inadequate #'s	☐ Disease Absent
Safety	☒ Yes	☐ No	☐ Inadequate #'s	☐ Disease Absent

Was age-based analysis included in labeling?	
Yes	No
☐	☒
☐	☒

Is a dosing modification based on age recommended in the label? ☐ Yes ☒ No

If the analysis was completed, who performed the analysis ☐ Sponsor ☐ FDA

Race-Based Analyses *(Please provide information for each category listed below)*

Category	Was Analysis Performed?		If no is checked, indicate which applies or provide comment below	
Efficacy	☒ Yes	☐ No	☐ Inadequate #'s	☐ Disease Absent
Safety	☒ Yes	☐ No	☐ Inadequate #'s	☐ Disease Absent

Was race-based analysis included in labeling?	
Yes	No
☐	☒
☐	☒

Is a dosing modification based on race recommended in the label? ☐ Yes ☒ No

If the analysis was completed, who performed the analysis ☐ Sponsor ☐ FDA

In the comment section below, indicate whether an alternate reason (other than "inadequate numbers" or "disease absent") was provided for why a subgroup analysis was NOT performed, and/or if other subgroups were studied for which the metabolism or excretion of the drug might be altered (including if labeling was modified).

Comment:

*** The sponsor did not perform a subgroup analysis of Females > 50.**

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/s/

Kristen Buck
2/8/2006 03:42:34 PM

Ruyi He
2/8/2006 03:07:42 PM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: January 31, 2006

To: Robert Cormack, Ph.D.	**From:** Tanya D. Clayton, BS Regulatory Project Manager
Company: Sucampo Pharmaceuticals, Inc.	Division of Gastroenterology Products
Fax number: 301-961-3440	**Fax number:** 301-796-9905
Phone number: 301-961-3400	**Phone number:** 301-796-0871

Subject: NDA 21-908 Approval Letter

Total no. of pages including cover: 18

Comments:

Please find attached a copy of the Approval Letter for NDA 21-908, Amitiza, dated January 31, 2006.

Best regards.

Document to be mailed: ☑YES ☐NO

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/s/

Tanya Clayton
1/31/2006 05:16:11 PM
CSO

Sucampo Pharmaceuticals, Inc.
4733 Bethesda Avenue, Suite 450, Bethesda, MD 20814
▸ **Fax: 301-951-3480** ▸ **Phone: 301-961-3400**

To:	Tanya D. Clayton, B.S.
Company:	Division of Gastroenterology Products, CDER, FDA
Fax number:	301-796-9905
From:	Robert S. Cormack, Ph.D., RAC
Date:	31 January 2006
Pages:	1
Subject:	**Acknowledgement of Receipt of NDA Approval Letter**

FACSIMILE

Dear Tanya,

This fax is to inform you that Sucampo Pharmaceuticals, Inc., has received today the FDA Approval Letter for NDA 21-908, dated 31 January 2006.

Sincerely,

Robert S. Cormack, Ph.D., RAC
Regulatory Affairs Manager
Sucampo Pharmaceuticals, Inc.

SUCAMPO PHARMACEUTICALS

SUCAMPO
PHARMACEUTICALS, INC.

4733 BETHESDA AVE. • SUITE 450 • BETHESDA, MD • 20814
TEL 301-961-3400 • FAX 301-961-3440
WWW.SUCAMPO.COM

30 January 2006

NDA 21-908

Brian E. Harvey, M.D., Ph.D.
Director, Division of Gastroenterology Products
Center for Drug Evaluation and Research, FDA
5901-B Ammendale Road
Beltsville, MD 20705

Re: Post-marketing Commitments

Dear Dr. Harvey:

Sucampo is in agreement with all of the proposed AMITIZA™ post-marketing commitments as requested during the 26 January 2006 teleconference and in the facsimile from the Division of Gastroenterology Products.

Specifically, Sucampo agrees to perform the following post-marketing studies with AMITIZA™:

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

   Sucampo agrees to submit the protocol by 31 July 2006.
   Sucampo agrees to start the study by 31 January 2007.
   Sucampo agrees to submit the final report by 31 January 2008.

2. Phase 4 study to assess the need for potential dose adjustment in patients with renal impairment.

   Sucampo agrees to submit the protocol by 31 July 2006.
   Sucampo agrees to start the study by 31 January 2007.
   Sucampo agrees to submit the final report by 31 January 2008.

3. Phase 4 study to assess the need for potential dose adjustment in patients with hepatic impairment.

   Sucampo agrees to submit the protocol by 31 July 2006.
   Sucampo agrees to start the study by 31 January 2007.
   Sucampo agrees to submit the final report by 31 January 2008.

Sincerely,

Sachiko Kuno, Ph.D.
President & C.E.O.
Sucampo Pharmaceuticals, Inc.

R-Tech Ueno, Ltd.
4-1 TECHNO PARK, SANDA
HYOGO 669-1339 JAPAN
TEL 81-795-60-7181
FAX 81-795-60-7180

Sucampo Pharma, Ltd.
SAKURABASHI-TOYO BUILDING 4TH FLOOR
2-2-16 SONEZAKISHINCHI, KITA-KU
OSAKA 530-0002 JAPAN
TEL 81-6-6343-9181
FAX 81-6-6343-0663

Sucampo Pharma Europe, Ltd.
78 CANNON STREET
LONDON, EC4N6NQ, UK
TEL 44-207-618-6479
FAX 44-207-618-8661

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research

DATE: January 27, 2006

FROM: Brian E. Harvey, M.D., Ph.D.
Division Director, DGP/ODE III/OND

TO: Julie G. Beitz, M.D.
Deputy Director, ODE III/OND

SUBJECT: Division Director Concurrence Memo
NDA 21-908

APPLICANT: Sucampo Pharmaceuticals, Inc.

DRUG: Lubiprostone capsules (Amitiza™)

DATE SUBMITTED: March 31, 2005

DIVISION RECOMMENDATION

The primary Medical Officer and Medical Team Leader recommend that NDA 21-908, oral Lubiprostone capsules be approved for the treatment of chronic idiopathic constipation in the adult population. I am in agreement with this recommendation.

I. BACKGROUND:

Lubiprostone is a prostaglandin E_1 metabolite analogue. This drug product for oral administration is formulated in a soft gelatin capsule which also contains a medium-chain fatty acid triglyceride. Lubiprostone is classified as a locally acting chloride channel activator and is known to promote chloride-rich intestinal fluid secretion without altering sodium and potassium concentrations in the serum. It is believed that by increasing intestinal fluid secretion, lubiprostone increases motility in the intestine and therefore increase the passage of stool in those patients with chronic idiopathic constipation.

II. DISCIPLINE REVIEW SUMMARY AND COMMENTARY:

A. OPDRA/DDMAC/DMETS:

The DDMAC consultation concluded that the proprietary name, [redacted] was acceptable from a promotional perspective. However, the DMETS consultation

did not recommend use of the name — In response to their specific concerns, the sponsor submitted a new trade name; "AMITIZA" has been found to be acceptable by DMETS, as well as the clinical team.

Finally, Dr. Khairy Malek from the Division of Scientific Investigations conducted the clinical inspection. His report raised no concerns regarding the data submitted from the four investigational sites in support of this NDA.

B. CHEMISTRY AND MANUFACTURING:

Chemistry Review Team has recommended approval. There are no outstanding chemistry issues based upon their review.

C. PRE-CLINICAL PHARMACOLOGY/TOXICOLOGY:

The primary pharmacology/toxicology reviewer, his direct divisional supervisor, the pharmacology/toxicology consultant from the Division of Reproductive and Urology Products and upper pharmacology/toxicology management had numerous discussions regarding the pre-clinical data submitted in the NDA. The following is the resulting consensus based upon these discussions:

> "***Carcinogenesis:*** Two 2-year oral (gavage) carcinogenicity studies (one in Crl:B6C3F1 mice and one in Sprague-Dawley rats) were conducted with lubiprostone. In the 2-year carcinogenicity study in mice, lubiprostone doses of 25, 75, 200, and 500 mcg/kg/day (approximately 2, 6, 17, and 42 times the recommended human dose, respectively, based on body surface area) were used. In the 2-year rat carcinogenicity study, lubiprostone doses of 20, 100, and 400 mcg/kg/day (approximately 3, 17, and 68 times the recommended human dose, respectively, based on body surface area) were used. In the mouse carcinogenicity study, there was no significant increase in any tumor incidences. There was a significant increase in the incidence of interstitial cell adenoma of the testes in male rats at the 400 mcg/kg/day dose. In female rats, treatment with lubiprostone produced hepatocellular adenoma at the 400 mcg/kg/day dose Lubiprostone was not genotoxic in the in vitro Ames reverse mutation assay, the in vitro mouse lymphoma (L5178Y TK+/–) forward mutation assay, the in vitro Chinese hamster lung (CHL/IU) chromosomal aberration assay, and the in vivo mouse bone marrow micronucleus assay. Lubiprostone, at oral doses of up to 1000 mcg/kg/day, had no effect on the fertility and reproductive function of male and female rats. The 1000 mcg/kg/day dose in rats is approximately 166 times the recommended human dose of 48 mcg/day, based on the body surface area."

> "**Teratogenic Effects: Pregnancy Category C**: Teratology studies with lubiprostone have been conducted in rats at oral doses up to 2000 mcg/kg/day (approximately 332 times the recommended human dose,

based on body surface area), and in rabbits at oral doses of up to 100 mcg/kg/day (approximately 33 times the recommended human dose, based on body surface area). Lubiprostone was not teratogenic in rats and rabbits. In guinea pigs, lubiprostone caused fetal loss at doses of 10 and 25 mcg/kg/day (approximately 2 and 6 times the human dose, respectively, based on body surface area".

D. BIOPHARMACEUTICS:

Based upon the data submitted in the NDA, the review team concluded that lubiprostone is not detectable in plasma, urine or feces following oral administration of a radiolabeled dose of lubiprostone, even at a dose that is 3-fold higher than the proposed daily clinical dose. The mean Cmax and AUC values of M3 (active metabolite) were shown to increase in a dose dependent manner. The mass balance study demonstrated that approximately 2/3 of lubiprostone is excreted by the kidney in urine and 1/3 was found in the feces. The mean elimination half-life in plasma was 3 hours in this study. The data in this NDA supported the existence of a total of 18 lubiprostone metabolites following oral administration.

The findings of their dose-ranging study indicated that the dose of 24 mcg twice daily provided a clinically significant improvement in the primary endpoint, spontaneous bowel movements (SBM) for week 1, over the dose of 24 mcg once daily. In addition, there was a clear dose-related incidence of gastrointestinal adverse events, such as nausea and diarrhea, with lubiprostone administration.

In summary, the review team and their management in the Office of Clinical Pharmacology and Biopharmaceutics, concluded that the sponsor provided adequate Clinical Pharmacology and Biopharmaceutics data in support of the proposed indication.

E. CLINICAL & STATISTICAL:

Both the primary Medical Officer and the Medical Team Leader provided a detailed review and analysis of the clinical data submitted in support of this NDA. Their reviews summarized the data as follows. A total of 1688 subjects, which included 1491 patients with constipation and 197 healthy volunteers, were involved with the clinical development program of lubiprostone. They also stated that there were a total of 606 subjects in the Well-Controlled group cohort (WCG) and 878 subjects in the Long-Term-Safety group cohort (LTS). Following a 2-week baseline/washout period, subjects were randomized to receive 4 weeks of double-blind treatment with either lubiprostone 24 mcg BID or placebo. The primary endpoint of the studies was SBM frequency for Week 1. The sponsor defined an SBM as any bowel movement that did not occur within 24 hours of rescue medication use. The data demonstrated that subjects treated with lubiprostone had a higher frequency of SBMs during Week 1 than the placebo

subjects. In both studies, higher frequency of SBMs in the treatment group was also observed in Weeks 2, 3 and 4 of therapy. In both studies, the median SBM frequency rates in the treatment group for Weeks 1, 2, 3, and 4 were higher than that in the placebo group. These differences between the two groups were statistically significant at Weeks 1 – 4 in both studies.

The primary Medical Officer and the Medical Team Leader summarized the safety data as follows. There were a total of 1688 subjects treated in the overall safety population of which 1321 received active treatment and 367 received placebo. Of the 1321 subjects who received treatment, 1119 received lubiprostone 48 mcg daily, while 494 subjects remained on lubiprostone 48 mcg daily at 24 weeks trial duration and 221 subjects remained on lubiprostone at a dose of 48 mcg daily for the 48 weeks trial duration.

The medical review team reported that no subjects died during the treatment period or follow-up period for any of the studies included in this NDA, and that the occurrence of serious adverse events in the studied population was relatively low. Among all of the actively treated subjects (N=1175), the most commonly reported adverse events were nausea (30.9%), diarrhea (13.2%), headache (13.0%), abdominal distension (6.8%), abdominal pain (6.8%), and flatulence (5.9%). There were no significant abnormalities noted in the clinical and laboratory data presented in this NDA. There was no evidence that lubiprostone had an effect on heart rate, cardiac conduction, cardiac repolarization, or ECG morphologies.

Although pregnant women were excluded from all clinical trials of lubiprostone, 4 pregnancies were reported in the NDA database. In all 4 cases, lubiprostone was discontinued upon detection of the pregnancy. Two of the women were reported to have had healthy babies, one had an uneventful pregnancy while being monitored, but was lost to follow-up one month post-discontinuation and fourth patient delivered a baby with bilateral club feet.

F. PEDIATRIC USE:

The medical team leader stated that the safety and effectiveness of lubiprostone in the pediatric population has not been evaluated and recommended that the sponsor conduct a PK and/or a safety and efficacy study of lubiprostone in the pediatric population as a post- marketing study commitment. The sponsor requested, and was granted a deferral of pediatric studies and has agreed to submit a pediatric development plan.

G. REPRODUCTIVE CONSULTATION:

The consult obtained by the review team from the Division of Reproductive and Urology Products, contained input from both the pharmacology/toxicology and medical officer consultants in that division. This consult concluded the following:

"While lubiprostone may have played a role in the abortions observed in guinea pigs and monkeys, the data is not conclusive. In guinea pigs the abortions could have been related to maternal toxicity, and the single abortion and early deliveries in monkeys are within historical control limits and could have been spontaneous. In vitro pharmacology data would indicate that when compared to natural prostaglandins and misoprostol, lubiprostone has only weak agonist activity in guinea pig ileum smooth muscle. The only definitive study would be a comparison of lubiprostone with a know abortifacient...It is my recommendation that all reproductive data generated in the rat, rabbit, guinea pig [redacted] be included in labeling, [redacted] Other drugs which cause fetal death but do not cause teratogenicity are generally labeled under Pregnancy Category C, and not recommended for use in pregnant women".

III. SUMMARY

The studies demonstrated that subjects treated with lubiprostone had a higher frequency of SBMs during Week 1 than the placebo subjects that were both statistically and clinically significant. In both studies, results similar to those in Week 1 were also observed in Weeks 2, 3 and 4 of therapy. The occurrence of serious adverse events in the studied population was relatively low and the majority of these side effects were mild and of short duration.

IV. RECOMMENDATIONS FOR REGULATORY ACTIONS

I concur that this NDA 21-908 for oral Lubiprostone capsules should be approved for the treatment of chronic idiopathic constipation in the adult population. I agree with the review team that as a post-marketing study commitment, the sponsor needs to conduct a PK and/or a safety and efficacy study of lubiprostone in the pediatric population. In addition, the sponsor needs to perform a Phase IV study to assess the need for potential dose adjustment in subjects with renal and hepatic impairments.

Since the safety of lubiprostone in pregnancy has not been evaluated in humans and lubiprostone has been shown to have the potential to cause fetal loss in animal studies, I agree with the final review team recommendation that this product be Pregnancy Category C.

IV. Labeling Recommendations:

The proposed changes to the product label have been outlined in both the primary Medical Officer review and the Medical Officer Team Leader memo. After discussions

with the sponsor and the review team, I concur with the negotiated label as attached to the approval letter for this NDA 21-908.

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Brian Harvey
1/30/2006 04:24:00 PM
MEDICAL OFFICER

Sucampo Pharmaceuticals, Inc.
4733 Bethesda Avenue, Suite 450, Bethesda, MD 20814
▸ **Fax: 301-951-3480** ▸ **Phone: 301-961-3400**

To:	Tanya D. Clayton, B.S.
Company:	Division of Gastroenterology Products, CDER, FDA
Fax number:	301-796-9905

From:	Robert S. Cormack, Ph.D., RAC
Date:	27 January 2006
Pages:	3 (including cover sheet)
Subject:	**Final Package Labeling**

FACSIMILE

Tanya,

Here is the letter stating Sucampo's agreement to make changes to the final package labeling as requested by the FDA. A formal eCTD submission to the NDA will follow next week.

Regards,

Robert

SUCAMPO PHARMACEUTICALS

SUCAMPO
PHARMACEUTICALS, INC.
4733 BETHESDA AVE. • SUITE 450 • BETHESDA, MD • 20814
TEL 301-961-3400 • FAX 301-961-3440
WWW.SUCAMPO.COM

27 January 2006

NDA 21-908

Tanya D. Clayton, B.S.
Regulatory Project Manager
Division of Gastroenterology Products
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705

Re: Revision to Final Carton and Container Labels
Lubiprostone (SPI-0211; RU-0211) Capsules (Amitiza)

Dear Ms. Clayton:

Please find below our response to the Division's request dated 27 January 2006 in regards to the final carton and container labels for Amitiza (lubiprostone) capsules.

Request #1:

Response:

Request #2:

Increase the prominence (*i.e.*, font size) of the product strength commensurate with the proprietary and established name.

Response:

The prominence of the font for product strength, *i.e.*, 24 mcg, was increased in all instances in accordance with the request. The color of the text was also changed from white to green.

R-Tech Ueno, Ltd.
4-1 TECHNO PARK, SANDA
HYOGO 669-1339 JAPAN
TEL 81-795-60-7181
FAX 81-795-60-7180

Sucampo Pharma, Ltd.
SAKURABASHI-TOYO BUILDING 4TH FLOOR
2-2-16 SONEZAKISHINCHI, KITA-KU
OSAKA 530-0002 JAPAN
TEL 81-6-6343-9181
FAX 81-6-6343-0663

Sucampo Pharma Europe, Ltd.
78 CANNON STREET
LONDON, EC4N6NQ, UK
TEL 44-207-618-6479
FAX 44-207-618-8661

Request #3:

Include a "Usual Dosage" statement. (for the 100 count container).

Response:

The following text was added to the 100-count container label: " "

In addition to the above revisions, the following text was added to the container label, carton, and display tray: " This text was deemed acceptable by the Agency as communicated in an e-mail message dated 27 January 2006.

Sincerely,

Robert S. Cormack, Ph.D., RAC
Regulatory Affairs Manager
Sucampo Pharmaceuticals, Inc.
Tel: 301-961-3400, ext. 163
Fax: 301-951-3480
E-mail: r.cormack@sucampo.com

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: January 25, 2006

To: Robert Cormack, Ph.D.	**From:** Tanya D. Clayton, BS Regulatory Project Manager
Company: Sucampo Pharmaceuticals, Inc.	Division of Gastroenterology Products
Fax number: 301-961-3440	**Fax number:** 301-796-9905
Phone number: 301-961-3400	**Phone number:** 301-796-0871

Subject: NDA 21-908

Total no. of pages including cover: 2

Comments:

Please find attached a list of the Postmarketing Commitments as requested in today's teleconference. Please respond by submitting a formal submission to the NDA stating your commitment to these commitments.

Best regards.

Document to be mailed: ☐YES ☑NO

Your Postmarketing Commitments include the following:

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

   Final Report Submission: January 31, 2008

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

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

3. Perform a Phase IV study to assess the need for potential dose adjustment in patients with hepatic impairment.

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

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

/s/

Tanya Clayton
1/31/2006 05:05:03 PM
CSO

****
*** TX REPORT ***
****

TRANSMISSION OK

TX/RX NO	0574
RECIPIENT ADDRESS	93019613440
DESTINATION ID	
ST. TIME	01/24 16:24
TIME USE	00'20
PAGES SENT	2
RESULT	OK

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: January 24, 2006

To: Robert Cormack, Ph.D.	**From:** Tanya D. Clayton, BS Regulatory Project Manager
Company: Sucampo Pharmaceuticals, Inc.	Division of Gastroenterology Products
Fax number: 301-961-3440	**Fax number:** 301-796-9905
Phone number: 301-961-3400	**Phone number:** 301-796-0871

Subject: NDA 21-908

Total no. of pages including cover: 2

Comments:

Please find attached the response regarding your proposed container labels.

Document to be mailed: ☐YES ☑NO

Please make the following change regarding your Package labeling submitted 01/23/06:

For the three markups, including final art for Amitiza™ 24 mcg/100 count, Amitiza™ display tray and Amitiza™ carton, the USAN name lubiprostone should be in parenthesis, capsules should be next to it. The strength, 24 mcg, can follow one line under as shown below:

Amitiza™
(lubiprostone) Capsules
24 mcg

****
*** TX REPORT ***
****

TRANSMISSION OK

TX/RX NO	0573
RECIPIENT ADDRESS	93019613440
DESTINATION ID	
ST. TIME	01/24 16:11
TIME USE	02'16
PAGES SENT	16
RESULT	OK

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: January 24, 2006

To: Robert Cormack, Ph.D.	**From:** Tanya D. Clayton, BS Regulatory Project Manager
Company: Sucampo Pharmaceuticals, Inc.	Division of Gastroenterology Products
Fax number: 301-961-3440	**Fax number:** 301-796-9905
Phone number: 301-961-3400	**Phone number:** 301-796-0871

Subject: NDA 21-908

Total no. of pages including cover: 15

Comments:

Please find attached a list of labeling request as well as a copy of the revised draft label dated 1.24.06. This draft includes our response to your proposed revisions.

Best regards.

Document to be mailed: ☐YES ☑NO

Please address the following regarding your Package Insert:

- Throughout the label, please adjust your medical abbreviations to "BID" and "TID".
- Replace "subjects" with "patients" throughout the clinical sections.
- Please provide clarification of 1429 patients as mentioned within the label.

Appears This Way
On Original

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; White Oak 22, Mail Stop 4447)

DATE RECEIVED:	**DESIRED COMPLETION DATE:**	**ODS CONSULT #:** 05-0134-1
November 30, 2005	December 30, 2005	
DATE OF DOCUMENT:	**PDUFA DATE:** January 31, 2006	
November 28, 2005		

TO: Brian Harvey, MD, PhD.
Director, Division of Gastroenterology Products
HFD-180

FROM: Todd D. Bridges, R.Ph., Safety Evaluator
Division of Medication Errors and Technical Support

THROUGH: Kristina Arnwine, Pharm.D., Acting Team Leader
Denise Toyer, Pharm.D., Deputy Director
Carol Holquist, R.Ph., Director
Division of Medication Errors and Technical Support

PRODUCT NAME:	**NDA SPONSOR:** Sucampo Pharmaceuticals, Inc.
ıitiza™ .ubiprostone Capsules) 24 mcg **NDA#:** 21-908	

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, Amitiza™. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.

2. DMETS recommends implementation of the label and labeling revisions outlined in Section III of this review in order to minimize potential errors with the use of this product.

3. DDMAC finds the proprietary name, Amitiza™, acceptable from a promotional perspective.

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; White Oak 22, Mail Stop 4447
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: December 8, 2005

NDA#: 21-908

NAME OF DRUG: Amitiza™
(Lubiprostone Capsules)
24 mcg

NDA HOLDER: Sucampo Pharmaceuticals, Inc.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Gastroenterology Products (HFD-180), for assessment of the proprietary name, Amitiza™, regarding potential name confusion with other proprietary or established drug names. Amitiza™ is the second name submitted for this NDA. The sponsor initially submitted the proprietary name, [redacted], which was reviewed by DMETS (see ODS Consult # 05-0134, dated June 23, 2005) and found unacceptable. DMETS did not recommend use of the proprietary name, [redacted], due to its potential look-alike and/or sound-alike similarities to [redacted]. Package insert labeling was provided and re-reviewed. Additionally, DMETS notes that the container label, carton, and insert labeling recommendations made in ODS Consult # 05-0134, dated June 23, 2005, were not forwarded to the sponsor in the discipline review letter dated November 22, 2005. Thus, those recommendations are restated in Section III of this review.

PRODUCT INFORMATION

Amitiza™ is a locally acting chloride channel activator that enhances a chloride-rich intestinal fluid secretion without altering sodium and potassium concentrations in the serum. Amitiza™ is indicated for [redacted] chronic idiopathic constipation [redacted]. This medication is supplied as 24 mcg capsules which are orally administered twice a day, for a total daily dose of 48 mcg. Amitiza™ is available in bottles of 100 capsules.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2], as well as several FDA databases[3] for existing drug names which sound-alike or look-alike to Amitiza™ to a degree where potential confusion between drug names could occur

[1] MICROMEDEX Integrated Index, 2005, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.
[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.
[3] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, and the electronic online version of the FDA Orange Book.

under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[4]. The Saegis[5] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, Amitiza. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proposed proprietary name, Amitiza, acceptable from a promotional perspective.

2. The Expert Panel identified two proprietary names that were thought to have the potential for confusion with Amitiza. These products are listed in Table 1 (see below), along with the dosage forms available and usual dosage.

Table 1: Potential Look-Alike Names Identified by DMETS Expert Panel

Product Name	Established name, Dosage form(s)	Usual adult dose*	Other*
Amitiza	Lubiprostone Capsules: 24 mcg	One capsule twice a day.	N/A
Avinza	Morphine Sulfate Capsules: 30 mg, 60 mg, 90 mg, and 120 mg.	Individualized dose administered once daily.	LA
Antizol	Fomepizole Injection: 1 gram/mL.	Administer a loading dose of 15 mg/kg, followed by doses of 10 mg/kg every 12 hours for 4 doses, then 15 mg/kg every 12 hours thereafter until ethylene glycol or methanol concentrations are undetectable or have been reduced to < 20 mg/dL, and the patient is asymptomatic with normal pH. Administer all doses as a slow IV infusion over 30 minutes.	LA
*Frequently used, not all-inclusive. **LA (look-alike).			

[4] WWW location http://www.uspto.gov/tmdb/index.html.

[5] Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

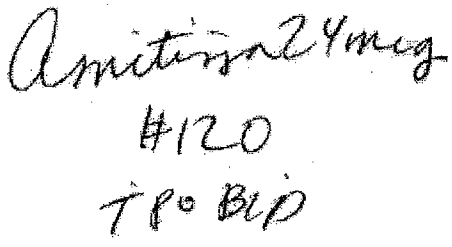
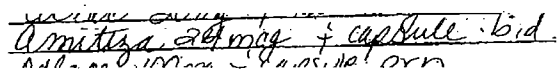
B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to Amitiza were discussed by the Expert Panel (EPD).

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Amitiza with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 119 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Amitiza (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: 	Amitiza 24 mcg #120 Take one capsule twice a day.
Inpatient RX: 	

2. Results:

None of the interpretations of the proposed name overlap, sound similar, or look similar to any currently marketed U.S. product. See Appendix A (page 9) for the complete listing of interpretations from the verbal and written studies.

D. SAFETY EVALUATOR RISK ASSESSMENT

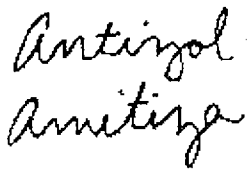
In reviewing the proprietary name Amitiza, the primary concerns related to look-alike confusion with Avinza and Antizol.

Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with any of the aforementioned names. However, negative findings are not predictive as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Amitiza.

1. Avinza may look similar to Amitiza when written (see below). Avinza capsules are a modified-release formulation of morphine sulfate intended for once daily administration. Avinza is indicated for the relief of moderate to severe pain requiring continuous, around-the-clock, opioid therapy for an extended period of time. Avinza is supplied as 30 mg, 60 mg, 90 mg, and 120 mg capsules in bottles of 100. The usual dose of Avinza is patient specific and must be limited to a maximum of 1600 mg/day. Both names begin with the letter "A-" and end with the letters "-za" which contributes to the look-alike similarity between the two names. The third letter of each name (-i-) is also the same. However, the upstroke letter "t" of Amitiza may help to distinguish the name from Avinza. Also, because Avinza is supplied in multiple strengths (30 mg, 60 mg, 90 mg, and 120 mg), a strength would need to be indicated on a prescription prior to filling and dispensing the medication, unlike Amitiza, which is available in only one strength (24 mcg). Thus, the necessity of a strength on Avinza prescriptions may help to differentiate the two drug names. Furthermore, the dosage of Avinza is patient specific while the usual dosage of Amitiza (one capsule twice daily) is invariant and thus, the patient specific dosage of Avinza indicated on a prescription may lessen any confusion stemming from look-alike similarities involving this name pair. Moreover, these products have a differing frequency of administration (once daily vs. twice daily). The dosing frequency, which will likely be indicated on a prescription, may help to distinguish Avinza from Amitiza. These products also differ in indication for use (pain vs. constipation) and unit of measure (mg vs. mcg). The lack of convincing look-alike similarities between these names, in addition to differences in strength and dosing regimen, minimize DMETS concerns regarding the potential for confusion and error between these two products.

Avinza
Amitiza

2. Antizol may look similar to Amitiza when written (see below). Antizol is indicated as an antidote for ethylene glycol (e.g., antifreeze) or methanol poisoning, or for use in suspected ethylene glycol or methanol ingestion, either alone or in combination with hemodialysis. Antizol, approved in 1997 as an orphan drug, is supplied in vials containing 1.5 mL (1 gram/mL) of preservative-free Fomepizole solution. The orthographic similarity stems from the fact that both names begin with the letter "A" and share the letter combination "tiz". Although the letter "n" in Antizol may look similar to the letter "m" in Amitiza when scripted, the letter "i" which follows the letter "m" in Amitiza and the upstroke letter "l" in Antizol may help to differentiate these product names on an order. Furthermore, Antizol has a unique context of use compared to Amitiza in that Antizol is not dispensed directly to patients and is only administered in an emergency room, intensive care unit or similar setting. Additionally, a prescriber may order Amitiza with "as directed" for the directions of use while an order for Antizol, which is dosed based upon patient weight, will likely include the route of administration (IV infusion) and a patient specific dose based on the patient's weight. This indication of an individualized dosing and route of administration on an order may help to differentiate these names from one another. Furthermore, the duration of therapy for Antizol, unlike Amitiza, will be based on lab results (e.g., ethylene glycol/ methanol concentrations and pH level). Thus, an order for Antizol will likely indicate how frequently blood is to be drawn in order to measure the serum ethylene glycol/methanol level and endpoints at which the medication is to be discontinued (e.g., pH, ethylene glycol/methanol levels every 12 hours. XX mg via IV infusion over 30 minutes every 12 hours *until pH level is normal and ethylene glycol/methanol concentration has been reduced to < 20 mg/dL).* The specification of how frequently blood is to be collected and when to discontinue Antizol will aid in distinguishing this name pair on an order. Moreover, these products differ with respect to indication for use (ethylene glycol or methanol poisoning vs. constipation), unit of measure (mg vs. mcg), duration of treatment (acute vs. chronic), dosage form (solution for injection vs. capsule), route of administration (intravenous vs. oral), and strength (1 gram/mL vs. 24 mcg). DMETS believes that the aforementioned product differences in combination with the patient specific dosing will minimize the risk of confusion and error due to look-alike similarities between Antizol and Amitiza.



III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container labels, carton and insert labeling of Amitiza, DMETS has attempted to focus on safety issues relating to possible medication errors. Additionally, DMETS notes that the container label, carton, and insert labeling recommendations made in ODS Consult # 05-0134, dated June 23, 2005, were not forwarded to the sponsor in the discipline review letter dated November 22, 2005. Thus, those recommendations are restated below. DMETS has identified the following areas of possible improvement, in the interest of minimizing potential user error and patient safety.

A. GENERAL COMMENTS

1. Ensure that the established name is at least ½ the size of the proprietary name and that it appears prominently in accordance with CFR 21 201.10(g)(2).

2. Avoid the use of abbreviations and acronyms (e.g., SBMs, q.d., b.i.d., t.i.d., etc.) throughout the labeling. As evidenced by our post-marketing surveillance, abbreviations and acronyms may be misinterpreted. We note that the Joint Commission for Accreditation of Hospitals (JCAHO), 2006 Hospitals National Patient Safety Goals includes the goal: Improve the effectiveness of communication among caregivers. A requirement to meet this goal is that each hospital must 'Standardize a list of abbreviations, acronyms and symbols that are not to be used throughout the organization'. The abbreviation "q.d." is specifically listed as a dangerous abbreviation, acronym or symbol. Additionally, the Institute for Safe Medication Practices also publishes an "ISMP List of Error-Prone Abbreviations, Symbols, and Dose Designations" in which they also recommend avoiding the use of the abbreviation "q.d." Postmarketing experience has shown that "q.d." (once daily) may be confused with "q.i.d." (four times daily), especially if the period after the letter "q" or the tail of the letter "q" is misinterpreted as the letter "i". Revise accordingly (i.e., "q.d." to read daily, "SBMs" to read spontaneous bowel movements, etc.).

B. CONTAINER (100 count)

1. See GENERAL COMMENT A1.

2. Include a "Usual Dose" statement.

3. Sucampo Pharmaceuticals, Inc., and Takeda Pharmaceuticals America, Inc., appear on the container label as marketers of this product. Revise labeling to meet the requirements of 21 CFR 201.1, with regard to name and place of business of manufacturer, packer, or distributor.

C. CONTAINER LABEL (Professional Sample Blister 6 count)

The proposed proprietary and established names and strength are difficult to read as currently presented. DMETS recommends increasing the prominence of this information. In order to provide additional space on the blister, DMETS recommends listing only one name (e.g., manufacturer, distributor, etc) on the blister.

D. CARTON LABELING (Sample Carton)

See GENERAL COMMENT A1.

E. CARTON LABELING (Display Tray)

1. See GENERAL COMMENTS A1, B2, and B3.

2. DMETS notes inconsistency in the presentation of the dosage form. Both ' 'capsule' are included in this draft presentation. Revise to provide consistency with the supplied dosage form (capsule).

F. INSERT LABELING

1. See GENERAL COMMENT A2.

2. Precautions Section

The information found in the Precautions, Patient Information subsection should be repeated at the end of the insert labeling in accordance with 21 CFR.57(f)(2).

3. Dosage and Administration

a. After the recommended dosage statement, include a statement about the effect of food on Lubiprostone (e.g., "Amitiza may be taken with or without food.").

b.

Appendix A:

Inpatient Written	Voice	Outpatient Written
Amiteza	Amateeza	Amiti(n?)a
Amiteza	Amateeza	Amitina
Amiteza	Amatesa	Amitirza
Amiteza	Amatesa	Amitison
Amiteza	Amateza	Amitisyn
Amiteza	Amateza	Amitisyn
Amitiza	Amatiza	Amitisyn
Amitiza	Amatiza	Amitiza
Amitiza	Amitaza	Amitiza
Amitiza	Amitesa	Amitiza
Amitiza	Amitesa	Amitiza
Amitiza	Amitisa	Amitiza
Amitiza	Amitisa	Amitizin
Amitiza	Amitiza	Amitizon
Amitiza	Amitiza	Amitrizan
Amitiza	Amitrex	Antimina
Amittiza		
AMITTZA		
Amittza		

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/s/

Todd Bridges
12/23/2005 12:52:29 PM
DRUG SAFETY OFFICE REVIEWER

Kristina Arnwine
12/23/2005 12:55:21 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
12/23/2005 01:10:59 PM
DRUG SAFETY OFFICE REVIEWER

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: December 23, 2005

To: Robert Cormack, Ph.D.	**From:** Tanya D. Clayton, BS Regulatory Health Project Manager
Company: Sucampo Pharmaceuticals	Division of Gastrointestinal and Coagulation Drug Products
Fax number: 301-961-3440	**Fax number:** 301-443-9285
Phone number: 301-961-3400	**Phone number:** 301-827-4005

Subject: NDA 21-908
Information Request

Total no. of pages including cover: 2

Comments:

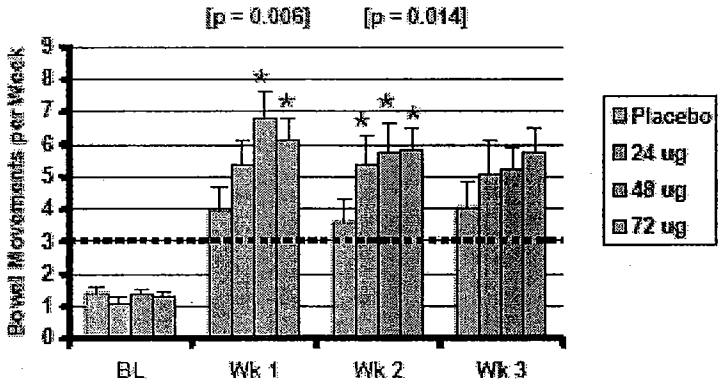
Please find the following information request pertaining to the NDA mentioned above.

Document to be mailed: YES √NO

Information Request

Please provide the following information:

- A revised version of the graph depicting the dose/response relationship following administration of varying regimens of lubiprostone in the dose-finding Phase 2b study (study SC9921). We would like you to reconstruct the dose/response graph using median response values instead of mean response values.



- Please revise and submit the graph as (24 mcg q.d./ 24 mcg b.i.d./ and 24 mcg t.i.d.) instead of the total cumulative doses.

- Please heighten the ordinate axis (y-axis) to help the reviewers better visualize the differences.

Appears This Way
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/s/

Tanya Clayton
1/10/2006 06:07:08 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Dan A. Morton, M.D.
Gastroenterology Associates of North Texas
1201 Summit, Suite 500
Fort Worth, TX 76102

Dear Dr. Morton:

Between September 19 and 23, 2005, Mr. Stephen Beekman, representing the Food and Drug Administration (FDA), conducted an investigation to review your conduct of a clinical investigation (protocol # SC0131 entitled: "Multi-Center, Double-Blind, Randomized, Placebo-Controlled Phase III Study of the Efficacy and Safety of Oral RU-0211 for the Treatment of Occasional Constipation") of the investigational drug (lubiprostone, RU-0211), performed for Sucampo Pharmaceuticals. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Beekman during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

{See appended electronic signature page}

Ni A. Khin, M.D.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

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/s/

Ni Aye Khin
12/23/2005 03:24:11 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Robert Holmes, M.D.
Piedmont Medical Research Associates
1901 S. Hawthorne Road, Suite 306
Winston-Salem, NC 27103

Dear Dr. Holmes:

Between September 6 and 9, 2005, Ms. Michelle Haamid, representing the Food and Drug Administration (FDA), conducted an investigation to review your conduct of a clinical investigation (protocol # SC0232 entitled: "Multi-Center, Double-Blind, Randomized, Placebo-Controlled Phase III Study of the Efficacy and Safety of Oral RU-0211 for the Treatment of Occasional Constipation" of the investigational drug (lubiprostone), performed for Sucampo Pharmaceuticals. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We are aware that at the conclusion of the inspection, Ms. Haamid presented and discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

You did not prepare and maintain adequate case histories that record all observations and other data pertinent to the investigation [21 CFR 312.62(b)].

> For 15 subjects (# 701-715) enrolled in the study, respiration rate for each of these subjects was recorded as 16 per minute for visits 1, 2, 3 and 5, except for subject #707 at visit 3.
>
> We note that during the inspection, you stated that respiration rates were taken by listening to the subject's respiration for 15 seconds; then the number was multiplied by 4 to obtain total number of respiration per minute.

We request that you inform this office, in writing, of the actions you have taken or plan to take in your procedures so that the finding noted above is not repeated in any ongoing or future studies.

We appreciate the cooperation shown Investigator Haamid during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact

me by letter at the address given below.

Sincerely,

{See appended electronic signature page}

Ni A. Khin, M.D.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

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/s/

Ni Aye Khin
12/21/2005 06:59:19 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

John F. Johanson, M.D., MSc
401 Roxbury Road
Rockford, IL 61107

Dear Dr. Johnson:

Between September 28 and October 5, 2005, Ms. Lisa Hayka, representing the Food and Drug Administration (FDA), conducted an investigation to review your conduct of a clinical investigation (protocol # SC0131 entitled: "Multi-Center, Randomized, Placebo-Controlled Phase III Study of the Efficacy and Safety of Oral RU-0211 for the Treatment of Occasional Constipation") of the investigational drug (lubiprostone, RU-0211), performed for Sucampo Pharmaceuticals. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We are aware that at the conclusion of the inspection, Ms. Hayka discussed with you inspectional observations. We wish to emphasize the following:

1. You did not ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].

    a. Two subjects (#120 and 124) took an enema, a prohibited medication in the Week 1 of the Treatment period.

    b. Three subjects did not have complete physical exams at Visit 1 in that # 0103 and 0124 did not have their neurological and muscloskeletal exams while # 0107 did not have neurological, muscloskeletal and EENT examinations.

    c. Laboratory reports of three subjects (# 0101, 0104 and 0106) did not appear to have been reviewed by the Investigator until 5-7 weeks after randomization and the lab reports of subject 0118 was not reviewed prior to randomization.

2. You did not prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation [21 CFR 312.62(b)].

    In the final report to the IRB, the site reported that two subjects dropped out of the study, one for lack of efficacy and the other for family problems. The Case Report Forms (CRFs) show

that subject #0111 dropped out of the study for lack of efficacy and subject #0118 for adverse events (nausea and vomiting).

Please make appropriate corrections in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies.

We appreciate the cooperation shown Investigator Hayka during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

{See appended electronic signature page}

Ni A. Khin, M.D.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

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/s/

Ni Aye Khin
12/14/2005 10:46:06 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-908

DISCIPLINE REVIEW LETTER

Sucampo Pharmaceuticals, Inc.
Attention: Robert S. Cormack, Ph.D., RAC
Regulatory Affairs Manager
4733 Bethesda Ave, Suite 450
Bethesda, MD 20814

Dear Dr. Cormack:

Please refer to your March 31, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lubiprostone.

Our review of the Chemistry, Manufacturing and Controls section of your submission is complete, and we have identified the following deficiencies:

1. For the Drug Product, the deficiencies for DMF — must be resolved before this NDA can be approved.
2. For the Drug Substance, the deficiencies for DMF — must be resolved before this NDA can be approved.
3. Provide data to justify that — of the fill weight is needed for 24 mcg/ — Capsules.
4. You should commit to reporting to the Agency any changes in MCT (e.g. changes in vendor or grade of MCT) via prior approval supplements and provide comparable —

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the Prescription Drug User Fee Reauthorization Agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the User Fee Reauthorization Agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Tanya Clayton, B.S., Regulatory Health Project Manager, at (301) 796-0871.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Chief, Branch III
Pre-Marketing Quality Assessment Division II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Moo-Jhong Rhee
12/9/2005 04:50:17 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO (Division/Office):	FROM:
Scott Dallas and Diane Smith, White Oak Rm 4421	Tanya Clayton, Regulatory Health Project Manager White Oak, Rm 5103

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
November 29, 2005		21-908	Tradename Review	November 28, 2005

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Lubiprostone	High	Laxative	December 30, 2005

NAME OF FIRM: — (Sucampo Pharmaceuticals, Inc.)

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE–NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: See comments below.

COMMENTS/SPECIAL INSTRUCTIONS:

This is a type 1New Drug Application that is indicated for the treatment of chronic idiopathic constipation — The sponsor is previously proposed — as the tradename. Your November 18, 2005 review denied — as the tradename. Consequently, the firm is now proposing Amitiza or — as the proposed tradename. The PDUFA goal date is 01/31/06. Please note that this application was submitted electronically, consequently, it may be found on the EDR pathway – N 21908/31March2005 . I'm attaching a copy of the email forwarded by the firm. The official copy should arrive early next week. Please let me know if you require additional information. Thank you in advance.

Tanya Clayton – 301-796-0871.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☒ MAIL (e-mail) ☐HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

Dear Tanya,

In light of DMETS disapproval of the proposed proprietary name for lubiprostone capsules — , Sucampo intends to submit the following new trade name and back-up trade name to the FDA:

proposed proprietary name is AMITIZA, pronounced am-i-'tE-za. The proposed back-up proprietary name is —

These proposed proprietary names will be formally submitted to NDA 21-908, along with supporting background research material. The submission, Instance 0008, is expected to be prepared by the end of this week. In the meantime, please forward Amitiza — to the appropriate Project Manager at DMETS for consideration.

Warm Regards,

> Robert S. Cormack, Ph.D., RAC
> Regulatory Affairs Manager
> Sucampo Pharmaceuticals, Inc.
> 4733 Bethesda Avenue, Suite 450
> Bethesda, MD 20814
> 301-961-3400 ext. 163

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/s/

Tanya Clayton
11/29/2005 02:01:31 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-908

DISCIPLINE REVIEW LETTER

Sucampo Pharmaceuticals, Inc.
Attention: Robert S. Cormack, Ph.D.
4733 Bethesda Ave, Suite 450
Bethesda, MD 20814

Dear Dr. Cormack:

Please refer to your March 31, 2005, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lubiprostone Capsules.

Our review of your proposed tradename submitted March 31, 2005, under NDA 21-908 is complete, and we have the following comments:

We do not recommend use of the proposed proprietary name, — The name chosen has sound-alike and look-alike similarities to — The name also has look-alike similarity to — . Please consider proposing an alternate proprietary name and submitting it to NDA 21-908.

We recommend that you submit another proprietary name to the Agency for review.

If you have any questions, call Tanya Clayton, Regulatory Health Project Manager, at (301) 796-0871.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Brian Strongin
11/22/2005 01:31:40 PM

22 Page(s) Withheld

____ § 552(b)(4) Trade Secret / Confidential

___✓ § 552(b)(5) Deliberative Process

____ § 552(b)(4) Draft Labeling

Department of Health and Human Services Public Health Service
Food and Drug Administration
Rockville, MD 20857

OCT 31 2005

Robert S. Cormack, Ph.D.
Regulatory Affairs Manager
Sucampo Pharmaceuticals, Inc.
4733 Bethesda Avenue, Suite 450
Bethesda, MD 20814

RE: Sucampo Pharmaceuticals, Inc., Small Business Waiver Request 2005.050, NDA 21-908, — (lubiprostone)

Dear Dr. Cormack:

This responds to your July 21, 2005, letter requesting a waiver and refund of the human drug application fee for new drug application (NDA) 21-908, — (lubiprostone), under the small business waiver provision, section 736(d)(1)(D)[1] of the Federal Food, Drug, and Cosmetic Act (the Act) (Waiver Request 2005.050). For the reasons described below, the Food and Drug Administration (FDA) grants the Sucampo Pharmaceuticals, Inc. (Sucampo) request for a small business waiver of the application fee for NDA 21-908, — (lubiprostone).

According to your letter, you certify that Sucampo is a small business submitting its first human drug application to the FDA for review. You note that Sucampo submitted its first NDA 21-908 for — on March 31, 2005, and paid the application user fee of $672,000 (UFID # 3006034) at the same time. The application was submitted under section 505(b)(1) of the Act and required clinical data for approval. You did not identify any affiliates of Sucampo.

Under section 736(d)(3) of the Act,[2] a waiver of the application fee is granted to a small business for the first human drug application that it or its affiliate[3] submits to the FDA for review. The small business waiver provision entitles a small business to a waiver when the business meets the following criteria: (1) the business must employ fewer than 500 persons, including employees of its affiliates, and (2) the marketing application must be the first human drug application, within the meaning of the Act, that a company or its affiliate submits to FDA.

---

[1] 21 U.S.C. 379h(d)(1)(D).
[2] 21 U.S.C. 379h(d)(3).
[3] "The term 'affiliate' means a business entity that has a relationship with a second business entity if, directly or indirectly — (A) one business entity controls, or has the power to control, the other business entity; or (B) a third party controls, or has the power to control, both of the business entities" (21 U.S.C. 379g(9)).

FDA's decision to grant Sucampo's request for a small business waiver for NDA 21-908 is based on the following findings. First, the Small Business Administration (SBA) determined and stated in its letter dated September 13, 2005, that Sucampo and its affiliates, S&R Technology Holdings, LLC; Sucampo Pharma Europe, Ltd.; Sucampo Pharma Ltd., Japan; R-Tech Ueno, Ltd., Japan; Sucampo AG, Switzerland; Sucampo AG Japan, Ltd.; Sucampo Pharma Ophthalmics, Ltd.; and Sucampo AG USA have fewer than 500 employees.[4] Second, according to FDA records, the marketing application for NDA 21-908, — is the first human drug application, within the meaning of the Act, to be submitted to FDA by Sucampo or its affiliates. Consequently, your request for a small business waiver of the application fee for NDA 21-908, — (lubiprostone), is granted.

We have notified the FDA Office of Financial Management (OFM) of this waiver decision and have asked them to waive the application fee for Sucampo's NDA 21-908, — (lubiprostone). FDA records show that Sucampo submitted NDA 21-908 on March 31, 2005. We have confirmed that FDA was notified of the application fee payment of $672,000 on the same date and have asked OFM to refund the application fee in the amount of $672,000. If you do not receive a refund within 30 days of the date of this letter, please contact Dianne Taylor, OFM at 301-827-0430.

FDA plans to disclose to the public information about its actions granting or denying waivers and reductions of user fees. This disclosure will be consistent with the laws and regulations governing the disclosure of confidential commercial or financial information.

If any billing questions arise concerning the marketing application or if you have any questions about this small business waiver, please contact Beverly Friedman or Michael Jones at 301-594-2041.

Sincerely,

Jane A. Axelrad

Jane A. Axelrad
Associate Director for Policy
Center for Drug Evaluation and Research

[4] SBA noted that Sucampo AG Japan, Ltd.; Sucampo Pharma Ophthalmics, Ltd.; and Sucampo AG USA, have all been closed.

BCC:
HFD-5 M. Jones
HFD-7 B. Friedman
HFD-7 Chron file
HFD-5 Sucampo waiver file
HFD-540 Tanya Clayton, Project Manager for NDA 21-908
HFM-110 C. Vincent/R. Eastep
HFA-100 M. Louviere, P. Joseph (Refund pending – UFID 3006034)
HFA-103 K. Boyd (RECORD ON PAYMENT AND ARREARS LIST)
HF-20 F. Claunts
HFV-3 T. Forfa
HFV-100 D. Newkirk

Drafted: B. Friedman 9/16/2005
CDER Application Check: R-Tech Ueno ' — no other applications 9/16/2005
CBER Application Check: C. Vincent: No applications – 9/16/2005
Edited: F. Purdie 10/24/2005
Revised: B. Friedman 10/24/2005
Reviewed and Signed: J. Axelrad

P:\waiver\Pending\Sucampo\2005.50\05A0721v2.doc
10/24/2005

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

OCT 28 2005

Neil Price, M.D.
300 Twentieth Avenue North
Suite 105
Nashville, TN 37203-2162

Dear Dr. Price:

Between August 31 and September 8, 2005, Mr. George Flynn representing the Food and Drug Administration (FDA), conducted an investigation to review your conduct of a clinical investigation (protocol # SC0232 entitled: "Multi-Center, Double-Blind, Randomized, Placebo-Controlled Phase III Study of the Efficacy and Safety of Oral RU-0211 for the Treatment of Occasional Constipation") of the investigational drug — lubiprostone, RU-0211), performed for Sucampo Pharmaceuticals. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our evaluation of the establishment inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Flynn during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

Ni A. Khin, M.D.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

2 Page(s) Withheld

____ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(5) Deliberative Process

____ § 552(b)(4) Draft Labeling

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Robert Orleans
Margaret Kober/Jennifer Mercier
Division of Reproductive and Urologic Drug Products,
ODE III, HFD-580

FROM:
Tanya Clayton (Regulatory Health Project Manager)
Gastroenterology Drug Products, HFD-180

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
October 17, 2005		21-908	New Drug Application	March 31, 2005

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
— ubiprostone)	Standard	Laxative	October 30, 2005

NAME OF FIRM: Sucampo Pharmaceuticals — US Agent)

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

COMMENTS/SPECIAL INSTRUCTIONS:

Amendment to original consult dated May 13, 2005

This New Drug Application provides for the treatment of chronic idiopathic constipation — . Our division has concerns because this formulation is a softgel capsule which may be inserted into the vagina for off-label use. Preclinical studies in the guinea pig suggest that the drug may be an abortifacient. As a result, our clinical review team has requested a consult. Our original request was sent to you May 13, 2005. However, as the review has progressed, our division is now able to identify specific questions. They are as follows:

1. Can you provide guidance as to the adequate clinical trial design to capture the abortifacient adverse events of concern regarding this drug?

2. Can you provide additional clinical trial requirements for evaluation of the abortifacient safety concerns?

3. Can you provide guidance to increase the probability of safe use in the drug label given the drug's potential as an abortifacient?

4. If pre-clinical data suggests that this drug has abortifacient potential; do you recommend any further clinical study to evaluate this effect? If you do, should these studies be done prior to approval or as Phase 4 commitments?

5. Can you provide guidance with a risk management plan for this drug regarding its abortifacient potential?

The User Fee Goal Date is January 31, 2006, our Divisional Goal Date is December 30, 2005, thus we are requesting to receive your consult by October 30, 2005. The medical reviewer is Kristen Buck. This NDA is fully Electronic and can be accessed through the EDR.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☒ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Tanya Clayton
10/17/2005 06:40:21 PM

MEMORANDUM OF MEETING MINUTES

Meeting Date: October 5, 2005

Time: 12:00-1:00 PM

Location: Conference Room 1415, White Oak

Application: NDA 21-908; Lubiprostone Capsules.

Type of Meeting: Type A

Meeting Chair: Ruyi He, M.D.

Meeting Recorder: Tanya Clayton, B.S.

FDA Attendees, Titles, and Office/Division:

Office of Drug Evaluation III

Julie Beitz, M.D.	Deputy Director

Division of Gastroenterology Drug Products

Brian E. Harvey, M.D., Ph.D.	Division Director
Joyce Korvick, M.D., M.P.H.	Deputy Division Director
Ruyi He, M.D.	Medical Team Leader
Kristen Buck, M.D.	Medical Reviewer
Suliman Al-Fayoumi, Ph.D.	Biopharm Reviewer
Jasti Choudary, Ph.D.	Supervisory Pharmacologist
Sushanta Chakder, Ph.D.	Pharmacology Reviewer
Sonia Castillo, Ph.D.	Statistical Reviewer
Tanya Clayton, B.S.	Regulatory Health Project Manager

Division of Pharmacology/Toxicology, Office of New Drugs

David Jacobson-Kram, Ph.D.	Acting Director

Office of Drug Safety/Division of Drug Risk Evaluation

Lanh Green, PharmD, M.P.H.	Team Leader, Safety Evaluator
Ann Corken Mackey, R.Ph., M.P.H.	Safety Evaluator

Division of Reproductive and Urologic Products

Lynnda Reid, Ph.D.	Supervisory Pharmacologist

External Constituent Attendees and Titles:

Sucampo Pharmaceuticals:

Kory J. Engelke, Ph.D., D.A.B.T.	Director of Pharmacology and Toxicology Ryuji Ueno, M.D., Ph.D., C.S.O.
Robert S. Cormack, Ph.D.	Regulatory Affairs Manager Consultant

Sachiko Kuno, Ph.D.	C.E.O.
Birgit Roerig, Ph.D.	Senior Scientist
Taryn R. Joswick, B.S.	Clinical Trial Manger
Lana Gloukhova, M.D.	Medical Director

Takeda Pharmaceutical Company

Masaki Yamamuto Ph.D.	Director, Development Research Center
Toshiro Heya, Ph.D.	Manager, Strategic Development

Background:

On August 8, 2005 the firm requested a Type A meeting to discuss their detailed results of both the guinea pig and monkey abortifacient studies for the purpose of defending their position that lubiprostone is unlikely to be used off-label as an abortifacient. This topic is the result of concerns raised by the FDA review team during the firms orientation presentation on July 12, 2005.

A subsequent September 9, 2005 background package was submitted, which contained 3 questions for discussion.

Following introductions, the attendees proceeded directly to their slide presentation. For convenience, the slides presented are attached to these minutes. Following the presentation, further discussion took place regarding the presentation as well as the Agency's responses to the 3 questions posed.

Discussion Points: (bullet format):

1. Based upon the concerns noted in the guinea pig studies, does the Division feel that lubiprostone possesses direct abortifacient activity in the guinea pig?

   Agency Response

   Based upon our initial review of the data presented in your NDA, there were dose related abortifacient effects.

2. Does the Division feel that sufficiently high doses of lubiprostone were evaluated in the monkey study to determine the abortifacient potential of the product?

   Agency Response

   The dose selection based on the rat teratology study is not appropriate or acceptable. Specifically, the highest dose should have been chosen to induce mild maternal toxicity or an acceptable level of exposure.

3. Based upon the results of the complete reproduction toxicology package (standard developmental and reproductive toxicology studies in rats and rabbits and FDA-requested abortifacient studies in guinea pig

and rhesus monkey), does the Division feel that lubiprostone is an abortifacient (especially when compared to a known abortifacient) and could be potentially used off-label to terminate a pregnancy?

Agency Response

The standard reproductive toxicology studies in rats and rabbits are not designed to detect the abortifacient effects relevant to humans. In these species, the sustenance of pregnancy is dependent on ovarian endocrine activity throughout gestation and a precipitous withdrawal of progesterone is a prerequisite for the onset of parturition. It is therefore not possible to clearly assess the abortifacient effects or to distinguish the abortifacient effects from luteolytic effects. In species like human, monkey and guinea pig, the endocrine function of the ovary is shifted to the feto-placental unit after a certain lag period during pregnancy and pregnancy can continue even in the absence of ovaries. Premature parturition can be induced in these species without a precipitous decline in progesterone. Thus, pregnant guinea pigs and rhesus monkeys are reliable experimental models for assessing and predicting the potential for abortifacient effects in humans.

The guinea pig study of lubiprostone is positive, while the rhesus monkey study may not be adequate.

MeetingUpdate

These answers are based upon the Agency's review to date and the review is currently ongoing.

14 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

____ § 552(b)(5) Deliberative Process

____ § 552(b)(4) Draft Labeling

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/s/

Tanya Clayton
11/2/2005 04:24:17 PM

Ruyi He
11/2/2005 05:05:38 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-908

Sucampo Pharmaceuticals, Inc.
(Agent, —
Attention: — Regulatory Agent
—
—

Dear Mr. —

Please refer to your March 31, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for — lubiprostone, 24 mcg).

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on May 30, 2005 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We are concerned about the potential for off label use of your drug as an abortifacient. The guinea pig model demonstrated this potential, while the monkey model may not have tested sufficiently high doses to resolve this issue. We are currently reviewing this data in detail. There may be additional safety issues which will need further discussion with you during the review regarding this potential off label use.

If you have any questions, call Tanya Clayton, B.S., Regulatory Health Project Manager, at (301) 827-4005.

Sincerely,

{See appended electronic signature page}

Joyce Korvick, M.D., M.P.H.
Deputy Director
Division of Gastrointestinal and Coagulation
Drug Products, HFD-180
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Joyce Korvick
6/13/05 04:54:02 PM
for Dr. Brian E Harvey

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-908 Supplement # N/A Efficacy Supplement Type SE- N/A

Trade Name: —
Established Name: Lubiprostone
Strengths: 24 mcg

Applicant: Sucampo Pharmaceuticals
Agent for Applicant: —

Date of Application: March 31, 2005
Date of Receipt: March 31, 2005
Date clock started after UN:
Date of Filing Meeting: May 12, 2005
Filing Date: May 30, 2005
Action Goal Date (optional): User Fee Goal Date: January 31, 2006

Indication(s) requested: treatment of Chronic idiopathic constipation and associated symptoms

Type of Original NDA: (b)(1) ☒ (b)(2) ☐
OR
Type of Supplement: (b)(1) ☐ (b)(2) ☐

NOTE:

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.

(2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

☒ NDA is a (b)(1) application OR ☐ NDA is a (b)(2) application

Therapeutic Classification: S ☒ P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.)
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES ☒ NO ☐

User Fee Status: Paid ☒ Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling.*

If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES ☐ NO ☒
  If yes, explain:

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES ☐ NO ☐

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐

- Was form 356h included with an authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES ☒ NO ☐
  If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A ☐ YES ☒ NO ☐
  If an electronic NDA, all forms and certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  Additional comments:

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A ☐ YES ☐ NO ☐

- Is it an electronic CTD (eCTD)? N/A ☐ YES ☒ NO ☐
  If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.

  Additional comments:

- Patent information submitted on form FDA 3542a? YES ☒ NO ☐

- Exclusivity requested? YES, _____ Years NO ☒
  NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES ☐ NO ☐
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Financial Disclosure forms included with authorized signature? YES ☒ NO ☐
  (Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)
  NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section)? Y ☒ NO ☐

- PDUFA and Action Goal dates correct in COMIS? YES ☒ NO ☐
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 59,623

- End-of-Phase 2 Meeting(s)? Date(s) April 11, 2001 and June 18, 2001 NO ☐
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) May 24, 2004 NO ☐
  If yes, distribute minutes before filing meeting.

Project Management

- Was electronic "Content of Labeling" submitted? YES ☒ NO ☐
  If no, request in 74-day letter.

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?
  YES ☒ NO ☐

- Risk Management Plan consulted to ODS/IO? N/A ☒ YES ☐ NO ☐

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y ☒ NO ☐

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A ☒ YES ☐ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  N/A ☒ YES ☐ NO ☐

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A ☒ YES ☐ NO ☐

- Has DOTCDP been notified of the OTC switch application? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES ☐ NO ☐

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☒ NO ☐
  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐
  If EA submitted, consulted to Florian Zielinski (HFD-357)? YES ☐ NO ☐
- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☒ NO ☐
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES ☐ NO ☐

ATTACHMENT

MEMO OF FILING MEETING

DATE: May 12, 2005

BACKGROUND: — . is indicated for the treatment of chronic idiopathic constipation —
— This is a Type 1 NME.
(Provide a brief background of the drug, e.g., it is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES: Tanya Clayton, Joyce Korvick, Florence Houn, Ruyi He, Kristen Buck, Liang Zhou, Zhengfang Ge, Suliman Al-Fayoumi, Jasti Choudary, Stella Grosser, Sushanta Chakder, Milton Fan, Brian Harvey (tcon)

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline	**Reviewer**
Medical:	Kristen Buck
Secondary Medical:	
Statistical:	Milton Fan
Pharmacology:	Sushanta Chakder
Statistical Pharmacology:	Mushifiqur Rashid
Chemistry:	Zhengfang Ge
Environmental Assessment (if needed):	
Biopharmaceutical:	Suliman Al-Fayoumi
Microbiology, sterility:	Bryan Riley
Microbiology, clinical (for antimicrobial products only):	
DSI:	Khairy Malek
Regulatory Project Management:	Tanya Clayton
Other Consults:	DDMAC, DMETS, HFD-580

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐
If no, explain:

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site inspection needed? YES ☒ NO ☐
- Advisory Committee Meeting needed? YES, date if known _____ NO ☒
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
  N/A ☐ YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A ☒ FILE ☐ REFUSE TO FILE ☐

STATISTICS N/A ☐ FILE ☒ REFUSE TO FILE ☐

BIOPHARMACEUTICS FILE ☒ REFUSE TO FILE ☐

- Biopharm. inspection needed? YES ☐ NO ☒

PHARMACOLOGY N/A ☐ FILE ☒ REFUSE TO FILE ☐

- GLP inspection needed? YES ☐ NO ☐

CHEMISTRY FILE ☒ REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES ☐ NO ☐
- Microbiology YES ☒ NO ☐

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

- ☐ No filing issues have been identified.
- ☐ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
2. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. ☒ Convey document filing issues/no filing issues to applicant by Day 74.

Tanya Clayton, B.S.
Regulatory Project Manager, HFD-180

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/s/

Tanya Clayton
6/7/05 12:58:47 PM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
annon Benedetto and Elaine Hu,
D-42, Parklawn Building, Room 17B-17

FROM:
Tanya Clayton (Regulatory Health Project Manager)
GI and Coagulation Drug Products, HFD-180,
PKLN 6B-45

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
June 3, 2005		21-908	New Drug Application	March 31, 2005

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
(Lubiprostone)	Standard	Laxative	October 30, 2005

NAME OF FIRM: Sucampo Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
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- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: Labeling Review

COMMENTS/SPECIAL INSTRUCTIONS:

This is a type 1New Drug Application that is indicated for the treatment of chronic idiopathic constipation. The PDUFA goal date is 01/31/06. I'm attaching a copy of the proposed package and PI labeling. Also, please note that this application was submitted electronically, consequently, may be found on the EDR pathway – N 21908/21March2005 . Please let me know if you require additional information. Thank you in advance.
nya Clayton – 827-4005.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Tanya Clayton
6/3/05 01:36:10 PM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: May 16, 2005

To: Regulatory Agent for Sucampo Pharmaceuticals	**From:** Tanya D. Clayton, BS Regulatory Health Project Manager
Company:	Division of Gastrointestinal and Coagulation Drug Products
Fax number:	**Fax number:** 301-443-9285
Phone number:	**Phone number:** 301-827-4005

Subject: NDA 21-908
Information Request

Total no. of pages including cover: 2

Comments:

Please find the following information request pertaining to the submission mentioned above.

Document to be mailed: YES √NO

Information Request

Please provide the historical control incidences of tumors, in the same strain of rat and mouse used in the carcinogenicity study. This data come from studies conducted during the last 3 to 5 years in the laboratory which conducted the carcinogenicity studies.

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/s/

Tanya Clayton
1/10/2006 06:01:12 PM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Margaret Kober/Jennifer Mercier
'ision of Reproductive and Urologic Drug Products,
)E III, HFD-580, Parklawn Building, Room 17B-45

FROM:
Tanya Clayton (Regulatory Health Project Manager)
GI and Coagulation Drug Products, HFD-180

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
May 13, 2005		21-908	New Drug Application	March 31, 2005

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
' — ,ubiprostone)	Standard	Laxative	September 30, 2005

NAME OF FIRM: Sucampo Pharmaceuticals —

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
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- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

COMMENTS/SPECIAL INSTRUCTIONS:

This New Drug Application provides for the treatment of chronic idiopathic constipation Our division has concerns because this formulation is a softgel capsule which may be inserted into the vagina for off-label use. Preclinical studies in the guinea pig suggest that the drug may be an abortifacient. As a result, our clinical review team has requested a 'nsult. Please advise us if you think additional preclinical or clinical studies are necessary to address this issue (ie. intra-ginal studies in animals).

The User Fee Goal Date is January 31, 2006, our Divisional Goal Date is December 30, 2005, thus we are requesting to receive your consult by September 30, 2005. The medical reviewer is Kristen Buck. This NDA is fully Electronic and can be accessed through the EDR. The hard copy of this consult will be hand delivered.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☒ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Tanya Clayton
5/13/05 03:38:45 PM

3 Page(s) Withheld

___ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-908

Sucampo Pharmaceuticals, Inc.
(Agent,
Attention: , Regulatory Agent

Dear Mr.

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

Name of Drug Product: RU-0211 Capsules (lubiprostone, 24 mcg)

Review Priority Classification: Standard (S)

Date of Application: March 31, 2005

Date of Receipt: March 31, 2005

Our Reference Number: NDA 21-098

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May 30, 2005 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be January 30, 2005.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We acknowledge receipt of your request for a deferral of pediatric studies for this application. Once the application has been filed, we will notify you whether we have deferred the pediatric study requirement for this application.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Send all electronic or mixed electronic and paper submissions to the Central Document Room at the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room (CDR)
5901-B Ammendale Road
Beltsville, MD 20705-1266

If your submission only contains paper, send it to the following address:

Courier/Overnight Mail/U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: Division Document Room, 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-4005.

Sincerely,

{See appended electronic signature page}

Tanya D. Clayton, BS
Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Tanya Clayton
4/11/05 12:32:22 PM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: July 7, 2005

To: Regulatory Agent for Sucampo Pharmaceuticals	**From:** Tanya D. Clayton, BS Regulatory Health Project Manager
Company:	Division of Gastrointestinal and Coagulation Drug Products
Fax number:	**Fax number:** 301-443-9285
Phone number:	**Phone number:** 301-827-4005

Subject: NDA 21-908
Information Request

Total no. of pages including cover: 2

Comments:

Please find the following information request pertaining to the submission mentioned above, per our statistical reviewer.

Document to be mailed: YES √NO

Information Request

- Please provide the carcinogenicity data electronically in Biometrics format.

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

/s/

Tanya Clayton
1/10/2006 06:16:05 PM
CSO

MEMORANDUM OF MEETING MINUTES

Meeting Date: May 24, 2004

Time: 1:00-2:30 PM

Location: Parklawn Building, Conference Room C

Application: IND 56,623; RU-0211 Capsules

Type of Meeting: Type B, Pre-NDA

Meeting Chair: Ruyi He, M.D..

Meeting Recorder: Tanya Clayton, B.S.

FDA Attendees, Titles, and Office/Division:

Division of Gastrointestinal and Coagulation Drug Products

Robert Justice, M.D., M.Sc.	Division Director
Ruyi He, M.D.	Medical Team Leader
Robert Prizont, M.D.	Medical Reviewer
Jasti Choudary, Ph.D., B.V.Sc.	Supervisory Pharmacologist
Sushanta Chakder, Ph.D.	Pharmacology Reviewer
Suresh Doddapaneni, Ph.D.	Biopharmaceutical Team Leader
Raymond Frankewich, Ph.D.	Chemistry Reviewer
Mushfiqur Rashid, Ph.D.	Statistical Reviewer
Zei-Pao Huang	Review Technologist (Office of Information Management)
Alice Kacuba, R.N., M.S.N., RAC	Regulatory Health Project Manager
Tanya Clayton, B.S.	Regulatory Project Manager

External Constituent Attendees and Titles:

Sucampo Pharmaceuticals:

Ryu Hirata, MSc., Chief Operating	CEO, R-Tech Urno, Ltd.
Michele Gargano, M.S.	Director, Clinical Development
Patrick Thomas	Regulatory Affairs Consultant
Kory J. Engelke, Ph.D., DABT	Senior Manager, Pharmacology and Toxicology
Myra L .Patchen, Ph.D.	CEO
P. Christopher Holland, M.S.	Associate Director, Biostatistics and Clinical Data
George P. Perentesis, Pharm.D., F.C.P.	Vice President, Research and Development
Thomas W. MacAllister	COO, General Counsel

Kristin A. Pribyla — Regulatory Affairs Associate

BACKGROUND:

On February 27, 2004, the firm requested a Pre-NDA meeting for the purpose of discussing their Phase III results as well as obtaining the Agency's guidance on their proposed plans for NDA submission including the format, content and timing of the submission.

A subsequent April 26, 2004 background package was submitted, which contained 11 questions for discussion.

Following introductions, the attendees proceeded directly to the questions for response.

DISCUSSION POINTS: (BULLET FORMAT):

1. Does the Division concur that the pre-clinical package of pharmacology, toxicology, ADME, reproduction and carcinogenicity studies is complete for the NDA filing?

FDA Response

- **Under safety pharmacology, in vitro cardiac electrophysiology studies are missing. Please refer to " ICH Guidance for Industry, S7A Safety Pharmacology Studies for Human Pharmaceuticals, July 2001" and "Safety Pharmacology Studies for Assessing the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) By Human Pharmaceuticals, February 2002".**

1A. At the End of the Phase II meeting in April 2001, the only reprotoxicology study Sucampo had performed was the Rat Seg I Study.[55] (located in Preclinical Summary). The Division stated that Sucampo needed to perform Rat Seg II, III, Rabbit Seg II, and also determine the abortifacient potential of RU-0211 in rhesus monkeys and guinea pigs. Subsequent to the April meeting, Sucampo has completed the necessary rat and rabbit reproduction studies (Segment I, II and III in rats and Segment II in rabbits). These studies established that RU-0211 had no adverse effects in the reproduction function of rats and/or rabbits at doses up to 125 to 2500-fold the intended clinical dose[54,56,57,59] (study report texts are included for reference in Appendix E, F, G, and H).

In addition to the above mentioned reproduction studies, Sucampo respectfully asks the Division to reconsider the following facts about RU-0211:

- In comparison to the most active native prostaglandins or prostaglandin analogues, RU-0211 has <1 to 5 percent of the relative receptor activity on the classical PG receptors.[6] (located in Pre-Clinical Summary)

- Similar to other PGE_1 metabolites, RU-0211 has a much-reduced ($\leq$ 10 percent) relative biological activity on isolated tissues, including the ileum, uterus, and trachea.[15,16,17] (located in Pre-Clinical Summary)

Based on this data, RU-0211 would not be expected to induce abortion and/or parturition that are characteristic of prostaglandin receptor activators.

As requested by the Division at the April 2001 meeting, Sucampo is planning to perform a study to address the abortifacient potential of RU-0211 in pregnant rhesus monkeys. As per the correspondence from the Division to Sucampo dated 8 January 2003, the animals will be dosed on gestation days 110 to 130 and a Cesarean section will be performed on gestation day 150 (if necessary); progesterone levels will be monitored throughout the dosing period. Currently, the breeding of these monkeys, which are seasonal breeders, is occurring and as of 14 April 2004 (the latest information), there are 24 pregnant animals. This number of animals will allow the design of the study to have 3 dose groups (vehicle, low and high dose RU-0211) with 8 animals per group. However, the results of the mating on an additional 12 animals are pending; any additional pregnant animals will be assigned to the study. Sucampo plans to submit the results of the study outlined above at the time of the NDA filing.

Given that RU-0211 does not appear to have prostaglandin-like activities and did not appear to affect the reproductive function in rats and rabbits at doses as high as 2500-fold the intended clinical dose, Sucampo believes that the above study design (pregnant rhesus monkey model with 3 dose groups [vehicle, low and high dose RU-0211] containing eight animals per group with dose administration occurring on gestation days 110 to 130) will properly address the abortifacient potential of RU-0211. Does the Division concur?

FDA Response

- **No. The proposed abortifacient study in rhesus monkeys will assess it only partially. From the standpoint of uterine anatomy, myometrial organization, general hemodynamics during pregnancy, utero-placental hemodynamics and placental structure, the rhesus monkey is a good model. However, from a endocrine standpoint, guinea pig is more similar to human than monkey. In guinea pigs, serum progesterone levels increase from 4-8 ng/mL during the cycle to about 266 ng/mL during pregnancy. These changes are similar to the changes in women and prostaglandin derivatives are capable of inducing abortion in both species without prior decrease in progesterone. In other laboratory species prostaglandins produce such an effect only after a precipitous decline in progesterone. For a complete and comprehensive assessment of the abortifacient potential of RU-0211, it needs to be tested in both rhesus monkeys and guinea pigs.**

1B. The published literature states in studies with antifertility prostaglandins in pregnant guinea pigs and pregnant rhesus monkeys, that a good correlation of abortifacient effects can be observed between the two animal models[1] (study report text is included in Appendix B). These data do not suggest that one model is better than the other; rather, that the data from both the pregnant rhesus monkey and the pregnant guinea pig are very sensitive and that both are relevant models. These data additionally support the use of either model for assessing the abortifacient potential of prostaglandins.

Based upon the facts presented above, and the fact that Sucampo is planning to perform the abortifacient study in pregnant rhesus monkeys, Sucampo does not believe that a study in pregnant guinea pigs will yield additional relevant data regarding the abortifacient potential of RU-0211. Therefore, Sucampo respectfully requests reconsideration from performing the guinea pig study. Does the Division agree to Sucampo's request?

FDA Response

- **No. Please see response to 1A. The two models complement each other.**

1C. At the End of the Phase II meeting in April 2001, the Division also requested that Sucampo further explore the potential genotoxic effects observed in the CHL cell chromosomal aberration test and mouse lymphoma cell forward mutation test. In addition, the Division suggested that Sucampo perform a study to evaluate the clastogenic potential in human lymphocytes. However, Sucampo has recently completed two 104-week carcinogenicity studies in mice and rats,[52,53] (located in Pre-Clinical Summary) respectively, and believes that the results of these studies will address the long-term effect of any genotoxic activities that RU-0211 may possess and that these *in vitro* assays will yield little additional relevant data. Therefore, Sucampo respectfully requests reconsideration for performing these additional studies. Does the Division agree to Sucampo's request?

FDA Response

- **Yes, no additional genotoxicity studies are needed.**

1D. To address potential drug-drug interactions in which RU-0211 may participate, Sucampo has conducted a study to evaluate the potential of RU-0211 to competitively inhibit eight specific isoforms of cytochrome P450 in pooled human liver microsomes[21] (study report text is included in Appendix D.

In this study, the IC_{50} values for CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 were measured using the relevant substrates (phenacetin, coumarin, bupropion, tolbutamide, (*S*)-mephenytoin, dextromethorphan, chlorzoxazone, midazolam, and testosterone, respectively) at single concentrations approximating their respective apparent K_m values. The

concentrations of RU-0211 used for these IC_{50} studies were 0, 0.1, 1, 10, 100, 1000, and 10,000 pg/mL. The metabolite formation for each activity was monitored by a validated LC-MS/MS method, and the specificity of these experimental conditions for an appropriate metabolite formation was also evaluated in the presence of specific inhibitors.

Samples for mechanism-based inhibition screening were pre-incubated for 15 minutes, at 37 °C with RU-0211 (10 or 100 pg/mL) in the presence or absence of NADPH. The percent remaining activity of microsomes pre-incubated for 15 minutes at 37 °C with RU-0211 and NADPH were compared to microsomes pre-incubated with RU-0211 without NADPH. In addition, the pre-incubated samples were compared to samples prepared at the same test article concentrations without pre-incubation (co-incubation samples).

Incubation of RU-0211 in human hepatic microsomal suspensions at concentrations up to 10,000 pg/mL resulted in no significant concentration dependent inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4. Mechanism-based inactivation screening of RU-0211 showed possible mechanism-based inactivation of CYP2A6. This screening is based on a single time and test article concentration incubations. The percentage contribution of CYP2A6 to the total cytochromes in human liver is small and only small numbers of drugs are known to be metabolized by CYP2A6. Thus, the possibility of a clinical drug-drug interaction due to mechanism-based inactivation of CYP2A6 should be limited. In addition, the highest concentration of RU-0211 in these studies (10,000 pg/mL) is greater than 2000-fold the plasma level of RU-0211 measured in the clinical studies. Therefore, Sucampo does not intend to perform any clinical or additional preclinical studies to further define the drug-drug interaction profile of RU-0211. Does the Division concur?

FDA Response

- **Comment if there are data addressing the potential to induce metabolic enzymes. Indicate the extent of metabolism and specific pathways so as to be able assess the potential for other coadministered drugs to affect the metabolism of RU-0211.**
- **The sponsor will provide a rationale as to why drug-drug interactions are not significant.**

2. Does the Division concur that the plans for the integrated safety summary and methods for analyzing and presenting the data are appropriate and sufficient for the NDA filing?

FDA Response

- **The presentation of the ISS appears acceptable.**

3. Does the Division concur that the plans for the integrated efficacy summary and methods for analyzing and presenting the data are appropriate and sufficient for the NDA filing?

FDA Response

- **Although, we recognize that a different primary efficacy endpoint was specified in the protocol, an important analysis is the proportion of responders in the placebo and RU-0211 treatment groups. A responder is a patient who has ≥3 spontaneous bowel movements (BM) per week for 4 weeks on average and ≥3 spontaneous BMs for at least 2 weeks. You may perform two separate analyses. One would classify drop-outs due to lack of efficacy as non-responders. The other would classify all drop-outs as non-responders. Please include this analysis in the NDA.**
- **Additional secondary efficacy analyses may include: (a) number and the proportion of (responders) patients who has ≥3 bowel movements (BM) per week at the end of week 1 (7 days), week 2 (14 days) and week 3 (21 days) in the placebo and RU-0211 treatment groups; (b) increase in the number of BMs from baseline per week for each week in the placebo and RU-0211 treatment groups.**

4. Does the Division concur that the identified efficacy and safety studies support labeling for — (24 µg BID) of RU-0211 for the —

FDA Response

- **The indication — is too broad. The proposed indication should reflect the type of constipation studied in the pivotal clinical trials, e.g., idiopathic constipation, — onstipation predominant. The label should reflect the duration of treatment in the clinical trials.**

  Please conduct a sub-group analyses of IBS-c patients and IBS-like patients.

4A. At the End of Phase II meeting in April 2001, the Division also requested that Sucampo further address the potential to affect the bone metabolism. Following the Division's suggestion, Sucampo has performed pre/post treatment x-rays of the hands of subjects exposed to RU-0211 at longer durations of treatment. Specifically, approximately 215 sets of pre/post treatment x-rays have been assessed for subjects dosed with RU-0211 out to 6 months and approximately 177 sets of pre/post treatment x-rays have been assessed for subjects dosed with RU-0211 out to 12 months. Writing of the final clinical reports for the studies in which these subjects participated in, is ongoing and will be submitted to the FDA. Data analysis has been completed and across both the 6- and 12-month treatment groups, no clinically significant trends have been seen in terms of changes from baseline.

In addition to the above-mentioned clinical data, there has been no evidence of altered bone metabolism in any of the preclinical toxicology studies performed with RU-0211. Specifically, there were no apparent changes in the histopathological examination of bones (sternum and femur) in rats and dogs administered oral RU-0211 at doses approximately 500 and 63-fold the planned clinical dose for 26 and 39 weeks, respectively[46,47] (located in Pre-Clinical Summary). Furthermore, there were no fetal skeletal variations or malformations that were attributable to RU-0211 at doses up to approximately 2500 and 125-fold the planned clinical dose in the rat and rabbit Segment II reproduction studies, respectively[55,58] (located in Pre-Clinical Summary).

Therefore, Sucampo believes that they have properly addressed the Division's question. Does the Division concur?

FDA Response

- **You don't seem to have generated any in vitro pharmacology data on bone growth and dissolution. You also need to subject the bone tissues from the carcinogenicity studies to histopathology examination.**

4B. Due to the recent regulatory initiatives by the FDA on the use of ECGs in clinical trials, Sucampo has proactively opted to ascertain the cardiac safety of RU-0211. In this regard, Sucampo has conducted a retrospective study of the pre/post treatment ECGs that were conducted as part of the Phase IIb constipation study described in the Summary of Clinical Package, Section II.D.1. Additionally, Sucampo is planning to conduct the same retrospective study of the ECGs conducted as part of its [redacted] Summary of Clinical Package, Section II.D.2.). The draft final report for the Phase IIb constipation ECG study is included in this package (Appendix P). In summary, the ECG analysis showed no evidence of any effect of RU-0211 on ECG parameters. RU-0211 at doses of 24, 48, and 72 µg per day, for 3 weeks, as studied in the protocol, show no evidence of any effects on heart rate, cardiac conduction (PR and QRS duration) or cardiac repolarization (QTc analysis) and no evidence of new morphological changes.

In addition to the above clinical data, Sucampo evaluated the QTc interval at various time points (10, 20, 30, 45, 60, 90, and 120 minutes) after a single intraduodenally-administered dose of 10, 100, or 1000 µg/kg RU-0211 in the anesthesized dog[13] (located in Pre-Clinical Summary). Additionally, Sucampo evaluated the effect of orally administered 2, 10 or 50 µg/kg RU-0211 on the QTc interval in the 39-week dog study[7] (located in Pre-Clinical Summary). The QTc interval was evaluated pre-dose, at week 13, 26 and 39. There was no apparent effect on QTc by RU-0211 at doses 125- and 63-fold, single or chronic doses, respectively, the intended clinical dose.

Therefore, due to the results of this proactive assessment of the cardiac safety and the preclinical studies, Sucampo believes that the administration of RU-0211 will not adversely compromise cardiac function and does not intend to perform additional studies (clinical or preclinical) to further address the cardiac safety of RU-0211. Does the Division concur?

FDA Response

- **ECG measurements obtained pre and post treatment will not rule out QTc prolongation.**
- **Serial QTc measurements should be obtained pre and at intervals post dosing and over a range of doses to ascertain the potential QTc prolongation effects.**
- **Please see the preliminary concept paper entitled "The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-antiarrythmic Drugs." The link to the website where this paper can be found is given below:**
  http://[illegible]t.cder.fda.gov/QTWG/QT%20Workshop/qt4jam.pdf

5. Does the Division concur that the NDA can be submitted in an electronic CTD format? Does the Division have any specific procedures or requirements, in addition to those outlined in FDA's Guidances on electronic submissions?

FDA Response:

- **Please clarify whether your NDA will be:**
  1) A "fully electronic CTD (eCTD) NDA" according to Guidance for Industry: M2 eCTD: Electronic common Technical Document Specification (April 2003), or
  2) A "[illegible] submitted in electronic format" according to the 1999 Guidance for Industry: Regulatory Submissions in Electronic Format; General Considerations (January 1999) and Guidance for Industry: Regulatory Submissions in Electronic Format; New Drug Application, (January, 1999).
- **Because adherence to the eCTD specification is critical, a fully eCTD NDA requires that you meet with CDER and submit a sample eCTD submission to be processed by CDER's [illegible] validation tool prior to submitting the eCTD. (Sample submission is to be sent to [illegible]@cder.fda.gov).**

Sponsor clarified they will be submitting the statement mentioned in #1.

6. Does the Division require the ISS/ISE to be placed in a specific section in the electronic CTD?

FDA Response:

- **The ISS/ISE as required by 21 CFR 314.50(d)(5)(v) and (vi) are not the same as Module 2, Section 2.7: Clinical Summary.**
- **Sections 2.7.3 and 2.7.4 are Summary of Clinical Efficacy and Summary of Clinical Safety, which may not be the integrated analyses that are the ISS/ISE.**
- **The placement of the ISS/ISE may also be dependant on the size of the document. If the documents exceed 500 pages, the documents should be placed in Module 5 and clearly labeled as ISS and ISE.**
- **Please review the following references:**
  1) Guidance for Industry: M4: The CTD-Efficacy (August 2001)
  2) Guidance for Industry: M4: CTD-Efficacy Questions and Answers (May 2004)

3) June 2002 DIA slides of presentations from Justina Molzen and Robert Temple on CTD issues. The slides can be found at http://www.fda.gov/cder/present/DIA62002/default.htm

7. Does the Division concur with the developmental dissolution test for the RU-0211 capsules?

FDA Response

- **Analytical procedure and acceptance criterion will be evaluated as part of the NDA review. Justification should be provided for the presence of — in the dissolution medium.**

8. Does the Division concur with the specifications for RU-0211 drug substance?

FDA Response

- **We recommend that you amend the drug substance specification to include tests and acceptance criteria for individual Specified Identified Impurities — — and Total Impurities. Reference is made to ICH Q3A(R). We also recommend that each drug substance lot be evaluated with both — — so that it can be confirmed that — — are present, and that the main peak (RU-0211) is pure.**

9. Does the Division concur with the specifications for RU-0211 drug product?

FDA Response

- **We recommend that you amend the drug product specification to include tests and acceptance criteria for individual Specified Degradation Products — Individual Unspecified Degradation Products, and Total Degradation Products. Reference is made to ICH Q3B(R). Impurities — are described as potential degradation products. It appears that no testing for them has been performed on any lot of drug product to date.**

- **Validation data for specificity should be submitted for both of the analytical procedures for identification (of the drug substance) in the drug product specification.**

10. Additional structural information on RU-0211 drug product by — is presented, which documents the — during the primary stability tests and will confirm — for the process validation batches. Does the Division concur that upon confirmation of the — will be omitted as a specification test for RU-0211 drug product?

FDA Response

- **It appears that the — in the recent batches. If possible, — some of the earlier batches (used for Phase 1 and 2 studies) should also be tested and submitted. When the data is complete, a decision regarding — in stability testing will be made.**

11. A minimum of — long-term stability data for RU-0211 drug product will be submitted in the NDA. During the NDA review period, — of stability data will become available. Does the Division concur this data can be submitted during the review period in support of a 36-month expiry period?

FDA Response

- **Yes, you can submit this data during the review process. Whether or not we will be able to grant a 36 month expiry period depends on whether we will have adequate time to review the data. When during the review process do you plan to submit it?**

Additional Chemistry Comments:

1. **Describe the — on commercial scale for both drug substance and drug product.**

2. **Clarify whether the container and closure used in the stability analysis of the drug product — are the same as those intended for market. Describe and justify any differences.**

3. **The drug substance (RU-0211) is manufactured by R-Tech Ueno, Ltd. by performing — obtained from —). Because — cGMP inspection of — is anticipated.**

4. **It is noted that the drug product used in each of the three IND phases was produced at a different facility — for Phase 1; — Provide a description of any differences between the process and — of material produced at the three facilities.**

5. **Initiate the process of obtaining a nonproprietaty (established) name for the proposed drug substance as soon as possible. Assignment of a nonproprietary name by the USAN council should be completed before an NDA is filed.**

<u>Additional Clinical pharmacology and Biopharmaceutics Comments:</u>

It is not clear if the following information is obtained yet:

1. **Absolute or relative bioavailability of RU-011.**
2. **If the metabolism is completely elucidated and the enzymes involved in the metabolism are identified.**
3. **Effect of hepatic impairment and renal impairment on the pharmacokinetics of RU-0211.**
4. **Effect of age, gender, and race on the pharmacokinetics of RU-0211.**
5. **Extent and nature of human plasma protein binding.**
6. **Pharmacologic activity of major metabolite(s) seen in humans.**

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/s/

Tanya Clayton
6/22/04 03:42:02 PM

Ruyi He
6/22/04 04:32:02 PM

Methods Validation

The Method Validation is pending. This will be fulfilled post-approval.

Tanya Clayton

Tanya Clayton, B.S.
Regulatory Health Project Manager

Statistical Review (Stability)

This section is discussed within the Chemistry review on Page 36.

Tanya Clayton

Tanya Clayton, B.S.
Regulatory Health Project Manager

Environmental Assessment

This section is discussed in the Chemistry review dated, December 5, 2005, page 41.

Tanya Clayton, B.S.
Regulatory Health Project Manager

Micro Review (s) – Validation of Sterilization

This section is not applicable.

Tanya Clayton, B.S.
Regulatory Health Project Manager

Abuse Liability Review

This section is not applicable.

Tanya Clayton, B.S.
Regulatory Health Project Manager

NDA 21-908
Amitiza™ (Lubiprostone)

Safety Update Review

This update is discussed in the Clinical review dated December 19, 2005, page 132.

Tanya Clayton, B.S.
Regulatory Health Project Manager

Advisory Committee Meeting

This section is not applicable.

Tanya Clayton, B.S.
Regulatory Health Project Manager

Federal Register Notice (s)

This section is not applicable.

Tanya Clayton

Tanya Clayton, B.S.
Regulatory Health Project Manager

AIP

The sponsor is not on AIP.

Tanya Clayton, B.S.
Regulatory Health Project Manager