CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 21214/S-006

Trade Name: RESCULA

Generic Name: unoprostone isopropyl ophthalmic solution

Sponsor: Sucampo Pharma Americas, LLC

Approval Date: 12/07/2012

Indication: Rescula (unoprostone isopropyl ophthalmic solution) 0.15% is indicated for the lowering of intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21214/S-006

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21214/S-006

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21-214/S-006
NDA 21-214/S-007

SUPPLEMENT APPROVAL

Sucampo Pharma Americas, LLC
Attention: Jeff Carey
Senior Director, Regulatory Affairs
4520 East-West Highway, Suite 300
Bethesda, MD 20814

Dear Mr. Carey:

Please refer to your Supplemental New Drug Applications (sNDAs) dated and received August 21, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Rescula (unoprostone isopropyl ophthalmic solution) 0.15%.

We acknowledge receipt of your amendments to Supplement-006 dated August 26 and October 20, 2009, September 16, 2010, and November 19, 2012.

We also acknowledge receipt of your amendments to Supplement-007 dated July 25 and August 27, 2012. The August 27, 2012, submission to Supplement-007 constituted a complete response to our March 20, 2012, action letter.

These "Prior Approval" supplemental new drug applications provide for the following changes:

(1) Supplement-006: Requests approval of the following lots listed below manufactured at R-Techs Ueno, Ltd Eye Drop Plant. This supplement also proposes to change the bottle container from a polypropylene to low-density polyethylene.

List of 44 Rescula Ophthalmic Solution 0.15% batches produced at R-Tech Ueno, Ltd Eye Drops plant

	Lot number	Date of Manufacturing	Number of Bottles	Expiration date
1	U04BA	(b) (4)		
2	U05BA			
3	U06BA			
4	U07BA			
5	U08BA			
6	U09BA			
7	U10BA			
8	U11BA			

		(b) (4)
9	U12BB	
10	U13BB	
11	U14BB	
12	U15BB	
13	U16BB	
14	U17BB	
15	U18BB	
16	U19BB	
17	U20BB	
18	U21BB	
19	U22BB	
20	U23BB	
21	U24BB	
22	U25BB	
23	U26BB	
24	U27BB	
25	U28BB	
26	U29BB	
27	U30BB	
28	U31BB	
29	U32BB	
30	U33BB	
31	U34BC	
32	U35BC	
33	U36BC	
34	U37BC	
35	U38BC	
36	U39BC	
37	U40BC	
38	U41BC	
39	U42BC	
40	U43BC	
41	U44BC	
42	U45BC	
43	U46BC	
44	U47BC	

We note that the R-Tech Ueno Eye Drop Plant, located in Sanda, Japan, was closed as of October 31, 2012, after manufacturing 44 lots of Rescula 0.15%.

(2) Supplement-007: Provides for a package insert which complies with the Physician's Labeling Rule (PLR) format.

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

We note your August 27, 2012, submission for the following administrative change: the corporate name "Sucampo Pharma Americas, Inc." has changed to "Sucampo Pharma Americas, LLC." This change is reflected in the associated labeling for this product.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions regarding these supplemental applications, please contact the following individuals:

Supplement-006: Ms. Althea Cuff, Regulatory Health Project Manager, at (301) 796-4061
Supplement-007: Ms. Judit Milstein, Chief, Project Management Staff, at (301) 796-0763

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, M.D.
Deputy Director
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

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

/s/

WILEY A CHAMBERS
12/07/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21214/S-006

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use RESCULA safely and effectively. See full prescribing information for RESCULA.

Rescula (unoprostone isopropyl ophthalmic solution) 0.15%
Initial U.S. Approval: 2000

---------- INDICATIONS AND USAGE ----------
- Rescula (unoprostone isopropyl ophthalmic solution) 0.15% is indicated for the lowering of intraocular pressure in patients with open-angle glaucoma or ocular hypertension. (1)

---------- DOSAGE AND ADMINISTRATION ----------
- One drop in the affected eye(s) twice daily (2)

---------- DOSAGE FORMS AND STRENGTHS ----------
- Unoprostone isopropyl ophthalmic solution, 1.5 mg/mL (3)

---------- CONTRAINDICATIONS ----------
- Hypersensitivity to unoprostone isopropyl or any of the excipients (4)

---------- WARNINGS AND PRECAUTIONS ----------
- Rescula has been reported to increase pigmentation of the iris (5.1)
- Rescula has been reported to increase pigmentation of the periorbital tissues and eyelashes (5.2)
- Rescula should be used with caution in patients with active intraocular inflammation because the inflammation may be exacerbated (5.3)

---------- ADVERSE REACTIONS ----------
- Most common adverse reactions (incidence 10–25%) are burning/stinging, burning/stinging upon drug instillation, dry eyes, itching, increased length of eyelashes and injection (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sucampo Pharma Americas at 1-855-RESCULA (1-855-737-2852) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 11/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Rescula (unoprostone isopropyl ophthalmic solution) 0.15% is indicated for the lowering of intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

2 DOSAGE AND ADMINISTRATION

The recommended dosage is one drop in the affected eye(s) twice daily.

Rescula may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If two drugs are used, they should be administered at least five (5) minutes apart *[see Patient Counseling Information (17.5)]*.

3 DOSAGE FORMS AND STRENGTHS

Unoprostone isopropyl ophthalmic solution 1.5 mg/mL.

4 CONTRAINDICATIONS

Rescula is contraindicated in patients with hypersensitivity to unoprostone isopropyl or any other ingredient in this product.

5 WARNINGS AND PRECAUTIONS

5.1 Iris Pigmentation

Unoprostone isopropyl ophthalmic solution may gradually increase the pigmentation of the iris. The pigmentation change is believed to be due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. The long term effects of increased pigmentation are not known. Iris color changes seen with administration of unoprostone isopropyl ophthalmic solution may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts of the iris become more brownish. Neither nevi nor freckles of the iris appear to be affected by treatment. Treatment with Rescula solution can be continued in patients who develop noticeably increased iris pigmentation.

Patients who receive treatment with Rescula should be informed of the possibility of increased pigmentation *[see Patient Counseling Information (17.2)]*.

5.2 Lid Pigmentation

Unoprostone isopropyl has been reported to cause pigment changes (darkening) to periorbital pigmented tissues and eyelashes. The pigmentation is expected to increase as long as unoprostone isopropyl is administered, but has been reported to be reversible upon discontinuation of unoprostone isopropyl ophthalmic solution in most patients.

5.3 Intraocular Inflammation

Rescula should be used with caution in patients with active intraocular inflammation (e.g., uveitis) because the inflammation may be exacerbated.

5.4 Macular Edema

Macular edema, including cystoid macular edema, has been reported. Rescula should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

5.5 Contamination of Tip And Solution

To minimize contaminating the dropper tip and solution, care should be taken not to touch the eyelids or surrounding areas with the dropper tip of the bottle. Keep bottle tightly closed when not in use. There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products *[see Patient Counseling Information (17.1)]*.

5.6 Use with Contact Lenses

Rescula contains benzalkonium chloride, which may be absorbed by soft contact lenses. Contact lenses should be removed prior to application of solution and may be reinserted 15 minutes following its administration *[see Patient Counseling Information (17.4)]*.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

In clinical studies, the most common ocular adverse reactions with use of Rescula were burning/stinging, burning/stinging upon drug instillation, dry eyes, itching, increased length of eyelashes, and injection. These were reported in approximately 10–25% of patients. Approximately 10–14% of patients were observed to have an increase in the length of eyelashes (≥ 1 mm) at 12 months, while 7% of patients were observed to have a decrease in the length of eyelashes.

Ocular adverse reactions occurring in approximately 5–10% of patients were abnormal vision, eyelid disorder, foreign body sensation, and lacrimation disorder.

Ocular adverse reactions occurring in approximately 1–5% of patients were blepharitis, cataract, conjunctivitis, corneal lesion, discharge from the eye, eye hemorrhage, eye pain, keratitis, irritation, photophobia, and vitreous disorder.

Other ocular adverse reactions reported in less than 1% of patients were acute elevated intraocular pressure, color blindness, corneal deposits, corneal edema, corneal opacity, diplopia, hyperpigmentation of the eyelid, increased number of eyelashes, iris hyperpigmentation, iritis, optic atrophy, ptosis, retinal hemorrhage, and visual field defect.

The most frequently reported nonocular adverse reaction associated with the use of Rescula in the clinical trials was flu-like syndrome that was observed in approximately 6% of patients. Nonocular adverse reactions reported in the 1–5% of patients were accidental injury,

allergic reaction, back pain, bronchitis, increased cough, diabetes mellitus, dizziness, headache, hypertension, insomnia, pharyngitis, pain, rhinitis, and sinusitis.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Rescula. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Voluntary reports of adverse reactions occurring with the use of Rescula include corneal erosion.

There have been rare spontaneous reports with a different formulation of unoprostone isopropyl (0.12%) of chemosis, dry mouth, nausea, vomiting and palpitations.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C
Teratogenic effects: There were no teratogenic effects observed in rats and rabbits up to 5 and 0.3 mg/kg/day (approximately 1,000 and 60 fold the recommended human dose of 0.005 mg/kg/day in the rat and rabbit, respectively). There was an increase in the incidence of miscarriages and a decrease in live birth index in rats administered unoprostone isopropyl during organogenesis at subcutaneous doses of 5 mg/kg. There was an increase in incidence of miscarriages and resorptions and a decrease in the number of live fetuses in rabbits administered unoprostone isopropyl during organogenesis at subcutaneous doses of 0.3 mg/kg. The no observable adverse effect level (NOAEL) for embryofetal toxicity in rats and rabbits was 2 and 0.1 mg/kg (approximately 400 and 20 fold the recommended human dose of 0.005 mg/kg/day in the rat and rabbit, respectively).

There was an increase in incidence of premature delivery, a decrease in live birth index, and a decrease in weight at birth and through postpartum Day 7 in rats administered unoprostone isopropyl during late gestation through postpartum Day 21 at subcutaneous doses of 1.25 mg/kg. In addition, pups from rats administered 1.25 mg/kg subcutaneously exhibited delayed growth and development characterized by delayed incisor eruption and eye opening. There was an increase in the number of stillborn pups and a decrease in perinatal survival in rats administered unoprostone isopropyl during late gestation through weaning at subcutaneous doses of $\geq$ 0.5 mg/kg. The NOAEL for pre- and postnatal toxicity in rats was 0.2 mg/kg (approximately 40 fold the recommended human dose of 0.005 mg/kg/day).

There are no adequate and well-controlled studies in pregnant women. Because animal studies are not always predictive of human response, Rescula should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers

It is not known whether Rescula is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Rescula is administered to a nursing woman.

8.4 Pediatric Use

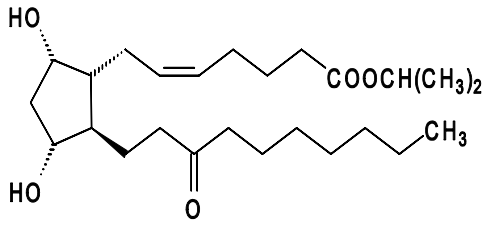
Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

No overall differences in safety or effectiveness have been observed between elderly and other adult patients.

11 DESCRIPTION

Rescula (unoprostone isopropyl ophthalmic solution) 0.15% is a synthetic docosanoid. Unoprostone isopropyl has the chemical name isopropyl (+)-(*Z*)-7-[(1*R*,2*R*,3*R*,5*S*)-3,5-dihydroxy-2-(3-oxodecyl)cyclopentyl]-5-heptenoate. Its molecular formula is $C_{25}H_{44}O_5$ and its chemical structure is:



Unoprostone isopropyl is a clear, colorless, viscous liquid that is very soluble in acetonitrile, ethanol, ethyl acetate, isopropanol, dioxane, ether, and hexane. It is practically insoluble in water. Rescula (unoprostone isopropyl ophthalmic solution) 0.15% is supplied as a sterile, isotonic, buffered, aqueous solution of unoprostone isopropyl with a pH of 5.0–6.5 and an osmolality of 235–300 mOsmol/kg.

Each mL of Rescula contains 1.5 mg of unoprostone isopropyl. Benzalkonium chloride 0.015% is added as a preservative. Inactive ingredients are mannitol, polysorbate 80, edetate disodium, sodium hydroxide or hydrochloric acid (to adjust pH), and water for injection.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Rescula is believed to reduce elevated intraocular pressure (IOP) by increasing the outflow of aqueous humor through the trabecular meshwork. Unoprostone isopropyl (UI) may have a local effect on BK (Big Potassium) channels and ClC-2 chloride channels, but the exact mechanism is unknown at this time.

12.3 Pharmacokinetics

Absorption

After application to the eye, unoprostone isopropyl is absorbed through the cornea and conjunctival epithelium where it is hydrolyzed by esterases to unoprostone free acid.

A study conducted with 18 healthy volunteers dosed bilaterally with unoprostone isopropyl ophthalmic solution twice daily for 14 days demonstrated little systemic absorption of unoprostone isopropyl. The systemic exposure of its metabolite unoprostone free acid was minimal following the ocular administration. Mean peak unoprostone free acid concentration was less than 1.5 ng/mL. Little or no accumulation of unoprostone free acid was observed.

Metabolism

Following ocular application, unoprostone isopropyl is hydrolyzed by esterases in the cornea to its biological active metabolite, unoprostone free acid. Unoprostone free acid is further metabolized to several inactive metabolites with lower molecular weight and increased polarity via ω- or β-oxidation. No secondary conjugation is found and no significant effect on hepatic microsomal enzyme activity has been observed.

Elimination

Elimination of unoprostone free acid from human plasma is rapid, with a half-life of 14 minutes. Plasma levels of unoprostone free acid dropped below the lower limit of quantitation (< 0.25 ng/mL) 1 hour following ocular instillation. The metabolites are excreted predominately in urine.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Unoprostone isopropyl was not carcinogenic in rats administered oral doses up to 12 mg/kg/day for up to 2 years (approximately 580 and 240 fold the recommended human dose of 0.005 mg/kg/day based on $AUC_{0–24}$ in male and female rats, respectively).
Under the conditions tested, unoprostone isopropyl and unoprostone free acid were neither mutagenic in an Ames assay nor clastogenic in a chromosome aberration assay in Chinese hamster lung–derived fibroblast cells. Under the conditions tested, unoprostone isopropyl was not genotoxic in a mouse lymphoma mutation assay or clastogenic in an *in vivo* chromosomal aberration test in mouse bone marrow.
Unoprostone isopropyl did not impair male or female fertility in rats at subcutaneous doses up to 50 mg/kg (approximately 10,000 fold the recommended human dose of 0.005 mg/kg/day).

14 CLINICAL STUDIES

In six (6) month randomized controlled clinical studies in patients with a mean baseline intraocular pressure of 23 mmHg, Rescula lowered intraocular pressure by approximately 3–4 mmHg throughout the day. Rescula appeared to lower intraocular pressure without affecting cardiovascular or pulmonary function.

16 HOW SUPPLIED/STORAGE AND HANDLING

Rescula (unoprostone isopropyl ophthalmic solution) 0.15% is supplied sterile in a low-density polyethylene bottle with a low-density polyethylene dropper tip, a turquoise polypropylene closure, and a clear tamper-evident shrinkband.

5 mL in a 7.5 mL bottle NDC 17350-015-05

Storage: Store between 2° - 25°C (36° - 77°F).

17 PATIENT COUNSELING INFORMATION

17.1 Handling the Bottle

Patients should be instructed that the Rescula bottle must be maintained intact and to avoid allowing the tip of the bottle to contact surrounding structures, fingers, or any other unintended surface in order to avoid contamination of the bottle or applicator by common bacteria known to cause ocular infections. Serious infections may result from using contaminated solutions.

17.2 Potential for Iris Darkening

Patients should be advised about the potential for increased brown iris pigmentation which is likely to be permanent.

17.3 Potential For Eyelid Skin Darkening

Patients should be informed about the possibility of eyelid skin darkening, which may be reversible after discontinuation of Rescula.

17.4 Use with Contact Lenses

Patients should be advised that Rescula contains benzalkonium chloride, which may be absorbed by soft contact lenses. Contact lenses should be removed prior to application of Rescula and may be reinserted 15 minutes following its administration.

17.5 Multiple Therapies

If more than one topical ophthalmic therapy is being used patients should be instructed to administer the drugs at least 5 minutes apart.

Marketed by:
Sucampo Pharma Americas, LLC
Bethesda, MD 20814

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21214/S-006

CHEMISTRY REVIEW(S)

Chemistry Review: # 3 Addendum	**1. Division:** HFD-520	**2. NDA Number:** **21-214**

3. Name and Address of Applicant:
Sucampo Pharma Americas, Inc.
4520 East-West Highway
Suite 300
Bethesda, MD 20814

4. Supplement(s):
Number: SCM-006
Date(s): August 21, 2009
Addendum: December 7, 2012

5. Name of Drug:
Rescula

6. Nonproprietary name:
Unoprostone Isopropyl

7. Supplement Provides for: the addition of R-Techs Ueno, Ltd Eye Drop Plant (Sanda, Hyogo, Japan) as the manufacturer of 0.15% Rescula for the U.S. market and proposes to change the bottle container from polypropylene to low-density polyethylene.

8. Amendment(s): None

9. Pharmacological Category: Reducction of elevated intraocular pressure in open-angle glaucoma or ocular hypertension

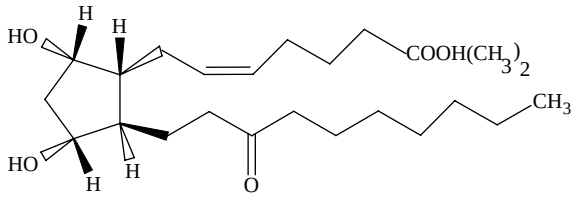
10. How Dispensed:
R_x

11. Related Documents:
None

12. Dosage Form:
Ophthalmic Topical

13. Potency(es):
Unoprostone Isopropyl 0.15%

14. Chemical Name and Structure: Unoprostone Isopropyl, (+)-Isopropyl (*Z*)-7-[(1*R*,2*R*,3*R*,5*S*)-3,5-dihydroxy-2-(3-oxodecyl)cyclopentyl]hept-5-enoate, **$C_{25}H_{44}O_5$,** M.W. 424.61



15. Comments: This drug product, Rescula, was approved for Novartis by the FDA in August 2000 as Isopropyl Unoprostone (Rescula) Ophthalmic Solution 0.15%, in NDA 21-214. Rescula was then marketed in the USA until 2004, when Novartis ceased distribution of this drug product in the U.S. due to discontinued manufacturing of the drug product at the approved Ciba Vision Sterile Manufacturing, CVSM plant in Mississauga, ON, Canada. Ownership of NDA 21-214 was then transferred to R-Tech Ueno, Ltd., in 2006, and thereafter, to Sucampo Pharma Americas Inc. in July, 2009.

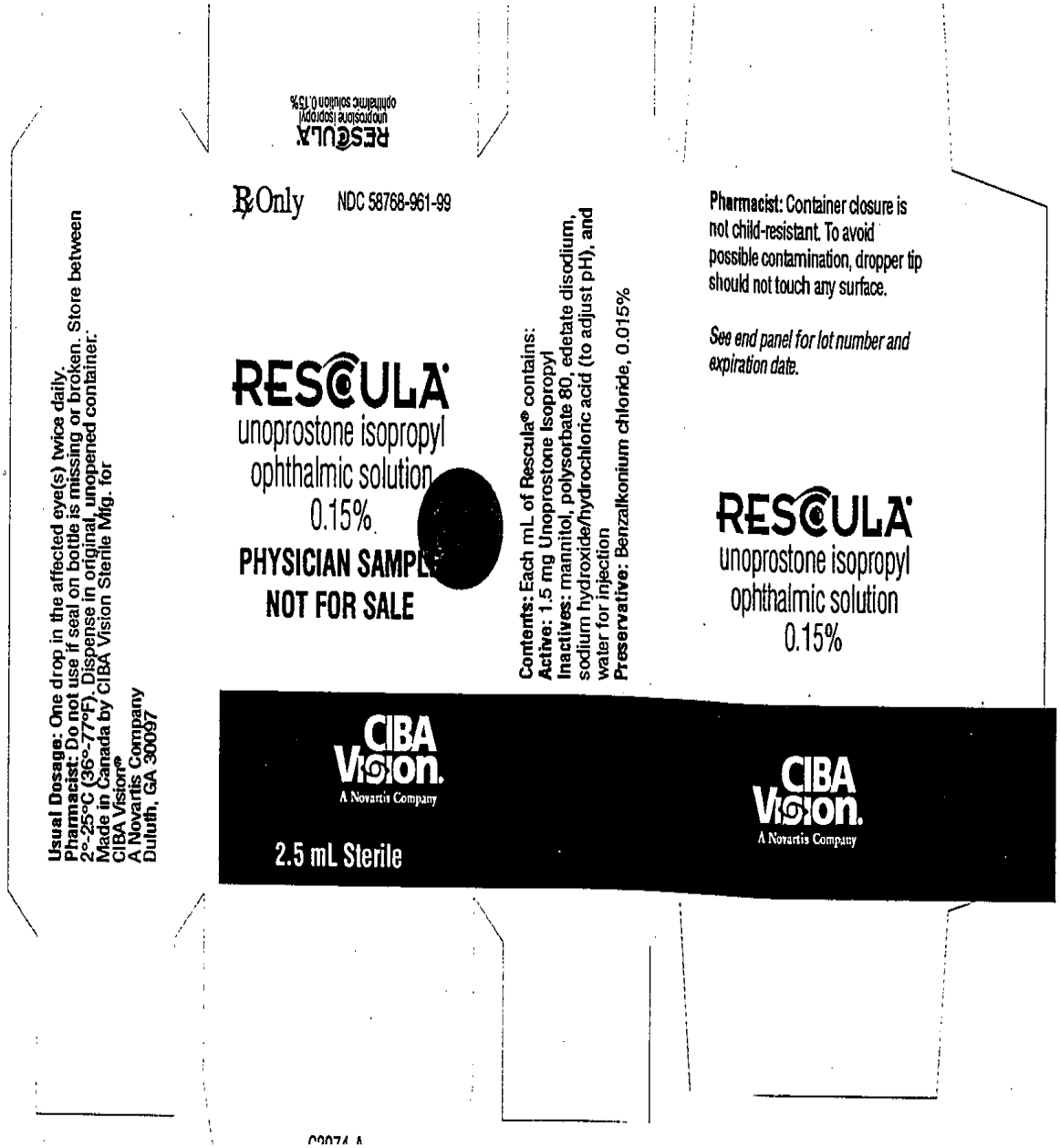
This addendum to review #3 compares the labeling from the previously approved Rescula unoprostone isopropyl Ophthalmic Solution 0.15% manufactured at the approved Ciba Vision Sterile Manufacturing, CVSM plant in Mississauga, ON, Canada, to the labeling for the same drug product manufactured at the R-Tech Ueno, Ltd., proposed manufacturing facility. See Chemistry Review Notes below for the side by side comparison.

16. **Conclusions and Recommendations: T**his addendum to review # 3 of this supplemental application clarifies final details raised during the completion of the evaluation of this application. The CMC recommendation for **approval** in this review #3 remains unchanged.

17. Name: **Signature:** **Date:**
Libaniel Rodriguez, Ph.D., Review Chemist/ONDQA/DII/BVI

18. Concurrence: **Signature:** **Date:**
Thomas Oliver, Ph.D., Branch Chief/ONDQA/DII/BVI

Chemistry Review Notes: The following are the commercial and physician carton for the Rescula Ophthalmic Solution 15%, currently approved (first two cartons) and the proposed cartons (third and fouth cartons).



1 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

Comment: Side by side comparison of the two sets of cartons (approved and proposed), indicate that the proposed carton label has been appropriately revised to indicate the logo and name of the new company that owns the brand, Sucampo Pharma Americas, LLC, at the front and back of the carton and the side panel of the carton has been revised to indicate the new owner and place of manufacturing as follows: "Manufactured for Sucampo Pharma Americas, LLC. Bethesda, MD 20814"
Followed two lines below by: "Made in Japan".

All other aspects (components, storage, dosage, caution.. etc) of the carton label approved in the original product remain unchanged in this proposed carton label.

The CMC relevant sections of the Package Insert (sections 3, 11 and 16) remain acceptable. Section 16 was initially revised to reflect the change in container from polypropylene to Low density polyethylene. This change was found acceptable in the microbiology and CMC reviews.

The applicant did not have a current container label available. However, the applicant has PI and carton label with the correct update company name. As the applicant has two of the labeling components updated and the change is very minor; CMC finds labeling acceptable. Note: Updating the name could actually be covered via an annual report.

Conclusion: This addendum to review # 3 of this supplemental application clarifies final details raised during the completion of the evaluation of this application. The CMC recommendation for approval in this review #3 remains unchanged.

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/s/

LIBANIEL RODRIGUEZ
12/07/2012

THOMAS F OLIVER
12/07/2012

Chemistry Review: # 3	**1. Division:** HFD-520	**2. NDA Number:** **21-214**

3. Name and Address of Applicant:
Sucampo Pharma Americas, Inc.
4520 East-West Highway
Suite 300
Bethesda, MD 20814

4. Supplement(s):
Number: SCM-006
Date(s): August 21, 2009

5. Name of Drug:
Rescula

6. Nonproprietary name:
Unoprostone Isopropyl

7. Supplement Provides for: the addition of R-Techs Ueno, Ltd Eye Drop Plant (Sanda, Hyogo, Japan) as the manufacturer of 0.15% Rescula for the U.S. market and proposes to change the bottle container from polypropylene to low-density polyethylene.

8. Amendment(s): None

9. Pharmacological Category: Reducction of elevated intraocular pressure in open-angle glaucoma or ocular hypertension

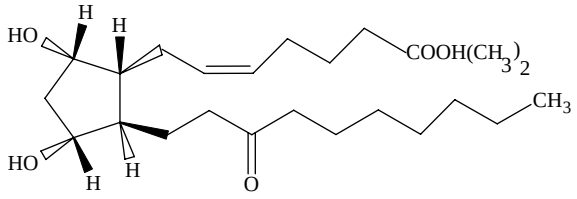
10. How Dispensed:
R_x

11. Related Documents:
None

12. Dosage Form:
Ophthalmic Topical

13. Potency(es):
Unoprostone Isopropyl 0.15%

14. Chemical Name and Structure: Unoprostone Isopropyl, (+)-Isopropyl (*Z*)-7-[(1*R*,2*R*,3*R*,5*S*)-3,5-dihydroxy-2-(3-oxodecyl)cyclopentyl]hept-5-enoate, **$C_{25}H_{44}O_5$,** M.W. 424.61



15. Comments: This drug product, Rescula, was approved for Novartis by the FDA in August 2000 as Isopropyl Unoprostone (Rescula) Ophthalmic Solution 0.15%, in NDA 21-214. Rescula was then marketed in the USA until 2004, when Novartis ceased distribution of this drug product in the U.S. due to discontinued manufacturing of the drug product at the approved Ciba Vision Sterile Manufacturing, CVSM plant in Mississauga, ON, Canada. Ownership of NDA 21-214 was then transferred to R-Tech Ueno, Ltd., in 2006, and thereafter, to Sucampo Pharma Americas Inc. in July, 2009.

This supplement requests approval of R-Techs' Ueno, Ltd., Eye Drop Plant located in Sanda, Japan (R-Tech) as the manufacturer of 0.15% Rescula for the U.S. market. R-Tech has been producing Rescula Eye Drops 0.12% for the Japanese and world market since 1994.

The CMC information and stability data provided indicate that the proposed manufacturing facility, R-Tech Ueno, can manufacture Rescula 0.15% ophthalmic solution of the same quality as the Rescula drug product manufactured at the previously approved facility (Ciba Vision Sterile Manufacturing, CVSM plant in Mississauga, ON, Canada); it also demonstrates that manufacture of Rescula 0.15% Opthalmic Solution at the proposed R-Tech Ueno facility does not have any adverse effect on the quality of the final drug product. See CMC reviews (dated 16-DEC-09 and 11-JAN-10 by Dr. Libaniel Rodriguez).

Reviews #1 and #2, raised issues regarding the microbiology information missing in this application.

All of the microbiology issues were satisfactorily resolved in the amendment submitted on December 17, 2010.
Dr. Robert J. Mello (microbiology) reviewed the responses and issued an approval recommendation on July 11, 2012.

The R-Tech Ueno site was inspected in July 2012. The Office of Compliance (OC) issued an overall recommendation of **ACCEPTABLE** for the proposed R-Tech Ueno manufacturing facility on December 5, 2012. See OC report below.

After the R-Tech Ueno facility, inspected above, manufactured 44 lots of drug product Rescula Ophthalmic Solution 0.15% (see list of lots manufactured with dates of manufacture and proposed shelf life attached), this facility was closed to manufacturing of the drug product Rescula 15% (see statement attached).

The applicant proposed a 30 months shelf life for these lots of Rescula 15%, with future extension to (b) (4) through satisfactory data provided in annual reports.

The proposed 30 months shelf life and further extension through compliant data in annual reports for the 44 lots above is acceptable.

16. **Conclusions and Recommendations:** All the issues concerning CMC raised during the first review cycle of this supplement have been resolved satisfactorily. For this reason, from the point of view of CMC, this supplement is recommended for approval. The approval letter should contain the list of lots of Rescula batches manufactured at the proposed R-Tech Ueno facility prior to closure and a statement that there will be no further manufacturing of Rescula 0.15% at the same facility (as stated by the applicant).

17. Name: **Signature:** **Date:**
Libaniel Rodriguez, Ph.D., Review Chemist/ONDQA/DII/BVI

18. Concurrence: **Signature:** **Date:**
Thomas Oliver, Ph.D., Branch Chief/ONDQA/DII/BVI

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 21214/006	**Sponsor:**	SUCAMPO PHARMS
Org. Code:	590		4520 EAST-WEST HWY 3RD FL
Priority:	1P		BETHESDA, MD 20814
Stamp Date:	21-AUG-2009	**Brand Name:**	RESCULA(UNOPROSTONE ISOPROPYL OPHTHALMIC
PDUFA Date:	21-DEC-2009	**Estab. Name:**	
Action Goal:		**Generic Name:**	UNOPROSTONE ISOPROPYL OPHTHALMIC SOLUTIO
District Goal:	16-NOV-2009	**Product Number; Dosage Form; Ingredient; Strengths**	
		001; SOLUTION, DROPS; UNOPROSTONE ISOPROPYL; .15%	

FDA Contacts:	A. CUFF	Project Manager	(HF-01)	3017964061
	L. RODRIGUEZ	Review Chemist		3017961445
	S. DE	Team Leader		3017961664

Overall Recommendation:	ACCEPTABLE	on 05-DEC-2012	by T. GOOEN	(HFD-320)	3017963257
	WITHHOLD	on 02-NOV-2012	by D. SMITH	(HFD-323)	3017965321
	PENDING	on 31-OCT-2012	by EES_PROD		
	PENDING	on 20-MAR-2012	by EES_PROD		
	ACCEPTABLE	on 26-JUL-2011	by M. STOCK	(HFD-320)	3017964753
	ACCEPTABLE	on 29-JUN-2010	by A. INYARD	(HFD-323)	3017965363
	WITHHOLD	on 15-DEC-2009	by JOHNSONE		

Establishment:	**CFN:** 9614764	**FEI:** 3004520523	
	R-TECH UENO, LTD. 4-1 TECHNO PARK SANDA, HYOGO, JAPAN		
DMF No:	14611	**AADA:**	
Responsibilities:	FINISHED DOSAGE MANUFACTURER		
Profile:	STERILE LIQUID (EXCLUDE SUSPENSIONS & EMULSIONS)	**OAI Status:**	NONE
Last Milestone:	NO FURTHER EVALUATION		
Milestone Date:	05-DEC-2012		

R-Tech Ueno Response

Information on Rescula (unoprostone isopropyl) ophthalmic solution 0.15% manufactured for Sucampo at R-Tech Ueno Eye drops plant located in Sanda Japan.

List of Rescula Ophthalmic Solution 0.15% batches produced at R-Tech Eye Drops plant

	Lot number	Date of Manufacturing	Number of Bottles	Expiration date
1	U04BA	(b) (4)		
2	U05BA			
3	U06BA			
4	U07BA			
5	U08BA			
6	U09BA			
7	U10BA			
8	U11BA			
9	U12BB			
10	U13BB			
11	U14BB			
12	U15BB			
13	U16BB			
14	U17BB			
15	U18BB			
16	U19BB			
17	U20BB			
18	U21BB			
19	U22BB			
20	U23BB			
21	U24BB			
22	U25BB			
23	U26BB			
24	U27BB			
25	U28BB			
26	U29BB			
27	U30BB			
28	U31BB			
29	U32BB			
30	U33BB			
31	U34BC			
32	U35BC			
33	U36BC			
34	U37BC			

35	U38BC	(b) (4)
36	U39BC	
37	U40BC	
38	U41BC	
39	U42BC	
40	U43BC	
41	U44BC	
42	U45BC	
43	U46BC	
44	U47BC	

The eye drops plant is now closed and there is no more Rescula 0.15% batch production at the plant.

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/s/

LIBANIEL RODRIGUEZ
12/06/2012

THOMAS F OLIVER
12/06/2012

Chemistry Review: # 2	**1. Division:** HFD-520	**2. NDA Number:** 21-214

3. Name and Address of Applicant:
Sucampo Pharma Americas, Inc.
4520 East-West Highway
Suite 300
Bethesda, MD 20814

4. Supplement(s):
Number: SCM-006
Date(s): August 21, 2009

5. Name of Drug:
Rescula

6. Nonproprietary name:
Unoprostone Isopropyl

7. Supplement Provides for: Re-listing of Rescula (uniprostone Isopropyl). Review #2, microbiological review and conclusions.

8. Amendment(s): None

9. Pharmacological Category: Reducction of elevated intraocular pressure in open-angle glaucoma or ocular hypertension

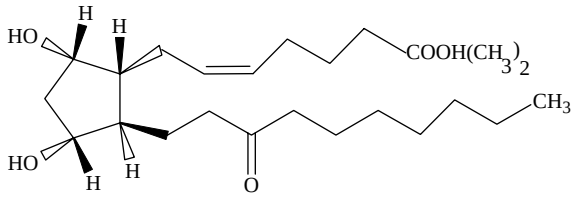
10. How Dispensed:
R_x

11. Related Documents:
None

12. Dosage Form:
Ophthalmic Topical

13. Potency(es):
Unoprostone Isopropyl 0.15%

14. Chemical Name and Structure: Unoprostone Isopropyl, (+)-Isopropyl (*Z*)-7-[(1*R*,2*R*,3*R*,5*S*)-3,5-dihydroxy-2-(3-oxodecyl)cyclopentyl]hept-5-enoate, **$C_{25}H_{44}O_5$,** M.W. 424.61



15. Comments: This drug product, Rescula, was approved for Novartis by the FDA in August 2000 as Isopropyl Unoprostone (Rescula) Ophthalmic Solution 0.15%, in NDA 21-214. Rescula was then marketed in the USA until 2004, when Novartis ceased distribution of this drug product in the U.S. due to discontinued manufacturing of the drug product at the approved Ciba Vision Sterile Manufacturing, CVSM plant in Mississauga, ON, Canada. Ownership of NDA 21-214 was then transferred to R-Tech Ueno, Ltd., in 2006, and thereafter, to Sucampo Pharma Americas Inc. in July, 2009.

This supplement requests approval of R-Techs' Ueno, Ltd., Eye Drop Plant located in Sanda, Japan (R-Tech), the currently approved manufactuctured of Rescula 0.15% Ophthalmic Solution, as the manufacturer of 0.15% Rescula for the U.S. market. R-Tech has been producing Rescula Eye Drops 0.12% for the Japanese and world market since 1994.

Changes in the container/closure materials from polypropylene (PP) to low-density polyethylene (LDPE) to accommodate manufacturing at the proposed site are also requested.

There are no changes to the approved (NDA 21-214) manufacturer and manufacture and acceptance criteria of the drug substance, and no changes to the component/composition, manufacturing, process controls, acceptance criteria and (b) (4) of the drug product will be made as a result of this manufacturing transfer.

Information and data provided in support of this request includes the following:

- Updated manufacturer/manufacture at the proposed facility. See this review.
- Detailed information on the proposed container/closure (extractables and leachables) changes, made as a result of the manufacturing transfer. See review # 1.

Details and discussion of the information and data provided in support of the proposed change are addressed in the Chemistry Review Notes section below. **This review (review #2) deals mainly with the conclusions of the microbiology review.**

Microbiological aspects related to the transfer of manufacturing and change of materials for the container/closure for this (b) (4) drug product were sent for consult to microbiology team in OPS/NDMS/HFD-805 on September 21, 2009. The information was reviewed by Dr. R. Mello on December 31, 2009 and recommended for a complete response (CR), with the following deficiencies to be conveyed to the applicant: (See Conclusions and Recommendations section below).

The proposed manufacturing facility was submitted to the **Office of Compliance (OC) for inspection** on September 28, 2009. The OC inspected the facility and recommended withhold on December 15, 2009. See report attached to this review. See copy of report in Chemistry Review Notes below.

Clinical review of labeling changes was conducted by Dr. W. Boyd of HFD-520. Conclusion about labeling from the clinical review will be available when a "Citizens Petition" involving the type of drug substance used in this drug product is resolved.

The clinical information in this submission and the CMC information need to be split from each other and reviewed on their own.

16. **Conclusions and Recommendations:** The CMC information and stability data provided indicate that the proposed manufacturing facility, R-Tech Ueno, can manufacture Rescula 0.15% ophthalmic solution of the same quality as the Rescula drug product manufactured in the currently approved facility; it also demonstrates that manufacture of Rescula 0.15% Opthalmic Solution at the propose R-Tech Ueno facility does not have any adverse effect on the quality of the drug product. See review #1.

The microbiology review of the information provided recommended the application for a CR with the following deficiencies to be conveyed to the applicant:

- **The applicant did not provide sufficient details of the dye ingress or microbial ingress container closure tests. The applicant should provide the study protocols and summary reports of the completed studies (English Translations). The information should contain sufucient detail (temperatures/hold times/pressures) to assess the quality of the studies.**
- **DMF # 22987 for the drug product manufacturing was not adequate to support the submission. The DMF holder will be notified, separately, of the deficiencies.**

Splitting of the CMC section of this application from the clinical sections (labeling) is pending.

The Office of Compliance recommended the proposed manufacturing facility for withhold on December 15, 2009.

Based on the withhold recommendation by the Office of Compliance and the microbiology recommendation and deficiencies, this supplement is recommended for a Complete Response (CR) letter.

17. Name: **Signature:** **Date:**
Libaniel Rodriguez, Ph.D., Review Chemist

18. Concurrence: **Signature:** **Date:**
David Lewis, Ph.D., Pharmaceutical Assessment Lead, for Hasmukh Patel, Ph.D., Branch Chief, ONDQA/DPME/VIII

Chemistry Review Notes:

Detailed information on the proposed container/closure (extractables and leachables) changes, made as a result of the manufacturing transfer.

The original bottle approved for commercial distribution of Rescula 0.15% Ophthalmic Solution was made of polypropylene. Upon transfer, due to mechanical incompatibilities of the polypropylene bottle (b) (4), the bottle will be changed to a low density polyethylene (LDPE)made bottle.

All the details for the materials, construction and sterilization of the proposed LDPE bottle are described in DMF (b) (4). Letter of Authorization (LOA) dated August 6, 2009 is appropriately included in this application.

Because of the microbiological aspects related to the manufacturing of the LDPE container/closure, review of DMF (b) (4) was consulted to the microbiology team in OPS/NDMS.HFD-805, on November 29, 2009. DMFs related to this application were reviewed by Dr. R. Mello an recommended as **not adequate.** Defiencies to be sent separately to DMF holder.

Labeling: Updated labeling, Carton label, Bottle label and Package Insert (How Supplied section) , reflecting the change in manufacturing facility are provided in this application.

Comment: The updated labeling is acceptable from the point of view of CMC. However, there are labeling revisions and issues related to a Citizen's Petition involving this drug product. For this reason, the review by the clinical reviewer will be detached from the CMC sections of this application, so that CMC conducts an independent review of this application.

Conclusion: The CMC information and stability data provided indicate that the proposed manufacturing facility, R-Tech Ueno, can manufacture Rescula 0.15% ophthalmic solution of the same quality as the Rescula drug product manufactured in the currently approved facility; it also demonstrates that manufacture of Rescula 0.15% Opthalmic Solution at the propose R-Tech Ueno facility does not have any adverse effect on the quality of the drug product. See review #1.

The microbiology review of the information provided recommended the application for a CR with the following deficiencies to be conveyed to the applicant:

- **The applicant did not provide sufficient details of the dye ingress or microbial ingress container closure tests. The applicant should provide the study protocols and summary reports of the completed studies (English Translations). The information should contain sufucient detail (temperatures/hold times/pressures) to assess the quality of the studies.**
- **DMF # 22987 for the drug product manufacturing was not adequate to support the submission. The DMF holder will be notified, separately, of the deficiencies.**

Splitting of the CMC section of this application from the clinical sections (labeling) is pending.

The Office of Compliance recommended the proposed manufacturing facility for withhold on December 15, 2009.

Based on the withhold recommendation by the Office of Compliance and the microbiology recommendation and deficiencies, this supplement is recommended for a Complete Response (CR) letter.

Attachment:

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 21214/006	**Sponsor:**	R TECH UENO LTD
Org. Code:	520		7361 CALHOUN PL STE 500
Priority:	1P		ROCKVILLE, MD 208552765
Stamp Date:	21-AUG-2009	**Brand Name:**	RESCULA(UNOPROSTONE ISOPROPYL OPHTHALMIC
PDUFA Date:	21-DEC-2009	**Estab. Name:**	
Action Goal:		**Generic Name:**	UNOPROSTONE ISOPROPYL OPHTHALMIC SOLUTIO
District Goal:	16-NOV-2009	**Product Number; Dosage Form; Ingredient; Strengths**	
		001; SOLUTION, DROPS; UNOPROSTONE ISOPROPYL; .15%	

FDA Contacts:	A. CUFF	Project Manager	(HF-01)	301-796-4061
	L. RODRIGUEZ	Review Chemist		301-796-1445
	S. DE	Team Leader		301-796-1664

Overall Recommendation: WITHHOLD on 15-DEC-2009 by E. JOHNSON (HFD-320) 301-796-3334

Establishment:	**CFN:** 9614764 **FEI:**		
	R TECH UENO LTD 4-1 TECHNO PARK , , JAPAN		
DMF No:	14611	**AADA:**	
Responsibilities:	FINISHED DOSAGE MANUFACTURER		
Profile:	OPHTHALMIC/STERILE NON-INJECTABLE	**OAI Status:**	POTENTIAL OAI
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	15-DEC-2009		
Decision:	WITHHOLD		
Reason:	DISTRICT RECOMMENDATION		

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21214	SUPPL-6	R TECH UENO LTD	RESCULA(UNOPROSTONE ISOPROPYL OPHTHALMIC

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/s/

LIBANIEL RODRIGUEZ
01/11/2010

DAVID B LEWIS
01/11/2010
Concur; recommend CR due to micro deficincies and WH from OC. Signing for H. Patel.

Chemistry Review: # 1	**1. Division:** HFD-520	**2. NDA Number:** 21-214

3. Name and Address of Applicant:
Sucampo Pharma Americas, Inc.
4520 East-West Highway
Suite 300
Bethesda, MD 20814

4. Supplement(s):
Number: SCM-006
Date(s): August 21, 2009

5. Name of Drug:
Rescula

6. Nonproprietary name:
Unoprostone Isopropyl

7. Supplement Provides for: Re-listing of Rescula (uniprostone Isopropyl)

8. Amendment(s): None

9. Pharmacological Category: Reducction of elevated intraocular pressure in open-angle glaucoma or ocular hypertension

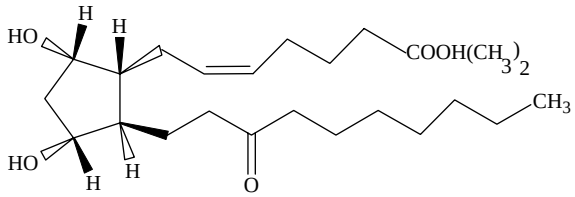
10. How Dispensed:
R_x

11. Related Documents:
None

12. Dosage Form:
Ophthalmic Topical

13. Potency(es):
Unoprostone Isopropyl 0.15%

14. Chemical Name and Structure: Unoprostone Isopropyl, (+)-Isopropyl (*Z*)-7-[(1*R*,2*R*,3*R*,5*S*)-3,5-dihydroxy-2-(3-oxodecyl)cyclopentyl]hept-5-enoate, **$C_{25}H_{44}O_5$,** M.W. 424.61



15. Comments: This drug product, Rescula, was approved for Novartis by the FDA in August 2000 as Isopropyl Unoprostone (Rescula) Ophthalmic Solution 0.15%, in NDA 21-214. Rescula was then marketed in the USA until 2004, when Novartis ceased distribution of this drug product in the U.S. due to discontinued manufacturing of the drug product at the approved Ciba Vision Sterile Manufacturing, CVSM plant in Mississauga, ON, Canada. Ownership of NDA 21-214 was then transferred to R-Tech Ueno, Ltd., in 2006, and thereafter, to Sucampo Pharma Americas Inc. in July, 2009.

This supplement requests approval of R-Techs' Ueno, Ltd., Eye Drop Plant located in Sanda, Japan (R-Tech), the currently approved manufactuctured of Rescula 0.15% Ophthalmic Solution, as the manufacturer of 0.15% Rescula for the U.S. market. R-Tech has been producing Rescula Eye Drops 0.12% for the Japanese and world market since 1994.

Changes in the container/closure materials from polypropylene (PP) to low-density polyethylene (LDPE) to accommodate manufacturing at the proposed site are also requested.

There are no changes to the approved (NDA 21-214) manufacturer and manufacture and acceptance criteria of the drug substance, and no changes to the component/composition, manufacturing, process controls, acceptance criteria and (b) (4) of the drug product will be made as a result of this manufacturing transfer.

Information and data provided in support of this request includes the following:

- Updated manufacturer/manufacture at the proposed facility.
- Data on validation of the methods transferred for testing of the drug product to the proposed facility.
- Detailed information on the proposed container/closure (extractables and leachables) changes, made as a result of the manufacturing transfer.
- Stability data for drug product manufactured at the proposed facility.

Details and discussion of the information and data provided in support of the proposed change are addressed in the Chemistry Review Notes section below.

Microbiological aspects related to the transfer of manufacturing and change of materials for the container/closure for this (b) (4) drug product were sent for consult to microbiology team in OPS/NDMS/HFD-805 on September 21, 2009. The information under review by Dr. R. Mello as of the date of this review, December 16, 2009.

The proposed manufacturing facility was submitted to the **Office of Compliance (OC) for inspection** on September 28, 2009. The OC inspected the facility and recommended withhold on December 15, 2009. See report attached to this review. See copy of report in Chemistry Review Notes below.

Clinical review of labeling changes was conducted by Dr. W. Boyd of HFD-520. Conclusion about labeling from the clinical review will be available when a "Citizens Petition" involving the type of drug substance used in this drug product is resolved.

The clinical information in this submission and the CMC information need to be split from each other and reviewed on their own.

16. **Conclusions and Recommendations:** The CMC information and data provided indicate that the proposed manufacturing facility, R-Tech Ueno, can manufacture Rescula 0.15% ophthalmic solution of the same quality as the Rescula drug product manufactured in the currently approved facility; it also demonstrate that manufacture of Rescula 0.15% Opthalmic Solution at the propose R-Tech Ueno facility does not have any adverse effect on the quality of the drug product.

The microbiology review of the information provided is pending.

Splitting of the CMC section of this application from the clinical sections (labeling) is pending.

The Office of Compliance recommended the proposed manufacturing facility for withhold on December 15, 2009.

Because of the withhold recommendation by the Office of Compliance, this supplement is recommended for a Complete Response (CR) letter.

17. Name: **Signature:** **Date:**
Libaniel Rodriguez, Ph.D., Review Chemist

18. Concurrence: **Signature:** **Date:**
David Lewis, pH.D. Pharmaceutical Assessment Lead, for Hasmukh Patel, Ph.D., Branch Chief, ONDQA/DPME/VIII

Chemistry Review Notes:

DRUG SUBSTANCE

(b) (4)

[redacted]

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(b) (4)

Labeling: Updated labeling, Carton label, Bottle label and Package Insert (How Supplied section) , reflecting the change in manufacturing facility are provided in this application.

Comment: The updated labeling is acceptable from the point of view of CMC. However, there are labeling revisions and issues related to a Citizen's Petition involving this drug product. For this reason, the review by the clinical reviewer will be detached from the CMC sections of this application, so that CMC conducts an independent review of this application.

Environmental Assessment: The applicant requests categorical exclusion from filing an environmental assessment based on 21 CFR 2531(b), this action does not "increase the use of the active moiety, but the estimated concentrationof substance at the point of entry into the aquatic environment will be below 1 ppb"

Comment: Based on the CFR section quoted, the request for categorical exclusion is granted.

Conclusion: The CMC information and data provided indicate that the proposed manufacturing facility, R-Tech Ueno, can manufacture Rescula 0.15% ophthalmic solution of the same quality as the Rescula drug product manufactured in the currently approved facility. The information and data provided also demonstrate that manufacture of Rescula 0.15% Opthalmic Solution at the propose R-Tech Ueno facility does not have any adverse effect on the quality of the drug product.

The microbiology review of the information provided is pending.

Splitting of the CMC section of this application from the clinical sections (labeling) is pending.

The Office of Compliance recommended the proposed manufacturing facility for withhold on December 15, 2009.

Because of the withhold recommendation by the Office of Compliance, this supplement is recommended for a Complete Response (CR) letter.

Attachment:

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 21214/006	**Sponsor:**	R TECH UENO LTD
Org. Code:	520		7361 CALHOUN PL STE 500
Priority:	1P		ROCKVILLE, MD 208552765
Stamp Date:	21-AUG-2009	**Brand Name:**	RESCULA(UNOPROSTONE ISOPROPYL OPHTHALMIC
PDUFA Date:	21-DEC-2009	**Estab. Name:**	
Action Goal:		**Generic Name:**	UNOPROSTONE ISOPROPYL OPHTHALMIC SOLUTIO
District Goal:	16-NOV-2009	**Product Number; Dosage Form; Ingredient; Strengths**	
		001; SOLUTION, DROPS; UNOPROSTONE ISOPROPYL; .15%	

FDA Contacts:	A. CUFF	Project Manager	(HF-01)	301-796-4061
	L. RODRIGUEZ	Review Chemist		301-796-1445
	S. DE	Team Leader		301-796-1664

Overall Recommendation: WITHHOLD on 15-DEC-2009 by E. JOHNSON (HFD-320) 301-796-3334

Establishment:	**CFN:** 9614764	**FEI:**	
	R TECH UENO LTD 4-1 TECHNO PARK , , JAPAN		
DMF No:	14611	**AADA:**	
Responsibilities:	FINISHED DOSAGE MANUFACTURER		
Profile:	OPHTHALMIC/STERILE NON-INJECTABLE	**OAI Status:**	POTENTIAL OAI
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	15-DEC-2009		
Decision:	WITHHOLD		
Reason:	DISTRICT RECOMMENDATION		

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21214	SUPPL-6	R TECH UENO LTD	RESCULA(UNOPROSTONE ISOPROPYL OPHTHALMIC

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/s/

LIBANIEL RODRIGUEZ
12/16/2009

DAVID B LEWIS
12/16/2009
Concur; recommend for COMPLETE RESPONSE since the facility was recommended for withhold. Signing for H. Patel.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21214/S-006

PHARMACOLOGY REVIEW(S)

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

DATE: June 22, 2012

TO: Judit R Milstein
DTOP, OND

FROM: Sushanta Chakder Ph.D.
Supervisory Pharmacologist, DGIEP

THROUGH:

Andrew E. Mulberg, M.D.
Division Deputy Director, DGIEP

NDA 21214

Drug: Rescula (unoprostone isopropyl) ophthalmic solution

SUBJECT: Consult request from the Division of Transplant and Ophthalmology Products (DTOP) regarding the quantity and quality of scientific evidence (nonclinical and clinical information) that was considered sufficient to support (b) (4)

Background: (b) (4)

The Division of Transplant and Opthalmology Products has approved (b) (4) (unoprostone isopropyl/ Rescula ophthalmic solution) indicated for the lowering of intraocular pressure in patients with open-angle glaucoma or ocular hypertension (NDA 21214). Sucampo Pharma Americas, Inc is the holder (b) (4) NDAs. Sucampo submitted a (b) (4)

The DTOP has asked the following question to the DGIEP.

1. What was the quantity and quality of scientific evidence you judged to be sufficient to support these labeling statements?

2. How did you reach the conclusion that the information provided for [redacted] was scientifically valid and clinically meaningful?
3. Did you consider that clinical evidence was needed in order to provide for the [redacted] If not, what was the minimum in-vitro data you would have accepted in support of this labeling change?

Nonclinical Studies:

Several *in vitro* and *in vivo* studies were conducted with [redacted], and are summarized below.

In vitro Studies:

The mechanism of the [redacted]

[redacted]

[redacted]

[redacted]

In vivo studies:

(b) (4)

Several other *in vivo* studies were conducted in rats and mice to examine the (b) (4) in both rats and mice.

Questions from the DTOP:

1. What was the quantity and quality of scientific evidence you judged to be sufficient to support these labeling statements?

Response: The role of (b) (4) was mainly based on the above-mentioned nonclinical studies conducted by the sponsor.

2. How did you reach the conclusion that the information provided for (b) (4) was scientifically valid and clinically meaningful?

Response: The role of (b) (4) was justified.

3. Did you consider that clinical evidence was needed in order to provide for the (b) (4)? If not, what was the minimum in-vitro data you would have accepted in support of this labeling change?

Response: (b) (4). Please see our response to Questions 1 and 2.

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/s/

SUSHANTA K CHAKDER
06/22/2012

ANDREW E MULBERG
06/22/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21214/S-006

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review

11 July 2012

NDA: 21-214/S-006

Drug Product Name
Proprietary: Rescula®
Non-proprietary: Unoprostone Isopropyl Ophthalmic Solution 0.15%

Review Number: 2

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
16 September 2010	17 December 2010	01 February 2011	01 February 2011

Submission History (for amendments only)

Submit Date(s)	Microbiology Review #	Review Date(s)
21 August 2009	1	30 December 2009

Applicant/Sponsor
Name: Sucampo Pharma Americas, Inc.
Address: 4520 East-West Highway, 3rd Floor
Bethesda, MD 20814
Representative: Robert S. Cormack, Ph.D.
Dir. Regulatory Affairs
Telephone: 301-961-3400

Name of Reviewer: Robert J. Mello, Ph.D.

Conclusion: The application is recommended for approval from microbiology product quality standpoint.

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Prior Approval Supplement

2. SUBMISSION PROVIDES FOR: (1) Re-listing of the approved Drug Product (Rescula®); (2) Change of drug product manufacturing site; (3) Change in the bottle container from poly-propylene to low-density polyethylene; (4) Updating of the labeling text.

3. MANUFACTURING SITE: R-Tech Ueno, Ltd., Sanda Plant
4-1 Techno-Park
Sanda, Hyogo 669-1339
Japan

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Sterile Ophthalmic Solution, topical ophthalmic; 0.15% (w/v), 5 ml fill in a (b) (4) low density polyethylene (LDPE) bottle with a LDPE dropper tip and (b) (4) cap.

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: Ocular hypertension

B. SUPPORTING/RELATED DOCUMENTS:

- DMF #22987 Unoprostone Isopropyl Ophthalmic Solution 0.15% (R-Tech Ueno, Ltd. (Letter of Authorization to reference DMF #22987 dated 07 AUGUST, 2009, was provided in the original submission.) An amendment to this DMF was submitted on August 10, 2010 (Volume B2.1) in response to a DMF Deficiency letter from the Agency dated June 28, 2010. In addition, this DMF was updated on August 10, 2010 (received September 30 2010, Volumes B3.1 and B3.2) and again on September 27, 2011 (Volume B4.1). There are no other submissions listed for this DMF in the DARRTS system as of the time of this review.
- Microbiology Review #2 of DMF #22987, dated 11 July 2012.

C. REMARKS:

- The current submission is a paper technical submission and is not in CTD format.
- NDA 21-214 was originally approved in August 2000 (CIBA Vision Corp.) for manufacture at the CIBA Vision Sterile Manufacturing facility in Mississauga, Ontario, Canada. In 2004, the (then) applicant Novartis Pharmaceuticals withdrew the product from the US market (but still sold internationally). R-Tech Ueno gained the rights to the product in 2006. In July 2009, Sucampo Pharma Americas acquired the rights to the drug product from R-Tech Ueno. R-tech Ueno (Japan) is the proposed new site for manufacture of the drug product.

Filename: N21214S006R2.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability - Recommend Approval

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable - N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology - The manufacturing site is changed to R-Tech Ueno, Japan. The drug product is preserved with benzalkonium chloride (BAC). The formulated drug product is (b) (4) into ophthalmic "dropper bottles." The bottles are (b) (4)

B. Brief Description of Microbiology Deficiencies - None

C. Assessment of Risk Due to Microbiology Deficiencies - N/A

III. Administrative

A. Reviewer's Signature: _____

Robert J. Mello, Ph.D.
Senior Microbiology Reviewer

B. Endorsement Block: _____

John W. Metcalfe, Ph.D.
Senior Microbiology Reviewer

C. CC Block

NDA 21-214

Product Quality Microbiology Assessment

Details of the container closure integrity testing were not provided in the original submission. In addition, the DMF #22987 for the drug product manufacturing and the validations of the container/closure component sterilization processes were not adequate to support the original submission.
In the current submission the applicant has responded to the deficiency concerning the container closure integrity studies (communicated to them via email on June 30, 2010 by the ONDQA Project Manager). The response to the deficiencies in DMF #22987 is reviewed in a separate report (see microbiology review #2 of DMF #22987, dated 11 July 2012).
In this review, the deficiency is listed in bold italics. Review of the Applicant's response is listed in normal type.

Deficiency #1

1. ***The applicant did not provide sufficient details of the dye ingress or microbial ingress container closure tests. The applicant should provide the study protocols and summary reports of the completed studies (English translations). The information should contain sufficient detail (temperatures/ hold times / pressures) to assess the adequacy of the studies.***

Applicant's response #1

(b) (4)

[redacted]

- Acceptable -

Deficiency #2

2. DMF #22987 for the drug product manufacturing was not adequate to support the submission. The DMF holder will be notified, separately, of the deficiencies.

Applicant's response #2

The Applicant provided no response to this deficiency as it was the responsibility of the DMF holder (R-Tech Ueno, Limited) to provide a response.

The DMF holder has responded to the cited deficiencies and has made corrections and updates to DMF #22987. That DMF is now ADEQUATE to support NDA 21-214 Supplement 006.

- Acceptable -

3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:

None

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/s/

ROBERT J MELLO
07/11/2012

JOHN W METCALFE
07/11/2012
I concur.

Product Quality Microbiology Review

30 DECEMBER 2009

NDA: 21-214/S-006

Drug Product Name
Proprietary: Rescula®
Non-proprietary: Unoprostone Isopropyl Ophthalmic Solution 0.15%

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
21 AUG 2009	21 AUG 2009	28 SEPT 2009	28 SEPT 2009
26 AUG 2009	27 AUG 2009	-	-

Submission History (for amendments only): N/A

Applicant/Sponsor
Name: Sucampo Pharma Americas, Inc.
Address: 4520 East-West Highway, 3rd Floor
Bethesda, MD 20814
Representative: Robert S. Cormack, Ph.D.
Dir. Regulatory Affairs
Telephone: 301-961-3400

Name of Reviewer: Robert J. Mello, Ph.D.

Conclusion: The application is approvable pending receipt of additional information (See Review Section 3)

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Prior Approval Supplement

2. SUBMISSION PROVIDES FOR: (1) Re-listing of the approved Drug Product (Rescula®); (2) Change of drug product manufacturing site; (3) Change in the bottle container from poly-propylene to low-density polyethylene; (4) Updating of the labeling text.

3. MANUFACTURING SITE: R-Tech Ueno, Ltd., Sanda Plant
4-1 Techno-Park
Sanda, Hyogo 669-1339
Japan

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Sterile Ophthalmic Solution, topical ophthalmic; 0.15% (w/v), 5 ml fill in a (b) (4) low density polyethylene (LDPE) bottle with a LDPE dropper tip and (b) (4) cap.

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: Ocular hypertension

B. SUPPORTING/RELATED DOCUMENTS:

- DMF #22987 Unoprostone Isopropyl Ophthalmic Solution 0.15% (R-Tech Ueno, Ltd. (Letter of Authorization to reference DMF #22987 dated 07 AUGUST, 2009, was provided in the submission.)
- DMF # (b) (4), Type III DMF for the eye drop container (b) (4) (b) (4) (b) (4)) (Letter of Authorization to reference DMF # (b) (4) dated 06 AUGUST, 2009, was provided in the submission.)
- NDA 21214, Microbiology Review #1 dated July 7, 2000 (N. Sweeney).
- NDA 21214, Chemist's Review #1 dated June 30, 2000 (A. Fenselau).

C. REMARKS:

- The submission is a paper technical submission in CTD format. An Amendment was submitted 27 AUGUST 2009 and included copies of the original 1997 filter validation studies performed for the sterilizing filters by the (b) (4).
- A Type II DMF #22987 was filed with the agency on 29 July 2009. An Amendment was filed on 15 OCTOBER 2009. The review of DMF #22987 was performed by this reviewer and was filed separately in DARRTS.
- A Type III DMF # (b) (4) was filed with the agency on 28 July 2009. It was consulted to confirm the container/closure sterilization parameters used in routine production. The sterilization validation information was contained in the R-Tech Ueno DMF #22897. A formal review of DMF # (b) (4) was not performed.
- NDA 21-214 was originally approved in August 2000 (CIBA Vision Corp.) for manufacture at the CIBA Vision Sterile Manufacturing facility

in Mississauga, Ontario, Canada. In 2004, the (then) applicant Novartis Pharmaceuticals withdrew the product from the US market (but still sold internationally). R-Tech Ueno gained the rights to the product in 2006. In July 2009, Sucampo Pharma Americas acquired the rights to the drug product from R-Tech Ueno. R-tech Ueno (Japan) is the proposed new site for manufacture of the drug product.

- **filename:** N21214S006R1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability – Approvable pending receipt of additional information

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – The manufacturing site is changed to R-Tech Ueno, Japan. The drug product is preserved with benzalkonium chloride (BAC). The formulated drug product is [redacted] (b) (4) into ophthalmic "dropper bottles." The bottles are [redacted] (b) (4) The dropper tip and the cap [redacted] (b) (4)

B. Brief Description of Microbiology Deficiencies - Details of the container closure integrity testing were not provided in the submission. The labeled storage temperature range of 2°C-25°C is not supported by stability or container closure integrity studies. The DMF #22987 for the drug product manufacturing and the validations of the container/closure component sterilization processes were not adequate to support the submission.

C. Assessment of Risk Due to Microbiology Deficiencies – There is a risk of producing a non-sterile product. There is also a risk that storage of the product at refrigerated temperatures could compromise the container closure integrity with respect to the maintenance of drug product sterility.

III. Administrative

A. Reviewer's Signature _____

Robert J. Mello, Ph.D.
Review Microbiologist

B. Endorsement Block _____

James L. McVey
Microbiology Team Leader

C. CC Block

NDA 21214

Product Quality Microbiology Assessment

1. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 3.2: BODY OF DATA

S DRUG SUBSTANCE: (b) (4).

P DRUG PRODUCT

(b) (4)

3 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

P.7 Container Closure System: See Section P.1

P.8 Stability

P.8.1 Stability Summary and Conclusion

Three 20 liter stability batches (US-1, US-2, and US-3) were, in error, formulated with an overage (b) (4) of EDTA. A total of 12 months of long term (25°C/40% RH) and 6 months of accelerated (40°C/20% RH) data were collected. In June of 2009, the error was detected and three additional 20 liter batches were prepared (US-4, US-5, and US-6). At the time of submission, only the release data were available were available for these June 2009 batches. Sterility testing would not be expected to be affected by the (b) (4) excess in EDTA in the 3 initial batches.

P.8.2 Post-Approval Stability Protocol and Stability Commitment

The applicant commits to continue the stability program on all six of the pilot scale lots (US-1 through US-6). In addition the applicant commits to placing the first three commercial lots and one lot (annually) into the long term stability program. (b) (4)

P.8.3 Stability Data

All lots tested for sterility, BAC content and preservative effectiveness conformed to specifications.

- ACCEPTABLE -

A APPENDICES: N/A

R REGIONAL INFORMATION

R.1 Executed Batch Record: The Master Batch Record was referenced to Section 2.4 of R-tech Ueno's DMF #22987.

2. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 1

A. PACKAGE INSERT: A copy of the package insert was provided for review and indicated that the unopened product is sterile. Storage temperature was indicated to be 2°C-25°C (36°-77°F).
Draft copies of the container and carton labeling were provided and indicated that the contents were sterile. Storage temperature was indicated to be 2°C-25°C (36°-77°F).

- ACCEPTABLE -

3. LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:

DEFICIENCIES:

1. The applicant did not provide sufficient details of the dye ingress or microbial ingress container closure tests. The applicant should provide the study protocols and summary reports of the completed studies (English translations). The information should contain sufficient detail (temperatures/ hold times / pressures) to assess the adequacy of the studies.

2. DMF #22987 for the drug product manufacturing was **not adequate** to support the submission. The DMF holder will be notified, separately, of the deficiencies.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21214	SUPPL-6	R TECH UENO LTD	RESCULA(UNOPROSTONE ISOPROPYL OPHTHALMIC

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/s/

ROBERT J MELLO
12/31/2009

JAMES L MCVEY
12/31/2009
I concur.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21214/S-006

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Division of Transplant and Ophthalmology Products
Preliminary Meeting Comments

Meeting Date/Time: June 26, 2012 at 10:00am
Meeting Location: White Oak Building 22 Room 1415
10903 New Hampshire Avenue
Silver Spring, Maryland 20903

Meeting Type: Post-action (post-decisional) meeting

Applications: NDA 21-214/S-007 (package insert in physician labeling rule format)
NDA 21-214/S-006 (CMC supplement)

Drug: Rescula (unoprostone isopropyl ophthalmic solution) 0.15%
Applicant: Sucampo Pharma Americas, Inc.
Date of Submission: May 21, 2012 (21/214/S-007)
August 21, 2009 and September 16, 2011 (21-214/S-006)

Dear Ms. Buc:

The following are the Division's preliminary responses and comments to the issues identified in your package dated May 21, 2012: the mechanism of action, the pharmacologic class, and the adverse reactions included in the WARNINGS AND PRECAUTIONS sections of the package insert for Rescula.

Please note that if there are any major changes to the purpose of the meeting, or to the issues you included in your submission based on our responses herein, we may not be prepared to discuss or reach agreement on such changes at the meeting.

The minutes of the June 26, 2012, meeting will reflect agreements, key issues, and any action items discussed during the formal meeting and may not be identical to these preliminary comments.

This document also includes for reference Attachment A: Deficiencies listed in Complete Response (CR) letter of March 20, 2012 for NDA 21-214/S-007,and Attachment B Labeling Comparison Document.

TOPICS FOR DISCUSSION

The Division comments are in *italicized* font.

1) Mechanism of Action (PLR Section 12 CLINICAL PHARMACOLOGY)

Sucampo proposed in the January 17, 2012, PLR submission to include the following text in section 12, under Mechanism of Action:

12.1 Mechanism of Action

(b) (4)

[redacted]

[redacted]

(b) (4)

[redacted]

The Division proposed alternative wording to the Mechanism of Action (MOA) section in the PLR included in the March 20, 2012 CR letter as follows:

12.1 Mechanism of Action

Rescula is believed to reduce elevated intraocular pressure (IOP) by increasing the outflow of aqueous humor. Unoprostone isopropyl (UI) may have a local effect on BK potassium channels and ClC-2 chloride channels, but the exact mechanism is unknown at this time.

Division's Comments:

The Division does not agree with the information provided by you in the May 21, 2012, submission. Page 3 of your letter states that (b) (4) [redacted] *However, as noted above, the Division has proposed to include the statement, Rescula is believed to reduce elevated intraocular pressure (IOP) by increasing the outflow of aqueous humor." This language is consistent with the approved timolol, latanoprost, travoprost, bimatoprost, and tafluprost ophthalmic products. The Division continues to disagree with what is known about unoprostone for the following reasons:*

1) A cause and effect relationship between (b) (4) [redacted]

(b) (4)

[redacted]

(b) (4)

[redacted]

2 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

2) Pharmacologic Class, (PLR HIGHLIGHTS OF PRESCRIBING INFORMATION, Indications and Usage)

Sucampo proposed in the January 17, 2012 PLR submission to include the following text in section **HIGHLIGHTS OF PRESCRIBING INFORMATION**:

> **INDICATIONS AND USAGE**----------
> - (b) (4)

The Division proposed alternative wording to the **HIGHLIGHTS OF PRESCRIBING INFORMATION** in the PLR included in the March 20, 2012 CR letter as follows:

> **INDICATIONS AND USAGE**----------
> - Rescula (unoprostone isopropyl ophthalmic solution) 0.15% is indicated for the lowering of intraocular pressure in patients with open-angle glaucoma or ocular hypertension. (1)

Division's Comments:

The Division acknowledges that Sucampo (b) (4)

As discussed previously regarding the mechanism of action for Rescula, (b) (4)

3) Adverse Reactions (PLR Section 5 WARNINGS AND PRECAUTIONS, and related sections of labeling)

Sucampo proposed in the January 17, 2012 PLR submission (b) (4)

[1] Guidance for Industry and Review Staff Labeling for Human Prescription Drug and Biological Products — Determining Established Pharmacologic Class for Use in the Highlights of Prescribing Information http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM186607.pdf

The Division included the following wording on iris pigmentation and eyelid pigmentation in Section 5 WARNINGS AND PRECAUTIONS and related sections of the labeling in the PLR included with the March 20, 2012 CR letter:

5.1 Iris Pigmentation

Unoprostone isopropyl ophthalmic solution may gradually increase the pigmentation of the iris. The pigmentation change is believed to be due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. The long term effects of increased pigmentation are not known. Iris color changes seen with administration of unoprostone isopropyl ophthalmic solution may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts of the iris become more brownish. Neither nevi nor freckles of the iris appear to be affected by treatment. Treatment with Rescula solution can be continued in patients who develop noticeably increased iris pigmentation.

Patients who receive treatment with Rescula should be informed of the possibility of increased pigmentation *[see Patient Counseling Information (17.2)]*.

5.2 Lid Pigmentation

Unoprostone isopropyl has been reported to cause pigment changes (darkening) to periorbital pigmented tissues and eyelashes. The pigmentation is expected to increase as long as unoprostone isopropyl is administered, but has been reported to be reversible upon discontinuation of unoprostone isopropyl ophthalmic solution in most patients.

Division's Comments:

(b) (4) *These adverse reactions are clinically meaningful because they are readily apparent to the patient* (b) (4) *The Division considers these reactions to be potentially serious even if they are infrequent.*

The Division also considers (b) (4) *to be a serious reaction even if it is infrequent because it can lead to decreased vision and is often best treated by stopping a contributing factor, and therefore has retained information on this adverse reaction in Section 5.*

4) CMC supplement for Low Density Polyethylene Vial presentation (S-006)

Division's Comments:

CMC has received responses to its requests for information from both Sucampo and the DMF holder. The responses are currently under review.

ATTACHMENT A:

Deficiencies listed in Complete Response (CR) letter of March 20, 2012 for NDA 21-214/S-007:

- Head to head comparison in a clinical trial between (b) (4) The Warnings and Precautions for Rescula are therefore appropriate as previously recommended and should remain unchanged.
- (b) (4) Therefore, the clinical significance of these theories remains unknown and statements suggesting a (b) (4) should be removed from the proposed package insert.
- (b) (4)
- Clinical trials which demonstrate the impact of changes in (b) (4) have not been submitted, (b) (4)

8 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/ TS) immediately following this page

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/s/

JUDIT R MILSTEIN
06/25/2012
NDA 21214/S-007 Preliminary Comments

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 21-214/S-006
NDA 21-214/S-007

ACKNOWLEDGEMENT --
PRIOR APPROVAL SUPPLEMENTS

Sucampo Pharma Americas, Inc.
Attention: Robert S. Cormack, PhD
Director Regulatory Affairs
4520 East-West Highway
Suite 300
Bethesda, MD 20814

Dear Dr. Cormack:

We have received your August 21, 2009, Supplemental New Drug Applications (sNDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 21-214

SUPPLEMENT NUMBERS: 006 and 007

PRODUCT NAME: Rescula (unoprostone isopropyl ophthalmic solution) 0.15%

DATE OF SUBMISSION: August 21, 2009

DATE OF RECEIPT: August 21, 2009

This supplemental application proposes the following change(s):

(1) Supplement #006: Requests approval of R-Techs Ueno, Ltd Eye Drop Plant as the manufacturer of 0.15% Rescula for the U.S. market and proposes to change the bottle container from a polypropylene to low-density polyethylene.

(2) Supplement #007: Provides for updated labeling text (package insert) and Physician Labeling Rule format.

Please note that for administrative purposes your submission has been split as identified above. All future correspondence should be identified by the above supplement numbers.

Additionally, please be advised that your request for re-listing should be directed to the following:

U.S. Food and Drug Administration
Office of Generic Drugs
Attention: Orange Book Staff
7620 Standish Place
Rockville, MD 20855

Your applications were filed on October 20, 2009, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3).

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective and Ophthalmology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have questions regarding these supplements, please contact the following project managers:

Supplement #006 - Althea Cuff, #301-796-4061
Supplement #007 – Raphael Rodriguez, #301-796-0798

Sincerely,

{See appended electronic signature page}

Maureen Dillon-Parker
Chief, Project Management Staff
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

MAUREEN P DILLON PARKER
03/23/2011

ALTHEA CUFF
03/23/2011

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

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Sylvia Gantt, HFD-003, Rm 3549

FROM (*Name, Office/Division, and Phone Number of Requestor)*: Althea Cuff, ONDQA, 301-796-4061

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
9/28/09		21-214	S-006	8/21/09

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Rescula			11/21/09

NAME OF FIRM: Sucampo

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 2a MEETING
- ☐ END-OF-PHASE 2 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)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: This supplement provides for use of the following:

- Re-list Rescual
- Supply of product will be manufactured by R.Tech Ueno;s Eyedrrop Pllant in Sanda, Japan
- The bottle container is changed from polypropylene to low-density polyethylene.
- The labeling is updated

Please review.

PDUFA Date: 12/21/2009

SIGNATURE OF REQUESTOR
Althea Cuff

METHOD OF DELIVERY (Check one)
☐ DFS ☒ EMAIL ☐ MAIL ☐ HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

	PRINTED NAME AND SIGNATURE OF DELIVERER

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21214	SUPPL-6	R TECH UENO LTD	RESCULA(UNOPROSTONE ISOPROPYL OPHTHALMIC

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/s/

ALTHEA CUFF
09/28/2009