CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-908

CHEMISTRY REVIEW(S)

NDA 21-908

Amitiza (Lubiprostone) Capsules, 24mcg

Sucampo Pharmaceutical, Inc

Zhengfang Ge, Ph.D.

Office of New Drug Quality Assessment
for
Division of Gastroenterology Products

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Chemistry Review Data Sheet

1. NDA # 21-908

2. REVIEW # 2

3. REVIEW DATE: January 25, 2006

4. REVIEWER: Zhengfang Ge

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original submission	March 31, 2005
N 21-908 N-000-BZ	September 30, 2005

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
N 21-908 N-000-BC	November 16, 2005
N 21-908 N-000-BC	December 21, 2005

7. NAME & ADDRESS OF APPLICANT:

Name:	SUCAMPO PHARMACEUTICAL, INC
Address:	4733 Bethesda Ave, Suite 450, Bethesda MD 20814
Representative:	—
Telephone:	—

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Amitiza
b) Non-Proprietary Name (USAN): Lubiprostone Capsules
c) Code Name/# (ONDC only): RU-0211
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: This application was filed under the provisions of section 505(b)(1) of Federal Food, Drug and Cosmetic act and 21 CFR 314.50.

10. PHARMACOL. CATEGORY: Chronic idiopathic constipation

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 24 mcg

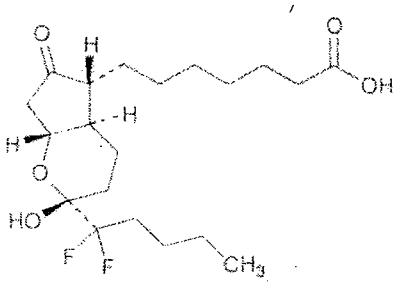
13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Name:

(-)-7-[(2R, 4aR, 5R, 7aR)-2-(1,1-difluoropentyl)-2-hydroxy-6-oxooctahydrocyclopenta[b]pyran-5-yl]heptanoic acid

Molecular Formula: $C_{20}H_{32}F_2O_5$

Molecular Weight: 390.46

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
/	II	R-Tech Ueno Ltd	RU-0211	1	Adequate	December 22, 2005	
/	II	/	/	1	Adequate	January 6, 2005	

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
CMC EOP-2 meeting minutes	IND 59, 623	

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not Applicable		
EES	Satisfactory	3-January-2006	
Pharm/Tox	Not Applicable		
Biopharm	Not Applicable		
LNC	Not Applicable		
Methods Validation	To be validated		
DMETS	See review notes for labeling comments	8-Dec-2005	Todd D. Bridges
EA	See review notes		
Microbiology	Approval	30-Sep-2005	Bryan S. Riley, Ph. D.

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

Appears This Way
On Original

The Chemistry Review for NDA 21-908

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The sponsor has adequately addressed all the CMC issues found in review #1. The inspection of the manufacturing sites were found satisfactory dated 3-Jan-2006. Subsequently, the sponsor revised the labeling based on the CMC requests during this review circle. From the CMC point of view, this NDA may be approved.

1. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Lubiprostone (RU-0211) is classified as a locally acting chloride channel activator that promotes a chloride-rich intestinal fluid secretion without altering sodium and potassium concentrations in the serum. Lubiprostone acts by specifically activating ClC-2, which is a normal constituent of the apical membrane of the human intestine, in a protein kinase A-independent fashion. By increasing intestinal fluid secretion, lubiprostone increases motility in the intestine thereby increasing the passage of stool and alleviating symptoms associated with chronic idiopathic constipation. One clinical concern is the off-label use of Lubiprostone as abortifacient if inserted virginally. Therefore, a microbiological consult was requested to assess the — specifications in the context of the intravaginal administration. The comment from the consulting report is that the specifications are acceptable for approval.

The drug substance RU-0211 is a new molecular entity with 4 chiral centers. The sponsor provided characterization data including —

— to demonstrate the structure of RU-0211 molecule. The sponsor also provided physical chemical properties. RU-0211 is insoluble in water but soluble in certain organic solvent. RU-0211 has a pKa at approximately 4.4 calculated from extrapolation of RU-0211 titration in EtOH/water.

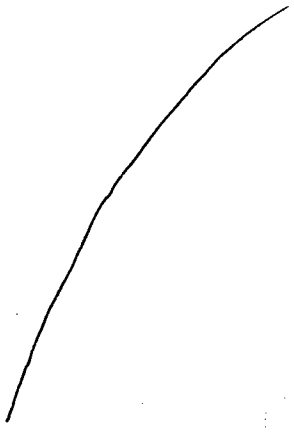
studies demonstrate that RU-0211 is a crystalline

Data about the structure elucidation and physical chemical properties were reviewed and were found acceptable. RU-0211 is

synthesized

RU-0211 is manufactured at R-Tech Ueno, Ltd. (Sanda, Hyogo, Japan), it's CMC information is provided in DMF The DMF is reviewed and found adequate after the applicant's adequate response to Agency's requests.

RU-0211 drug substance occurs as white crystals or crystalline powder RU-0211 is insoluble in water, but soluble in organic solvents such as ethanol and MCT



The drug product was developed as a soft gelatin capsule containing 24 mcg of liquid lubiprostone in MCT. The production of RU-0211 soft capsules is conducted by Some CMC information of the drug product, which includes composition of the drug product, control of materials, manufacturing process and process control, is provided in DMF The DMF is reviewed and found adequate after the applicant's adequate response to a list of requests by the Agency.

No degradation products were observed in drug substance under the proposed storage condition and drug product under room temperature. The impurities are controlled The drug substance is packaged in a The shelf life for the drug substance is granted for based on the updated stability data. The drug product is packaged in HDPE bottle with 100 capsules The expiration for the drug product is 36 months under 25 °C/60%RH based on the updated stability data.

B. Description of How the Drug Product is Intended to be Used

The drug product is indicated for chronic idiopathic constipation

The drug product is available as an oval, orange, soft gelatin capsule with "SPI" printed on one side. Each capsule contains 24 mcg lubiprostone. The recommended dosage for — is 24 mcg taken twice daily orally, for a total daily dose of 48 mcg.

C. Basis for Approvability or Not-Approval Recommendation

Based on the CMC review, this NDA can be approved.

III. Administrative

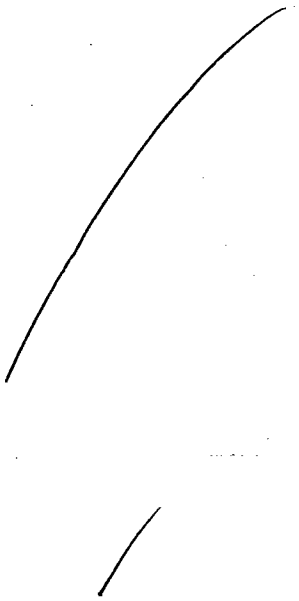
A. Reviewer's Signature

In DFS

B. Endorsement Block

Chemist: Zhengfang Ge
Chemistry Branch Chief: Moo-Jhong Rhee
ProjectManager: Tanya Clayton

C. CC Block



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___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

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/s/

Zhengfang Ge
1/25/2006 04:55:18 PM
CHEMIST

Moo-Jhong Rhee
1/26/2006 11:01:00 AM
CHEMIST
Chief, Branch III

NDA 21-908

— (Lubiprostone), 24mcg Capsule

Sucampo Pharmaceutical, Inc

Zhengfang Ge, Ph.D.

Office of New Drug Quality Assessment
for
Division of Gastroenterology Products
HFD-2411

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Chemistry Review Data Sheet

1. NDA # 21-908

2. REVIEW # 1

3. REVIEW DATE: November 30, 2005

4. REVIEWER: Zhengfang Ge

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original submission N 21-908 N-000-BZ	March 31, 2005 September 30, 2005

7. NAME & ADDRESS OF APPLICANT:

Name:	SUCAMPO PHARMACEUTICAL, INC
Address:	4733 Bethesda Ave, Suite 450, Bethesda MD 20814
Representative:	
Telephone:	

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: —
b) Non-Proprietary Name (USAN): Lubiprostone
c) Code Name/# (ONDC only): RU-0211
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: This application was filed under the provisions of section 505(b)(1) of Federal Food, Drug and Cosmetic act and 21 CFR 314.50.

10. PHARMACOL. CATEGORY: Chronic idiopathic constipation —

11. DOSAGE FORM: Soft Gel Capsules

12. STRENGTH/POTENCY: 24 mcg

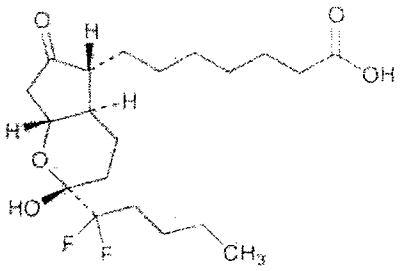
13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Name:

(-)-7-[(2R, 4aR, 5R, 7aR)-2-(1,1-difluoropentyl)-2-hydroxy-6-oxooctahydrocyclopenta[b]pyran-5-yl]heptanoic acid

Molecular Formula: $C_{20}H_{32}F_2O_5$

Molecular Weight: 390.46

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
—	II	R-Tech Ueno Ltd	RU-0211	1	Inadequate	November 7, 2005	Deficiencies sent to DMF holder
—	II	—	—	1	Inadequate	November 21, 2005	Deficiencies sent to DMF holder

[1] Action codes for DMF Table:
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B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
CMC EOP-2 meeting minutes	IND 59, 623	

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not Applicable		
EES	Pending		
Pharm/Tox	Not Applicable		
Biopharm	Pending		
LNC	Not Applicable		
Methods Validation	Pending		
DMETS	Pending		
EA	See review notes		
Microbiology	Approval	30-Sep-2005	Bryan S. Riley, Ph. D.

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for NDA 21-908

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Based on the CMC point of view this NDA is approvable pending acceptable manufacturing inspection and adequate response for the information requested in the list of deficiencies to be communicated to the applicant in section III of this review.

1. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Lubiprostone (RU-0211) is classified as a locally acting chloride channel activator that promotes a chloride-rich intestinal fluid secretion without altering sodium and potassium concentrations in the serum. Lubiprostone acts by specifically activating ClC-2, which is a normal constituent of the apical membrane of the human intestine, in a protein kinase A-independent fashion. By increasing intestinal fluid secretion, lubiprostone increases motility in the intestine thereby increasing the passage of stool and alleviating symptoms associated with chronic idiopathic constipation. One clinical concern is the off-label use of Lubiprostone as abortifacient if inserted virginally. Therefore, a microbiological consult was requested to assess the specifications in the context of the intravaginal administration. The comment from the consulting is approval.

The drug substance RU-0211 is a new molecular entity with 4 chiral centers. The sponsor provided characterization data including to demonstrate the structure of RU-0211 molecule. The sponsor also provided physical chemical properties. RU-0211 is insoluble in water but soluble in certain organic solvent. RU-0211 has a pKa at approximately 4.4 calculated from extrapolation of RU-0211 titration in EtOH/water. studies demonstrate that RU-0211 is a crystalline Data about the structure elucidation and physical chemical properties were reviewed and were found acceptable. RU-0211 is synthesized

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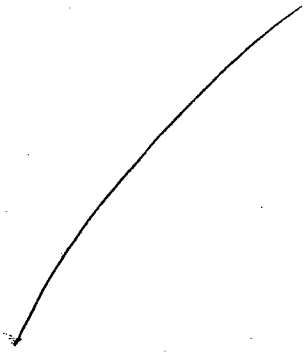

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B. Description of How the Drug Product is Intended to be Used

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The drug product is available as an oval, orange, soft gelatin capsule with "SPI" printed on one side. Each capsule contains 24 mcg lubiprostone. The recommended dosage for — is 24 mcg taken twice daily orally, for a total daily dose of 48 mcg.

C. Basis for Approvability or Not-Approval Recommendation

Based on the CMC review, there are a few deficiencies need to be resolved before this NDA can be approved. However, these deficiencies should be able to fix in this review circle.

III. Administrative

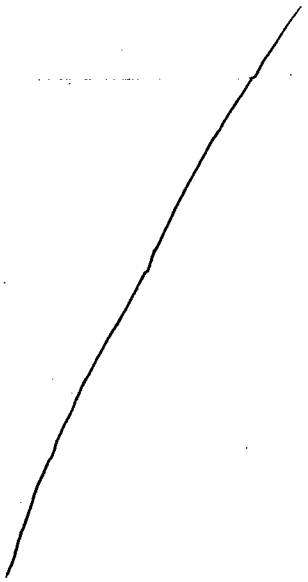
A. Reviewer's Signature

In DFS

B. Endorsement Block

Chemist: Zhengfang Ge
Chemistry Branch Chief: Moo-Jhong Rhee
ProjectManager: Tanya Clayton

C. CC Block



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___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

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/s/

Zhengfang Ge
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Moo-Jhong Rhee
12/5/2005 12:53:05 PM
CHEMIST
Chief, Branch III

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