CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 21214/S-007

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-007

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21214/S-007

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

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/s/

WILEY A CHAMBERS
12/07/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21214/S-007

OTHER ACTION LETTER(s)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21-214/S-007

COMPLETE RESPONSE

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

Dear Dr. Cormack:

Please refer to your Supplemental New Drug Application (sNDA) 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 dated May 25 and September 19, 2011, and January 19, 2012.

The September 19, 2011, submission constituted a complete response to our April 14, 2011, action letter.

We also acknowledge receipt of your amendment dated March 13, 2012, which was not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

This "Prior Approval" labeling supplemental new drug application proposes to revise the package insert to Physician's Labeling Rule (PLR) format and to label Rescula as a [redacted] (b) (4)

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. The submitted labeling does not fully comply with the requirements for content and format of labeling for human prescription drug and biological products [21 CFR 201.56 and 201.57] and some of the proposed statements are not supported by data in the application. Specifically:

- [redacted] (b) (4)

Rescula is reported to have caused a case of [redacted] (b) (4) as documented in the latest submission. The Warnings and Precautions for Rescula are therefore appropriate as previously recommended and should remain unchanged.

- [redacted] (b) (4)
- [redacted] (b) (4)
- [redacted] (b) (4)

Please submit draft labeling that incorporates the recommended revisions in the attached labeling. In addition, submit updated 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.

When responding to this letter, submit labeling that includes all previous revisions, as reflected in the most recently approved package insert. 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 include annotations with the supplement number for previously-approved labeling changes.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the supplemental application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants", May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change before approval of this supplemental application.

If you have any questions regarding this supplemental application, please contact Ms. Leanna M. Kelly, Consumer Safety Officer, at (301) 796-0471. For all other inquiries regarding this NDA, please call 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: Labeling

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/s/

WILEY A CHAMBERS
03/20/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21-214/S-007

COMPLETE RESPONSE – LABELING

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

Dear Dr. Cormack:

We acknowledge receipt on September 20, 2011, of your September 19, 2011, resubmission to your supplemental new drug application for Rescula (unoprostone isopropyl ophthalmic solution) 0.15%.

This amendment constitutes a complete response to our April 14, 2011, action letter.

If you have any questions, please call me at (301) 796-0471.

Sincerely,

{See appended electronic signature page}

Leanna M. Kelly
Consumer Safety Officer
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

LEANNA M KELLY
01/05/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21214/S-007 **COMPLETE RESPONSE**

Sucampo Pharma Americas, Inc.
Attn: Robert S. Cormack, Ph.D., RAC
4520 East-West Highway
3rd Floor, Suite 300
Bethesda, MD 20814

Dear Dr. Cormack:

Please refer to your Supplemental New Drug Application (sNDA) dated August 21, 2009, 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%.

This supplemental new drug application provides for revision of the current package insert in the Physician's Labeling Rule (PLR) format.

We have completed the review of your application, and have determined that we cannot approve it in its present form. The submitted labeling does not fully comply with the requirements for content and format of labeling for human prescription drug and biological products [21 CFR 201.56 and 201.57] as published in the Federal Register in January 2006 (FR notice: "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products," 71 FR 3922, January 24, 2006)[PLR].

Please submit draft labeling, identical to the enclosed, that includes the additional changes required under the PLR. In addition, submit updated content of labeling [21 CFR 314.50(1)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

When responding to this letter, submit labeling that includes all previous revisions, as reflected in the most recently approved package insert. 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 include annotations with the supplement number for previously-approved labeling changes.

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the supplemental application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants", May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change before approval of this supplemental application.

If you have any questions, call Raphael R. Rodriguez, Regulatory Project Manager, at (301) 796-0798.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, M.D.
Acting Director
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE: Labeling

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

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/s/

WILEY A CHAMBERS
04/14/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21214/S-007

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

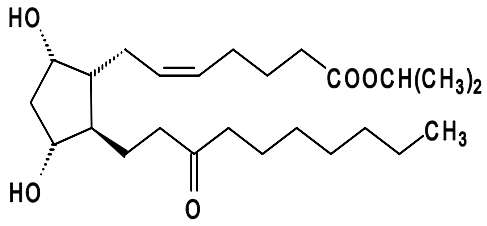
Safety and effectiveness in pediatric patients have not been established.

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-007

MEDICAL REVIEW(S)

Clinical Review of NDA 21-214
Prior Approval Labeling Supplement

NDA 21-214/S-007

SDN-142	**Submission Date:**	July 25, 2012
	Receipt Date:	July 26, 2012
SDN-143	**Submission Date:**	August 27, 2012
	Receipt Date:	August 28, 2012
	Review Date:	September 19, 2012

Applicant: Sucampo Pharma Americas, Inc.
4520 East-West Highway, Suite 300
Bethesda, MD 20814

Applicant's Representative: Jeff Carey
Senior Director, Regulatory Affairs
301-961-3400

Drug: Rescula (unoprostone isopropyl ophthalmic solution) 0.15%

Submitted:
The applicant has submitted amendments to a Prior Approval Labeling Supplement that requested the following changes:

- The applicant requests the Agency to re-list Rescula, subject to the provisions of the Prescription Drug User Fee Act, as currently enacted, and to update the status of the product in the Orange Book.
- Supply of the Rescula product (as approved) will be manufactured by R-Tech Ueno's Eye Drop plant located in Sanda, Japan.
- The bottle container is changed from polypropylene to low-density polyethylene.
- The labeling text (package insert) was updated in conformance with 21 C.F.R. §§ 201.56 and 201.57 and associated Guidances for Industry.

The applicant submitted an amendment, SDN-142, on July 25, 2012, which contained a copy of an email correspondence from Nancy L. Buc, Counsel to Sucampo, regarding follow-up information from the discussion at the July 24, 2012, meeting between Sucampo and the Division. The amendment also contained a copy of the presentation Ms. Buc gave at the meeting.

Refer to the following documents for more background on this history of this Supplement (S-007):

March 19, 2012 Clinical Review
March 20, 2012, Clinical Review
March 20, 2012, Complete Response Letter
August 7, 2012, Pharmacology/Toxicology Review

Based on a meeting with the applicant held on July 24, 2012, revised labeling was submitted on August 27, 2012 (see SDN-143). This revised labeling was previously found to be acceptable by the Division.

Following is the labeling submitted on August 27, 2012.

Reviewer additions are noted by underline and deletions by within the review.

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APPEARS THIS WAY ON ORIGINAL

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

Recommendations:

This supplement is recommended for approval.

Leanna M. Kelly
Consumer Safety Officer

William M. Boyd, M.D.
Clinical Team Leader

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/s/

LEANNA M KELLY
11/21/2012

WILEY A CHAMBERS
11/21/2012

Clinical Review of NDA 21-214
Prior Approval Labeling Supplement

NDA 21-214/S-007

SDN-106	**Submission Date:**	May 25, 2011
	Receipt Date:	May 26, 2011
SDN-133	**Submission Date:**	September 19, 2011
	Receipt Date:	September 20, 2011
SDN-135	**Submission Date:**	January 19, 2012
	Receipt Date:	January 19, 2012
SDN-136	**Submission Date:**	January 19, 2012
	Receipt Date:	January 25, 2012
	Review Date:	March 21, 2012

Applicant: Sucampo Pharma Americas, Inc.
4520 East-West Highway, Suite 300
Bethesda, MD 20814

Applicant's Representative: Robert S. Cormack, Ph.D., RAC
Director, Regulatory Affairs
301-961-3400

Gayle R. Dolecek, Ph.D., M.P.H.
Executive Advisor, R&D
301-961-3400

Drug: Rescula (unoprostone isopropyl ophthalmic solution) 0.15%

Submitted:

The applicant has submitted amendments to a Prior Approval Labeling Supplement that requested the following changes:

- The applicant requests the Agency to re-list Rescula, subject to the provisions of the Prescription Drug User Fee Act, as currently enacted, and to update the status of the product in the Orange Book.
- Supply of the Rescula product (as approved) will be manufactured by R-Tech Ueno's Eye Drop plant located in Sanda, Japan.
- The bottle container is changed from polypropylene to low-density polyethylene.

- The labeling text (package insert) was updated in conformance with 21 C.F.R. §§ 201.56 and 201.57 and associated Guidances for Industry.

This Supplement was administratively split on March 10, 2009, into Supplement 6 (Chemistry Manufacturing) and Supplement 7 (Labeling).

A labeling review dated March 19, 2012, was completed (see Clinical Review of NDA 21-214, NDA 21-214/S-007). In addition to the labeling changes suggested in that review, Section 16 "How Supplied/Storage and Handling" requires revision. The proposed change in the bottle container from polypropylene to low-density polyethylene has not been approved to date in Supplement 6; therefore, this change cannot appear in the recommended labeling.

Following is the clean, recommended labeling from the Clinical Review of NDA 21-214, NDA 21-214/S-007, dated March 19, 2012.

Reviewer additions are noted by underline and deletions by ~~strikethrough~~ within the review.

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

Recommendations:

This supplement is not recommended for approval. A Complete Response letter should be prepared; labeling consistent with the labeling found in this review should be attached to the letter.

Leanna M. Kelly
Consumer Safety Officer

William M. Boyd, M.D.
Clinical Team Leader

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/s/

LEANNA M KELLY
03/20/2012

WILLIAM M BOYD
03/20/2012

Clinical Review of NDA 21-214
Prior Approval Labeling Supplement

NDA 21-214/S-007

SDN-106	**Submission Date:**	May 25, 2011
	Receipt Date:	May 26, 2011
SDN-133	**Submission Date:**	September 19, 2011
	Receipt Date:	September 20, 2011
SDN-135	**Submission Date:**	January 19, 2012
	Receipt Date:	January 19, 2012
SDN-136	**Submission Date:**	January 19, 2012
	Receipt Date:	January 25, 2012
	Review Date:	March 15, 2012

Applicant: Sucampo Pharma Americas, Inc.
4520 East-West Highway, Suite 300
Bethesda, MD 20814

Applicant's Representative: Robert S. Cormack, Ph.D., RAC
Director, Regulatory Affairs
301-961-3400

Gayle R. Dolecek, Ph.D., M.P.H.
Executive Advisor, R&D
301-961-3400

Drug: Rescula (unoprostone isopropyl ophthalmic solution) 0.15%

Submitted:

The applicant has submitted amendments to a Prior Approval Labeling Supplement that requested the following changes:

- The applicant requests the Agency to re-list Rescula, subject to the provisions of the Prescription Drug User Fee Act, as currently enacted, and to update the status of the product in the Orange Book.
- Supply of the Rescula product (as approved) will be manufactured by R-Tech Ueno's Eye Drop plant located in Sanda, Japan.
- The bottle container is changed from polypropylene to low-density polyethylene.
- The labeling text (package insert) was updated in conformance with 21 C.F.R. §§ 201.56 and 201.57 and associated Guidances for Industry.

This Supplement was administratively split on March 10, 2009, into Supplement 6 (Chemistry Manufacturing) and Supplement 7 (Labeling).

The submitted labeling did not fully comply with the requirements for content and format of labeling for human prescription drug and biological products [21 CFR 201.56 and 201.57]. A Complete Response letter was issued on April 14, 2011.

The applicant submitted an amendment (SDN-106) on May 25, 2011, with revised labeling that reflects the (b) (4) SDN-106 contained published literature to support the applicant's proposed revisions to the label. However, some of the articles submitted were not in English, and therefore could not be reviewed.

The applicant submitted an amendment (SDN-133) on September 19, 2011, which contained the English translation of the Japanese articles submitted in SDN-106. This submission constituted a complete response to the April 14, 2011, action letter.

The applicant submitted an amendment (SDN-135) on January 19, 2012, which contained additional published literature to support the applicant's position that Rescula: (b) (4) This submission also contained revised labeling.

Following is the recommended labeling from the Division's April 14, 2011, Complete Response letter.

Applicant additions are noted by underline and deletions by within the review. Deleted: strikethrough

Reviewer additions are noted by underline and deletions by within the review. Deleted: strikethrough

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

Recommendations:

This supplement is not recommended for approval. A Complete Response letter should be prepared; labeling consistent with the labeling found in this review should be attached to the letter.

Leanna M. Kelly
Consumer Safety Officer

William M. Boyd, M.D.
Clinical Team Leader

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/s/

LEANNA M KELLY
03/19/2012

WILLIAM M BOYD
03/19/2012

Clinical Review of NDA 21-214
Prior Approval Supplement - Labeling

NDA 21-214/S-007
SDN-98

Submission Date: August 21, 2009
Receipt Date: August 21, 2009
Review Date: March 10, 2010

Applicant: Sucampo Pharma Americas, Inc.
4520 East-West Highway
Suite 300
Bethesda, MD 20814

Applicant's Representative: Robert S. Cormack, PhD
301-961-3400

Drug: Rescula (unoprostone isopropyl ophthalmic solution) 0.15%

Pharmacologic Category: prostaglandin analogue

Submitted:

Submitted is a Prior Approval Supplement requesting the following changes:

- The applicant requests the Agency to re-list Rescula, subject to the provisions of the Prescription Drug User Fee Act, as currently enacted, and to update the status of the product in the Orange Book.
- Supply of the Rescula product (as approved) will be manufactured by R-Tech Ueno's Eye Drop plant located in Sanda, Japan.
- The bottle container is changed from polypropylene to low-density polyethylene.
- The labeling text (package insert) was updated in conformance with 21 C.F.R. §§ 201.56 and 201.57 and associated Guidances for Industry.

This Supplement was administratively split on March 10, 2009, into Supplement 6 (Chemistry Manufacturing) and Supplement 7 (Labeling).

Proposed Package Insert

Following is the submitted package insert, presented for the first time in PLR format.

Reviewer additions are shown by underline. Reviewer deletions are shown by .

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

Recommendations:

This supplement (NDA 22-214/S-007) is not recommended for approval until the revisions noted in this review are incorporated into the labeling.

William Boyd, M.D.
Clinical Team Leader

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21214	SUPPL-7	SUCAMPO PHARMACEUTICALS INC	RESCULA(UNOPROSTONE ISOPROPYL OPHTHALMIC

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/s/

WILLIAM M BOYD
03/11/2010

WILEY A CHAMBERS
03/15/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21214/S-007

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	21-214
Supporting document/s:	SDN 136; SDN 140 (Supplement 7)
Applicant's letter date:	1-19-2012; 5-21-2012
CDER stamp date:	1-25-2012; 5-21-2012
Product:	Rescula® (unoprostone isopropyl)
Indication:	Treatment of elevated intraocular pressure in patients with open-angle glaucoma and ocular hypertension
Applicant:	Sucampo Pharmaceuticals 4520 East-West Hwy 3rd Fl Bethesda, MD 20814
Review Division:	DTOP
Reviewer:	Aaron M. Ruhland, Ph.D.
Supervisor/Team Leader:	Lori Kotch, Ph.D.
Division Director:	Renata Albrecht, M.D.
Project Manager:	Judit Milstein

TABLE OF CONTENTS

1 Executive Summary

1.1 Introduction

In this supplement, the applicant proposes new language in Section 12.1 of the labeling of Rescula (unoprostone isopropyl) to describe the mechanism of action. (b) (4)

[redacted]

1.2 Brief Discussion of Nonclinical Findings

Overall, the data suggest that Rescula possesses weak prostaglandin receptor agonist activity and acts as an activator of BK and CIC-2 channels. Through stimulation of the BK channel, Rescula was shown to inhibit endothelin-1 (ET-1) mediated contraction of ciliary muscle and trabecular meshwork strips *in vitro*. (b) (4)

[redacted]

This reviewer agrees with previous revisions to the labeling suggested to the applicant by the Division which update the labeling to describe these data more accurately and to remove all references to Rescula as a prostaglandin analogue. The applicant continues to protest these suggested revisions and seeks dispute resolution with the Agency to reach a solution.

1.3 Recommendations

1.3.1 Labeling

The Division has proposed the following labeling for Rescula in Section 12.1 Mechanism of Action:

> **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 CIC-2 chloride channels, but the exact mechanism is unknown at this time.

The applicant has proposed to the following labeling for Rescula in Section 12.1 Mechanism of Action:

12.1 Mechanism of Action

(b) (4)

Reviewer's note: (b) (4) Following review of the data included by the sponsor in this supplement, this reviewer agrees with the language previously proposed by the Division which (b) (4)

2 Drug Information

2.1 Drug

CAS Registry Number: 120373-36-6

Generic Name: Unoprostone isopropyl

Code Name: Rescula; UF-021

Chemical Name: Isopropyl (+)-(Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-(3-oxodecyl) cyclopentyl] hept-5-enoate

Molecular Formula/Molecular Weight: $C_{25}H_{44}O_5$ / 424.62

Structure or Biochemical Description:

*Pharmacologic Class: Originally classified as a docosanoid analogue of PGF-2α metabolite, (b) (4)

2.2 Relevant INDs, NDAs, BLAs and DMFs

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. 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.

2.3 Regulatory Background

Initial labeling changes by the applicant were proposed in Supplement 7 to the NDA dated 9-19-2011 (SDN 133). Following comments made by the Division in a letter dated 11-7-2011, the applicant submitted additional literature to support the proposed changes to the labeling on 1-19-2012 (SDN 135 and 136) and a request for dispute resolution in a submission to Supplement 7 (SDN 140) on 5-21-2012.

3 Studies Submitted

(studies shaded in gray were not submitted by the sponsor but found through an independent search of the literature)

3.1 Studies Reviewed

a. "Studies on receptor binding and signal transduction pathways of unoprostone isopropyl". Bhattacherjee P., et al., 2001, *J Ocul Pharmacol Ther.*, 17(5): 433-441.
b. "Affinity profile of unoprostone for prostaglandin receptors". Bhattacherjee P., 1999.
c. "Cellular and molecular effects of unoprostone as a BK channel activator". Cuppoletti, J., *et al.*, 2007, *Biochim Biophys Acta*, 1768(5): 1083-1092.
d. (b) (4)

e. “Effects of instillation of an isopropyl unoprostone on peripheral circulation in the human ocular fundus- A study using the laser speckle method”. Kojima S., *et al*., 1997, *J Jpn Ophthalmol Soc* 101: 605-610.
f. “Long-term effect of topically applied isopropyl unoprostone on microcirculation in the human ocular fundus”. Makimoto Y., *et al*., *Jpn J Ophthalmol*, 46: 31-35.
g. “Partial antagonism of endothelin-1-induced vasoconstriction in the human choroid by topical unoprostone isopropyl”. Polska, E., *et al*., 2002, *Arch Ophthalmol*, 120: 348-352.
h. “Human trabecular meshwork cell responses induced by bimatoprost, travoprost, unoprostone, and other FP prostaglandin receptor agonist analogues”. Sharif, N.A., *et al*., 2003, *Invest Ophthalmol Vis Sci*, 44: 715-721.
i. “Ocular hypotensive FP prostaglandin (PG) analogs: PG receptor subtype binding affinities and selectivities, and agonist potencies at FP and other PG receptors in cultured cells”. Sharif, N.A., *et al*., 2003, *J Ocul Pharmacol Ther*, 19(6): 501-515.
j. “Effects of unoprostone and endothelin 1 on L-type channel currents in human trabecular meshwork cells”. Thieme, H., *et al*., 2005, *Ophthalmic Res*, 37: 293-300.
k. “”Mechanisms of action of unoprostone on trabecular meshwork contractility”. Thieme, H., *et al*., 2001, *Invest Ophthalmol Vis Sci*, 42: 3193-3201.
l. “Increase in outflow facility with unoprostone treatment in ocular hypertensive patients”. Toris, C.B., *et al*., 2004, *Arch Ophthalmol*, 122(12): 1782-1787.
m. “Ocular hypotensive mechanism of topical isopropyl unoprostone, a novel prostaglandin metabolite-related drug, in rabbits”. Taniguchi, T., *et al*., 1996, *J Ocul Pharmacol Ther*, 12(4): 489-498.
n. “Real-time intracellular Ca^{2+} mobilization by travoprost acid, bimatoprost, unoprostone, and other analogs via endogenous mouse, rat, and cloned human FP prostaglandin receptors”. Kelly, C.R., *et al*., 2003, *J Pharmacol Exp Ther*, 304(1): 238-245.
o. “Metabolites of isopropyl unoprostone as potential ophthalmic solutions to reduce intraocular pressure in pigmented rabbits”. Kashiwagi, K., *et al*., 1999, *Jpn J Pharmacol*, 81: 56-62.
p. “The effects of prostaglandin analogues on IOP in prostanoid FP-receptor-deficient mice”. Ota, T., *et al*., 2005, *Invest Ophthalmol Vis Sci*, 46(11): 4159-4163.
q. “Effects of topical application of UF-021, a novel prostaglandin-related compound, on aqueous humor dynamics in rabbit”. Sakurai, M., *et al*., 1993, *Jpn J Ophthalmol*, 37: 252-258.

3.2 Citations submitted but not reviewed

a. “Similar effects of selective laser trabeculoplasty and prostaglandin analogs on the permeability of cultured Schlemm Canal cells”. Alvarado J., *et al*., 2010, *Am J Ophthalmol*, 150: 254-264.

b. “Comparison of iridial pigmentation between latanoprost and isopropyl unoprostone: a long term prospective comparative study”. Chiba T., *et al*., 2003, *Br J Ophthalmol*., 87: 956-959.
c. “Activation of the BK_{Ca} channel increases outflow facility and decreases trabecular meshwork cell volume”. Dismuke, WM and DZ Ellis, 2009, *J Ocul Pharmacol Ther*, 25(4): 309-314.
d. “Increased plasma endothelin-1 levels in patients with progressive open angle glaucoma”. Emre, M., *et al*., 2005, *Brit J Ophthalmol*, 89(1): 60-63.
e. “Efficacy of unoprostone switched from latanoprost”. Goseki T., *et al*., 2006, *Jpn J Clinic Ophthalmol*, 60(7): 1227-1230.
f. “The role of endothelin in the pathophysiology of glaucoma”, Good TJ and MY Kahook, 2010, *Expert Opin Ther Targets*, 14(6): 647-654.
g. “Acute Effects of PGF-2α on MMP-2 secretion from human ciliary muscle cells: A PKC- and ERK-dependent process”. Husain S., *et al*., 2005, *Invest Ophthalmol Sci*., 46(5): 1706-1713.
h. “Safety and efficacy of unoprostone switched from latanoprost in patients with latanoprost induced side effects”. Kuga H., *et al*., 2004, *Jpn J Ophthalmol*, 58(7): 1187-1191.
i. “Understanding trabecular meshwork physiology: A key to the control of intraocular pressure?”. Llobet, A., *et al*., 2003, *News Physiol Sci*, 18: 205-209.
j. “BK channel modulators: A comprehensive overview”. Nardi A., and S.P. Olesen, 2008, *Cur Med Chem*, 15: 1126-1146.
k. “Endothelin and its suspected role in the pathogenesis and possible treatment of glaucoma”. Shoshani, Y.Z., *et al*., 2011, *Curr Eye Res*, 37(1): 1-11.
l. “The retinal pigment epithelium in visual function”. Strauss, O., 2005, *Physiol Rev*, 85: 845-881.
m. “Regulation of trabecular meshwork contractility”. Stumpff, F. and M. Wiederholt, 2000, *Ophthalmologica*, 214(1): 33-53.
n. “Update on the mechanism of action of topical prostaglandins for intraocular pressure reduction”. Toris, C.B., *et al*., 2008, *Surv Ophthalmol*, 53 (SUPPL1): S107-S120.
o. “Effect of SPP 301, an endothelin antagonist, on intraocular pressure in glaucomatous monkey eyes”. Wang, R., *et al*., 2011, *Curr Eye Res*, 36(1): 41-46.
p. “Endothelin: is it a contributor to glaucoma pathophysiology”. Yorio, T., *et al*., *J Glaucoma*, 11: 259-270.
q. “VEGF Modulation of Retinal Pigment Epithelium Resistance”. Ablonczy, Z. and C.E. Crosson, 2007, *Exp Eye Res.,* 85(6): 762-771.
r. “Prostaglandin moieties that determine receptor binding specificity in the bovine corpus luteum”. Anderson, L., *et al*., 1999, *J Reprod Fertil*., 116(1): 133-141.
s. “Blood-aqueous barrier changes after the use of prostaglandin analogues in patients with pseudophakia and aphakia”. Arcieri E., *et al*., 2005, *Arch Ophthalmol*, 123(2):186-192.

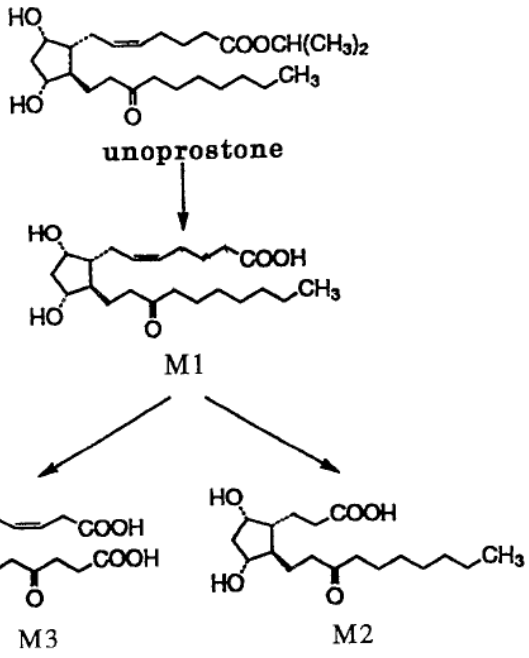
4. Review of pertinent studies

4.1 Metabolism

"**Metabolites of isopropyl unoprostone as potential ophthalmic solutions to reduce intraocular pressure in pigmented rabbits". Kashiwagi, K., et al., 1999, Jpn J Pharmacol, 81: 56-62.**

The intraocular metabolism of unoprostone isopropyl was investigated to determine which metabolites are produced and involved in activity in the eye. Three metabolites have been identified (Figure 1).

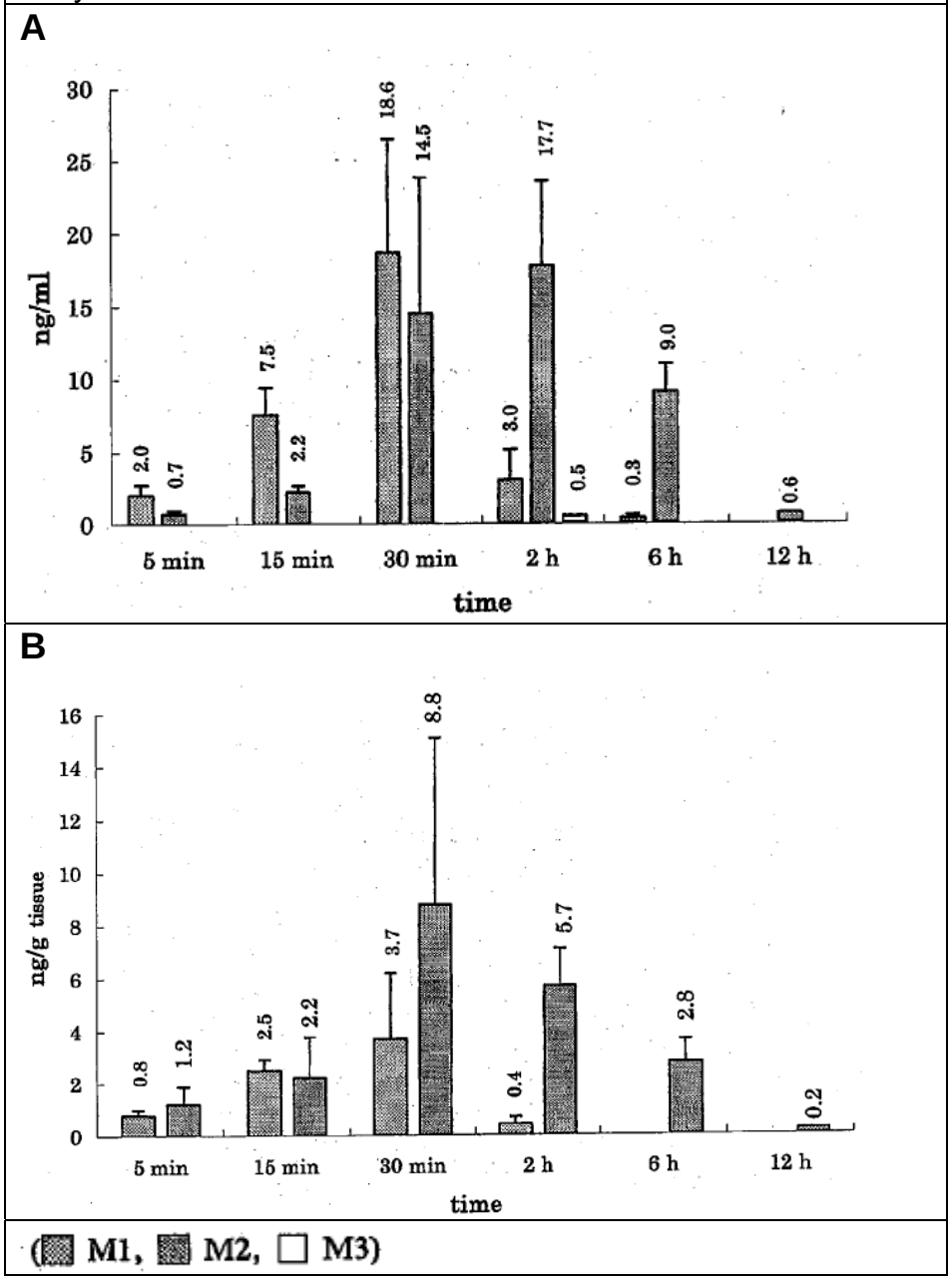
Figure 1. Metabolism of unoprostone isopropyl



[^{3}H]-unoprostone isopropyl (0.04%) was instilled in an eye of pigmented rabbits and the cornea, aqueous humor, iris, ciliary body and retina were collected at 5, 15, and 30 minutes as well as 2, 6, or 12 hours after administration. Through high performance liquid chromatography, the fraction of radioactivity and molecular species of unoprostone metabolite in each tissue was measured. Unmetabolized unoprostone isopropyl was not detected in any tissue at any time point. The de-esterified acid metabolite of unoprostone isopropyl, M1, and the further metabolized M2 were detected in the cornea (Figure 2). In the aqueous humor, M1, M2 and another metabolite M3 were detected with peak concentrations of M1 at 30 minutes and M2 at 2 hours. The iris and ciliary body had peak concentrations of M1 and M2 at 30 minutes. After 30 minutes, M2 was the dominant species present in the aqueous humor, ciliary body and

iris. In the retina, only total radioactivity was detected. Concentrations of each species in the most relevant tissues are shown in Figure 2 (data for cornea and iris were in citation but not shown in this review). Concentrations of M1 reached as high as 25 ng/mL (~60 nM) and ~6 ng/mL (~15 nM) in the aqueous humor and ciliary body at 30 minutes.

Figure 2. Time course of concentration of unoprostone isopropyl metabolites in the (A) aqueous humor and (B) ciliary body



Reviewer's note:
The highest concentration of [^{3}H]-unoprostone obtained in the aqueous humor was approximately 50 nM and 15 nM in the ciliary body. However, it should be noted that a solution of unoprostone isopropyl 0.04% was used in this study and additionally the authors note that "3H-Labeled unoprostone was diluted by non-radio-isotope-labeled unoprostone to prepare an ophthalmic solution with 1mM (0.0424%) of unoprostone and 6μCi/30μL of radioactivity". The authors state that the specific activity of the solution was 4.18 mCi/mg. Therefore 6μCi/30μL would calculate as 0.0478 mg unoprostone/mL. Since a 0.0424% solution contains 0.424 mg/mL, the radioactivity in the formulation in this study only comprised ~11% of the total unoprostone in the solution. Therefore levels obtained in the aqueous humor could be 9× higher in the aqueous humor (450 nM) and ciliary body (135nM). Taking into consideration that the clinical formulation of Rescula is 0.15% or 3.75× more concentrated than the formulation used in this study, intraocular concentrations of M1 following administration of the clinical formulation are likely to be even greater and could exceed 1μM in the aqueous humor. This is a very important consideration when determining whether unoprostone has prostaglandin receptor agonist activity.

4.2 Prostaglandin receptor binding/agonist activity

Studies on receptor binding and signal transduction pathways of unoprostone isopropyl. Bhattacherjee P., et al., 2001, *J Ocul Pharmacol Ther*., 17(5): 433-441.

This study examined the binding characteristics of unoprostone isopropyl and its main metabolite, M1, to bovine corpus luteum membranes. Unoprostone isopropyl and M1 mediated Ca^{2+} mobilization in human ciliary muscle cells and cyclic AMP generation following exposure to unoprostone isopropyl or M1 in isolated rabbit iris-ciliary body. The specific and nonspecific binding of ^{3}H-unoprostone isopropyl and ^{3}H -M1 to bovine corpus luteum membrane preparations was tested in the presence or absence of 1000-fold excess of unlabeled unoprostone isopropyl or M1. Parallel binding experiments were performed with ^{3}H-PGF2α in the presence or absence of 1000-fold excess of unlabeled PGF2a. Results showed linear total binding of unoprostone isopropyl as concentration of the labeled ligand was increased but this binding was not displaced by adding 1000× excess unlabeled ligand, i.e. the binding of unoprostone isopropyl to luteal membrane preparations was considered nonspecific (Table 1). Results for M1 were similar.

Table 1. Binding of ^{3}H-unoprostone isopropyl and ^{3}H-PGF-2α in bovine corpus luteal membranes as a function of concentration					
^{3}H-unoprostone isopropyl			^{3}H-PGF-2α		
Concentration (nM)	Total binding fmoles/mg protein	Specific binding fmoles/mg protein	Concentration (nM)	Total binding fmoles/mg protein	Specific binding fmoles/mg protein
8.0	19.4 ± 2	0	2.0	150.0 ± 16	120.0 ± 15
16.0	25.5 ± 4	0	4.0	325.0 ± 25	261.0 ± 27
32.0	40.0 ± 7	0	8.0	505.0 ± 75	423.0 ± 40

PGF-2α displayed specific binding capable of being displaced in a linear manner by increasing concentrations of unlabeled ligand (Table 2). Binding of unoprostone isopropyl, as demonstrated above, remained nonspecific.

Table 2. Competition for ^{3}H-unoprostone isopropyl or PGF-2α binding sites by unlabeled unoprostone isopropyl and PGF-2α					
Competing ligand unoprostone isopropyl (μM)	*Total ^{3}H-unoprostone binding fmoles/mg protein	Specific binding of ^{3}H-unoprostone isopropyl	Competing ligand PGF-2α (μM)	*Total binding of ^{3}H-PGF-2α fmoles/mg protein	Specific binding PGF-2α fmoles/mg protein
2.5	7.0	0	0.062	560	70
5.0	6.5	0	0.25	560	150
8.0	6.7	0	0.5	560	250
16.0	7.6	0	8.0	560	420
*Concentration of ^{3}H-unoprostone isopropyl or ^{3}H-PGF-2α used was 8 nM.					

Competition studies were performed with 8.0 nM ^{3}H-unoprostone isopropyl in the presence or absence of varying concentrations of different prostaglandin receptor agonists: 17-phenyl trinor PGE1 (EP1), butaprost (EP2), sulprostone (EP3), iloprost (IP), U46619 (TP), fluprostenol (FP) and BW245C (DP). None of the PG receptor agonists, at any concentration, was able to displace total bound ^{3}H-unoprostone isopropyl. Results for M1 were similar.

Primary cultures of human ciliary muscle cells were loaded with the Ca^{2+} sensitive dye, fura 2-AM. In a fluorometric assay, unoprostone isopropyl or M1, at 1,000 to 10,000 nM concentrations, mobilized 55 to 60 nM intracellular calcium in the human ciliary muscle cells which express EP1, EP2, EP4, and FP and muscarinic receptors. These values are not significantly different from the control value. In contrast, PGF2α, fluprostenol (FP receptor agonist) and carbachol (muscarinic receptor agonist) at 10 to 100 nM concentrations (Table 3) significantly mobilized intracellular calcium over basal levels.

Table 3. Mobilization of intracellular calcium by unoprostone isopropyl, M1, PGF-2α, fluprostenol, and carbachol		
Agonist	Concentration (nM)	Intracellular calcium (nM) Mean ± SEM
Control (Basal)		55.0 ± 2.5
Unoprostone isopropyl	1,000	60.25 ± 6.0
	10,000	50.75 ± 3.0
Metabolite M1	10,000	55.0 ± 3.0
PGF-2α	100	225.0 ± 15.0
Fluprostenol	100	300.5 ± 18.0
Carbachol	100	600.3 ± 40.0

Rabbit iris-ciliary body were dissected and placed in buffer. Following a 15 minute incubation with unoprostone isopropyl, M1 or prostaglandin controls, cAMP was measured using a commercially available kit. Unoprostone isopropyl or M1, at concentrations ranging from 0.125 (125 nM) to 8.0 mM, generated 37 to 105 pmoles of cyclic AMP in rabbit iris-ciliary body. The amount of cyclic AMP generated by unoprostone isopropyl or M1 is less than that produced by low concentrations of PGE2 (Table 4).

Table 4. Formation of cAMP in the rabbit iris-ciliary body by unoprostone isopropyl, M1 metabolite and PGE2				
Agonists	Concentrations (μM) of agonists			
	0.125	0.5	2.0	8.0
	pmoles cAMP/mg protein/15 minutes (Mean ± SEM)			
Unoprostone isopropyl	37.0 ± 10	48.5 ± 9.0	55.0 ± 14.0	45.0 ± 12
M1 metabolite	44.0 ± 1.0	51.0 ± 10.0	82.0 ± 20.0	105.0
PGE2	100.0 ± 10.0	206.0 ± 30.0	294.0 ± 45.0	394.0 ± 40.0
* It is important to note that the results are expressed as a net of stimulated – basal cAMP levels.				

Reviewer's note:
This experiment showed that neither unoprostone isopropyl nor M1 bind to PG receptors in luteal membranes with the same affinity as prostaglandin agonists. Neither unoprostone nor M1 were able to significantly displace other PGs from binding to their cognate receptors. Unoprostone isopropyl and M1 did not increase calcium mobilization at 15 minutes after addition to human ciliary muscle cells but did cause formation of cAMP in a manner similar to PGE2 in rabbit iris-ciliary body cells. It can not be discounted that cAMP generation stimulated by unoprostone or M1 may be mediated by the induction of endogenous PGE2. Exogenous PGs applied topically also stimulate PGE2 production and this has been postulated as a mechanism through which outflow facility is increased in response to PGs and may be due to trabecular meshwork relaxation mediated by PGE2. Overall, this experiment shows that while unoprostone

isopropyl/M1 may not act through similar pathways proximal to the cell membrane, their distal effects within the cell may have some overlap.

"Affinity profile of unoprostone for prostaglandin receptors". Bhattacherjee P., 1999.

This study report presented the same results described in the publication reviewed directly above this. The results of the cAMP assay were expanded to include PGF-2α and latanoprost. Additionally, results from the addition of lower concentrations of each agonist were included (Table 5).

Table 5. Formation of cyclic AMP in the rabbit-iris ciliary body stimulated by isopropyl unoprostone and its M1 metabolite

Agonists	Concentrations (μM)					
	0.0078	0.0312	0.125	0.5	2.0	8.0
	pmoles cAMP/mg protein/15 minutes (Mean ± SEM)					
Isopropyl unoprostone	-	0	37.0 ± 10	48.5 ± 9.0	55.0 ± 14	45.0 ± 12
Metabolite M1	-	0	44.0 ± 1.0	51.0 ± 10	82.0 ± 20	105.0 ± 26

Table 6. Formation of cyclic AMP in rabbit-iris ciliary body by PGE2, PGF-2α, and latanoprost

Agonist	Concentrations (nM)				
	0.0078	0.031	0.125	0.5	2.0
PGE2	-	-	206 ± 30	294 ± 45	394 ± 40
PGF-2α	0	10 ± 2.5	13.0 ± 3	20 ± 4.2	23.0 ± 5
Latanoprost	12.0 ± 3.5	20.0 ± 4	44 ± 10	47 ± 9	52.0 ± 12

Reviewer's note:
The results present here, particularly for PGE2, while identical nominally in regards to the amount of cAMP generated, are different in respect to the author's reported agonist concentration. For example, in the publication from *J Ocul Pharmacol Ther* reviewed above, PGE2 at 2.0 μM caused generation of 294.0 ± 45.0 pmoles of cAMP, however in this report, the author reports that 0.5 nM caused the exact same amount of cAMP to be generated. This discrepancy extends to other concentrations of PGE2 as well. This greatly affects interpretation of the results since a 1000× difference in concentration of agonists was reportedly used and the results seem to have been skewed to the right by one cell in the tables. However the observation that PGE2 generates a strong cAMP response and that PGF-2α, latanoprost, unoprostone isopropyl and M1 cause the generation of cAMP remains an important similarity between the different drugs since they have all been shown to generate PGE2 (see below) and PGE2 has been suggested to modulate trabecular meshwork contractility. The concentrations of

unoprostone isopropyl and M1 used in this experiment are physiologically relevant to concentrations achieved following topical administration of UI.

"Ocular hypotensive FP prostaglandin (PG) analogs: PG receptor subtype binding affinities and selectivities, and agonist potencies at FP and other PG receptors in cultured cells". Sharif, N.A., *et al*., 2003, *J Ocul Pharmacol Ther*, 19(6): 501-515.

Natural occurring prostaglandins were compared to unoprostone acid (M1), travoprost acid, bimatoprost, latanoprost, and S-1033 for binding to various prostaglandin receptors. Radioligand binding assays were employed. In general, each natural prostaglandin possessed the highest affinity for its respective receptor, however several natural prostaglandins displayed little selectively while the PG analogs in general were more selective (Table 7). Unoprostone isopropyl or its M1 acid metabolite displayed little affinity for any prostaglandin receptor including the FP receptor.

Table 7. PG receptor inhibition constants and relative selectivities of synthetic analogs of the FP-class

PG analog	PG receptor binding inhibition constants (K_i, nM) and FP receptor selectivity							
	DP	EP1	EP2	EP3	EP4	FP	IP	TP
Travoprost	52000	9540	nd	3501	41000	35	> 90000	> 121000
(±)-fluprostenol	> 50000	12300	> 100000	4533	14400	98	> 60500	121063
Bimatoprost acid	> 90000	95	nd	387	25700	83	>100000	> 77000
Latanoprost acid	> 43000	191002060	39667	7519	75000	98	> 90000	> 60000
Bimatoprost	90000	19100	nd	>100000	>100000	6310	>100000	>100000
Unoprostone acid (M1)	> 43000	11700	nd	> 22000	15200	5900	> 30000	> 30000
S-1033	90000	13500	nd	> 77000	6650	22000	> 30000	> 30000
Natural prostaglandins								
PGD_2	81	>19000	2973	115	2139	2500	>140000	>35000
PGE_2	>10000	26	4.9	3	0.9	3400	53708	>10000
PGF-2α	18000	594	964	24	433	130	> 50000	>190000
PGI_2	3537	>15000	nd	5375	8074	>86000	1398	>65000

A functional activity assay of PI turnover of each of the compounds was performed measuring [^{3} H]-inositol phosphate production (Table 8). Unoprostone isopropyl and metabolite M1 displayed comparatively little activity in each cell type except mouse 3T3 fibroblasts in which the M1 metabolite induced PI turnover with an EC_{50}= 617nM. As noted above for the Kashiwagi study on unoprostone ocular metabolism, this level may be physiologically achievable. The functional PI turnover activities of various PGs were blocked by the FP-receptor selective antagonist, AL-8810. Unoprostone also exhibited low potency in other prostaglandin receptor assays for DP-receptor (cAMP production), EP1 receptor (PI turnover), EP2 receptor (cAMP production), EP3 receptor (various

functional responses), EP4 receptor (cAMP production), IP receptor (cAMP production) and TP-receptor (PI turnover) (data not shown).

Table 8. Functional agonist potencies of various FP-class PG analogs at native or cloned FP receptors in different cell types

Compound	Agonist potency for stimulating PI turnover in different cell types (EC_{50}; nM)				
	Human ciliary muscle cells	Human trabecular meshwork cells	HEK-293 FP receptor transfectant	Mouse 3T3 fibroblasts	Rat A7r5 (vascular smooth muscle)
Travoprost acid	1.4	3.6	2.4	2.6	2.6
(±)-fluprostenol	4.3	11	4.6	3.7	4.4
Bimatoprost acid	3.8	26	3.3	2.8	2.8
Latanoprost acid	124	35	45.7	32	35
Travoprost	123	103	40.2	81	46
Latanoprost ester	313	564	173	142	110
Bimatoprost amide	9600	3245	681	12100	6850
Unoprostone acid (M1)	3503	3306	3220	617	878
Unoprostone isopropyl	8420	2310	9100	560	458
S-1033	4701	7000	2610	670	767
PGF-2α	104	62	29	26	31

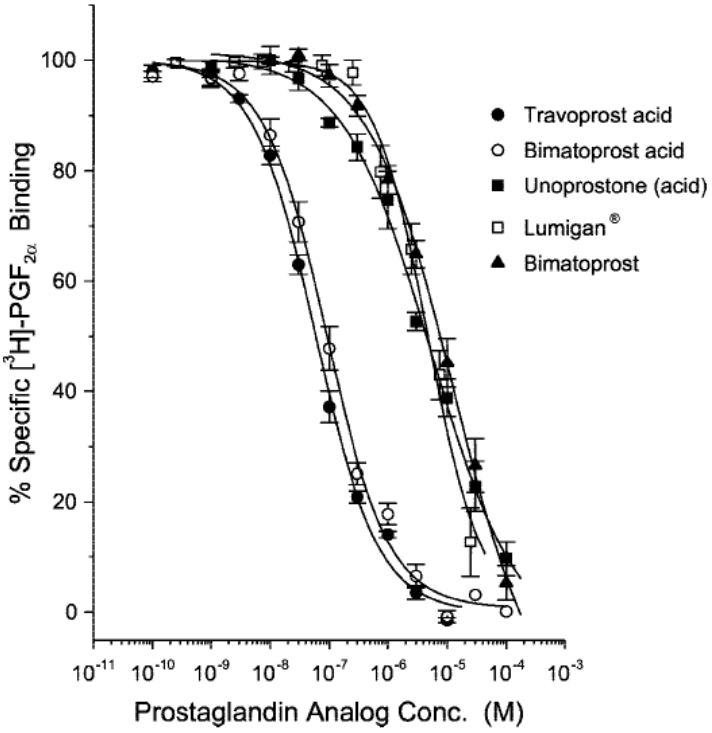
*pink shaded cell represents potential physiologically achievable concentration in the aqueous humor as inferred from the Kashiwagi paper reviewed above.

Reviewer's note:
The study provides data that suggest unoprostone does not bind prostaglandin receptors similar to natural or synthetic prostaglandin analogues nor induce similar proximal downstream signaling in cells at similar concentrations as other prostaglandin analogues such PI turnover or cAMP production. M1 displays some activity in inducing PI turnover in mouse 3T3 fibroblasts and rat vascular smooth muscle cells at potential physiologically achievable concentrations. While some stimulation of the prostaglandin receptor at physiological concentrations may be possible, unoprostone affects other targets such as BK, C1C-2 and L-type calcium channels at concentrations considerably lower than those required for prostaglandin agonist activity.

"Real-time intracellular Ca2+ mobilization by travoprost acid, bimatoprost, unoprostone, and other analogs via endogenous mouse, rat, and cloned human FP prostaglandin receptors". Kelly, C.R., et al., 2003, J Pharmacol Exp Ther, 304(1): 238-245.

The ability of PGF-2α analogs to compete for [^{3}H]PGF2α for binding to prostaglandin F2α receptors (FP) was investigated. Washed bovine corpus luteum membrane (BCLM) homogenates were incubated with [^{3}H]PGF-2α (1 nM) and increasing concentrations of a test compound for 2 h. Unoprostone competed with PGF-2α binding to bovine corpus luteum membranes with an EC_{50} binding constant of 3860 nM (Figure 3).

Figure 3. FP receptor binding activity of unoprostone isopropyl compared to other compounds

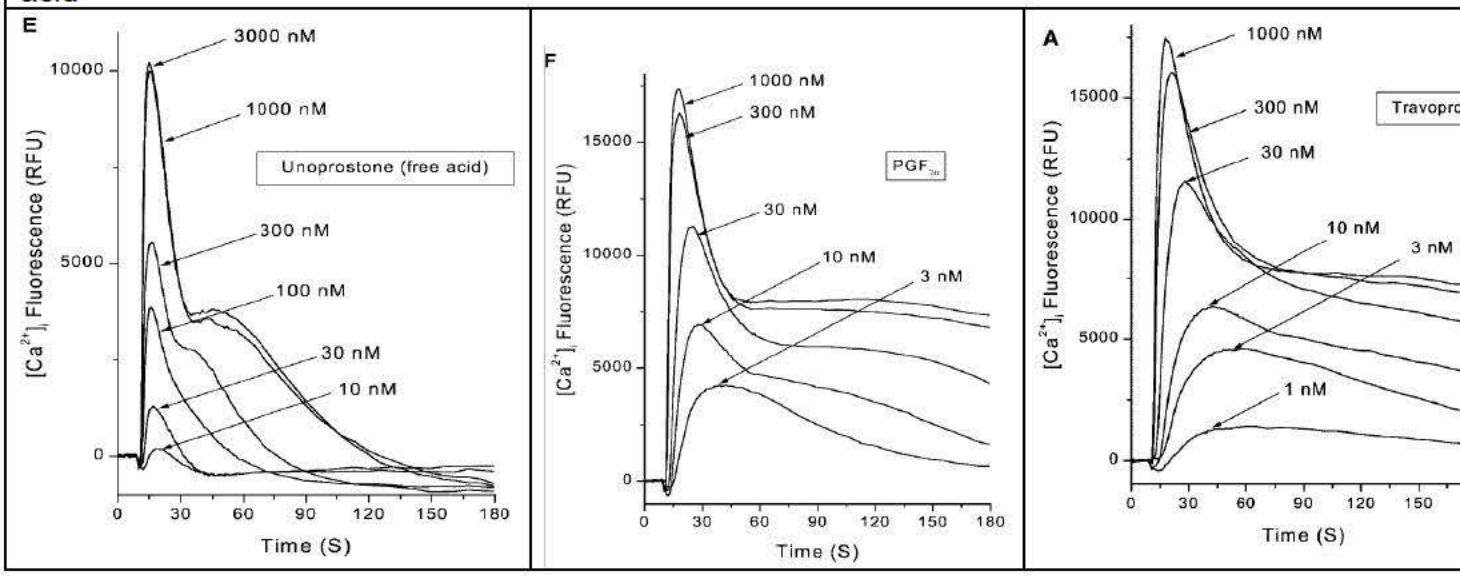


Compound	FP Receptor Binding Affinity (Ki ± SEM)
Travoprost acid [(+)-fluprostenol]	49.9 ± 3.3
Bimatoprost acid (17-phenyl trinor PGF-2α)	85.0 ± 14
Unoprostone acid (M1)	3860 ± 687
Lumigan (amide; bimatoprost; Allergan)	3426 ± 1225
Bimatoprost (amide; Cayman Chemical)	9862 ± 3738

The ability of the compounds to mobilize intracellular Ca^{++} was evaluated in rat smooth muscle (A7r5 cells) or mouse fibroblasts (3T3 cells) transfected with cloned human ocular FP prostanoid receptor. In both cell types, travoprost acid (EC_{50} = 17.5–37 nM), bimatoprost acid (EC_{50} = 23.3– 49.0 nM), unoprostone (EC_{50} = 306-1270 nM), bimatoprost (EC_{50} = 3070- 3940 nM), and Lumigan (EC_{50} = 1470–3190 nM)

concentration dependently stimulated Ca^{++} mobilization. In cells stimulated with prostaglandins such as PGF-2α or travoprost acid, concentrations as low as 3 nM induced a spike in intracellular Ca^{++} which was maintained above baseline for > 180 seconds, while on the other hand, unoprostone acid induced an initial spike in Ca^{++} even at concentrations as low as 10 nM but intracellular Ca^{++} returned to baseline levels within the 180 seconds of the assay. A clear difference can be seen (Figure 4).

Figure 4. Intracellular Ca++ accumulation in rat A7r5 cells treated with unoprostone, PGF-2α or travop acid



Reviewer's note:
Interestingly, it may be that the unoprostone acid metabolite, M1, at physiologically relevant concentrations (i.e. > 1000nM inferred from Kashiwagi et al reviewed above) is stimulating the FP receptor and mobilizing Ca^{++}. Initial Ca^{++} release following FP receptor stimulation occurs from intracellular stores within the endoplasmic reticulum and later maintenance of heightened intracellular Ca^{++} occurs through the influx of Ca^{++} through Ca^{++} channels (as seen for PGF-2α and travoprost acid in Figure 4). Unoprostone isopropyl or M1 may also be concurrently activating BK potassium channels and causing hyperpolarization of the cell and inhibition of Ca^{++} channels (see below). The result of these combined effects may manifest as an initial Ca^{++} spike due to FP receptor ligation and release of Ca^{++} from intracellular stores but a lack of maintenance of the intracellular Ca^{++} concentration due to inhibition of the Ca^{++} channel by BK channel mediated hyperpolarization of the cell.

"The effects of prostaglandin analogues on IOP in prostanoid FP-receptor-deficient mice". Ota, T., et al., 2005, Invest Ophthalmol Vis Sci, 46(11): 4159-4163.

This study was designed to determine the involvement of the prostanoid FP receptor in the intraocular pressure (IOP)- lowering activity of latanoprost, travoprost, bimatoprost, and unoprostone in prostaglandin FP-receptor– deficient (FPKO) mice. A 3µL drop of

each drug solution was topically applied to a randomly selected eye. IOP reduction was evaluated by the difference in IOP between the treated eye and the untreated contralateral eye in the same mouse. First, the diurnal variation and baseline IOP in WT and FPKO mice were measured. The baseline IOP (mean ± SEM) in WT and FPKO mice was 15.0 ± 0.2 and 15.0 ± 0.3 mm Hg, respectively, during the day, and 18.9 ± 0.4 and 19.2 ± 0.4 mm Hg, respectively, at night. In WT mice, isopropyl unoprostone significantly lowered IOP at night (13.7 ± 1.9%) but did not reach statistical significance during the day (5.3 ± 3.2%; Figure 5). In FPKO mice, latanoprost, travoprost, bimatoprost, and unoprostone showed no significant IOP-lowering effect (Figure 6).

Figure 5. Effects of latanoprost (LAT; 0.005%), travoprost (TRA; 0.004%), bimatoprost (BIM; 0.03%) and unoprostone isopropyl (UNO; 0.12%) on intraocular pressure in wild type mice

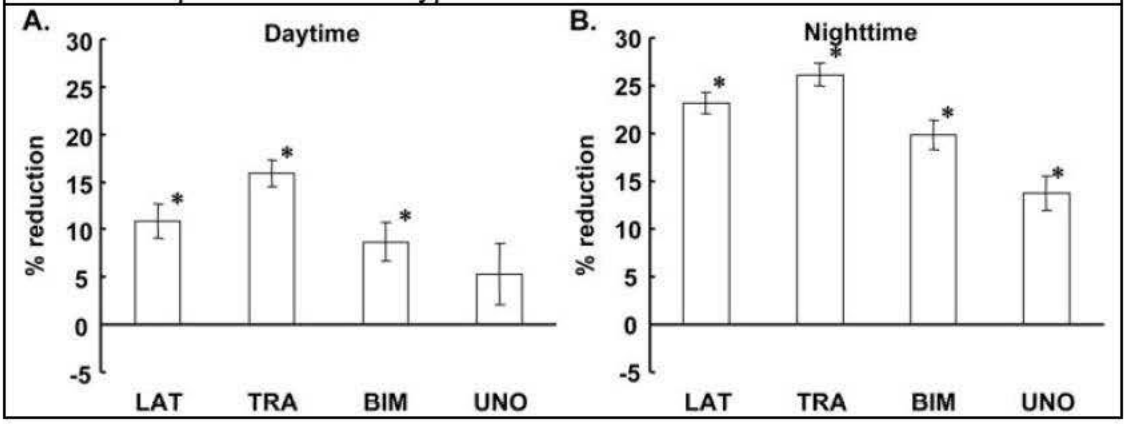
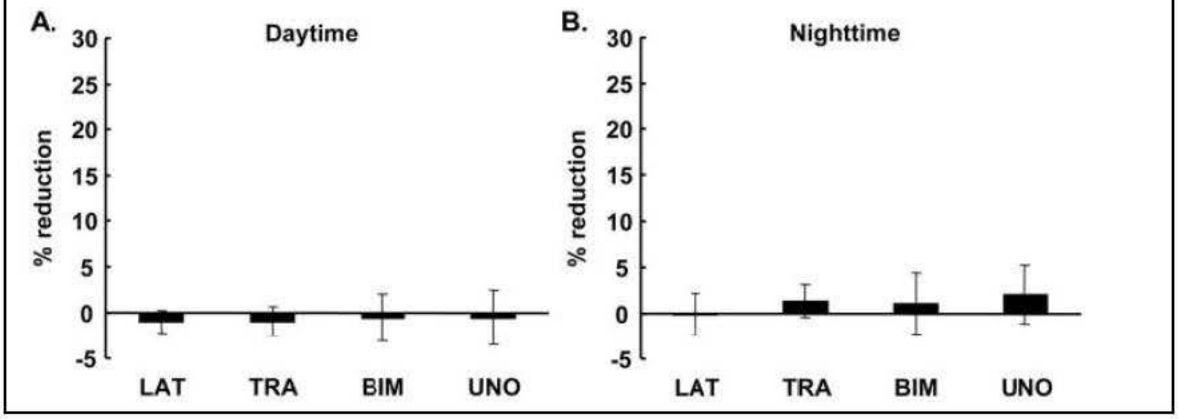


Figure 6. Effects of latanoprost (LAT; 0.005%), travoprost (TRA; 0.004%), bimatoprost (BIM; 0.03%) and unoprostone isopropyl (UNO; 0.12%) on intraocular pressure in prostaglandin FP-receptor knockout mice



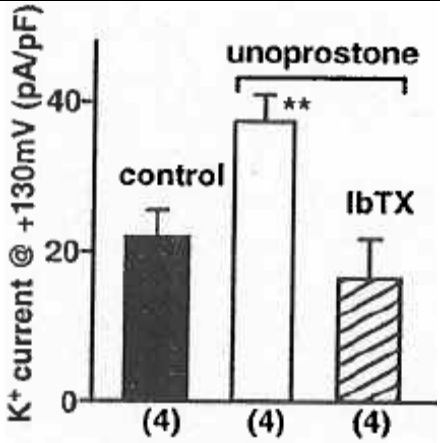
Reviewer's note:
This study demonstrated the dependence of unoprostone on the FP receptor following a single topical application in normotensive mice, this dependence may not apply to a clinical scenario in which patients with elevated IOP are administered multiple applications of the drug. While unoprostone isopropyl and its metabolites show low affinity for the FP receptor compared to other prostaglandins and their analogues, it remains possible that concentrations are achieved which allow some FP stimulation or that FP receptor agonists induced by unoprostone act on FP receptors via unknown signal pathways. To clarify this issue, determination of the endogenous production of PG analogues in the aqueous humor after instillation of bimatoprost and unoprostone in FPKO mice will be required.

4.3 Ion channel modulating activity

"Cellular and molecular effects of unoprostone as a BK channel activator". Cuppoletti, J., *et al*., 2007, *Biochim Biophys Acta*, 1768(5): 1083-1092.

This study compared the effects of unoprostone isopropyl and M1 with latanoprost and PGF-2α in HCN-1A cells, a human neuronal cell line commonly used in studies of membrane channels. In a whole cell patch clamp assay designed to measure K^+ channel currents, addition of 1nM unoprostone isopropyl to HCN-1 cells caused an increase in K^+ current which was inhibited by iberiotoxin, a scorpion toxin with specificity for the BK channel (Figure 7). There was no effect of 1 nM latanoprost or 1nM PGF-2α on iberiotoxin sensitive K^+ currents (data not shown in publication). The EC_{50} for unoprostone isopropyl stimulation of the BK channel was 0.6 ± 0.2 nM.

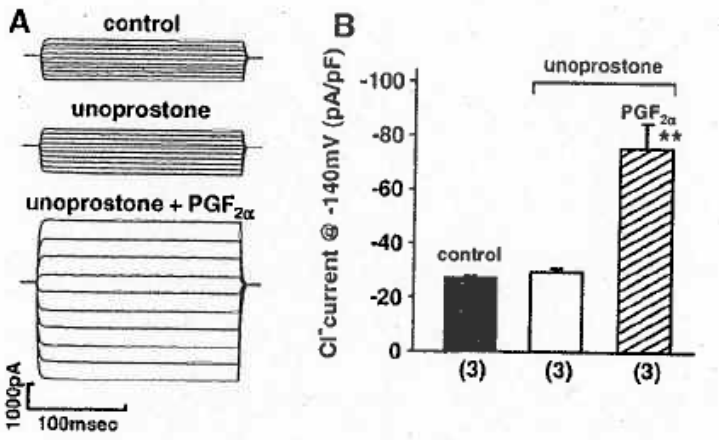
Figure 7. K^+ currents normalized to capacitance in HCN-1 cells following exposure to iberiotoxin



The ability of 1nM unoprostone isopropyl, latanoprost and PGF-2α to activate Cl^- currents in HCN-1A cells was then investigated. While latanoprost and PGF-2 were

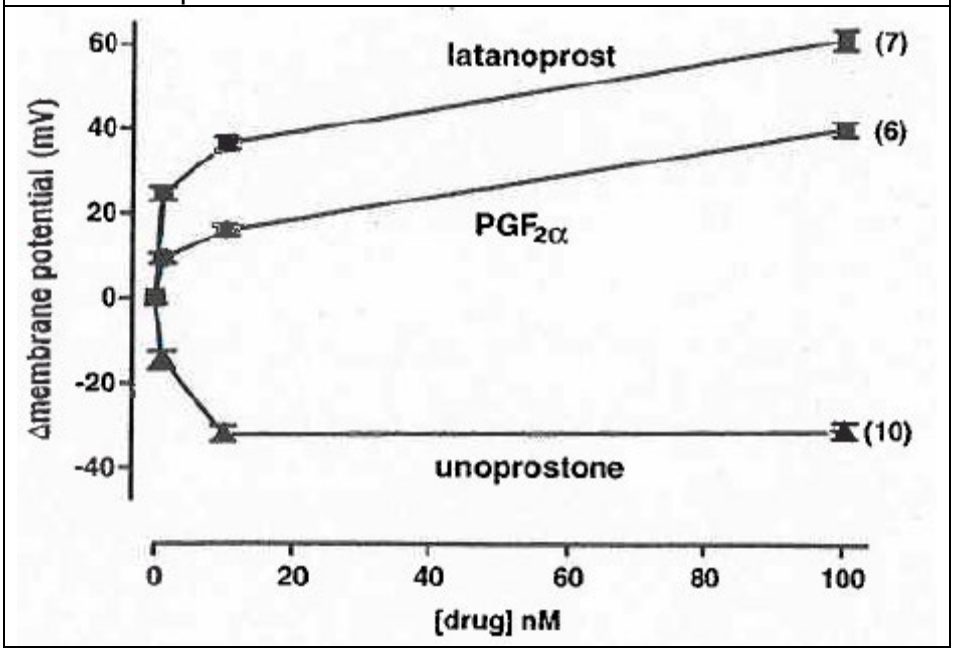
shown to activate Cl^- current in these cells as shown by a decrease in membrane potential, unoprostone had no effect (Figure 8, data shown for PGF2α only).

Figure 8. Effect of UI on Cl^- currents of HCN-1A cells



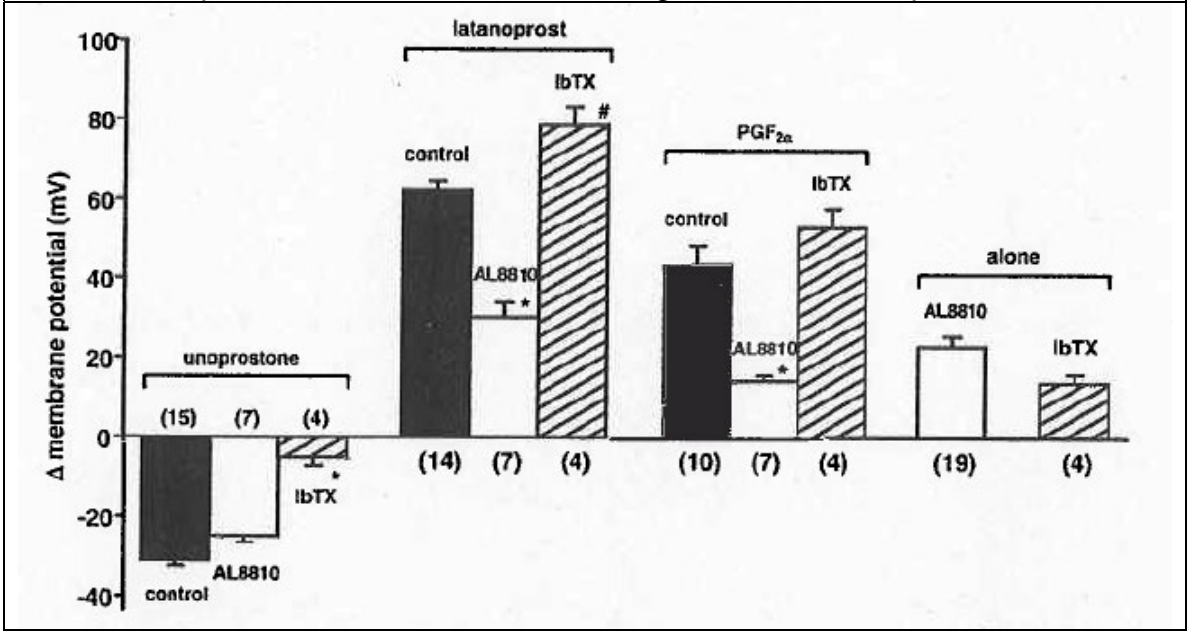
A fluorescent membrane potential sensitive dye, $DiBAC_4$, was used to measure membrane polarization following treatment with unoprostone isopropyl, latanoprost and PGF-2α. While unoprostone isopropyl caused a dose dependent hyperpolarization of HCN-1A cells, latanoprost and PGF-2α caused a depolarization of membrane potential (Figure 9).

Figure 9. Effect of UI, latanoprost and PGF-2α on changes in membrane potential in HCN-1A cells.



To further specify the mechanism through which membrane polarization is effected by unoprostone isopropyl, latanoprost and PGF-2α, specific inhibitors of BK channels (iberiotoxin) and PGF-FP receptor antagonists were added to HCN-1A cells treated with the drugs. Results showed that the FP receptor antagonist, AL-8810 blocked latanoprost and PGF-2α mediated membrane depolarization whereas AL-8810 did not significantly effect hyperpolarization mediated by unoprostone isopropyl. Iberiotoxin blocked unoprostone mediated membrane hyperpolarization whereas it did not effect depolarization mediated by the prostaglandins latanoprost and PGF-2α (Figure 10).

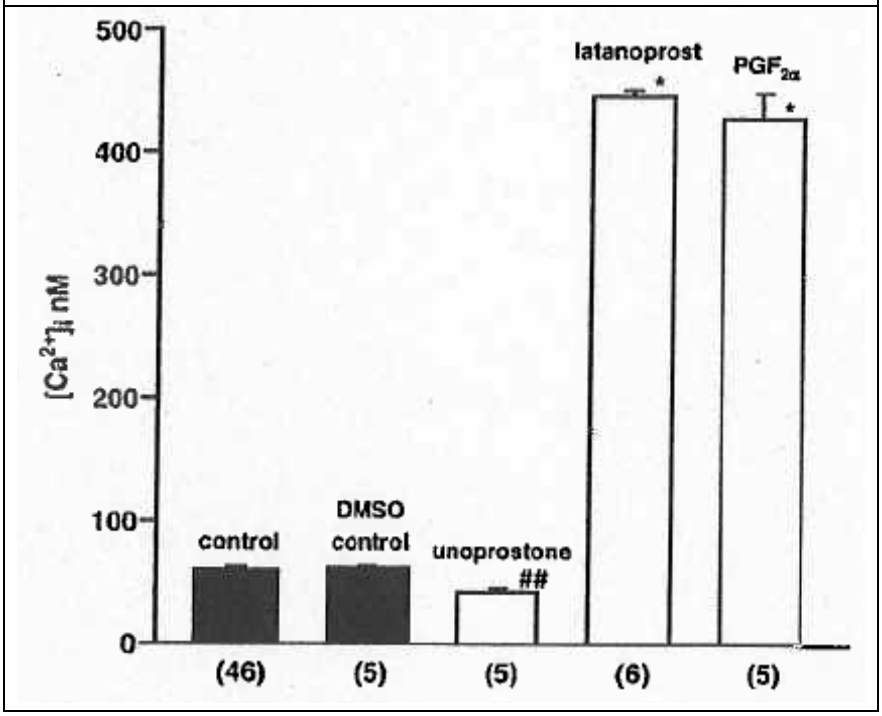
Figure 10. Effect of AL-8810, an FP receptor antagonist and iberiotoxin (IbTX) on UI, latanoprost and PGF-2α induced changes in membrane potential.



The effect of unoprostone isopropyl, latanoprost and PGF-2α on intracellular Ca^{++} accumulation was determined. HCN-1A cells loaded with the Ca^{++} sensitive dye indo-1/AM and treated with 100 nM of unoprostone isopropyl, latanoprost and PGF-2α were assayed for intracellular Ca^{++} after 60 minutes. Results showed that while latanoprost and PGF-2α caused an accumulation of intracellular Ca^{++} which was present at 60 minutes after treatment, unoprostone did not cause an apparent increase in intracellular Ca^{++} (Figure 11).

Reviewer's note: It is important to realize that intracellular Ca^{++} was measured 60 minutes following addition of the different compounds. As shown above in Kelly *et al* (2003), intracellular Ca^{++} is initially increased by unoprostone isopropyl, but quickly returns to baseline levels whereas the prostaglandins cause a sustained increase in intracellular Ca^{++} above baseline. See also the reviewer's note for the Kelly study regarding a possible mechanism for this observation.

Figure 11. Effect of UI, latanoprost, and PGF-2α on intracellular Ca^{++}



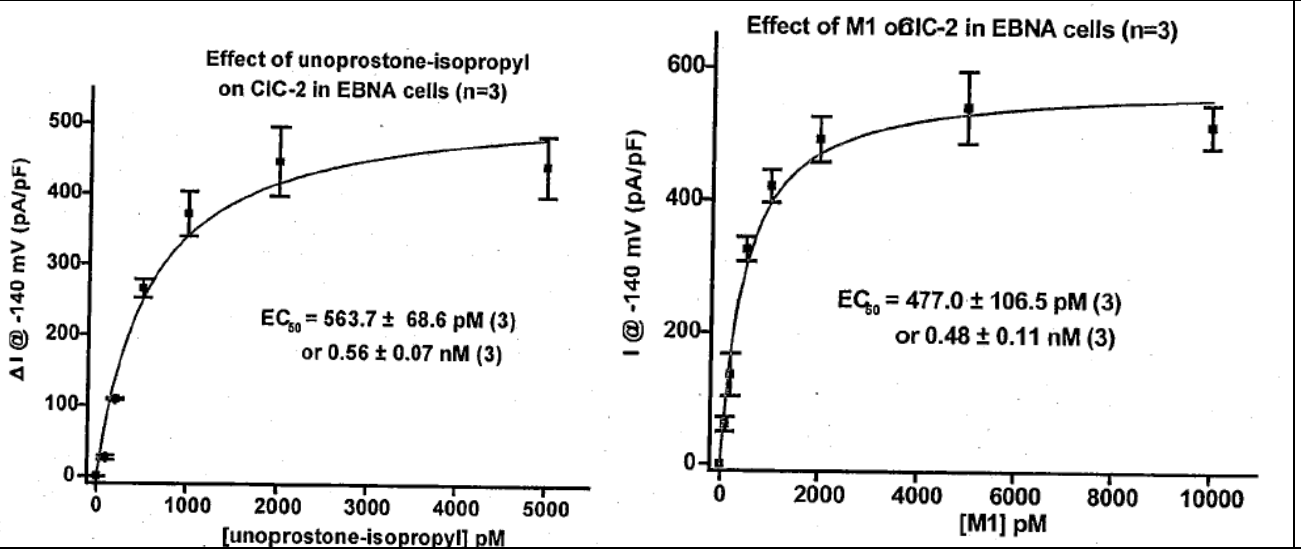
Reviewer's note:
These data suggest that unoprostone isopropyl does not induce similar changes in cell membrane polarization and membrane channel stimulation as latanoprost and PGF-2α. Whereas latanoprost and PGF-2α cause a depolarization of the cell membrane characterized by intracellular Ca^{++} accumulation and an increased Cl^- current, unoprostone causes hyperpolarization of the cell membrane and activation of BK channels. While latanoprost and PGF-2α stimulated Cl^- conductance at 1 nM, unoprostone isopropyl did not. However, given the observation that unoprostone displays reduced affinity for the prostaglandin receptors, higher concentrations of unoprostone and M1 should have been tested. These data suggest that unoprostone isopropyl does not act similar to prostaglandins at similar concentrations and induce opposing effects regarding membrane polarity.

"Draft technical report November 5, 2010 in support of FDA label change: Cellular and molecular effects of *cis*-unoprostone-isopropyl, *trans*-unoprostone and M1 as BK potassium channel and ClC-2 chloride channel activators with distinctly different molecular and cellular effects than latanoprost or travoprost", Cuppoletti J., 2010, *et al*.

The effect of unoprostone isopropyl and its acid metabolite (M1) on ClC-2 currents was investigated in EBNA293 human embryonic kidney (HEK) cells transfected with human recombinant ClC-2. Unoprostone isopropyl and M1 caused an increase in Cl^- current

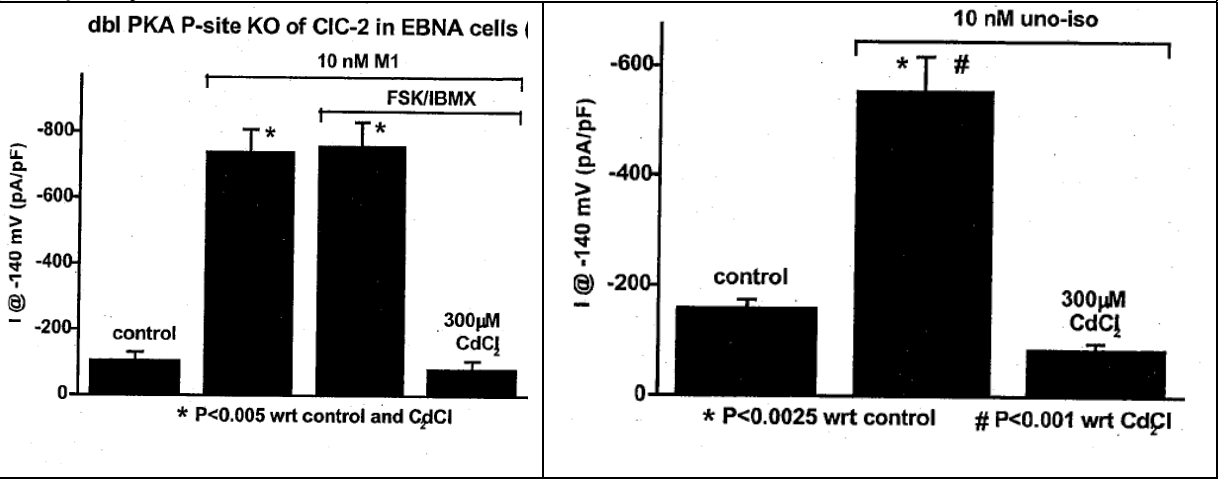
which was inhibited with 300 μM $CdCl_2$ which is consistent with activation of ClC-2 channels. The EC_{50} for unoprostone isopropyl and M1 were 0.48 ±0.11 nM and 0.56 ± 0.07 nM (Figure 12).

Figure 12. Activation of ClC-2 channels by unoprostone isopropyl and M1



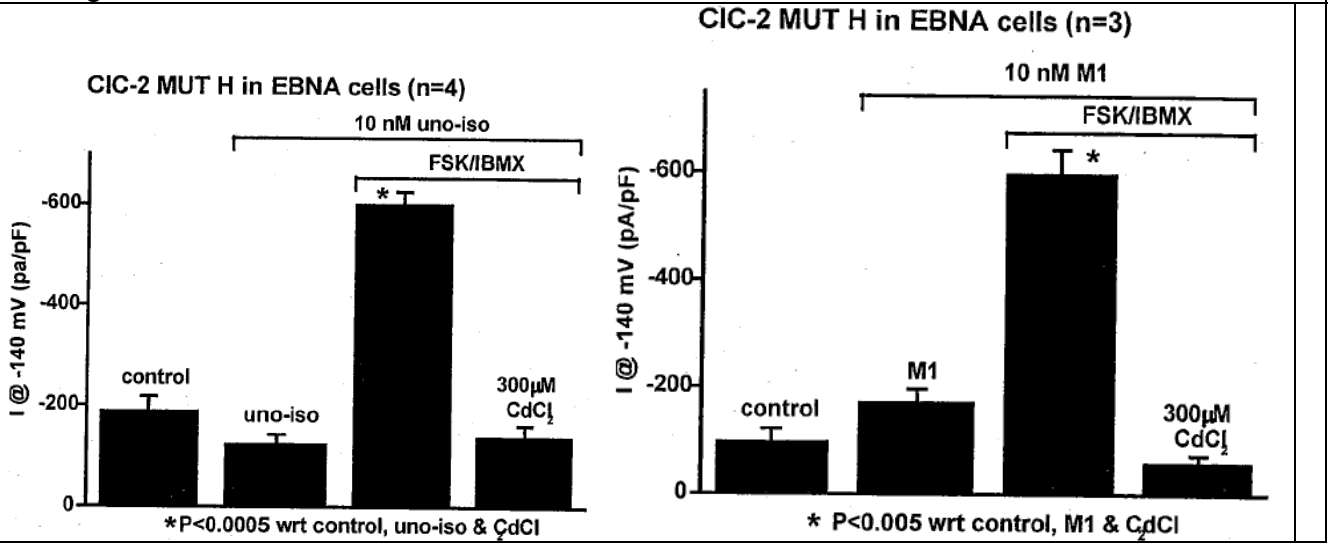
The stimulation of ClC-2 channels by unoprostone isopropyl and M1 was independent of protein kinase A (PKA) as shown by its stimulation of EBNA cells transfected with a ClC-2 mutant lacking PKA phosphorylation sites (Figure 13) . This experiment lacked a control which was dependent on PKA for stimulation of the ClC-2 channel which would have shown that the mutant was indeed characterized by a lack of PKA activation. A positive control, forskolin/ isobutylmethylxanthine (IBMX) did not increase ClC-2 currents over those stimulated with M1. Treatment with $CdCl_2$ inhibited the ClC-2 channel and returned chloride current to baseline levels.

Figure 13. Effect of M1 and unoprostone isopropyl on ClC-2 mutant lacking PKA phosphorylation sites



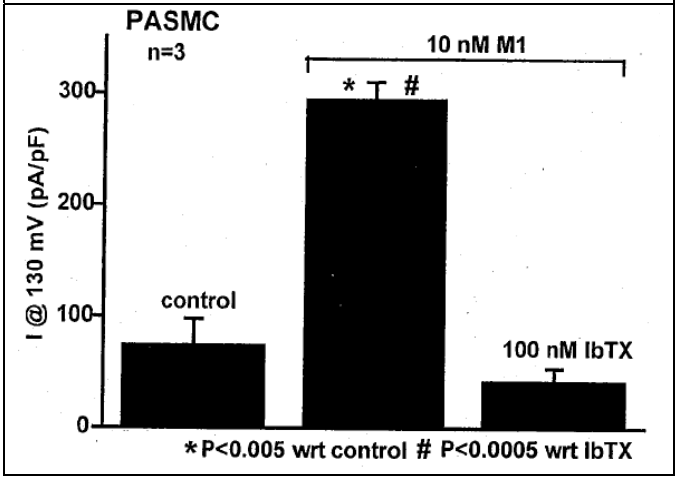
Activation of the ClC-2 channel was however dependent on a specific putative prostone binding site since a mutant lacking this activation site was also not activated by unoprostone isopropyl but was stimulated by forskolin/IBMX (Figure 14). The author did not include information regarding the characterization of this putative prostone binding site.

Figure 14. Effect of M1 and unoprostone isopropyl on ClC-2 mutant putative prostone binding site



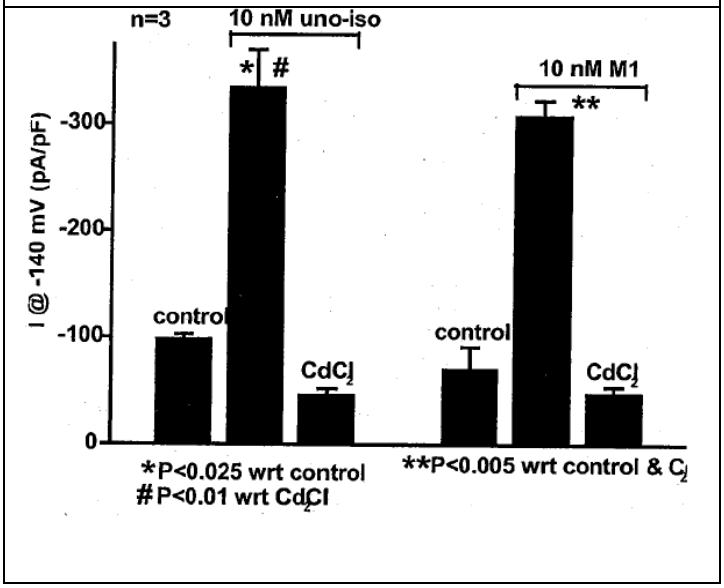
Patch clamp experiments were performed in a human pulmonary smooth muscle cell line that showed that M1 activates BK channels in an iberiotoxin sensitive manner (Figure 15).

Figure 15. M1 activates BK channels in smooth muscle cells



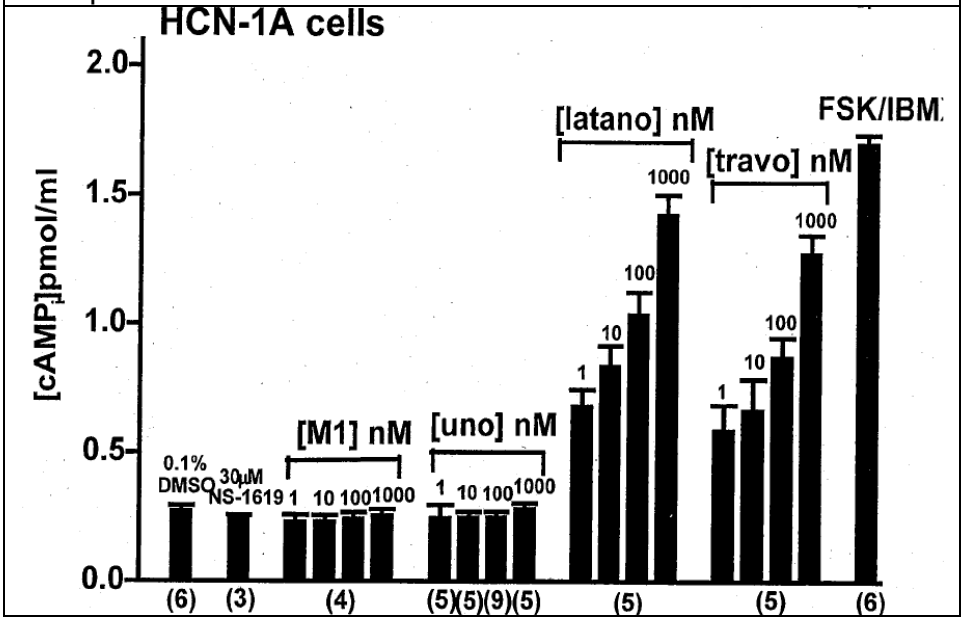
Similar experiments also revealed that unoprostone isopropyl and M1 also activate ClC-2 channels in the same human smooth muscle cell line (Figure 16).

Figure 16. Activation of ClC-2 in human smooth muscle cell line



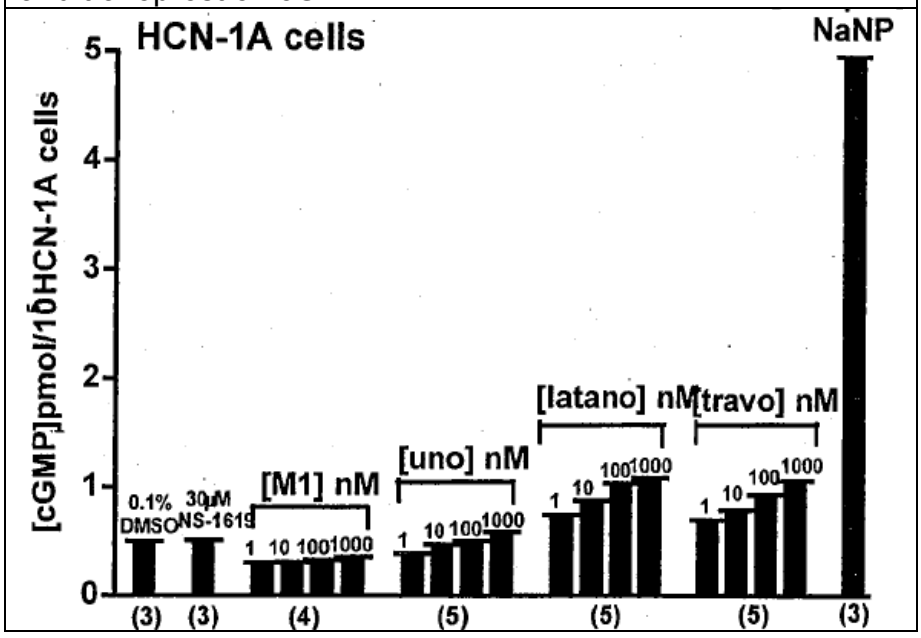
Cyclic AMP (cAMP) generation following exposure to unoprostone isopropyl, M1, latanoprost and PGF-2α were measured with ELISA. The results show that neither unoprostone isopropyl nor M1 increased intracellular cAMP at concentrations up to 1μM, whereas latanoprost and travoprost both increased intracellular cAMP (Figure 17).

Figure 17. Effect of unoprostone-isopropyl, M1 latanoprost and travoprost on cAMP.



In a similar experiment, data also suggest that unoprostone-isopropyl and M1 do not increase intracellular cGMP, while both latanoprost and travoprost appeared to cause a slight dose-dependent increase in intracellular cGMP (Figure 18).

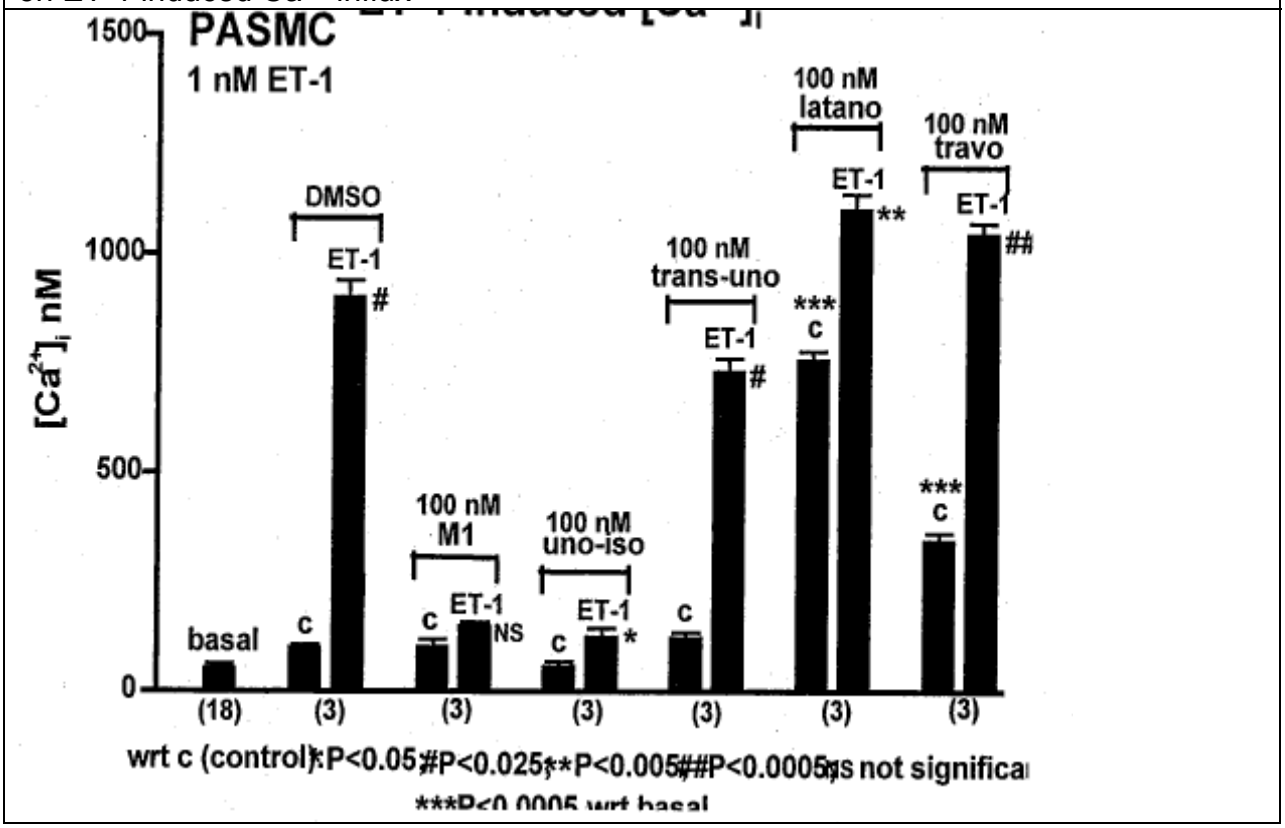
Figure 18. Effect of unoprostone isopropyl, M1, latanoprost and travoprost on cGMP



Cells* were loaded with indo-1/AM and then treated with 1 nM ET-1 and 100 nM M1, unoprostone-isopropyl, trans-unoprostone, latanoprost or travoprost or DMSO (vehicle for the drugs) for 30 min. Ca^{++} accumulation was then measured. Results showed that ET-1 caused an influx of Ca^{++} and the addition of latanoprost or travoprost increased this influx in response to ET-1 whereas treatment with unoprostone isopropyl or M1 abrogated the Ca^{++} influx associated with ET-1 treatment (Figure 19).

***Reviewer's note:** At one point the author states the cells used were HCN-1 cells (a neuronal cell line) whereas in the figure legend it states that smooth muscle cells were used. It is unknown which instance is correct.

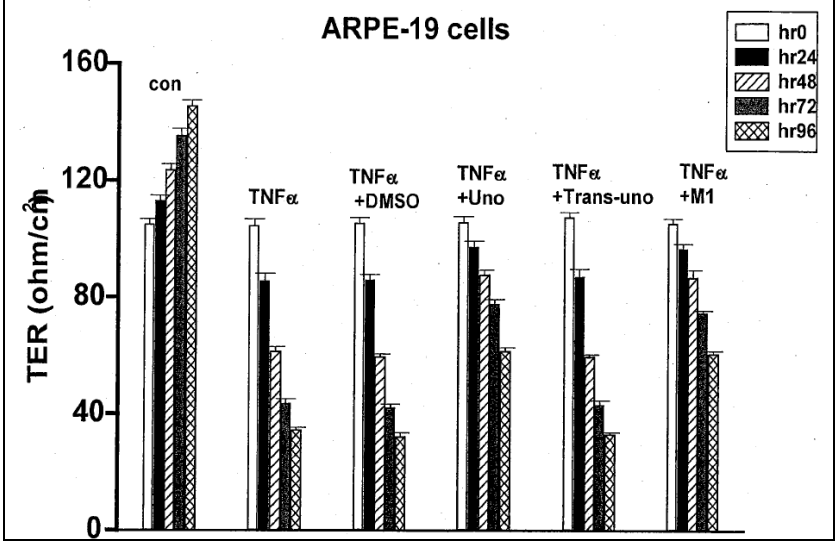
Figure 19. Effect of M1, unoprostone isopropyl, trans-unoprostone and prostaglandins on ET-1 induced Ca^{++} influx



The author also included agonist effects of unoprostone-isopropyl and M1 on prostaglandin receptors EP1-EP4, IP1, DP and FP studied using recombinant human receptors. The author did not specify the methodology used to determine these measurements. Unoprostone isopropyl and M1 were not strong EP1-EP 4 agonists (EC_{50}:1.25 µM). Unoprostone-isopropyl was not a strong FP receptor agonist (EC_{50}:1.25 µM) though M1 stimulated FP receptor with an EC_{50} = 600 nM. The author states that neither unoprostone-isopropyl nor M1 affected IP_1 or DP receptors.

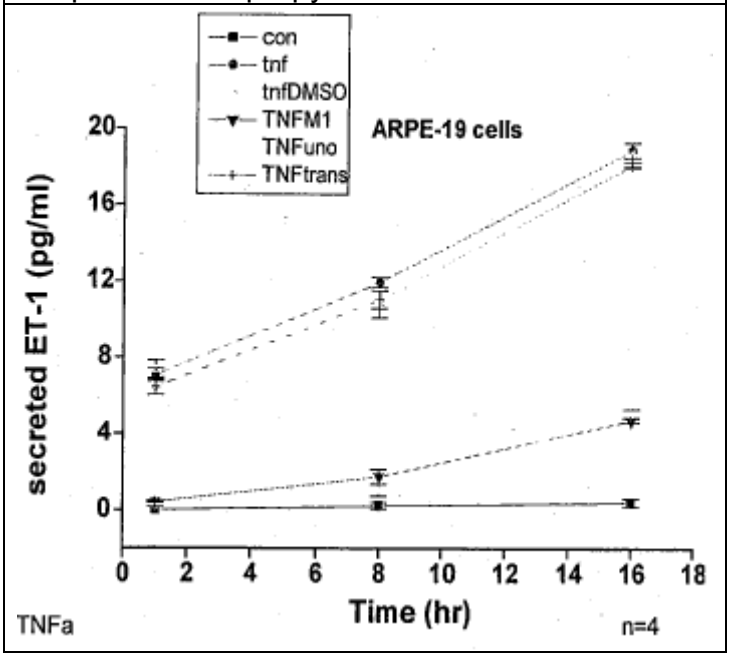
Treatment of a human retinal pigment epithelium cell line (ARPE-19 cells) with TNF-α causes a time dependent decrease in barrier function of the cells as shown by a decrease in transepithelial resistance (TER). Concurrent treatment of these cells with unoprostone isopropyl or M1 somewhat blunted this decrease in TER in response to TNF-α (Figure 20). A different isomer of unoprostone, trans-unoprostone did not mediate a similar effect.

Figure 20. Transepithelial resistance reduced by TNF-α is somewhat alleviated by unoprostone and M1



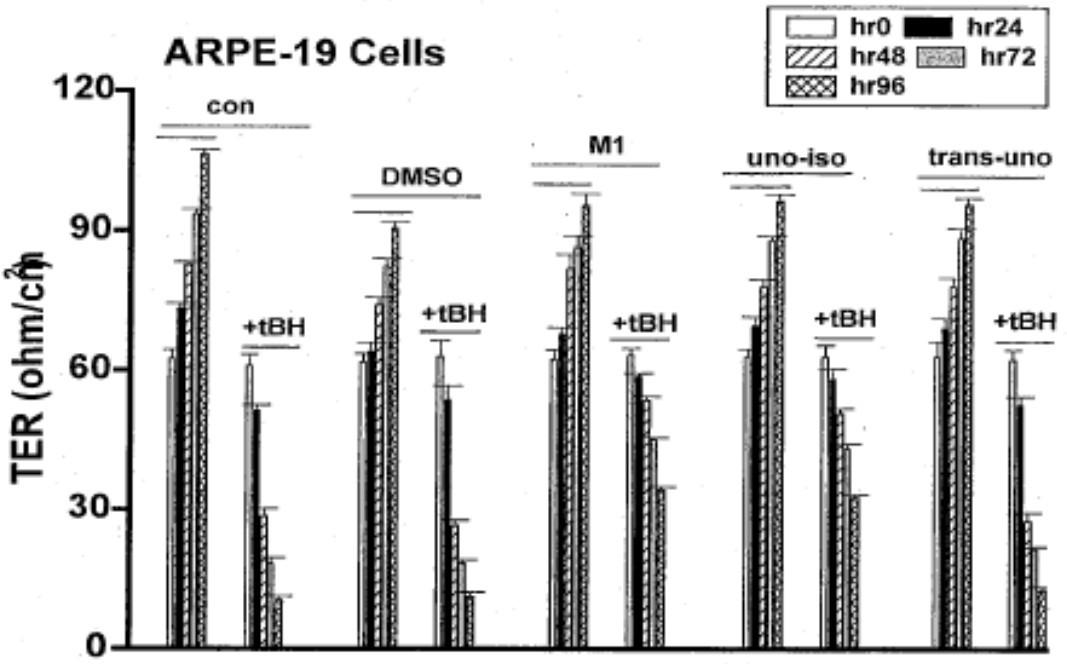
Furthermore, treatment of ARPE-19 cells with TNF-α stimulates secretion of ET-1. Secreted ET-1 in human ARPE-19 cells was measured using a quantitative chemiluminescent ELISA kit. Co-treatment of these cells with unoprostone isopropyl or M1 reduced ET-1 production in response to TNF-α (Figure 21).

Figure 21. ET-1 secretion stimulated by TNF-α in RPE cells in the presence or absence or unoprostone isopropyl or M1



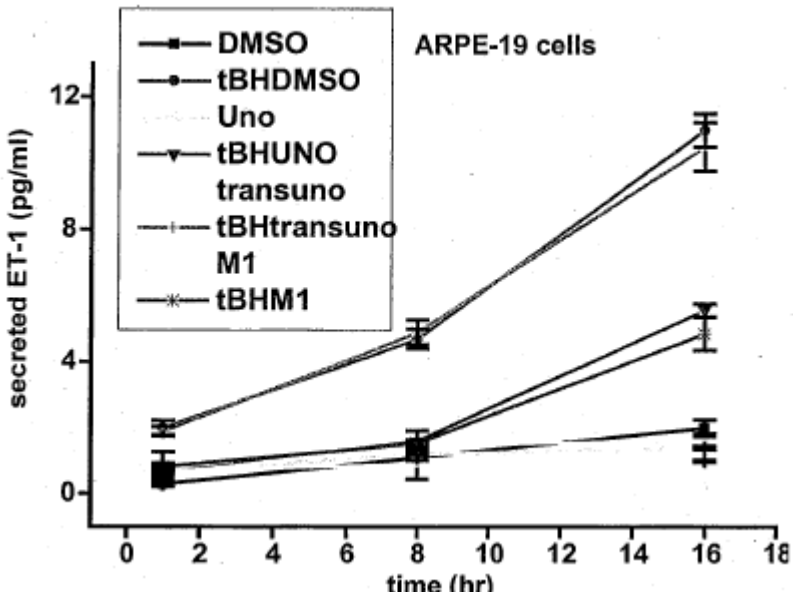
Another experiment to determine the effect of unoprostone on transepithelial resistance was conducted . ARPE-19 cells grown on Transwell 0.4 µM pore size filters for 7 days and then treated with tert-butylhydroperoxide (tBH), an oxidizing agent often used to reduce tight junction formation and decrease transepithelial resistance. Vehicle (DMSO), 100 nM unoprostone-isopropyl, M1 or trans-unoprostone, or a combination of tBH plus drugs were then added. At the indicated time points, TER was measured. Results showed that unoprostone and M1 protect against tBH induced loss of tight junction barrier function (Figure 22).

Figure 22. Effect of tBH, unoprostone isopropyl, M1, trans-unoprostone and combination of tBH and drugs on transepithelial resistance of ARPE-19 cells



The effect of unoprostone-isopropyl M1, and trans-unoprostone on tBH induced ET-1 secretion by ARPE-19 cells was determined. Cells were treated with either 100 μM tBH, 0.1 % DMSO, or 100nM unoprostone-isopropyl, M1 or trans-unoprostone or a combination of tBH and drug. Cell culture supernatants were collected at 1 hr, 8hr and 16hr after the drug treatment. Results showed that tBH induced ET-1 secretion and unoprostone and M1 reduced the amount of ET-1 secreted by ARPE-19 cells in response to tBH (Figure 23).

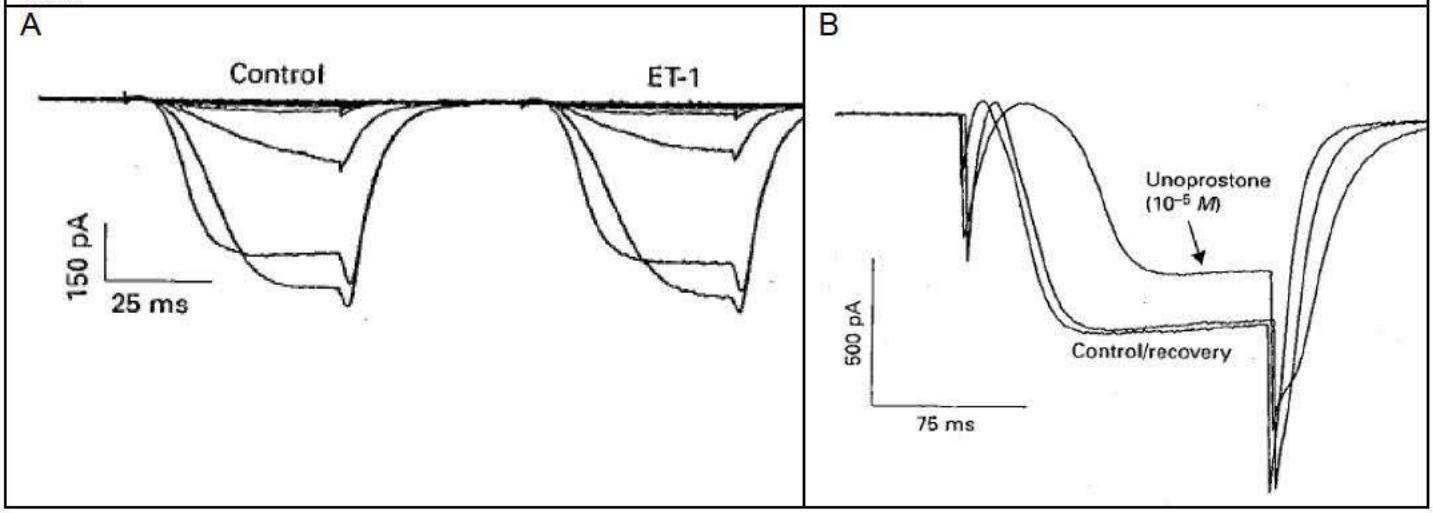
Figure 23. Effect of unoprostone, M1, and trans-unoprostone on tBH induced secretion of ET-1 in a human retinal pigment epithelium cell line



"Effects of unoprostone and endothelin 1 on L-type channel currents in human trabecular meshwork cells". Thieme, H., *et al*., 2005, *Ophthalmic Res*, 37: 293-300.

The effect of unoprostone and ET-1 on L-type channel currents was investigated in cultured human trabecular meshwork strips harvested from donor eyes. Patch clamp experiments were performed with intracellular K^+-free conditions to block superimposed outward K^+ currents which would inhibit detection of inward currents. When extracellular Ba^{++} (barium) is added to the solution, activation of L-type calcium channels occurs (Figure 24A Control). The addition of ET-1 (50nM) caused no change in Ca^{++} current (Figure 24A ET-1). Application of unoprostone led to a significant reduction in the control current (Figure 23B). In the presence of ET-1, unoprostone (10μM) reduced the control current. However, in the absence of ET-1, unoprostone (10μM) also led to a reduction in the control current which was not significantly different from that observed in the presence of ET-1. The authors conclude that ET-1 did not have any effect on the reduction in control current exerted by unoprostone.

Figure 24. Effect of ET-1 and unoprostone on L-type Ca^{++} current in human trabecular meshwork cells



Summary/Conclusions (Reviewer's note):
Two types of calcium channels that are responsible for the intracellular influx of Ca^{++} following cell stimulation are voltage gated calcium channels which are responsive to changes in membrane potential and store operated calcium channels (SOCS) which are responsive to depletion of intracellular calcium after some stimulus causes release from stores within the endoplasmic reticulum. L-type calcium channels are voltage gated calcium channels.

In this experiment, the L-type Ca^{++} channel was inhibited by unoprostone in K^{+}-free conditions which appear eliminate BK channel activation and subsequent hyperpolarization of the cell as being responsible for the lack of Ca^{++} influx. This is an important observation since it appears that unoprostone may have promiscuous channel activating/inhibiting properties. Since the tyrosine kinase inhibitor herbimycin A blunted the ability of unoprostone to inhibit the L-type calcium channel, a protein kinase, activated by unoprostone may be mediating the inhibition of Ca^{++} influx through L-type calcium channels. In a review of BK channel activators by Nardi and Olesen, (2008, *Curr Med Chem*, 15: 1126-1146), the authors specifically state:

> "the evaluation and classification of the BK channel modulators is further complicated by the lack of rigorous criteria in the literature which allows investigators the possibility to define a BK channel modulator as any drug modulating BK channels either directly or indirectly…Selectivity over other ion channels should also be investigated more thoroughly …the potency for relaxation of smooth muscle elicited by a BK-channel opener might be overestimated if the compound also inhibits Ca^{++} current."

Therefore it appears that unoprostone may be a molecule that these authors caution against categorizing as a BK channel activator. It may be that the drug displays multiple ion channel modulating capabilities of which the BK channel is only one or that

unoprostone acts on an upstream mediator which controls more global cellular functions. The sponsor has not submitted data which demonstrate that unoprostone has been screened against a panel of cellular targets including ion channels, protein kinases and receptors. At present, it appears that activation of the BK and C1C-2 channels and K^+-independent inhibition of L-type calcium channels have been identified. Further characterization of unoprostone specificity should be undertaken.

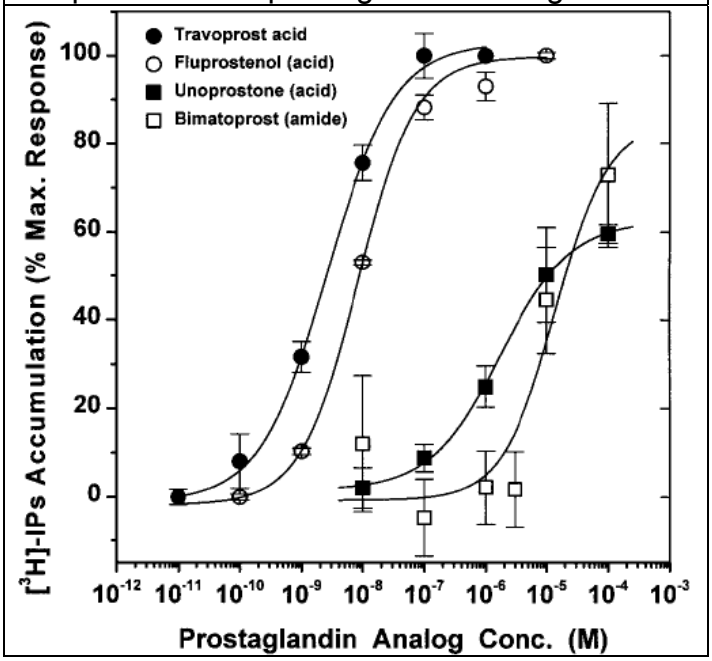
4.4 Effect on ocular tissues

"Human trabecular meshwork cell responses induced by bimatoprost, travoprost, unoprostone, and other FP prostaglandin receptor agonist analogues". Sharif, N.A., *et al*., 2003, *Invest Ophthalmol Vis Sci*, 44: 715-721.

The functional agonist properties of unoprostone isopropyl on human trabecular meshwork cells were compared to prostaglandin analogues. Human trabecular meshwork cell were obtained from dissected trabecular meshwork explants donated by various eye banks, and labeled with ^{3}[H]-phosphoinositol (PI). Different drugs were added at varying concentrations and turnover of PI, thought to be generated by prostaglandin receptor agonist activity was measured after 60 minutes by anion exchange chromatography. In another experiment in h-TM, Ca^{++} mobilization was determined by real-time fluorescence imaging.

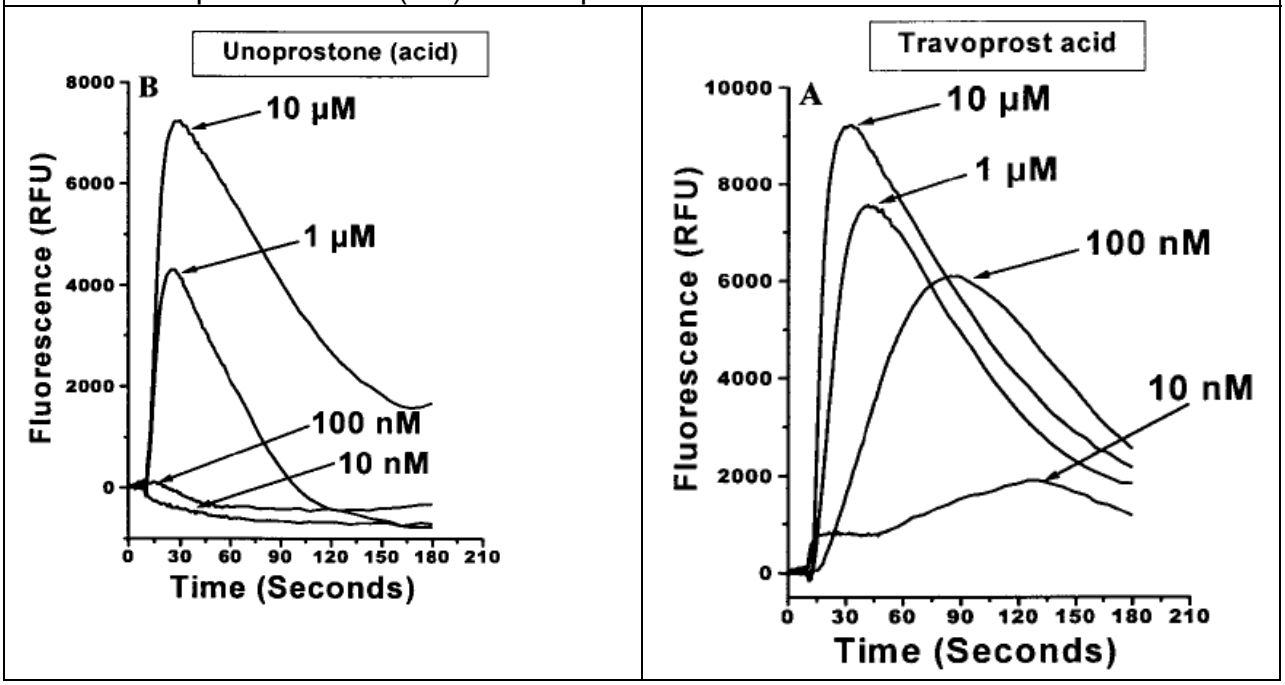
Generation of PI was concentration dependent for all compounds studied (Figure 25). The rank order of median effective concentration, EC_{50}, for PI turnover was travoprost acid (EC_{50}= 2.4 nM) > cloprostenol (EC_{50}=4.5 nM) (±)-fluprostenol (EC_{50} =10.8 nM) > latanoprost acid (EC_{50}=34.7 nM) > bimatoprost acid (EC_{50}=112 nM) > PGF2α (EC_{50}= 120 nM) >> **unoprostone isopropyl (EC_{50}=2310 nM) > unoprostone acid (M1; EC_{50}=3280 nM)** > S-1033 (EC_{50}=4570 nM).

Figure 25. Concentration-dependent stimulation of ^{3}[H]-phosphoinositol formation in human trabecular meshwork cells induced by unoprostone and prostaglandin analogues



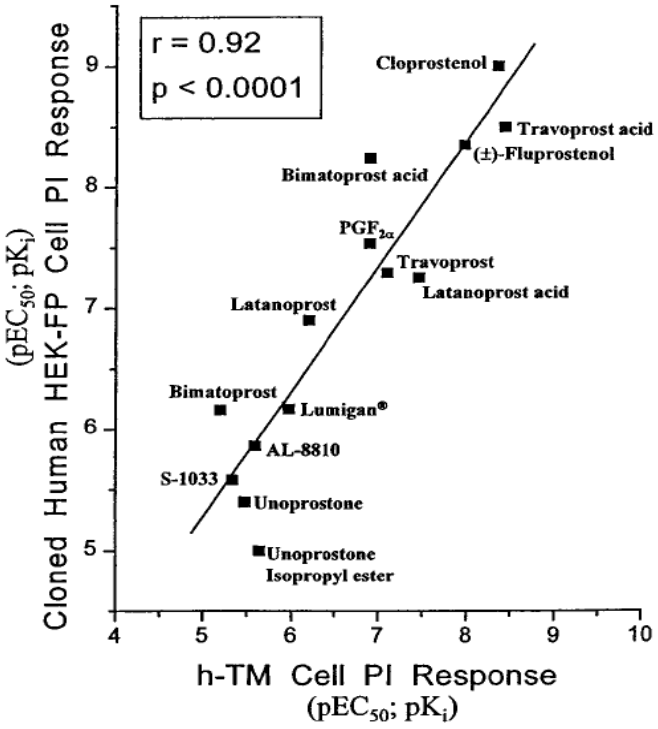
Unoprostone, travoprost acid, and S-1033 rapidly (within a few seconds) induced [Ca^{++}] mobilization in h-TM cells in a concentration dependent manner (Figure 26). The [Ca^{++}] mobilization was a transient response measured only over a 3-minute period and thus represented a non-equilibrium situation. Travoprost acid was found to be more potent than the other FP agonists studied, based on rank order of EC_{50} values: travoprost acid (EC_{50}=26nM) > PGF-2α (EC_{50}=98.6nM) > S-1033 (EC_{50}=1080nM) > unoprostone isopropyl (EC_{50}=2400nM). AL-8810, an FP receptor antagonist, concentration dependently antagonized the unoprostone induced PI turnover responses in the h-TM cells (K_i=2.4 μM) similar to prostaglandin analogues: (±)-fluprostenol– (K_i=2.56 μM), bimatoprost (K_i=1.0 μM), travoprost acid (K_i=2.5 μM) and latanoprost acid (K_i=4.3 └ M).

Figure 26. Ca^{++} mobilization in human trabecular meshwork cells in response to different unoprostone acid (M1) or travoprost acid



The authors compare the agonist properties of these drugs in human trabecular meshwork cells to agonist properties (PI turnover) seen in human embryonic kidney cells transfected with the human FP receptor (HEK-FP). Results showed correlation between both systems with unoprostone isopropyl and unoprostone acid (M1) having relatively little activity (high EC_{50} values) in each system (Figure 27).

Figure 27. Correlation between the agonist properties at FP receptors in normal human trabecular meshwork cells and an FP receptor transfected human cell line



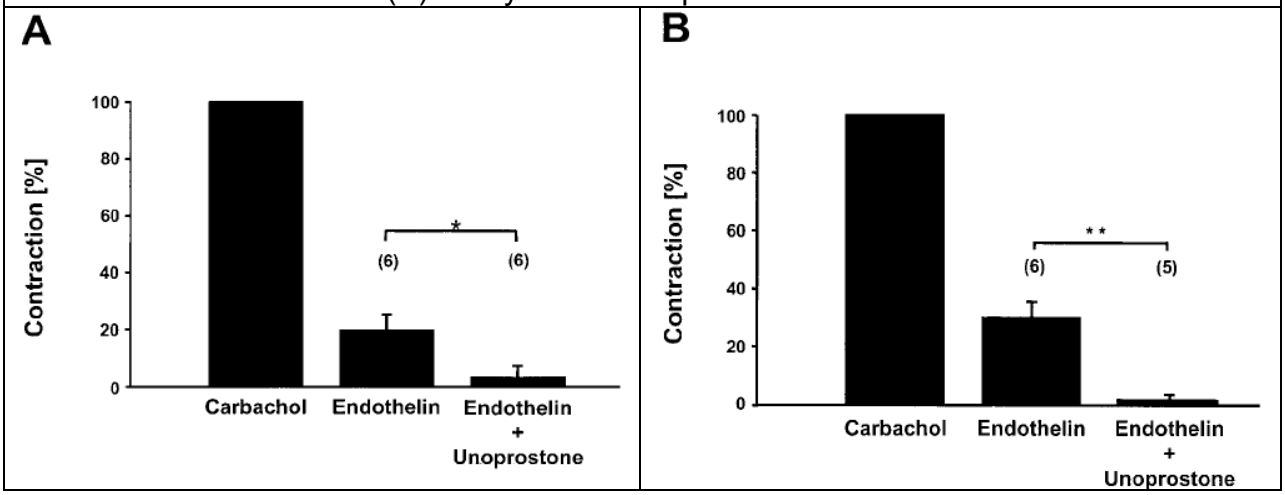
Summary/Conclusion (Reviewer's note):
This study provides data that unoprostone and its main metabolite, M1, do not act similar to prostaglandins and their analogues. EC_{50} values to induce PI turnover and Ca^{++} mobilization are higher than those which are thought to be achieved under physiologic circumstances following the approved dosage regimen (see Kashiwagi 1999, reviewed above). It is interesting to note that at the physiologically relevant concentration of 100 nM, unoprostone did induce some Ca^{++} mobilization which may be due to release from intracellular stores in the endoplasmic reticulum while still not allowing extracellular Ca^{++} to enter the cell either through hyperpolarization induced by BK channel activation or through the blockage of L-type Ca^{++} channels independent of BK channel activation (see Thieme 2005, reviewed above).

"Mechanisms of action of unoprostone on trabecular meshwork contractility". Thieme, H., *et al*., 2001, *Invest Ophthalmol Vis Sci*, 42: 3193-3201.

The effects of the acid metabolite of unoprostone, M1 (10 µM) and endothelin-1 (ET-1; 1 nM) on bovine TM (BTM) and ciliary muscle (CM) strips were investigated, by using a custom-made force-length transducer system. Isometric contractions were expressed relative to the response obtained with a maximally effective carbachol concentration

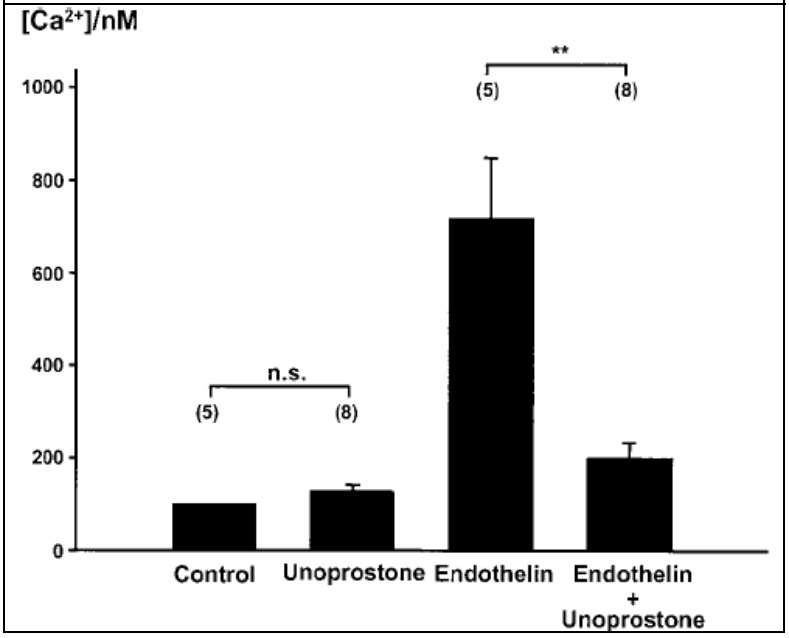
(1μM), which was tested in each tissue strip as a control (100% contractility). M1 had no influence on baseline tension in both tissues, nor did it influence carbachol-induced contraction. ET-1 caused contractions from baseline level in both tissues (TM: 19.6% ± 5.7%; CM: 30.1% ± 5.3%), which were completely blocked by unoprostone (TM: 2.9% ± 4.4%; CM: 1.4% ± 1.6% (Figure 28).

Figure 28. Effect of unoprostone acid (M1) on ET-1 mediated contraction in bovine (A) trabecular meshwork and (B) ciliary muscle strips



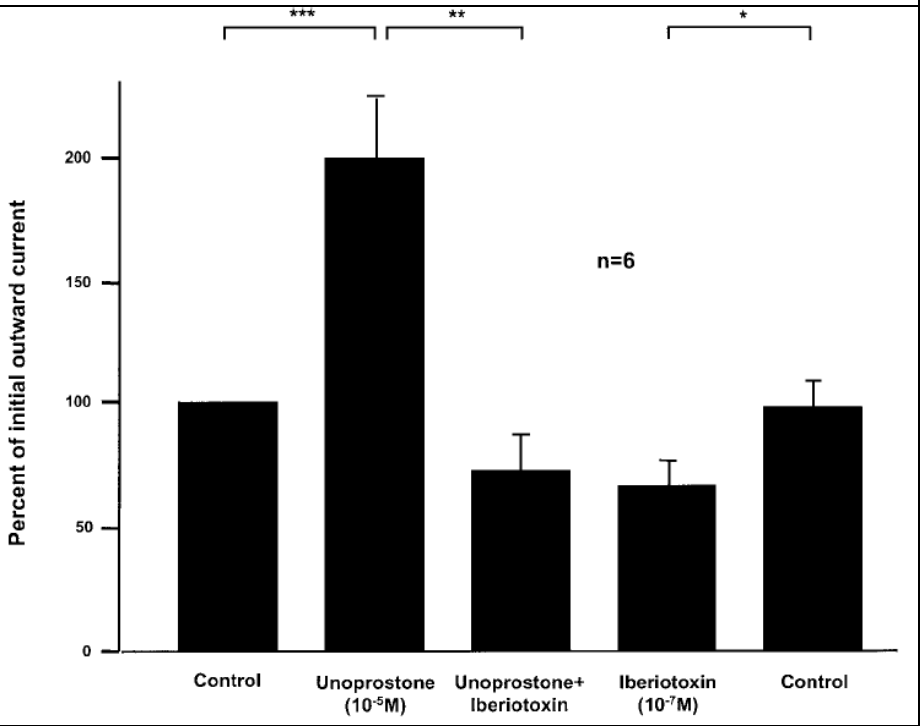
Human trabecular meshwork cells were isolated from multi-organ donors and cultured. Cells were then loaded fura-2AM for measurements of intracellular Ca^{++}. The effects of M1 (10μM) and ET-1 (50nM) on intracellular Ca^{++} mobilization in cultured human TM (HTM) were measured for 250 seconds. M1 almost completely inhibited influx of Ca^{++} induced by endothelin-1 treatment (Figure 29).

Figure 29. Effect of unoprostone acid (M1) on endothelin-1 mediated Ca^{++} influx



Patch clamp experiments were performed to detect outward movement of K^+ from human trabecular meshwork cells following treatment with ET-1 (50nM) and M1 (10μM). Results showed that treatment with M1 resulted in a significant increase in K^+ flux which was inhibited by iberiotoxin (Figure 30).

Figure 30. Effect of unoprostone acid (M1) on K^+ outflow in endothelin-1 stimulated human trabecular meshwork cells



Summary/Conclusions (Reviewer's note)

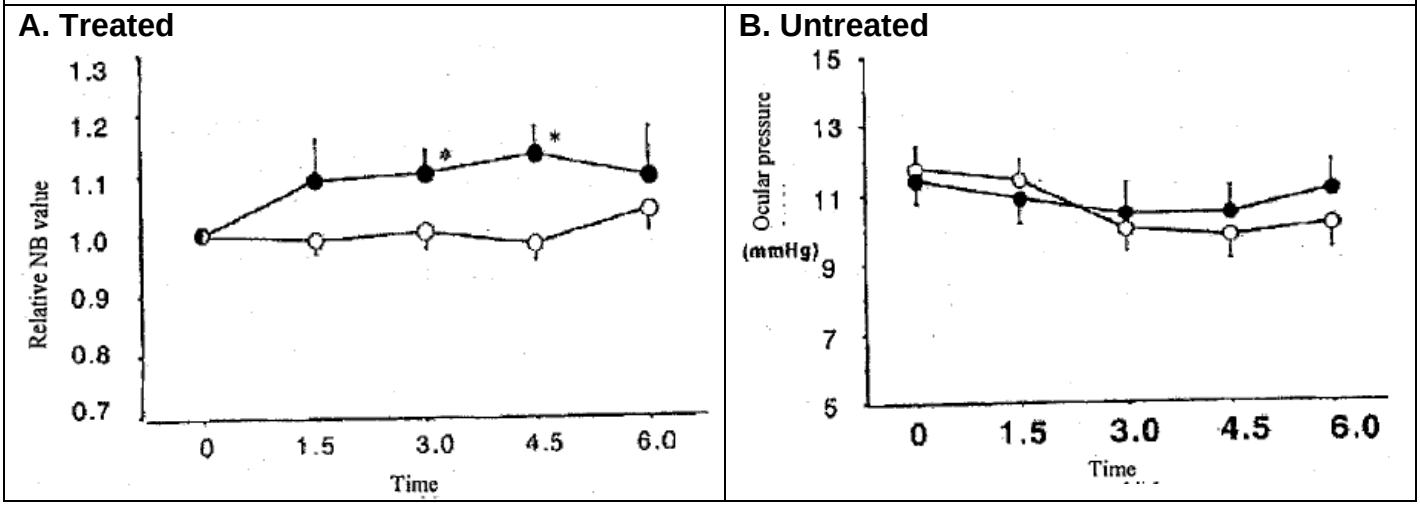
This experiment provides data supporting the observation that the acid metabolite of unoprostone (M1), which is the primary active ingredient present in the eye following topical application, activates BK K^+ channels in isolated human trabecular meshwork cells. Furthermore, the data show that ET-1 mediates contraction of isolated bovine trabecular meshwork and ciliary muscle strips and this contraction is inhibited by M1. The data do not show that this inhibition of ET-1 mediated contraction relieves elevated intraocular pressure. Furthermore, in a review by Weiderholt *et al.,* (2000, *Prog Retinal Eye Res.,*19: 271), the author offers conjecture on the dueling roles of contraction within the trabecular meshwork and ciliary muscle. The author hypothesizes that while contraction of the ciliary muscle relieves elevated intraocular pressure through its ability to relax the trabecular meshwork and increase aqueous humor outflow, contraction of the trabecular meshwork restricts aqueous humor outflow. Therefore, by relieving contraction of both the ciliary muscle and trabecular meshwork, due to these opposing roles in mediating aqueous humor outflow, a stalemate may result. More data should be gathered regarding the role of inhibiting the action of ET-1 on elevated intraocular pressure and if unoprostone or its metabolite contribute to lowering intraocular pressure through this pathway.

4.5 Mechanism of IOP lowering effects

"Effects of instillation of an isopropyl unoprostone on peripheral circulation in the human ocular fundus- A study using the laser speckle method". Kojima S., *et al*., 1997, *J Jpn Ophthalmol Soc* 101: 605-610.

A study used the laser speckle method in 9 volunteers to investigate the effect of unoprostone isopropyl (0.12%) on circulation within the human optic nerve head and choroid-retinal tissue. Baseline measurements of normalized blur value, an indicator of blood flow velocity, were made every 90 minutes over 6 hours. Normalized blur represents the blur in the speckle pattern formed through interference of laser light scattered from the ocular fundus. On a separate date, similar measurements were made following unilateral treatment with unoprostone. No significant differences were observed in mean blood pressure or pulse rate in comparison to the control or in comparison to the data obtained prior to instillation. For the optic nerve, no difference in normalized blur was observed between baseline and treatment with unoprostone. For the choroid-retina, a significant increase in normalized blur was noted in the treated eye at 3 (mean 8%) and 4.5 (mean 11%) hours after instillation (Figure 31). Intraocular pressure was also reduced during this period.

Figure 31. Change in normalized blur for choroid-retinal tissue in eye treated with unoprostone



Summary: These data provide evidence that treatment with unoprostone increases blood flow in the choroid but the exact mechanism remains unknown. The authors note that a distinction can not be made between the cause of this increased blood being due to the decrease in intraocular pressure or an actual effect on vascular resistance.

"Long-term effect of topically applied isopropyl unoprostone on microcirculation in the human ocular fundus". Makimoto Y., *et al*., 2002, *Jpn J Ophthalmol*, 46: 31-35.

This study investigated the effect of unoprostone isopropyl (0.12%) or placebo on microcirculation in the ocular fundus after 21 days of treatment in 11 healthy volunteers. Normalized blur, measured by the speckle method, of eleven healthy volunteers before and 4.5 hours after the instillation of a placebo into both eyes was measured to obtain a baseline blood flow. The intraocular pressure (IOP), blood pressure, and pulse rate were also recorded. Thereafter, unoprostone or a placebo was instilled into each eye in a double-blind manner twice a day for 21 days. After 21 days, NB was measured before and 4.5 hours after the daily dose of placebo or unoprostone was administered.

Results showed that the NB values in choroid-retina had increased significantly in both placebo and unoprostone treated eyes 4.5 hours after the last treatment (Table 9). IOP had decreased significantly only in the unoprostone-treated eyes. Ocular perfusion pressure showed no significant changes. The authors suggest that a decrease in vascular resistance could be responsible for the increased blood flow in the ocular fundus.

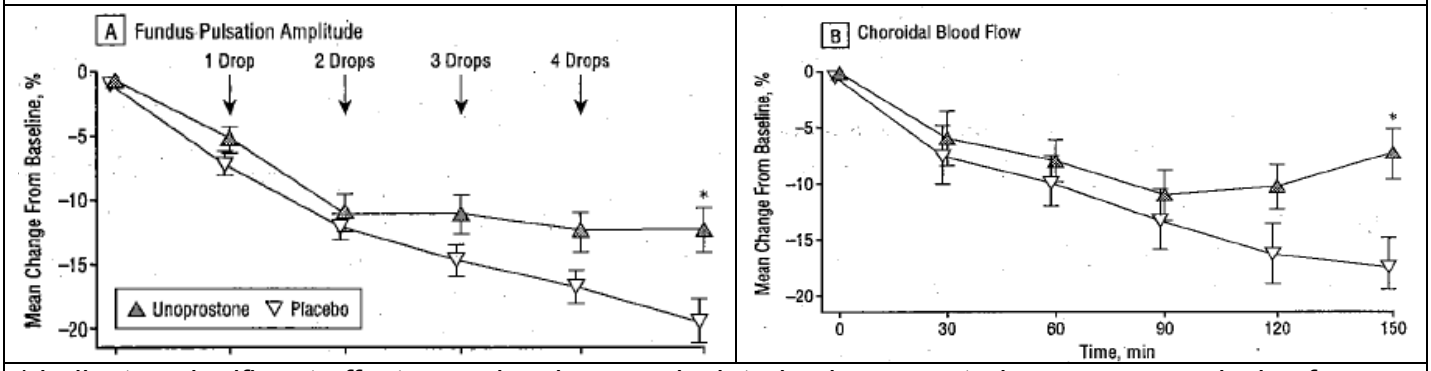
Table 9. Change in normalized blur in the optic nerve head (ONH) and choroid-retina (CHO) and IOP on day 21 compared to baseline before and 4.5 hours after treatment with placebo (P) or unoprostone (U)

	Pre-treatment	4.5 hours
ΔNB_{ONH} (U)	0.28 ± 0.10	0.44 ± 0.12
ΔNB_{ONH} (P)	-0.12 ± 0.20	0.43 ± 0.23
ΔNB_{CHO}(U)	0.51 ± 0.21	0.88 ± 0.24*
ΔNB_{CHO} (P)	0.20 ± 0.24	0.39 ± 0.20*
IOP (U)	-2.3 mm Hg*	-1.9 mm Hg*
IOP (P)	-1.3 mm Hg	-0.6 mm Hg
* $p < 0.05$ (paired *t*-test)		

"Partial antagonism of endothelin-1-induced vasoconstriction in the human choroid by topical unoprostone isopropyl". Polska, E., *et al*., 2002, *Arch Ophthalmol*, 120: 348-352.

In this study, 24 healthy volunteers underwent treatment with intravenous endothelin-1 (ET-1; 2.5 ng/kg per minute fro 150 minutes). Thirty minutes after the start of ET-1 infusion, 1 drop of unoprostone isopropyl (0.12%; Rescula) or placebo was instilled in the right eye. After each additional 30 minute period, an additional drop of placebo or unoprostone isopropyl was instilled until a total of 4 drops was reached. Subfoveal and pulsatile choroidal blood flow were assessed using Doppler flowmetry and laser interferometric measurement of fundus pulsation amplitude, respectively. Results showed that administration of ET-1 decreased choroidal blood flow and fundus pulsation amplitude. This effect was blunted by administration of unoprostone isopropyl but not by placebo (Figure 32).

Figure 32. Effect of unoprostone or placebo on (A) fundus pulsation amplitude and (B) choroidal blood flow in the presence of exogenous ET-1



* indicates significant effects vs. placebo as calculated using repeated measures analysis of variance

Summary/Conclusion: This study supports the observations of Makimoto and Kajima (reviewed above) in that unosprostone appears to influence choroidal blood flow and not blood flow of the optic nerve head. This study provides additional data regarding the ability of ET-1 to influence choroidal blood flow and the antagonistic properties of unoprostone in blunting these effects. It is important to note that IOP was not increased by administration of exogenous ET-1 and remained unaffected by treatment with topical unoprostone isopropyl when compared to placebo(12.8 mm Hg vs. 12.7 mm Hg, respectively). Mean brachial artery blood pressure and pulse rate also remained unchanged.

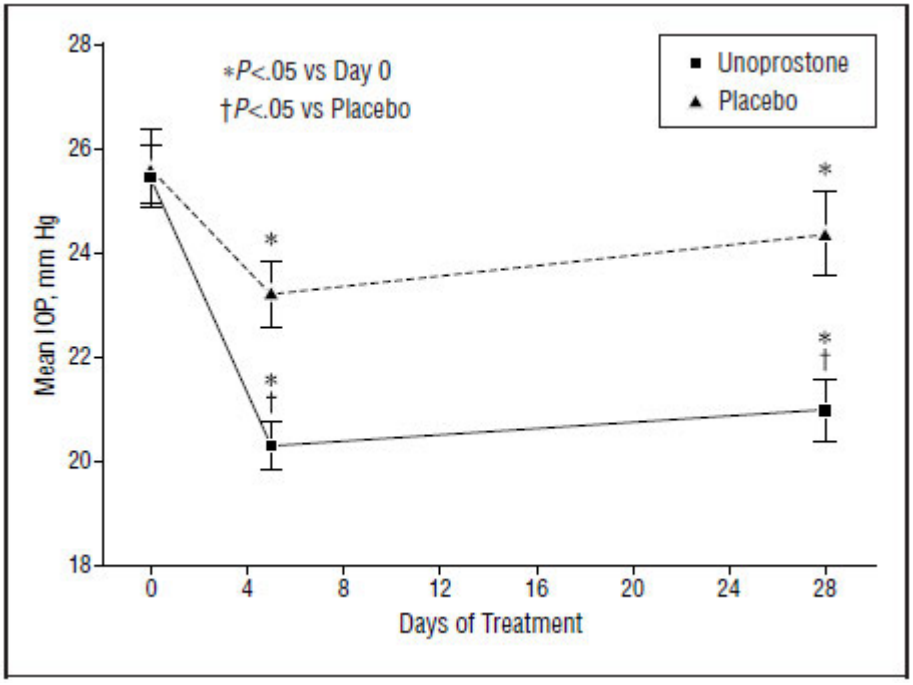
"Increase in outflow facility with unoprostone treatment in ocular hypertensive patients". Toris, C.B., *et al*., 2004, *Arch Ophthalmol*, 122(12): 1782-1787.

A single center clinical study was conducted in 33 patients with ocular hypertension or primary open-angle glaucoma to determine whether administration of 0.15% unoprostone isopropyl (Rescula) increased outflow facility. A group of patients were treated with Rescula BID for 5 days at which point a subgroup was chosen to continue to Day 28 on the basis of positive clinical response to Rescula shown as a decrease in IOP of ≥ 3 mmHg. Fluorophotometric scans were used to determine conventional outflow facility and, in combination with episcleral venous pressure, to calculate uveoscleral outflow. For analysis, IOP, conventional (trabecular) and uveoscleral outflow measurements made on Day 5 and Day 28 were compared.

Mean baseline IOP values were 25.5±0.6 mm Hg and 25.7±0.7 mm Hg in the unoprostone-treated eyes and placebo-treated eyes, respectively. Average reduction from baseline in eyes treated with unoprostone was 5.6±0.4mmHg (P <0.001) and 4.8±0.6mmHg (P< 0.001) on days 5 and 28, respectively, whereas the average reduction in the placebo treated eyes was 2.5±0.04mmHg (P < 0.001) and 1.7±0.1 mm Hg (P=.008), respectively (Figure 33). The baseline adjusted between-treatment

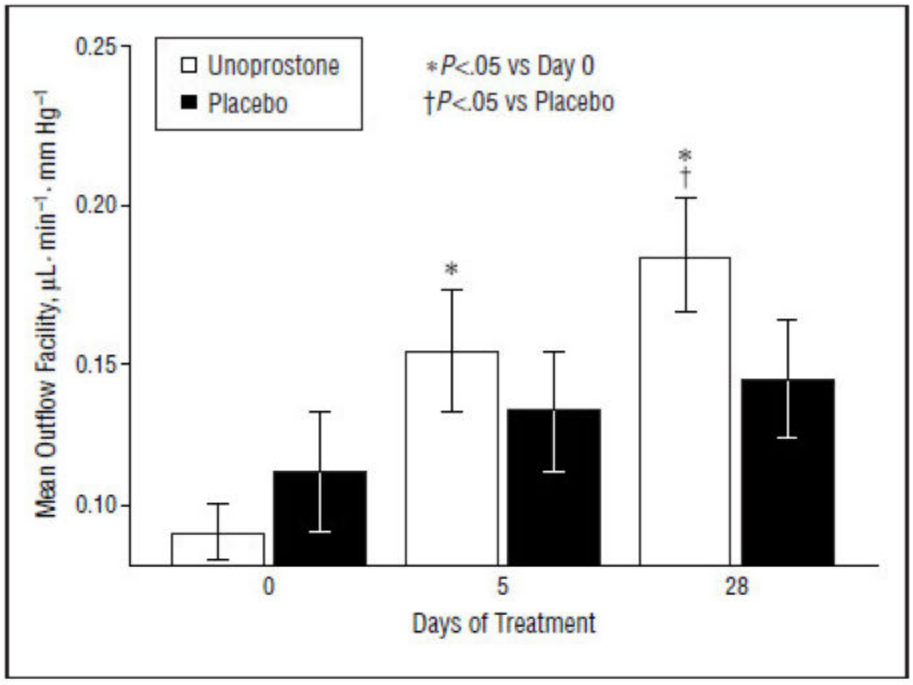
differences were statistically significant on day 5 (2.8±0.4mmHg; P ┌ .001) and on day 28 (3.2±0.5 mm Hg; P ┌ .001).

Figure 33. Mean IOP in patients with ocular hypertension or open angle glaucoma treated with Rescula or placebo



The average increases in outflow facility from baseline values in eyes treated with unoprostone were statistically significant (P < 0.001) on days 5 and 28, whereas the average changes in the placebo-treated eyes were not significant. The baseline-adjusted between treatment differences were statistically significant on day 28 (0.06±0.03 $\mu L \cdot min^{-1} \cdot mm\ Hg^{-1}$; P= 0.04) but not day 5. Both unoprostone and placebo reduced uveoscleral outflow on day 28 compared with baseline (P<.04; Table 2). However, the baseline- adjusted between-treatment differences were not statistically significant at day 5 or 28. Unoprostone and placebo did not significantly alter episcleral venous pressure.

Figure 34. Mean outflow facility in patients with ocular hypertension or open angle glaucoma treated with Rescula or placebo



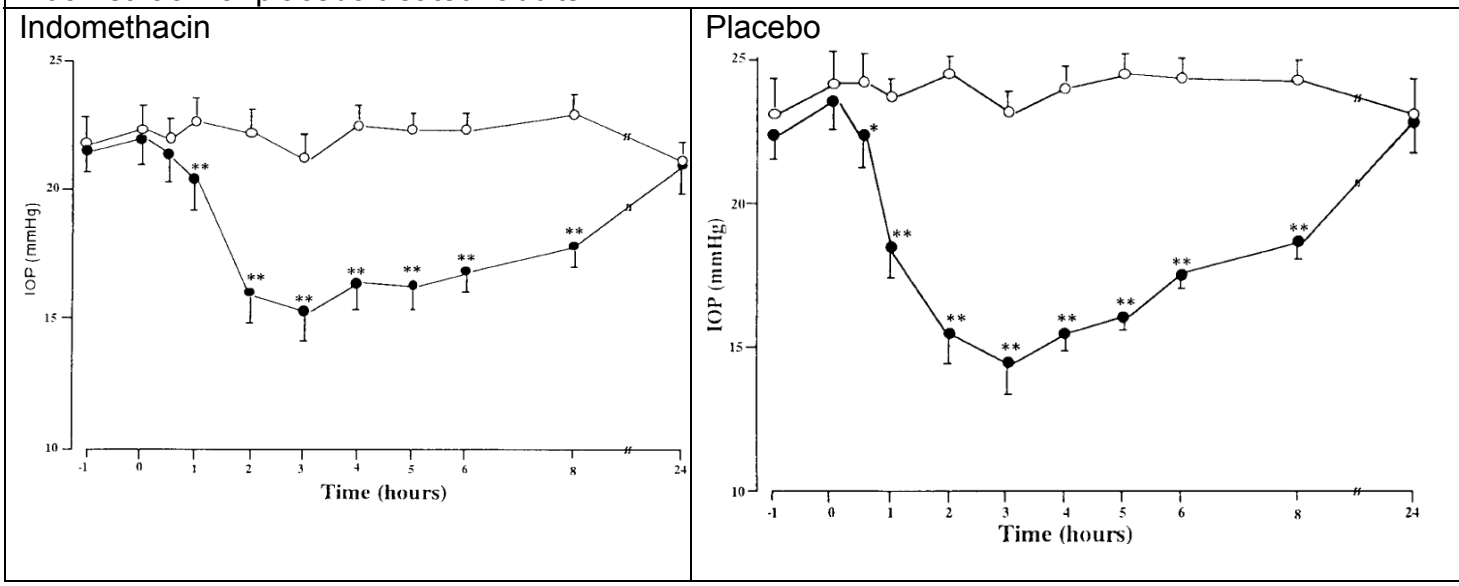
Reviewer's note:
While this study did show an increase in trabecular meshwork mediated conventional outflow facility, (b) (4)

"Ocular hypotensive mechanism of topical isopropyl unoprostone, a novel prostaglandin metabolite-related drug, in rabbits". Taniguchi, T., et al., 1996, J Ocul Pharmacol Ther, 12(4): 489-498.

This study investigated the mechanism of unoprostone and determined the outflow pathways affected by unoprostone isopropyl (0.12%) treatment in New Zealand White

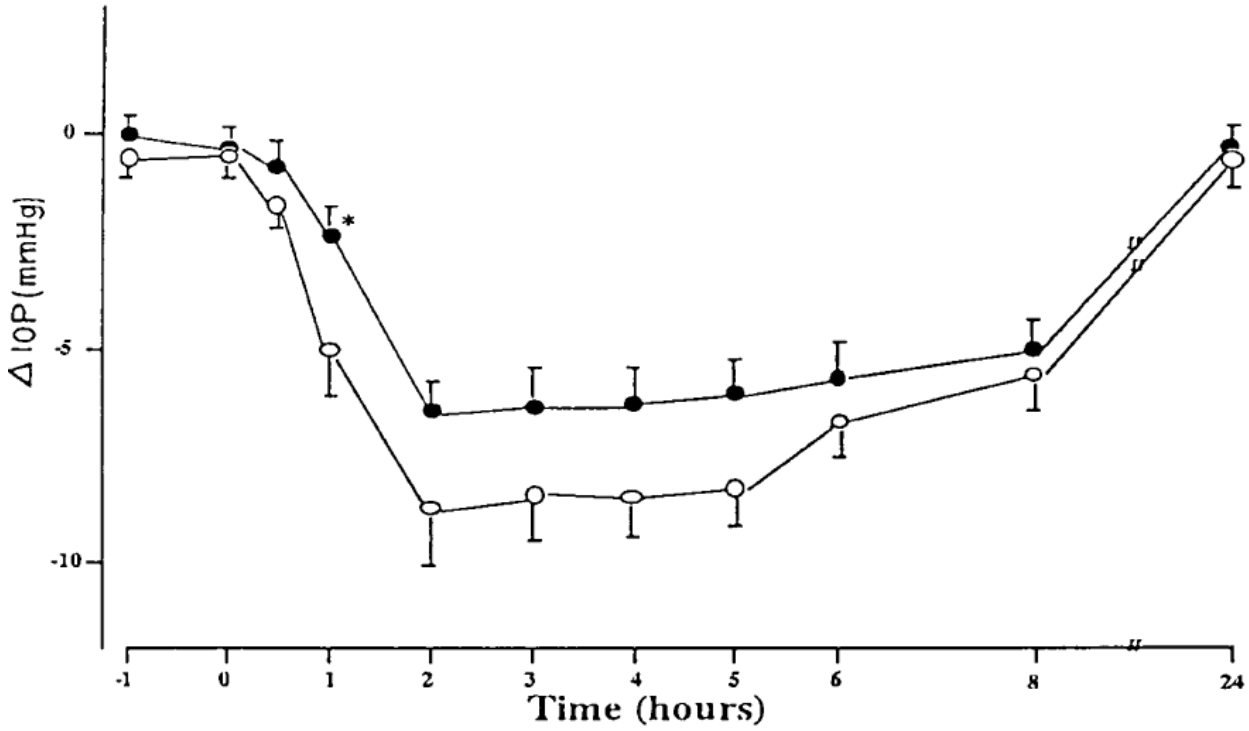
rabbits. Indomethacin (50 mg/kg; indomethacin group) or a placebo solution (0.01 M phosphate buffer; 10 ml/kg; placebo group) was administered intraperitoneally to six rabbits in both groups. One hour after administration, unoprostone was instilled into one randomly selected eye of each animal, and vehicle was instilled into the contralateral eye. Unoprostone caused a reduction in IOP without an early increase in IOP in both the indomethacin- and the placebo-pretreated groups. Unoprostone resulted in a significant difference in IOP between the treated and contralateral eyes, starting at 1 hour in the indomethacin-pretreated group and at 0.5 hour in the placebo-pretreated group, and lasting for more than 8 hours in both groups (Figure 35).

Figure 35. Changes in intraocular pressure after treatment with (●) unoprostone or (o) vehicle in indomethacin or placebo treated rabbits



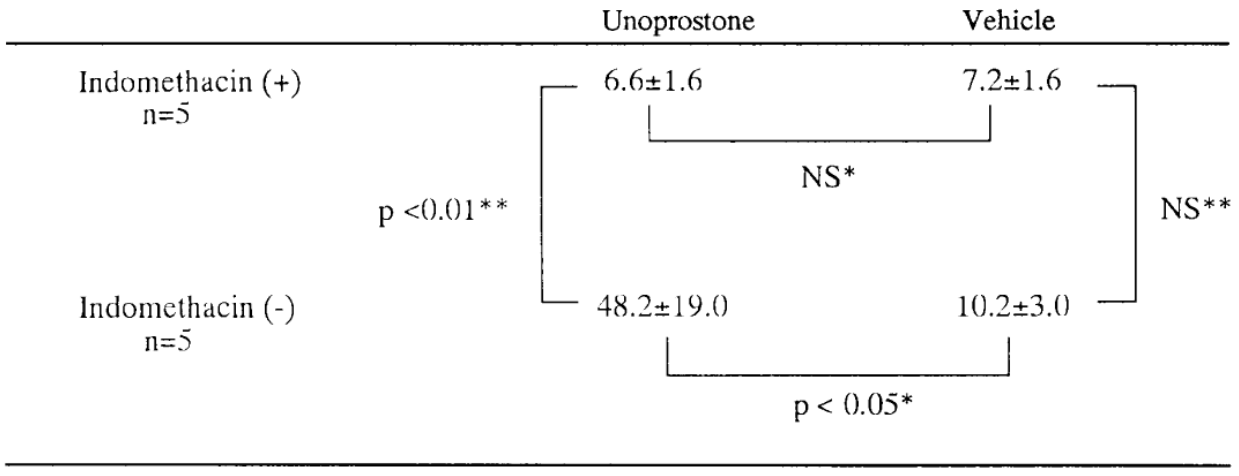
The maximum IOP differences between the unoprostone-treated and the contralateral eyes were 6.3 ± 0.8 mmHg at 2 hours in the indomethacin-pretreated group and 8.7 ± 1.3 mmHg at 2 hours in the placebo-pretreated group. The difference between those values did not reach statistical significance. At 1 hour, the IOP differences between the unoprostone-treated and the contralateral eyes were 2.2 ± 0.5 mmHg in the indomethacin-pretreated group and 5.0 ± 1.0 mmHg in the placebo-pretreated group ($p < 0.05$) (Figure 36). These data suggest that an indomethacin sensitive pathway is partially mediating the reduction in IOP by unoprostone.

Figure 36. Unoprostone mediated IOP difference between placebo and indomethacin treated rabbits



Unoprostone or vehicle were instilled in indomethacin- or placebo- pretreated rabbits followed 2 hours later by withdrawal of 100 µL of aqueous humor. PGE_2 concentrations in the aqueous humor were measured using a radioimmunoassay. In the placebo-pretreated group, topical unoprostone induced a significant elevation in the PGE_2 concentration at 2 hours compared with the vehicle. However, in the indomethacin-pretreated group, a significant difference in the PGE_2 concentration between the indomethacin- and the placebo-pretreated groups was observed in the unoprostone-treated eyes (Table 10).

Table 10. PGE_2 concentration (pg/mL) in the aqueous humor 2 hours after drug instillation



Aqueous flow, a function of aqueous humor production, was measured in rabbits using direct measurement of fluorescein flow rate. Fluorescein was given 10 hours before indomethacin treatment which was then followed 1 hour later with unoprostone. Total outflow facility was determined under similar conditions using two-level constant pressure perfusion for 1 hour. Starting 2 hours after the application of unoprostone and its vehicle, the bilateral anterior chambers of five rabbits anesthetized with 40% urethane were perfused with mock aqueous humor at constant pressures of either 25 or 35 mmHg alternately applied at 10-minute intervals. During each 10-minute period, fluid flow was measured for 8 minutes beginning 2 minutes after the pressure change was induced. Uveoscleral outflow was measured using a perfusion apparatus under constant pressure and a perfusion fluid containing fluorescein isothiocyanate-dextran (FITC-dextran) conjugate. Comparisons of FITC-dextran content in tissue specimens to the content in the initial perfusion fluid was used to calculate uveoscleral outflow.

Outflow facility increased by 46.7%, uveoscleral outflow increased by 6.6%, and aqueous flow was not significantly changed in the unoprostone-treated eyes (Table 11).

Table 11. Aqueous humor dynamics in indomethacin pre-treated rabbits

Treatment	Aqueous flow	Outflow facility	Uveoscleral outflow
Unoprostone	2.3 ± 0.3	0.20 ± 0.01	0.49 ± 0.02
Vehicle	2.4 ± 0.2	0.14 ± 0.01	0.46 ± 0.02
Significance	NS	p < 0.05	p < 0.05
% change		+46.7 %	+ 6.6 %

Reviewer's note:

Similar to the exogenous prostaglandins and their analogues, unoprostone induced the endogenous production of PGE_2 which was shown in this study to possibly contribute to the IOP lowering effects of unoprostone. While not completely mediating the reduction

in IOP, [redacted] (b) (4)

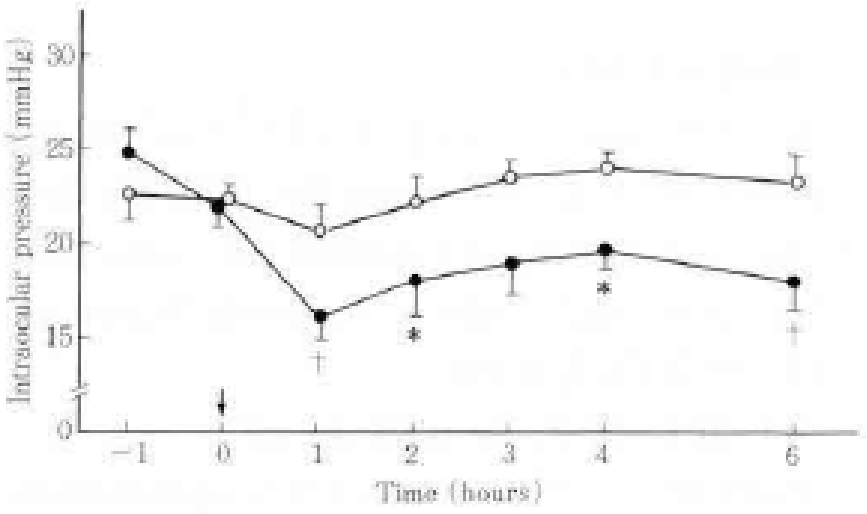
[redacted] (b) (4)

"Effects of topical application of UF-021, a novel prostaglandin-related compound, on aqueous humor dynamics in rabbit". Sakurai, M., et al., 1993, Jpn J Ophthalmol, 37: 252-258.

The mechanism of the IOP reducing effect of unoprostone isopropyl was studied in rabbits. A single instillation of unoprostone isopropyl (0.06%) to male Japanese albino rabbits. Aqueous flow rate, conventional and uveoscleral outflow were determined using fluorometric methods.

A single instillation of unoprostone isopropyl lowered IOP in the normotensive rabbit (Figure 37).

Figure 37. Time course of changes in IOP after single instillation of 0.06% unoprostone isopropyl (•) or vehicle (o)



Unoprostone isopropyl caused a slight, but significant, increase in aqueous flow rate (i.e. production of aqueous humor) compared to vehicle treated rabbits (Table 12). An increase in aqueous flow rate would elevate intraocular pressure but the authors note that when corrected for the iridial vessel dilating effects of unoprostone, the difference is likely negligible .

Table 12. Aqueous flow rate in rabbits following single instillation of unoprostone isopropyl or vehicle (µL/min)

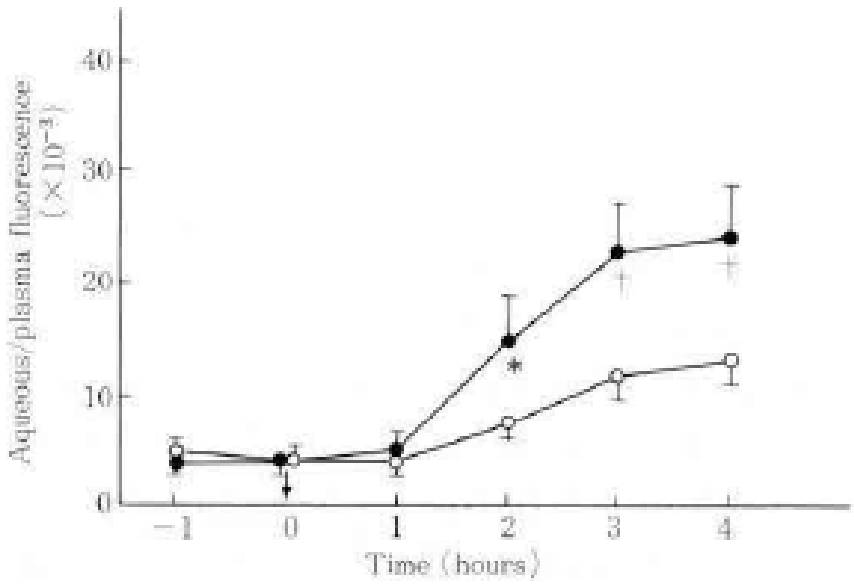
	Unoprostone isopropyl treated eyes	Vehicle treated eyes
Baseline measurement	2.9 ± 0.2	2.9 ± 0.3
Corrected baseline	3.0	3.0
After treatment	3.3 ± 0.2	2.9 ± 0.2
Corrected after treatment	3.0	3.0

Values obtained for uveoscleral outflow were 1.21 ±0.09 µL/min for unoprostone treated eyes and 0.25 µL/min for vehicle treated eyes. Conventional outflow to circulation was also increased in unoprostone treated eyes compared to vehicle (0.27 µL/min vs. 0.20 µL/min, respectively). The authors conclude that unoprostone exerts its effect through increasing both outflow facility to general circulation and uveoscleral outflow with no effect on aqueous humor production.

The ratio of fluorescence intensity in the anterior chamber to that in plasma after intravenous injection of FITC-dextran is a reflection of the integrity of the blood aqueous barrier (BAB). After a single dose of unoprostone isopropyl the ratio of fluorescence intensity in the anterior chamber to plasma was significantly higher in unoprostone

treated rabbits compared to vehicle (Figure 38). This suggests that the BAB is compromised in unoprostone isopropyl treated eyes which could explain increased uveoscleral outflow.

Figure 38. Ratio of fluorescence intensity in the aqueous humor to plasma following unoprostone (•) or vehicle (o) administration



Reviewer's note:
The results of this study suggest that in rabbits both conventional and uveoscleral outflow are increased in rabbits. Due to anatomical differences between higher primates and rabbits, extrapolating these results to humans may not be accurate. The authors of the above study note that the rabbit eye blood aqueous barrier is less stable than in humans and may account for the increase in uveoscleral outflow seen in rabbits but not reported in humans.

5 Integrated Summary

Overall, it appears that unoprostone isopropyl (Rescula) may mediate multiple mechanisms capable of lowering intraocular pressure, this conclusion is based upon the following experimental evidence:

- Unoprostone did not lower intraocular pressure in FP-receptor knockout mice
- The intraocular pressure reduction induced by unoprostone was partially inhibited by indomethacin (cyclooxygenase inhibitor; implicates prostaglandins)
- Unoprostone induced the production of PGE-2 which is known to reduce intraocular pressure
- Unoprostone inhibited L-type calcium channels in trabecular meshwork cells independently of BK channels (experiment performed in K^+ free conditions)

So it may be that unoprostone acts through multiple mechanisms or acts on a more global cellular regulator which mediates multiple pathways. Interestingly, the literature suggests that unoprostone acts similarly to a protein kinase inhibitor genistein, which was shown in trabecular meshwork cells to inhibit L-type calcium channels as well as activate BK channels independently of each other (Stumpff et al., 1999, *Invest Opthalmol Vis Sci*, 40: 1404 and Steinhausen *et al*., 2000, *Exp Eye Res*, 70: 285). The inhibition of L-type calcium channels is important, since these are directly activated in response to stimulation of muscarinic acetylcholine receptors found in the trabecular meshwork. Signaling through the acetylcholine receptor may be responsible for the normal tone of the trabecular meshwork and ciliary muscle or stimulate the ciliary muscle and through traction mediated interactions directly affect the tone of the trabecular meshwork.

The applicant has proposed the following Mechanism of Action to be included in the labeling for Rescula in Section 12.1:

(b) (4)

Following review of the data included by the sponsor in this submission, this reviewer agrees with the language proposed by the Division which (b) (4)

(b) (4)

In a previous communication to the applicant, the Division argued the limitations of the data in providing support for the changes to the mechanism of action section of the labeling proposed by the applicant. The applicant has responded to these arguments by providing literature references and making inferences in light of the data. These responses by the applicant will be listed and a counterargument made by this reviewer following review of the references provided by the applicant as well as through an independent literature review.

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Given the counterarguments made above, the following Mechanism of Action section in the labeling is appropriate:

12.1 Mechanism of Action
Rescula is believed to reduce elevated intraocular pressure (IOP) by (b) (4) 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.

Appendix A

The sponsor cites 21 CFR 201.57(c)(13)(A) as the basis for the proposed labeling changes:

> 201.57 Specific requirements on content and format of labeling for human prescription drug and biological products described in § 201.56(b)(1).
>
> (13) 12 Clinical pharmacology. (i) This section must contain information relating to the human clinical pharmacology and actions of the drug in humans. Pharmacologic information based on in vitro data using human biomaterials or pharmacologic animal models, or relevant details about in vivo study designs or results (e.g., drug interaction studies), may be included in this section if essential to understand dosing or drug interaction information presented in other sections of the labeling. This section must include the following subsections: (A) 12.1 Mechanism of action. This subsection must summarize what is known about the established mechanism(s) of the drug's action in humans at various levels (e.g., receptor, membrane, tissue, organ, whole body). If the mechanism of action is

> not known, this subsection must contain a statement about the lack of information.

The sponsor also cites Guidance for Industry: Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products— Content and Format:

> A. Mechanism of Action (How Therapeutic and Adverse Effects Occur) This subsection of the labeling should summarize what is known about the established mechanism or mechanisms of action in humans, focusing on the desired and adverse effects of the drug. The mechanism of action should be discussed at various levels, including the cellular, receptor, or membrane level (with a description of selectivity where important), the physiologic system level (target organ), and the whole body level, depending on what is known. Only reasonably well-characterized mechanisms should be described, and care must be taken to avoid speculative and undocumented suggestions of therapeutic advantages (21 CFR 201.56(a)(2)). If the relationship of the drug's mechanism of action to the desired effects is unknown, this also should be stated. Information from animals and in vitro studies can be included where helpful and clearly relevant to the human response. Although not generally needed, a brief description of disease pathophysiology can sometimes facilitate an understanding of the drug's pharmacology and its impact on that process. Speculation on the mechanism of drug action must be avoided (21 CFR 201.56(a)(2)). Any relevant pharmacogenomic factors affecting drug action should be included as well as whether established serologic correlates can be used to infer vaccine-induced protection against an infectious agent.

The sponsor further cites § 201.56 Requirements on content and format of labeling for human prescription drug and biological products:

> (a) General requirements. Prescription drug labeling described in § 201.100(d) must meet the following general requirements: (1) The labeling must contain a summary of the essential scientific information needed for the safe and effective use of the drug. (2) The labeling must be informative and accurate and neither promotional in tone nor false or misleading in any particular. In accordance with §§ 314.70 and 601.12 of this chapter, the labeling must be updated when new information becomes available that causes the labeling to become inaccurate, false, or misleading.

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/s/

AARON M RUHLAND
08/06/2012

LORI E KOTCH
08/07/2012

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 labeling supplement to the DTOP for labeling changes in the (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-007

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

COMMUNICATION SHEET

DATE: August 15, 2012

To: Nancy L. Buc FDA Counsel to Sucampo	**From:** Judit Milstein Chief, Project Management Staff
Company: Sucampo Pharma Americas, Inc.	Division of Transplant and Ophthalmology Products
Email: buclawpllc@gmail.com	**Email:** judit.milstein@fda.hhs.gov
Telephone number:	**Phone number:** 301-796-0763

Subject: Labeling comments for NDA 21214/S007- (b) (4)

Total no. of pages including cover: 4

Comments:

Document to be mailed: **YES** ☑ **NO**

Dear Ms. Buc,

Reference is made to the Sucampo Pharma Americas, Inc. (Sucampo) New Drug Application, NDA 21214/S007, and the meeting between Sucampo and the FDA on July 24, 2012, during which the proposed language for the (b) (4) section of the Rescula prescribing information was discussed.

At the meeting, you provided the following proposed language, referred to as (b) (4) and requested that the Division consider including this information in the (b) (4) section of the labeling.

(b) (4)

We have reviewed the proposed language and have the following comments:

(b) (4)

Until you have provided empirical data to establish (b) (4), we do not agree that this language should be included in the labeling.

We believe our conclusion is consistent with the statement in 21 CFR 201 regarding the (b) (4) section of labeling, as well as the related Guidance to Industry on labeling the (b) (4) section[1]

(b) (4)

Therefore, we recommend that the CLINICAL PHARMACOLOGY/Mechanism of Action section state the following:

> 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 potassium channels and ClC-2 chloride channels, but the exact mechanism is unknown at this time.

Please let me know if you have any questions regarding this communication.

Sincerely,

Judit Milstein
Chief, Project Management Staff
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration

[1] Guidance for Industry Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products— Content and Format, http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm109739.pdf

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/s/

JUDIT R MILSTEIN
08/16/2012
NDA 21214S007-Labeling comments

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21214/S-007

MEETING MINUTES

Sucampo Pharma Americas, Inc
Attention: Nancy Buc
Counsel
4520 East-West Highway, Suite 300
Bethesday, MD 20814

Dear Ms. Buc:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rescula (unoprostone isopropyl ophthalmic solution), 0.15%.

We also refer to the meeting between representatives of Sucampo Pharma Americas (Sucampo) and the FDA on July 24, 2012. The purpose of the meeting was to discuss the proposed changes to the Highlights, Mechanism of Action, and Warnings and Precautions sections of the product labeling.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Judit Milstein, Chief Project Management Staff at (301) 796-0763.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, MD
Director
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure: Minutes of the Meeting
Sucampo's presentation
Sucampo's proposed labeling

MEMORANDUM OF MEETING MINUTES

Meeting Category:	Post-Action Meeting
Meeting Date:	July 24, 2012
Meeting Location:	FDA Campus 10903 New Hampshire Avenue Building 22, Room 1415 Silver Spring, MD 20903
Application Number:	NDA 21214/S-007
Product Name:	Rescula (unoprostone isopropyl ophthalmic solution)
Sponsor/Applicant Name:	Sucampo Pharma Americas, Inc (Sucampo)
Meeting Chair:	Renata Albrecht, MD
Meeting Recorder:	Judit Milstein

FDA ATTENDEES

Edward M. Cox, MD, MPH, Director, Office of Antimicrobial Products
Renata Albrecht, MD, Director, Division of Transplant and Ophthalmology Products
Wiley A Chambers, MD, Deputy Director
William Boyd, MD, Clinical Team Leader
Martin Nevitt, MD, Clinical Reviewer
Lucious Lim, MD, Clinical Reviewer
Aaron Ruhland, PhD, Pharmacology/Toxicology Reviewer
Lori Kotch, PhD, Pharmacology/Toxicology Team Leader
Shukal Bala, PhD, Immunology/Toxicology
Hyun Son, Safety Project Manager
Ozlem Belen, MD, Deputy Director for Safety
Leanna Kelly, Labeling Reviewer
Libaniel Rodriguez, PhD, CMC Reviewer, Office of New Drug Quality Assessment (ONDQA)
Balajee Shanmugam, PhD, CMC Lead, ONDQA
Althea Cuff, Project Manager, ONDQA
Thomas Oliver, Branch Chief, ONDQA
Yan Wang, PhD, Biostatistics Team Leader, Office of Biometrics IV
Robert Mello, PhD, New Drug Microbiology Staff

SPONSOR ATTENDEES

Gayle Dolecek, PD, MPH, Executive Advisor, R&D, Sucampo
Birgit Roerig, PhD, Vice President of Pharmacology and Toxicology, Sucampo
Jeff Carey, Senior Director of Regulatory Affairs, Sucampo
Nancy L. Buc, BUCLAWPPLC, FDA Counsel to Sucampo

1. BACKGROUND

NDA 21214/S-007, submitted on August 21, 2009, received two Complete Response actions on April 14, 2011, and March 20, 2012, respectively. At issue are the proposed changes to the Highlights, Mechanism of Action (MOA) and Warnings and Precautions sections of the product labeling.

In preparation for this meeting, the applicant submitted a briefing document on May 21, 2012, and the Division sent preliminary responses on June 25, 2012. After receiving the preliminary comments, Sucampo requested that the post-decisional meeting originally scheduled for June 26, 2012 be rescheduled. The Division agreed and the meeting between Sucampo and FDA attendees took place on July 24, 2012.

2. DISCUSSION

After introductions, Ms. Buc made a presentation on behalf of Sucampo, noting that Sucampo was prepared to accept the language proposed by the Division for the Highlights and the Warnings and Precautions sections, but disagreeing with the currently-proposed language by the Division for the MOA section. Ms. Buc read a prepared document regarding Sucampo's assessment and interpretation of several of the studies provided in the May 21, 2012 submission[1] on the (b) (4). During that presentation, Ms. Buc provided handouts that proposed alternative language for the MOA section, which were said to be based on MOA language from (b) (4). Ms. Buc also requested (b) (4) (The text of the presentation, the MOA language (b) (4), and the (b) (4) language is attached.)

A discussion of some of the published data followed, and the Division noted some of the limitations identified in the studies including that some used (b) (4) instead of unoprostone. There was also discussion of the FDA-proposed labeling and how it differed from and was similar to the MOA language in approved products. The Division indicated that in principle they agreed to include the terms "trabecular meshwork" in the description of the aqueous humor outflow, but that they will need further internal discussion with regard to the proposed (b) (4).

3. ACTION ITEMS

The Division will internally discuss Sucampo's labeling proposals, including the proposed (b) (4).

The Division will issue the minutes of the meeting within 30 days.

4. ATTACHMENTS AND HANDOUTS

Sucampo's presentation (6 pages)

Sucampo's proposed wording for the MOA section of the labeling, including (b) (4) (2 pages)

[1] Also included in the January 19, 2012 submission to NDA 21214

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/s/

RENATA ALBRECHT
08/14/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21-214/S-007

MEETING REQUEST GRANTED

Sucampo Pharma Americas, Inc.
Attention: Ms. Nancy Buc
Counsel
4520 East-West Highway, Suite 300
Bethesda, MD 20814

Dear Ms. Buc:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rescula (unoprostone isopropyl ophthalmic solution), 0.15%.

We also refer to your June 1, 2012, correspondence requesting a Post-Action meeting to discuss the Complete Response letter issued on March 20, 2012, and the proposed changes for the product labeling in the Highlights, the Mechanism of Action (MOA) subsection of the Clinical Pharmacology section and the Warnings and Precautions section. This meeting was originally scheduled for June 26, 2012.

We make note that on June 25, 2012, the Division sent you preliminary comments and that on the same day you contacted me by telephone to request a postponement of the meeting, stating that Sucampo needed additional time to internally discuss the Division's preliminary comments.

Based on mutual agreement, the meeting is rescheduled as follows:

Date: July 24, 2012
Time: 12:00-1:00 PM
Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1421
Silver Spring, Maryland 20903

CDER participants:
Edward M. Cox, MD, MPH, Director, Office of Antimicrobial Products (OAP)
David Roeder, Associate Director for Regulatory Affairs, OAP
Renata Albrecht, MD, Director Division of Transplant and Ophthalmology Products (DTOP)
Wiley A. Chambers, MD, Deputy Director, DTOP
Ozlem Belen, MD, Deputy Director for Safety
William Boyd, MD, Clinical Team Leader
Yan Wang, PhD, Statistics, Team Leader
Lori Kotch, PhD, Pharmacology/Toxicology Team Leader

Aaron Ruhland, PhD, Microbiology/Immunology Reviewer
Leanna Kelly, Labeling Reviewer
Libaniel Rodriguez, PhD, Chemistry Reviewer
Robert Mello, PhD, Microbiology Reviewer
Judit Milstein, Chief, Project Management Staff

Please note that if based on the preliminary comments sent on June 25, 2012, Sucampo has major changes to the purpose of the meeting or to the issues included in the briefing document dated May 21, 2012, we may not be prepared to discuss or reach agreement on such changes at the July 24, 2012 meeting, and an additional meeting may be needed.

Please e-mail me any updates to your attendees at Judit.milstein@fda.hhs.gov, at least one week prior to the meeting. For each foreign visitor, complete and email me the enclosed Foreign Visitor Data Request Form, at least two weeks prior to the meeting. A foreign visitor is any non-U.S. citizen who does not have Permanent Resident Status or a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Upon arrival at FDA, provide the guards with my name and phone number to request an escort to the conference room: Judit Milstein, at 6-0763.

If you have any questions, call me at (301) 796-0763.

Sincerely,

{See appended electronic signature page}

Judit Milstein
Chief, Project Management Staff
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Foreign Visitor Data Request Form

FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH **(MM/DD/YYYY)**	
PLACE OF BIRTH **(city and country)**	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	
MEETING ENDING DATE AND TIME	
PURPOSE OF MEETING	
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	
HOSTING OFFICIAL **(**name, title, office/bldg, room number, and phone number)	
ESCORT INFORMATION (If different from Hosting Official)	

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/s/

JUDIT R MILSTEIN
06/28/2012
NDA 21214-Meeting Rescheduled

MEMORANDUM

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

DATE: June 26, 2012

FROM: Judit Milstein, Chief, Project Management Staff
Division of Transplant and Ophthalmology Products

SUBJECT: Request for postponement of a scheduled meeting

APPLICATION/DRUG: NDA 21214/S-007
Rescula (unoprostone isopropyl ophthalmic solution)

APPLICANT: Sucampo Pharma Americas, Inc.

BACKGROUND:
On August 21, 2009, Sucampo submitted a supplement which proposed changes to the labeling (which are reviewed by the Office of New Drugs) and changes to the manufacturer and bottle container for Rescula (which are reviewed by the Office of New Drug Quality Assessment-ONDQA)

In correspondence dated March 23, 2011, the applicant was informed that the August 21, 2009 submission was split into two supplements as follows:

1. NDA 21214/S-006 which provides for a change in the manufacturer and bottle container for Rescula.

2. NDA 21214/S-007, which provides for changes for the product labeling in the Highlights, Clinical Pharmacology/Mechanism of Action (MOA) and Warnings and Precautions sections.

NDA 21214/S-006 is currently under review by the Office of New Drug Quality Assessment.

NDA 21214/S-007 received two Complete Response actions on April 14, 2011, and March 20, 2012, and is the subject of this memorandum.

On May 21, 2012, the applicant submitted a request for Dispute resolution, which included a briefing document with literature references supporting their original labeling changes.
On June 1, 2012, the Office of New Drugs denied the request for dispute resolution based on the fact that no post-action meeting was held with the Division prior to appealing to a higher level (see procedures described in the *Guidance for Industry,"Formal Dispute Resolution: Appeals Above the Division Level."* The Office of New Drugs also recommended that the applicant request a post-action meeting with the Division.

On June 1, 2012, Sucampo submitted a request for a post-action meeting with the Division of Transplant and Ophthalmology Products (DTOP), and it was agreed that the information submitted on May 21, 2012 would constitute the briefing document for the meeting request. The June 1, 2012 submission also indicated that Ms. Nancy Buc, Counsel for Sucampo, would be the contact for this meeting request.

On June 8, 2012, correspondence was sent to Ms. Buc, confirming a June 26, 2012, meeting date.

On June 8 and June 20, 2012, the Division conducted internal meetings to discuss the issues and questions outlined in the May 21, 2012 briefing document. The Division's response to the issues and questions were finalized on June 25, 2012 and the same day were sent to Ms. Buc via e-mail as the Meeting Preliminary Comments which would be the basis for the discussions at the June 26, 2012 meeting regarding issues identified in S-007.

REQUEST FOR POSTPONEMENT OF THE MEETING:

Ms. Buc acknowledged receipt of the comments via an e-mail sent June 25, 2012. Also on June 25, 2012, Ms. Buc contacted me by telephone, requesting the postponement of the meeting. Ms. Buc acknowledged the detailed comments sent by the Division and stated that Sucampo will need more time to internally discuss these comments prior to meeting with the Division.

I replied that the Division was willing to work with Sucampo, and suggested that Ms. Buc provide me with a proposed timeline so we could reschedule the meeting.

In an e-mail sent by Ms. Buc on June 26, 2012, "Sucampo proposed the following dates for the postponed meeting, in order of preference:

> July 24 (any time), morning of 25th, 23rd (any time), 27th (any time), early morning of 30th."

Based on availability, the meeting was rescheduled for July 24, 2012, 12:00-1:00 pm.

A letter acknowledging the change in date and time will be entered into DARRTS and sent to Sucampo.

Milstein, Judit

From: buclawpllc@gmail.com
Sent: Monday, June 25, 2012 3:43 PM
To: Milstein, Judit
Subject: Re: Preliminary responses in preparation for tomorrow's meeting

To confirm our call, sucampo requests a postponement of tomorrow's meeting. I will call you by the end of this week to propose some dates.

Thank you.

Sent from my iPhone

On Jun 25, 2012, at 1:06 PM, "Milstein, Judit" <Judit.Milstein@fda.hhs.gov> wrote:

> NDA 21214/S-006 and S-007
> Rescula (unoprostone isopropyl ophthalmic solution)
> Sucampo Pharma Americas, Inc.
>
> Dear Ms. Buc,
> Find enclosed the Division's preliminary comments in preparation for tomorrow's meeting. These comments will serve as the basis for the discussion during the meeting
>
> I also wanted to alert you that we may have additional attendees. We have consulted other groups in CDER with regard to the issues related to the Pharmacologic Class and Mechanism of Action and as a courtesy, we extended them an invitation to the meeting. I am not sure yet who will be attending.
>
> I would appreciate a confirmation of receipt of these comments.
>
> Thank you
> Judit Milstein
> Chief, Project Management Staff
> DTOP/OAP/CDER
> Food and Drug Administration
> 10903 New Hampshire Avenue
> Building 22, Room 6170
> Silver Spring, MD 20993
> Phone: 301-796-0763
> Fax: 301-796-9881
>
> <NDA NDA 21214S007 Prelim Comments 26Jun12 meeting.pdf>

Milstein, Judit

From: Nancy L. Buc [buclawpllc@gmail.com]
Sent: Tuesday, June 26, 2012 4:33 PM
To: Milstein, Judit
Subject: Scheduling the postoned meeting

Dear Judit -

Sucampo proposes the following dates for the postponed meeting, in order of preference:

July 24 (any time), morning of 25th, 23 (any time), 27 (any time), early morning of 30.

Please let me know if any of those works for you.

Thanks.

Nancy

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/s/

JUDIT R MILSTEIN
06/28/2012
NDA 21214-Request for meeting postponement-Memo

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:

(b) (4)

(b) (4)

(b) (4)

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:

(b) (4)

Division's Comments:

(b) (4)

1) A cause and effect relationship between (b) (4)

(b) (4)

(b) (4)

(b) (4)

You cite a study by (b) (4)

2) Clinical trials do not appear to have been submitted demonstrating that (b) (4)

While there is no regulation which requires that the mechanism of action be demonstrated in clinical trials, the product's indication is for the reduction of IOP. As discussed, IOP is controlled by a multifactorial process. (b) (4)

3) Clinical trials do not appear to have been submitted which demonstrate that (b) (4)

(b) (4)

4) Clinical trials do not appear to have been submitted demonstrating that (b) (4)

(b) (4)

(b) (4)

5) Therefore, the clinical significance of these theories remains unknown and (b) (4)

While there is empirical evidence to support the concept (b) (4)

6) Stimulation of the (b) (4)

(b) (4)

(b) (4)

7) Clinical trials which demonstrate the impact of changes in (b) (4)

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* (b) (4) *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 21214/S-007

MEETING REQUEST GRANTED

Sucampo Pharma Americas, Inc.
Attention: Nancy Buc
Counsel
4520 East-West Highway, Suite 300
Bethesda, MD 20814

Dear Ms. Buc:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rescula (unoprostone isopropyl ophthalmic solution), 0.15%.

We also refer to your June 1, 2012, correspondence requesting a Post-Action meeting to discuss the Complete Response letter issued on March 20, 2012, and the proposed changes for the product labeling in the Highlights, the Mechanism of Action (MOA) subsection of the Clinical Pharmacology section and the Warnings and Precautions section. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type A meeting.

The meeting is scheduled as follows:

Date: June 26, 2012
Time: 10:00 am-11:00 am
Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1415
Silver Spring, Maryland 20903

CDER participants:
Edward M. Cox, MD, MPH, Director, Office of Antimicrobial Products (OAP)
David Roeder, Associate Director for Regulatory Affairs, OAP
Renata Albrecht, MD, Director Division of Transplant and Ophthalmology Products (DTOP)
Wiley A. Chambers, MD, Deputy Director, DTOP
Ozlem Belen, MD, Deputy Director for Safety
William Boyd, MD, Clinical Team Leader
Yan Wang, PhD, Statistics, Team Leader
Lori Kotch, PhD, Pharmacology/Toxicology Team Leader
Leanna Kelly, Labeling Reviewer
Libaniel Rodriguez, PhD, Chemistry Reviewer
Robert Mello, PhD, Microbiology Reviewer

Bryan Riley, PhD, Microbiology Team Leader
Judit Milstein, Chief, Project Management Staff

Please e-mail me any updates to your attendees at Judit.milstein@fda.hhs.gov, at least one week prior to the meeting. For each foreign visitor, complete and email me the enclosed Foreign Visitor Data Request Form, at least two weeks prior to the meeting. A foreign visitor is any non-U.S. citizen who does not have Permanent Resident Status or a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Upon arrival at FDA, provide the guards with the following number to request an escort to the conference room: Judit Milstein at 6-0763.

We note that your submission dated May 26, 2012, contains the background information for this meeting.

If you have any questions, call me at 301-796-0763

Sincerely,

{See appended electronic signature page}

Judit Milstein
Chief, Project Management Staff
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Foreign Visitor Data Request Form

FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH **(MM/DD/YYYY)**	
PLACE OF BIRTH **(city and country)**	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	
MEETING ENDING DATE AND TIME	
PURPOSE OF MEETING	
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	
HOSTING OFFICIAL **(**name, title, office/bldg, room number, and phone number)	
ESCORT INFORMATION (If different from Hosting Official)	

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/s/

JUDIT R MILSTEIN
06/08/2012
NDA 21214S007 Meeting Granted

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021214/S-007

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

Dear Mr. Carey:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rescula (unoprostone isopropyl ophthalmic solution) 0.15%.

We acknowledge receipt on May 21, 2012, of your May 21, 2012, request for formal dispute resolution. The appeal concerns the complete response action taken on March 20, 2012, specifically, changes that you had proposed for the product labeling in the Highlights, the Mechanism of Action (MOA) subsection of the Clinical Pharmacology section, and the Warnings and Precautions section.

In accordance with the procedures for dispute resolution described in the *Guidance for Industry, "Formal Dispute Resolution: Appeals Above the Division Level"* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079743.pdf), the appropriate course of action for a sponsor that disagrees with a decision is to first request reconsideration of the matter by the division before the issue may be appealed to the next higher management level. In instances where a sponsor disagrees with a complete response action, our practices have been that the sponsor requests a post-action meeting with the division to discuss the sponsor's concerns with the decision. If a sponsor chooses not to take the advice that the division provides at the post-action meeting, the sponsor may proceed with the formal dispute resolution process.

Since a post-action meeting has not been held between the Division of Transplant and Ophthalmology Products (DTOP) and you following the March 20, 2012 complete response action, it would be inappropriate to consider this matter under formal dispute resolution at this time. We believe that there is value in your having a post-action meeting with the DTOP to discuss your concerns. This will provide an opportunity for further productive discussion on the data in your application regarding the MOA.

Please submit a meeting request for a post-action meeting to the NDA administrative file. We will work to schedule this meeting as soon as a mutually agreed upon date can be found. Dr. Ed Cox, Director, Office of Antimicrobial Products (OAP), will attend that meeting in a non-

decisional capacity, so that he may hear your concerns directly. If you have any questions, contact Ms. Judit Milstein, Chief, Project Management Staff, at (301) 796-0763.

If, after this meeting, the issue is still not resolved to your satisfaction, you may appeal the matter to the Director of OAP. If you have any questions regarding the formal dispute resolution process, you may call me at (301) 796-1647.

Sincerely,

{See appended electronic signature page}

Amy Bertha
CDER Formal Dispute Resolution Project Manager
Office of New Drugs
Center for Drug Evaluation and Research

cc: Ms. Nancy L. Buc
BUCLAWPLLC
4200 Massachesetts Ave., NW #310
Washington, DC 20016

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/s/

AMY E BERTHA
06/01/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21214/S-007

MEETING MINUTES

Sucampo Pharma Americas, Inc.
Attention: Gayle Dolecek, P.D., MPH
Executive Advisor, Research & Development
4520 East-West Highway, 3rd Floor
Bethesda, MD 20814

Dear Dr. Dolecek:

Please refer to the labeling meeting between representatives of your firm and FDA on November 10, 2011. The purpose of the meeting was to discuss the proposed labeling revisions to Rescula (unoprostone isopropyl ophthalmic solution) 0.15%.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call 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
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure: Minutes of the meeting

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type C
Meeting Category:	Labeling meeting
Meeting Date and Time:	November 10, 2011, Start: 9:35, End: 10:20
Meeting Location:	Bldg #22, WO 1309
Application Number:	NDA 21214/S-007
Product Name:	Rescula (unoprostone isopropyl ophthalmic solution) 0.15%
Indication:	Reduction of elevated intraocular pressure in open-angel glaucoma or ocular hypertension.
Sponsor/Applicant Name:	Sucampo Pharma Americas, Inc.
Meeting Chair:	Wiley A. Chambers, M.D.
Meeting Recorder:	Raphael R. Rodriguez

FDA ATTENDEES
Wiley Chambers, M.D., Deputy Director, DTOP
William Boyd, M.D. Clinical Team Leader, DTOP
Jennifer Harris, M.D., Clinical Reviewer, DTOP
Martin Nevitt, M.D., Clinical Reviewer, DTOP
Raphael Rodriguez, MS, Senior Regulatory Project Manager, DTOP

SUCAMPO ATTENDEES
Birgit Roerig, Ph.D., Director of Pharmacology & Toxicology
Gayle Dolecek, P.D., Executive Advisor, R&D
Nancy Buc, Counsel to Sucampo Pharma Americas, Inc.

BACKGROUND

NDA 21-214/S-007 originally submitted on August 21, 2009, received a Complete Response action on April 14, 2011. This supplement was resubmitted on September 19, 2011, with a request for a meeting to discuss the proposed labeling. Preliminary responses on the questions posted in the September 19, 2011 resubmission were forwarded to the applicant on November 7, 2011.

For the purpose of these minutes, the questions posted by Sucampo in the briefing document dated September 19, 2011, are described in **bold** format, the Division's preliminary responses issued on November 7, 2011 are *italics* and the meeting discussions are in normal font.

DISCUSSION

1. Does the Division agree with the proposed changes as a general matter, i.e., in concept?

FDA Response: *The submitted prior approval supplement, S-007, is under review.*

The proposed changes to the labeling are not consistent with the data submitted to the original NDA application by CIBA Vision Corporation and which formed the basis for approval for Rescula (unoprostone isopropyl ophthalmic solution) 0.15%.

Most of the articles submitted (b) (4)

Meeting Discussion:
Sucampo believes that at the time of approval of this NDA, unoprostone isopropyl was (b) (4)

Sucampo proposed to submit additional literature in support of their position, and the Division agreed to review that information in the context of Supplement S-007

2. Which proposed changes are acceptable as proposed?

FDA Response: *The submitted prior approval supplement, S-007, is under review. The Agency is not able to commit that any of the proposed changes are acceptable as proposed until review of the supplement is completed. See response to Question 1.*

No additional discussion was held on this question

3. For any proposed changes which are not acceptable as proposed, can the Division suggest wording which would render them acceptable?

FDA Response: *The submitted prior approval supplement, S-007, is under review. The Agency is not able to commit that any of the proposed changes are acceptable as proposed until review of the supplement is completed. See response to Question 1*

No additional discussion was held on this question

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/s/

WILEY A CHAMBERS
04/09/2012

CLINICAL LABELING MEMORANDUM

DATE:	March 20, 2012
APPLICATION NUMBER:	NDA 21-214/S-007
DRUG:	Rescula (unoprostone isopropyl ophthalmic solution) 0.15%
APPLICANT:	Sucampo Pharma Amercias, Inc.
SUBJECT:	Discussion on Administrative Split

On March 20, 2012, Dr. William M. Boyd, Clinical Team Leader in the Division of Transplant and Ophthalmology Products (DTOP), and Ms. Leanna M. Kelly, Consumer Safety Officer (DTOP), spoke to Mr. Jeff Carey (sp?), the Director of Regulatory Affairs at Sucampo Pharma Americas, Inc., to remind the applicant that the August 21, 2009, Supplement New Drug Application (sNDA) was split on March 23, 2011.

> Supplement-6 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.
>
> Supplement-7 provides for updated labeling text (package insert) in Physician's Labeling Rule (PLR) format.

Dr. Boyd explained that as no action has been taken on Supplement-6, the applicant's proposal to include new bottle information in Supplement-7 is premature.

Dr. Boyd offered to speak to Mr. Carey (sp?) or another representative from Sucampo after action is taking for Supplement-7 if there are further questions.

Prepared by: Leanna M. Kelly
Consumer Safety Officer
Division of Transplant and Ophthalmology Products

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/s/

LEANNA M KELLY
03/27/2012

WILLIAM M BOYD
03/27/2012

Meeting Preliminary Comments

Division of Transplant and Ophthalmology Products

Meeting date:	March 13, 2012
Meeting Location:	Food and Drug Administration White Oak Campus, Building 22, Conference Room 1315 10903 New Hampshire Avenue Silver Spring, Maryland, 20903
Meeting Type:	Labeling
Application:	NDA 21214/S-007
Drug:	Rescula (unoprostone isopropyl ophthalmic solution)
Sponsor:	Sucampo Pharmaceuticals

The following are the Division's preliminary responses to the questions posted in your submission dated January 19, 2012, for Rescula (unoprostone isopropyl ophthalmic solution) 0.15%.

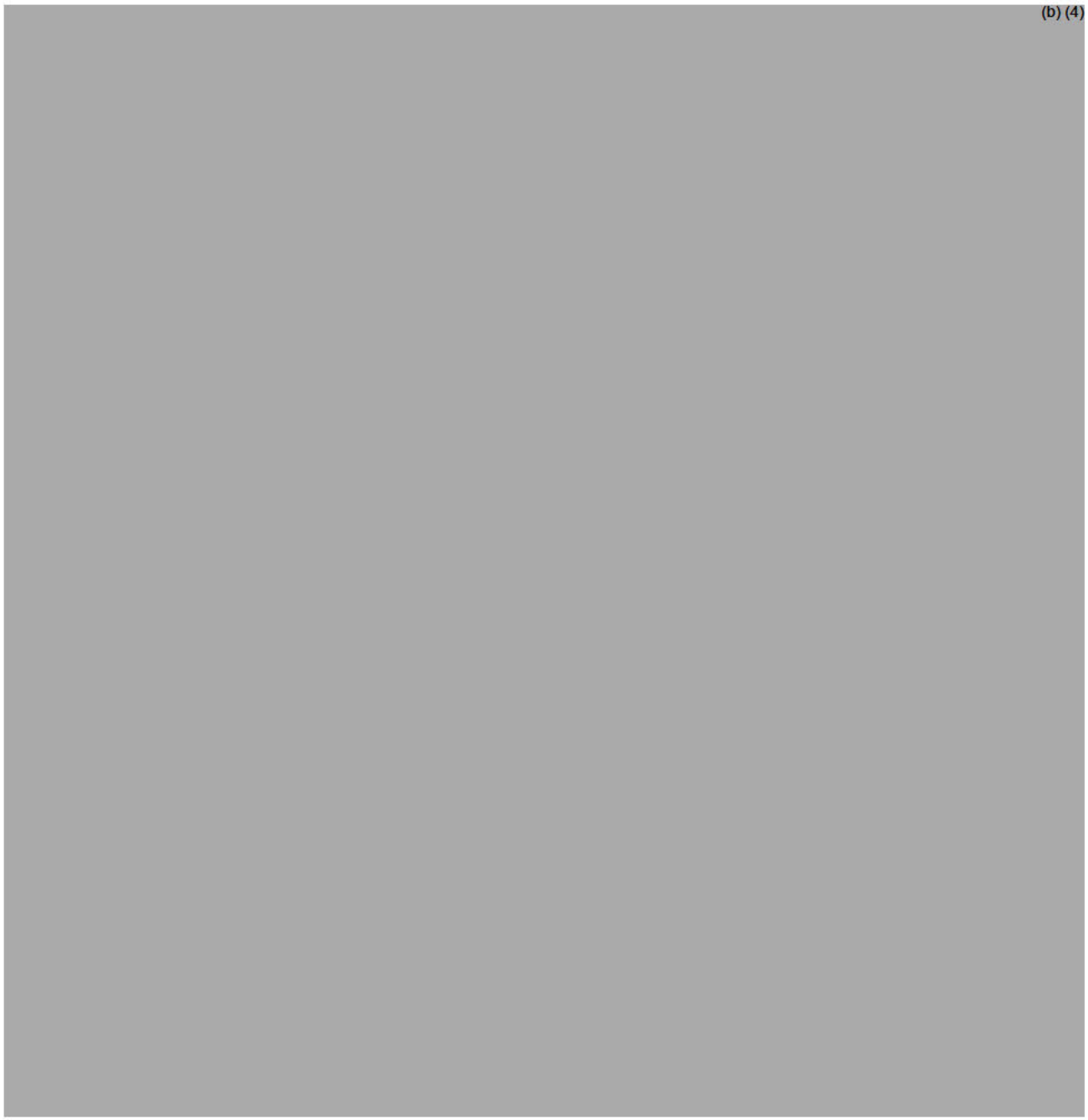
If these answers and comments to your questions are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting. You can also request that the face-to-face meeting be converted to a teleconference.

Please note that if there are any major changes to your development plan, or the purpose of the meeting, or new questions based on our responses herein, we may not be prepared to discuss or reach agreement on such changes at the meeting to be held on March 13, 2012. The minutes of the meeting will reflect agreements, key issues, and any action items discussed during the formal meeting and may not be identical to these preliminary comments.

For the purposes of this response, your questions are in **bold** font and our responses are in *italics* font.

1. Is the proposed labeling included in the January 19, 2012 submission acceptable?

FDA Response: *The proposed labeling is not acceptable. While a complete review of the amendment has not yet been completed, the following are preliminary comments:*



2. For any proposed changes that are not acceptable, why are they not acceptable and what changes does the Division suggest to make it acceptable.

FDA Response: *For the reasons described in the Response to Question 1 above, consideration will be given to* (b) (4) *for Rescula. Consideration will also be given to listing the mechanism of action for Rescula* (b) (4)*. It is anticipated that the Warnings and Precautions for Rescula will remain unchanged.*

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/s/

JUDIT R MILSTEIN
03/12/2012
NDA 21214/S007 Preliminary responses

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21214

MEETING REQUEST GRANTED

Sucampo Pharma Americas, Inc.
Attention: Gayle R. Dolecek
Executive Advisor, R&D
4520 East-West Highway, Suite 300
Bethesda, MD 20814

Dear Dr. Dolecek

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rescula (uniprostone isopropyl) ophthalmic solution.

We also refer to your January 24, 2012, correspondence requesting a meeting to discuss scientific and labeling wording issues related to Supplement S-007. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type B meeting.

The meeting is scheduled as follows:

Date: March 13, 2012
Time: 10:00 am-11:00 am
Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1315
Silver Spring, Maryland 20903

CDER participants:
Wiley A. Chambers, MD, Deputy Director
William Boyd, MD, Clinical Team Leader
Leanna Kelly, Labeling Reviewer
Judit Milstein, Chief, Project Management Staff

Please e-mail me any updates to your attendees at Judit.milstein@fda.hhs.gov, at least one week prior to the meeting. For each foreign visitor, complete and email me the enclosed Foreign Visitor Data Request Form, at least two weeks prior to the meeting. A foreign visitor is defined as any non-U.S. citizen or dual citizen who does not have a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Upon arrival at FDA, provide the guards with my name and telephone number to request an escort to the conference room.

If you have any questions, call me at (301) 796-0763.

Sincerely,

{See appended electronic signature page}

Judit Milstein
Chief, Project Management Staff
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE: Foreign Visitor Data Request Form

FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH **(MM/DD/YYYY)**	
PLACE OF BIRTH **(city and country)**	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	
MEETING ENDING DATE AND TIME	
PURPOSE OF MEETING	
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	
HOSTING OFFICIAL **(**name, title, office/bldg, room number, and phone number)	
ESCORT INFORMATION (If different from Hosting Official)	

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/s/

JUDIT R MILSTEIN
02/08/2012
NDA 21214 Meeting Granted

For Internal Use Only

Meeting Request Granted Form**

(Use this form to document the meeting granted via telephone.)

Complete the information below and check form into DARRTS.

Application Type	NDA
Application Number	21214/S-007
DATE Sponsor informed of meeting granted	November 2, 2011
Sponsor was informed of: • date/time & meeting location • expected FDA attendees • meeting briefing package due date • pre-meeting	November 11, 2011, CDER White Oak, RM #1309 Clinical reviewers September 19, 2011 November 7, 2011 11/2/2011 – Confirmation of this Type C - labeling meeting was granted and phone notification to Dr. Gayle Dolecek of Sucampo.
Project Manager	Raphael R. Rodriguez

Any follow-up letter must be checked into DARRTS as an advice letter, **NOT as a meeting request granted letter.

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/s/

RAPHAEL R RODRIGUEZ
11/10/2011

NDA 21-214/S-007 Sucampo Pharmaceuticals, Inc. Nov 10, 2011
Labeling meeting : Type C
RESCULA (unoprostone isopropyl ophthalmic solution) 0.15%

Dear Dr. Dolecek:

The following are the Division's preliminary responses to the questions posed in your briefing package dated September 19, 2011. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting. You also have the option of converting the face-to-face meeting to a teleconference.

Please note that if there are any major changes to your development plan, to the purpose of the meeting, or to the questions you submitted in your meeting package 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 November 11, 2011, meeting will reflect agreements, key issues, and any action items discussed during the formal meeting and may not be identical to these preliminary comments.

The questions outlined in your meeting package are presented **BOLD** font and our response are in *italicized* font.

TOPICS FOR DISCUSSION

1. **Does the Division agree with the proposed changes as a general matter, i.e., in concept?**

FDA Response: *The submitted prior approval supplement, S-007, is under review.*

The proposed changes to the labeling are not consistent with the data submitted to the original NDA application by CIBA Vision Corporation and which formed the basis for approval for Rescula (unoprostone isopropyl ophthalmic solution) 0.15%.

Most of the articles submitted [redacted] (b) (4)

2. **Which proposed changes are acceptable as proposed?**

FDA Response: *The submitted prior approval supplement, S-007, is under review. The Agency is not able to commit that any of the proposed changes are acceptable as proposed until review of the supplement is completed. See response to Question 1.*

3. **For any proposed changes which are not acceptable as proposed, can the Division suggest wording which would render them acceptable?**

FDA Response: *The submitted prior approval supplement, S-007, is under review. The Agency is not able to commit that any of the proposed changes are acceptable as proposed until review of the supplement is completed. See response to Question 1.*

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/s/

RAPHAEL R RODRIGUEZ
11/07/2011

From: Dolecek, Gayle [mailto:gdolecek@sucampo.com]
Sent: Thursday, July 28, 2011 2:44 PM
To: Rodriguez, Raphael R
Cc: Boyd, William M; Chambers, Wiley A
Subject: NDA 21214 labeling meeting sch'd July 29, 2011

Dear Mr. Rodriguez,

Sucampo does not agree with the reasoning in the Division's pre-meeting comments, but believes it would be more useful to respond to those comments in writing than to do so in the meeting now scheduled for Friday. Once we have responded in writing, we will again request a meeting. We will therefore forego the meeting scheduled for tomorrow.

Regards,

Gayle Dolecek

Gayle Robert Dolecek, PD, MPH
Senior VP, Research & Development
Sucampo Pharma Americas, Inc.

From:	Rodriguez, Raphael R
Sent:	Wednesday, July 27, 2011 2:25 PM
To:	'Dolecek, Gayle'
Cc:	'Knapp, Thomas'; 'Roerig, Birgit'; 'Ivanov, Tanya'
Subject:	NDA 21214 labeling meeting sch'd July 29, 2011

Gayle: attached are our written responses to NDA 21214, Rescula (unoprostone isopropyl ophthalmic solution) 0.15%, labeling meeting for July 29, 2011. These comments have been provided to help your team to prepare for the meeting. If you are satisfied with these responses and wish to forego the meeting, please let us know. If you would prefer to go forward, for the purpose of clarifying these comments, that is acceptable. We will NOT, however, be able to discuss any new information or answer new questions during this meeting. If you wish to present additional information or questions, a new meeting should be requested.

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NDA 21214/S-007 Labeling Meeting Sucampo Pharmaceuticals, Inc. July 29, 2011
RESCULA (unoprostone isopropyl ophthalmic solution) 0.15%

Questions:

1. Does the Division agree with the proposed changes as a general matter, i.e., in concept?

FDA Response: *The submitted prior approval supplement, S-007, is under review.*

The proposed changes to the labeling are not consistent with the data submitted to the original NDA application by CIBA Vision Corporation and which formed the basis for approval for Rescula (unoprostone isopropyl ophthalmic solution) 0.15%.

Most of the articles submitted (b) (4)

Please note that several of the submitted references are not translated into English. These references will not be reviewed in support of the supplement unless full English translations are provided.

2. Which proposed changes are acceptable as proposed?

FDA Response: *The submitted prior approval supplement, S-007, is under review. The Agency is not able to commit that any of the proposed changes are acceptable as proposed until review of the supplement is completed. See response to Question 1.*

3. For any proposed changes which are not acceptable as proposed, can the Division suggest wording which would render them acceptable?

FDA Response: *The submitted prior approval supplement, S-007, is under review. The Agency is not able to commit that any of the proposed changes are acceptable as proposed until review of the supplement is completed. See response to Question 1.*

Any questions, please contact me at (301) 796-0798, or simply reply back to this email.

Thanks. Raphael

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/s/

RAPHAEL R RODRIGUEZ
09/30/2011

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