

Subjects qualified for randomization at the baseline visit if their morning IOP measurement was 23 to 34 mm Hg, inclusive, in each eye with a difference in IOP of no more than 5 mm Hg between eyes. Each randomized subject was given one bottle of masked study medication and instructed on its proper instillation. The first dose of study medication was instilled after the morning IOP measurement on Day 0.

Study Medications

- Unoprostone isopropyl 0.06% ophthalmic solution [REDACTED]
- Unoprostone isopropyl 0.12% ophthalmic solution [REDACTED]
- Unoprostone isopropyl 0.15% ophthalmic solution [REDACTED]
- Vehicle placebo [REDACTED]
- Timolol maleate 0.5% ophthalmic solution [REDACTED]

Study Population

- Clinical diagnosis of primary open angle glaucoma or ocular hypertension in both eyes.
- Morning IOP of 23 to 34 mm Hg, inclusive, at the baseline visit after washout of prior therapy for glaucoma or ocular hypertension with no more than a 5 mm Hg difference between eyes.
- Best-corrected distance visual acuity (ETDRS) of 20/200 or better in each eye.

Efficacy Variables

The primary efficacy variable was the change from baseline in IOP, which was measured at screening and between 7 a.m. and 9 a.m. on Days 0 (baseline), 1, 7, and 28. On Days 7 and 28, IOP was measured 2, 4, 6, 8, 10, and 12 hours after instilling the morning dose of study medication.

Safety Variables

Ocular safety was determined from ophthalmic examinations including best-corrected distance visual acuity, slit lamp biomicroscopy, dilated ophthalmoscopy, and visual field exams. Ocular and systemic safeties were determined from adverse event reports.

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Table C97-UIOS-003-01 – Schedule of Assessments

| Procedure | Visit 1 Screen | Visit 2 Baseline Day 0 | Visit 3 Day 1 | Visit 4 Day 7 | Visit 5 ¹ Day 27 | Visit 6 Day 28 | Visit 7 ² |
|--|-------------------|------------------------------|------------------|------------------|--------------------------------|-------------------|----------------------|
| Informed Consent | x | | | | | | |
| Inclusion / Exclusion | x | x | | | | | |
| Demographics / Medical & Ocular History | x | | | | | | |
| Medication History | x | x | x | x | x | x | x |
| Ocular Symptom Assessment | x | x | x | x | x | x | x |
| Blood Pressure and Heart Rate | x | | | | | | |
| Best-Corrected Distance Visual Acuity | x | x | x | x | | x | x |
| Slit Lamp Biomicroscopy | x | x | x | x | | x | x |
| Morning IOP Measurement | x | x | x | x | | x | x ³ |
| 12-Hour Diurnal IOP Measurements | | | | x | | x | |
| Gonioscopy | x ⁴ | | | | | | |
| Dilated Fundoscopy | x | | | | | | |
| Visual Field (Humphrey) | x ⁵ | | | | | x | |
| Adverse Events | | | x | x | x | x | x |
| Instill Morning Drop at Office | | x | x | x | x | x | |
| Instill Evening Drop at Office | | | | x | x | | |
| Dispense Medication | | x | | x | | | |
| Recover Medication | | | | x | x | | |
| Exit Form | | | | | | | x ⁶ |

¹Visit 5 was a dosing day to insure compliance with study medication for Visit 6.

²Visit 7 was to be performed 7 days after trial medication was stopped, whether the subject discontinued early from the trial or completed the trial.

³This IOP measurement did not have to be taken between 7-9 a.m. in the morning.

⁴Required if gonioscopy examination was not performed within 12 months before screening.

⁵Required if visual field examination was not performed within 3 months before screening.

⁶Required for all subjects, regardless of exit status (i.e., early discontinuation).

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Subject Disposition and Demographics

Of the 237 randomized subjects, 46, 48, 49, 47, and 47 were assigned to treatment with UIOS 0.0%, 0.06%, 0.12%, 0.15% and TMOS 0.5%, respectively. All 237 randomized subjects received double-masked study medication, and 229 subjects completed the study. Subject disposition is summarized in the table below.

Table C97-UIOS-003-02 – Subject Disposition

| | Number of Subjects | | | | |
|---|--------------------|-------|-------|-------|------|
| | UIOS | | | | TMOS |
| | 0.0% | 0.06% | 0.12% | 0.15% | 0.5% |
| Randomized | 46 | 48 | 49 | 47 | 47 |
| Received masked study medication | 46 | 48 | 49 | 47 | 47 |
| Completed study | 45 | 47 | 46 | 47 | 44 |
| Analyzed for efficacy (Intent-to-Treat) | 46 | 47 | 49 | 46 | 47 |
| Analyzed for efficacy (Per Protocol) | 43 | 47 | 48 | 44 | 45 |
| Analyzed for safety | 46 | 48 | 49 | 47 | 47 |

Table C97-UIOS-003-03 – Discontinued Patients and Reason

| Investigator | Patient | Treatment | Reason |
|--------------|---------|------------|---|
| 116 | 114 | UIOS 0.00% | Other – would not return for Days 7, 27, 28 |
| 144 | 309 | UIOS 0.06% | Withdrawal of Consent – refused dilation |
| 140 | 215 | UIOS 0.12% | Adverse Event – corneal toxicity |
| 145 | 404 | UIOS 0.12% | Withdrawal of Consent – schedule conflicts |
| 146 | 534 | UIOS 0.12% | Protocol Violation – alteration in HTN meds |
| 145 | 433 | TMOS 0.5% | Withdrawal of Consent |
| 146 | 524 | TMOS 0.5% | Withdrawal of Consent – schedule conflicts |
| 148 | 706 | TMOS 0.5% | Adverse Event – A-fib |

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Table C97-UIOS-003-04 - Summary of Demographic Characteristics (Intent-to-Treat)

| | UIOS | | | | TMOS 0.5% | Total | P-value |
|---|-------|-------|-------|-------|--------------|-------|--------------------|
| | 0.00% | 0.06% | 0.12% | 0.15% | | | |
| No. of Subjects | 46 | 47 | 49 | 46 | 47 | 235 | |
| Gender | | | | | | | |
| Female | 70% | 60% | 63% | 72% | 51% | 63% | 0.251 |
| Male | 30% | 40% | 37% | 28% | 49% | 37% | |
| Race | | | | | | | |
| Caucasian | 59% | 77% | 65% | 61% | 60% | 64% | 0.336 ^A |
| Black | 17% | 9% | 8% | 9% | 11% | 11% | |
| Oriental | 2% | 0% | 4% | 0% | 0% | 1% | |
| Hispanic | 22% | 15% | 22% | 28% | 30% | 23% | |
| Native American | 0% | 0% | 0% | 2% | 0% | 0% | |
| Age (Years) | | | | | | | |
| N | 46 | 47 | 49 | 46 | 47 | 235 | 0.164 |
| Mean | 57.9 | 52.6 | 55.4 | 55.0 | 52.8 | 54.7 | |
| S.D. | 9.6 | 12.7 | 12.1 | 13.4 | 12.7 | 12.2 | |
| Median | 57.2 | 50.4 | 54.4 | 56.2 | 50.6 | 54.0 | |
| Iris Color | | | | | | | |
| Black | 0% | 2% | 0% | 0% | 0% | 0% | 0.135 ^B |
| Brown | 67% | 38% | 53% | 54% | 57% | 54% | |
| Hazel | 11% | 17% | 20% | 11% | 13% | 14% | |
| Green | 9% | 6% | 6% | 13% | 13% | 9% | |
| Blue | 13% | 32% | 20% | 17% | 15% | 20% | |
| Other | 0% | 4% | 0% | 4% | 2% | 2% | |
| Diagnosis | | | | | | | |
| POAG | 26% | 15% | 29% | 11% | 17% | 20% | 0.151 |
| OHT | 74% | 85% | 71% | 89% | 83% | 80% | |
| Gonioscopy | | | | | | | |
| 0-10 Degrees | 0% | 0% | 0% | 0% | 0% | 0% | 0.008 ^C |
| > 10 Degrees | 0% | 0% | 0% | 0% | 0% | 0% | |
| > 20 Degrees | 11% | 0% | 0% | 9% | 2% | 4% | |
| > 30 Degrees | 35% | 30% | 27% | 26% | 17% | 27% | |
| > 40 Degrees | 54% | 68% | 69% | 59% | 81% | 66% | |
| > 30 & >40 Deg | 0% | 0% | 4% | 4% | 0% | 2% | |
| Average IOP (mmHg) at Visit 1 (at any time during the day) | | | | | | | |
| N | 46 | 47 | 49 | 46 | 47 | 235 | 0.502 |
| Mean | 24.1 | 23.7 | 22.8 | 23.4 | 24.2 | 23.6 | |
| S.D. | 3.2 | 2.8 | 3.2 | 2.8 | 2.6 | 3.0 | |
| Median | 23.5 | 23.5 | 23.0 | 23.8 | 24.0 | 23.5 | |
| Minimum | 17.3 | 17.8 | 15.0 | 15.8 | 18.5 | 15.0 | |
| Maximum | 33.0 | 30.8 | 29.3 | 29.8 | 32.0 | 33.0 | |

^A Caucasians vs. others, Fisher's exact test

^B dark irides vs. light irides, Fisher's exact test

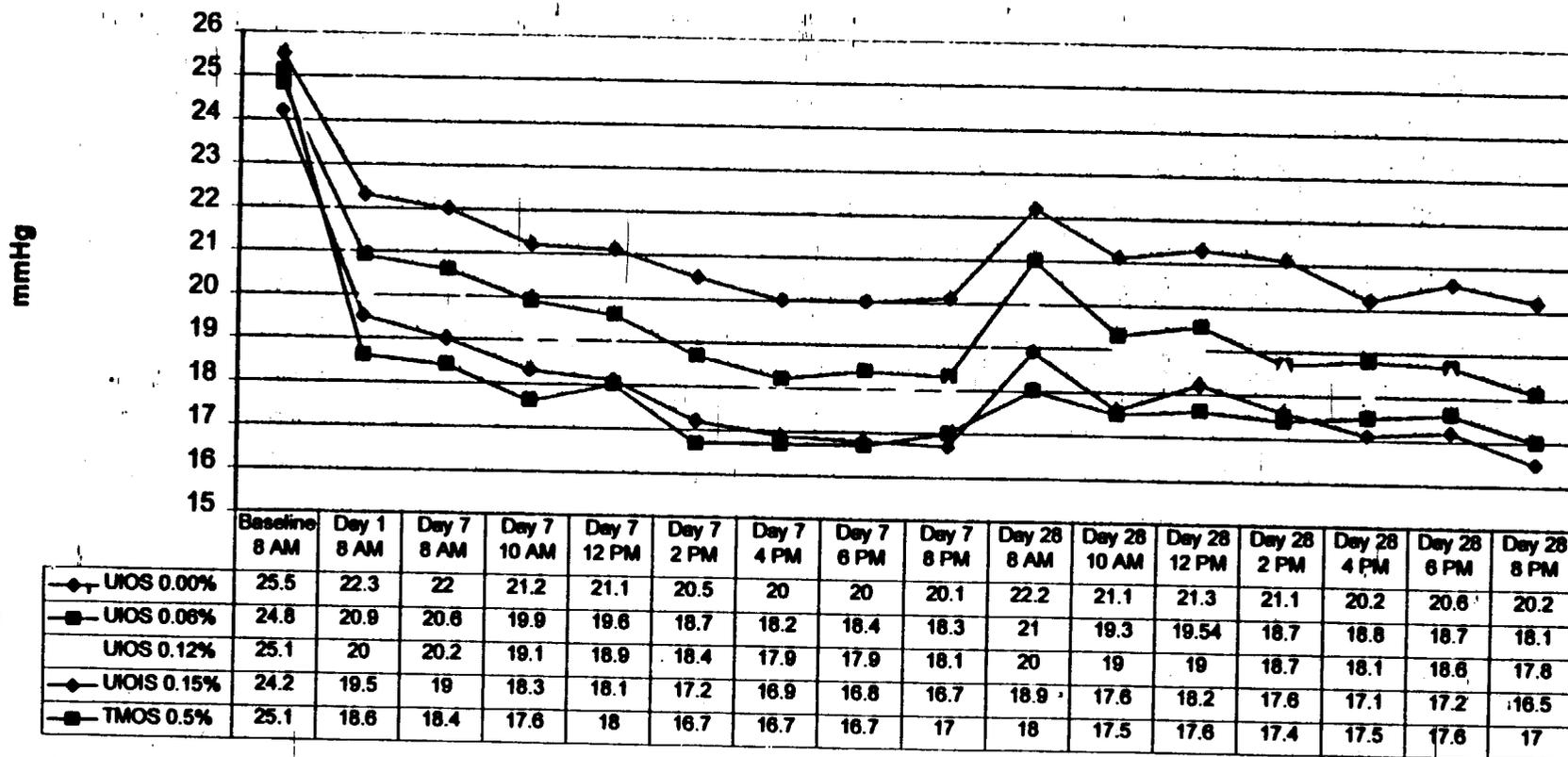
^C closed angles (< 30 degrees) vs. open angles (≥ 30 degrees), Fisher's exact test

8.1.3 Efficacy – Protocol C97-UIOS-003

Intent-to-Treat Population

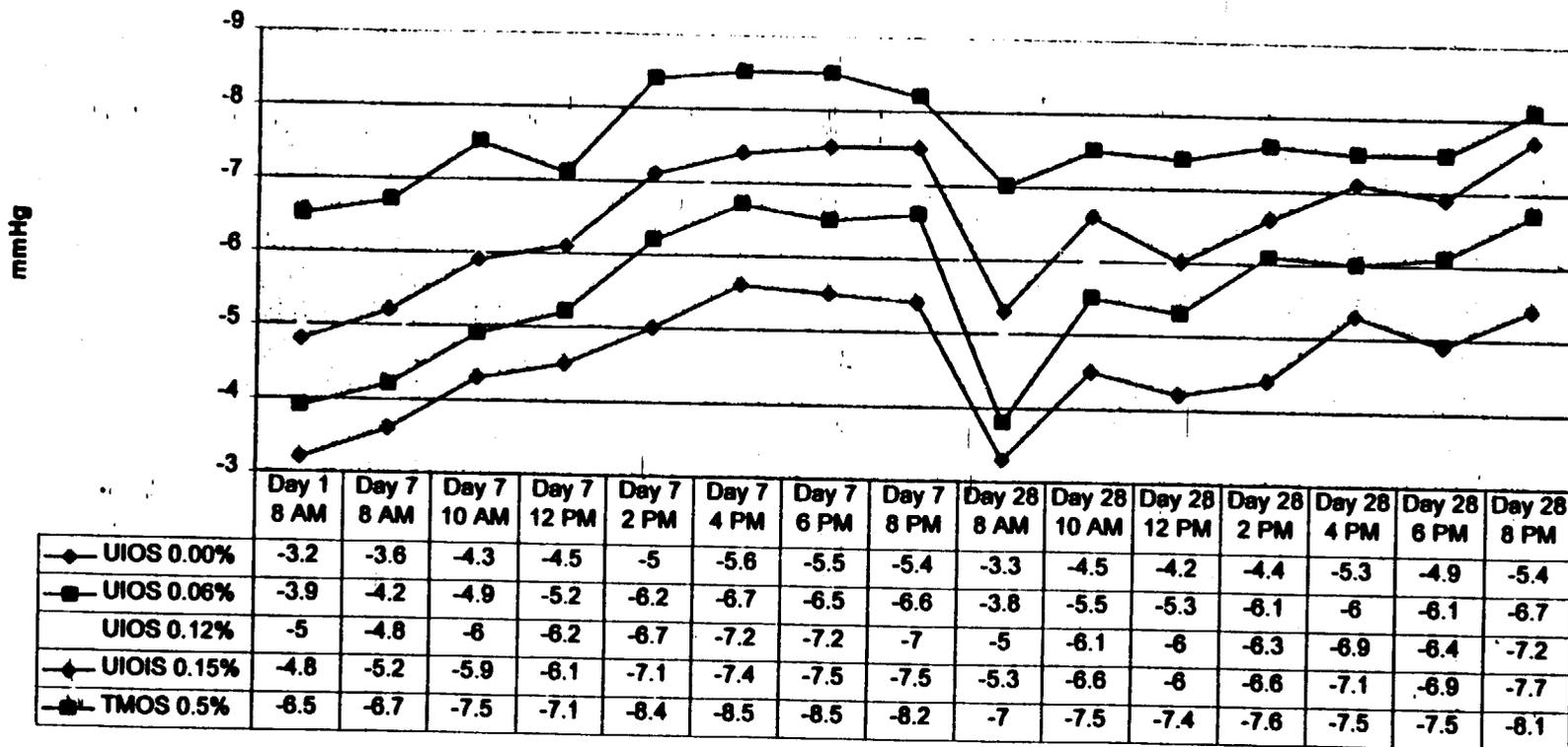
Primary Efficacy Variable

Mean IOP per Visit and Time



Reviewer's Comments: UIOS 0.15% was statistically significantly superior to vehicle placebo at each observation time and was the most effective UIOS concentration tested for reducing IOP. The baseline values in this study are highly questionable.

Change from Baseline IOP per Visit and Time



Reviewer's Comments: *The baseline values in this study are highly questionable. The study's only utility is in the comparison between UIOS treatment groups.*

8.1.3 Safety

Adverse Events

Serious adverse events other than death were reported for 0/190 (0%) subjects treated with UIOS at any concentration and for 1/47 (2.1%) subject treated with TMOS 0.5%.

Two serious adverse events were reported for Subject 706 (TMOS 0.5%) and led to his premature discontinuation from the study. During the evaluation of these adverse events, it was discovered that the subject had a history of illicit drug use and probably was using illicit drugs during study participation.

Table C97-UIOS-003-05- Serious Adverse Events

| Treatment | Investigator | Patient | AE Code | Final Outcome | D/C from Study |
|-----------|--------------|---------|--|--|----------------|
| TMOS | 148 | 706 | Atrial fibrillation Ventricular tachycardia | Lost to Follow-up Lost to Follow-up | Yes |

No deaths were reported during the study.

One subject receiving UIOS 0.12% (2.0%) discontinued from the study due to adverse events. One subject receiving TMOS 0.1.5% (2.1%) discontinued from the study due to adverse events (see above).

The most frequent ocular adverse events in subjects treated with UIOS 0.15% were burning and stinging upon instillation (28%), abnormal vision (9%), and foreign body sensation, itching, and keratitis (6% each).

The most frequent nonocular adverse event in subjects treated with UIOS 0.15% was headache (6%)

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Table C97-UIOS-003-06 – Summary of All Treatment Emergent Adverse Events Reported by Three or More Subjects in Any Treatment Group Regardless of Relationship to Study Treatment

| Body System/Preferred Term | Number (%) of Subjects | | | | |
|---|------------------------|----------------------|-------------------------|-------------------------|------------------------|
| | UIOS 0.0% (N=46) | UIOS 0.06% (N=48) | UIOS 0.12% (N=49) | UIOS 0.15% (N=47) | TMOS 0.5% (N=47) |
| <u>Body as a Whole</u> | | | | | |
| Headache | 4 (8.7%) | 5 (10.4%) | 4 (8.2%) | 3 (6.4%) | 4 (8.5%) |
| <u>Special Senses</u> | | | | | |
| Abnormal Vision | 3 (6.5%) | 3 (6.3%) | 3 (6.1%) | 4 (8.5%) | 3 (6.4%) |
| Blepharitis | 1 (2.2%) | 3 (6.3%) | 0 (0.0%) | 1 (2.1%) | 1 (2.1%) |
| Burning/stinging upon drug instillation | 5 (10.9%) | 8 (16.7%) | 18 (36.7%) | 13 (27.7%) | 6 (12.8%) |
| Eyelid disorder | 1 (2.2%) | 3 (6.3%) | 1 (2.0%) | 0 (0.0%) | 1 (2.1%) |
| Foreign body sensation | 0 (0.0%) | 1 (2.1%) | 1 (2.0%) | 3 (6.4%) | 0 (0.0%) |
| Injection | 3 (6.5%) | 2 (4.2%) | 4 (8.2%) | 2 (4.3%) | 3 (6.4%) |
| Irritation | 4 (8.7%) | 1 (2.1%) | 2 (4.1%) | 1 (2.1%) | 1 (2.1%) |
| Itching | 3 (6.5%) | 3 (6.3%) | 0 (0.0%) | 3 (6.4%) | 2 (4.3%) |
| Keratitis | 2 (4.3%) | 2 (4.2%) | 1 (2.0%) | 3 (6.4%) | 0 (0.0%) |

8.1.4 Reviewer's Summary of Efficacy and Safety

UIOS 0.15% was statistically significantly superior to vehicle placebo at each observation time and was the most effective UIOS concentration tested for reducing IOP.

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8.1.4 Study #4 Protocol C98-UIOS-012

Title: Effect of Unoprostone Isopropyl 0.15% Ophthalmic Solution, Timolol Maleate 0.5% Ophthalmic Solution, and Vehicle Placebo Ophthalmic Solution on Cardiovascular Function in Healthy Subjects

Test Drug Schedule: Subjects instilled single drop of study drug in each eye twice a day during the 5-day treatment period before each visit.

| Investigator Number | Investigator | Number Randomized |
|---------------------|--|-------------------|
| 116 | William C. Stewart, M.D. Charleston, South Carolina 29412 USA | 30 |

8.1.4 Study Design

This was a double-masked, single-center, active drug and placebo-controlled, three (3) treatment, three (3) period crossover design with randomized treatment sequences. Comparisons were to be made of the effects of mean change-from-baseline heart rate in healthy subjects treated with UIOS 0.15%, vehicle placebo, and TMOS 0.5%.

At baseline, a potential study participant was anyone who was able to successfully complete a modified Bruce treadmill test without: arrhythmias, ischemic ECG changes, marked blood pressure changes, excessive fatigue, chest pain, dyspnea or leg pain.

At Visit 1, all subjects were given a test drop of open label timolol 0.5% ophthalmic solution in each eye and observed for 15 minutes for untoward signs and symptoms to assure acceptable tolerance to β -blockers.

After completing screening/baseline examinations, subjects were randomized to one of six treatment sequences in a 3-treatment, 3-period crossover William's design.

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Table C98-UIOS-012-01 – Treatment Sequences

| Treatment Sequence | Treatment Period | | |
|--------------------|------------------|---------|---------|
| | 1 | 2 | 3 |
| 1 | Placebo | UIOS | TMOS |
| 2 | Placebo | TMOS | UIOS |
| 3 | UIOS | Placebo | TMOS |
| 4 | UIOS | TMOS | Placebo |
| 5 | TMOS | Placebo | UIOS |
| 6 | TMOS | UIOS | Placebo |

Approximately fifteen minutes after the final dose of the treatment period, each subject underwent a treadmill test (modified Bruce exercise protocol). Heart rate, measured continuously by an ECG machine, was recorded approximately every minute for a total of 15 minutes during the exercise testing period, and every 3 minutes for an additional 15 minutes during the recovery period.

Blood pressure was measured manually using a blood pressure cuff every 2 minutes during exercise testing and then every 3 minutes for an additional 15 minutes during the recovery period.

Study Medications

- Unoprostone Isopropyl, 0.15% ophthalmic solution, [REDACTED]
- Vehicle placebo ophthalmic solution, [REDACTED]
- Timolol maleate, 0.5% ophthalmic solution, [REDACTED]

A bulk supply of open label TMOS 0.5% ophthalmic solution was purchased and used by the site for the "test drop" at Visit 1. All other study medication was provided by the sponsor and was supplied in [REDACTED] polyethylene bottles [REDACTED]

Study Population – Inclusion and Exclusion Criteria

The following requirements had to be met in order for a subject to be enrolled into the study:

- able and willing to give written informed consent at screening
- willing to comply with the investigator's and protocol's instructions
- 18 to 45 years of age
- weight \leq 180 lbs (81.8 kg)
- not currently pregnant or lactating

- if female and of childbearing potential, agreed to use a reliable mechanical or hormonal form of contraception throughout the study
- considered by the investigator to be in good systemic health, particularly:
 - (a) did not have a history of cardiovascular, pulmonary or cerebrovascular disease
 - (b) did not have a history of systemic disease, especially hypertension or diabetes mellitus
 - (c) did not have an abnormally low or high heart rate or blood pressure, as defined by the following criteria (all measurements taken after 5-minutes of resting in a sitting position):
 - (d) heart rate ≤ 50 bpm or ≥ 100 bpm
 - (e) systolic blood pressure ≤ 70 or ≥ 140 mm Hg
 - (f) diastolic blood pressure ≤ 50 or ≥ 100 mm Hg
- before administration of any study medications, was able to successfully complete a modified Bruce treadmill test without arrhythmias, ischemic EKG changes, marked blood pressure changes, excessive fatigue, chest pain, dyspnea or leg pain developing
- considered by the investigator to be in good ocular health, particularly:
 - (a) did not have a history of glaucoma or any other chronic or progressive ocular disease or condition
 - (b) IOP ≤ 21 mm Hg
 - (c) did not have a clinical diagnosis of dry eye syndrome
 - (d) was not unocular, involving either a diagnosis of legal blindness in one eye or as having the use of only one eye secondary to previous trauma or congenital anomaly
- was not taking any medication, over-the-counter or prescribed by a physician, that in the opinion of the investigator would have had a clinically significant impact on study parameters (blood pressure, heart rate, etc.) OR that may have had a clinically significant impact on any major organ system, i.e., kidneys, liver, heart and lungs
- did not have a known hypersensitivity to α -adrenergic agonists, β -adrenergic blocking agents or any ingredient of any of the study medications or to any diagnostic agents to be used during the course of the study
- did not have psychological, medical, family, sociological or geographical conditions which would prohibit medical follow-up or compliance with study requirements
- had not had a problem with substance abuse (including alcohol) within the past two years
- had not received general anesthesia within the last 4 weeks
- had not received treatment with investigational medications or devices within the last 4 weeks
- had not been previously randomized for participation in this study.

CIBA Vision Corporation reserved the right to declare a subject ineligible or non-evaluable based on medical evidence indicating the subject would be unsuitable for the study.

Efficacy and Safety Variables

No efficacy data were collected in this study.

Safety variables, non-ocular and ocular, included:

- 1) heart rate, measured continuously by an ECG machine
- 2) blood pressure, measured manually using a blood pressure cuff
- 3) best-corrected ETDRS distance visual acuity,
- 4) slit-lamp biomicroscopy
- 5) dilated ophthalmoscopy.

Table C98-UIOS-012-02 – Schedule of Assessments

| Visit Number | 1 | | 2 | | 3 | | 4 |
|--|--------------------|--|------------------|--|------------------|--|------------------|
| Procedures | Screening Baseline | | Exercise Test #1 | | Exercise Test #2 | | Exercise Test #3 |
| Written Informed Consent | x | | | | | | |
| Inclusion/Exclusion Criteria Review | x | | | | | | |
| Demography and Past Medical and Ocular History | x | | | | | | |
| Coexistent Medical Conditions Query | x | | x | | x | | x |
| Coexistent Ocular Conditions Query | x | | x | | x | | x |
| Physical Exam | x | | | | | | |
| 12-lead ECG and Vital Signs | x | | x | | x | | x |
| IOP Check | x | | | | | | |
| Best-corrected ETDRS Visual Acuity | x | | x | | x | | x |
| Slit Lamp Biomicroscopy | x | | x | | x | | x |
| Dilated Ophthalmoscopy | x | | | | | | |
| Exercise Test | x | | x | | x | | x |
| Pregnancy Test | x | | | | | | |
| Medicine Dispensed | x | | x | | x | | x |
| Medicine Instilled | x | | x | | x | | x |
| Medicine Collected | | | x | | x | | x |
| Adverse Events | x | | x | | x | | x |
| Study Exit | | | | | | | x |

Subject Disposition and Demographics

Thirty-one subjects were screened, and all received the TMOS test drop at the screening visit. One subject was not randomized because the planned number of subjects had been enrolled.

From the 30 randomized subjects, post-treatment exercise data were available for 29 subjects with 1 being lost to follow-up. Twenty-seven subjects completed all 3 treatment periods. Two (2) subjects provided exercise data for only 1 treatment period (see below).

Table C98-UIOS-012-03 – Subject Disposition

| Disposition | Number of Subjects |
|--|--------------------|
| Screened | 31 |
| Received TMOS test drop | 31 |
| Randomized | 30 |
| Received masked study medication | 30* |
| Completed study | 27 |
| Analyzed for heart rate(Intent-to-Treat) | 29 |
| Analyzed for safety (Intent-to-Treat) | 29 |
| Evaluated after treatment with | |
| UIOS | 28 |
| TMOS | 28 |
| PL | 27 |

* Includes one subject lost to follow-up after Visit 1; use of study medication unknown; excluded from heart rate and safety population.

Table C97-UIOS-012-04 – Discontinued Patients and Reason

| Patient | Treatment Sequence | Reason |
|---------|--------------------|--------------------------------|
| 101 | P:U:T | Lost to Follow-up |
| 123 | T:U:P | Other – Prolonged P-R interval |
| 119 | U:T:P | Adverse Event – Blurred vision |

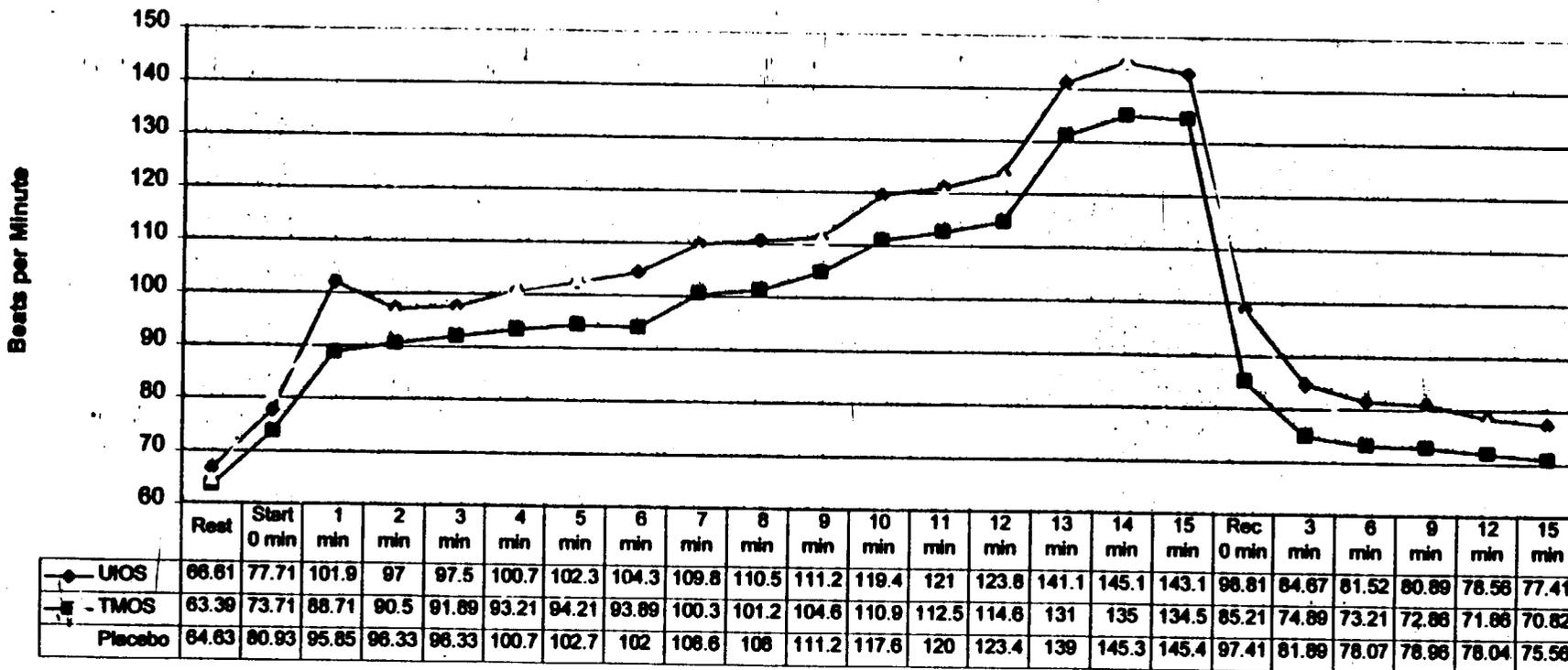
Table C97-UIOS-012-05 – Summary of Demographic Characteristics

| Characteristic | Total (N=30) |
|--|--------------|
| Gender | |
| % Female | 53% |
| % Male | 47% |
| Race | |
| % Caucasian | 87% |
| % Oriental | 10% |
| % Black | 3% |
| Age (Years) | |
| Mean (SD) | 24.1 (5.4) |
| Iris Color | |
| % Blue | 47% |
| % Brown | 37% |
| % Hazel | 17% |
| Response to Timoptic Test Drop at Visit 1 | |
| Heart Rate (beats per min): Mean (SD) | 65.3 (8.6) |
| Systolic Blood Pressure (mm Hg): Mean (SD) | 114.8 (8.6) |
| Diastolic Blood Pressure (mm Hg): Mean (SD) | 71.5 (5.7) |

8.1.4

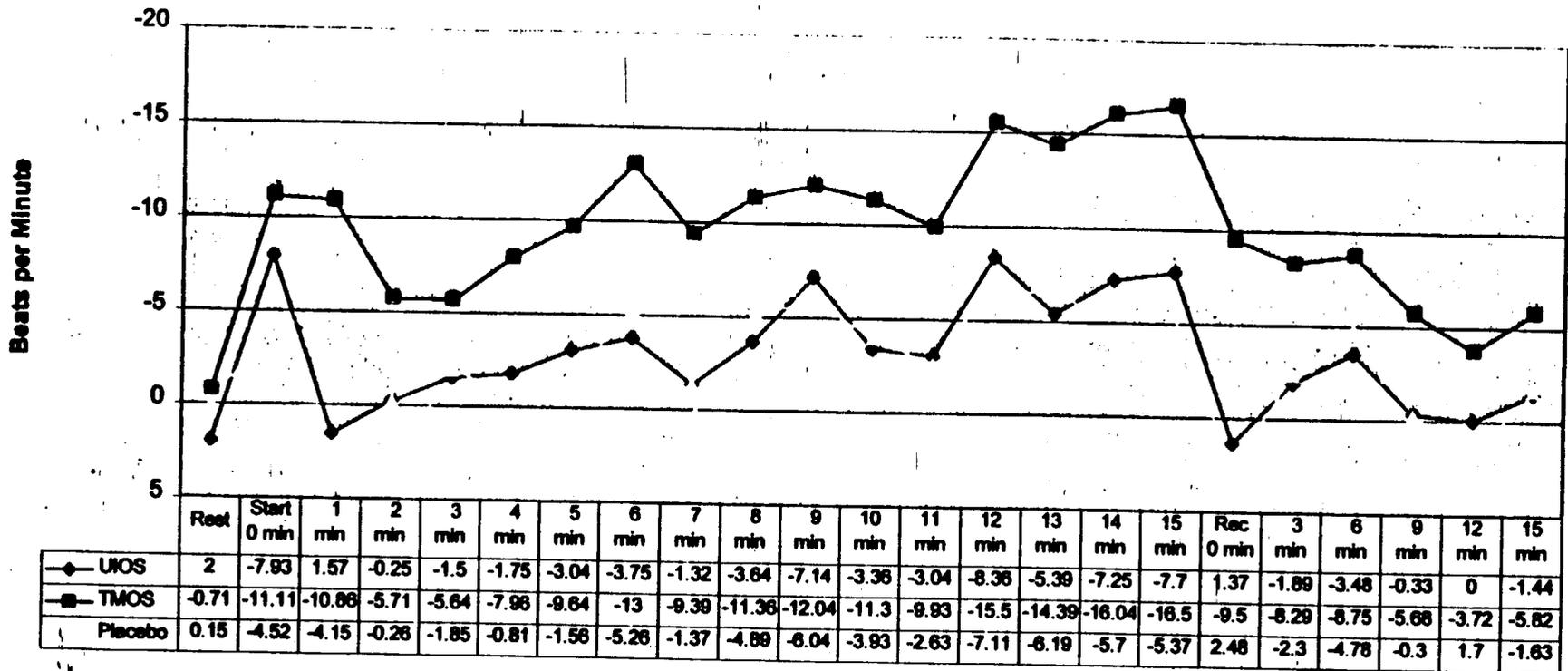
Safety – Protocol C98-UIOS-012

Heart Rate During Exercise and Recovery



Reviewer's Comments: Means shown above are the Pooled Means across all six treatment sequences. Screening (Baseline) Mean Heart Rate at Visit 1 was 64.2 bpm after five minutes rest. The mean heart rate for TMOS 0.5% subjects is lower than that of UIOS 0.15% subjects or Placebo subjects at Exercise Minutes 1-15 and at Recovery Minutes 0-15.

Heart Rate Change from Baseline During Exercise and Recovery



Reviewer's Comments: Change from Baseline was computed as the difference between time-matched values during exercise testing after drug treatment and during exercise testing at Screening Visit 1 (Day 0) before any study drug administration.

The Heart Rate Change from Baseline in TMOS 0.5% subjects was statistically significantly different than that of UIOS 0.15% subjects (i.e. Heart Rate was lower) at Exercise Minutes 1-15 and Recovery Minutes 0-15. Differences between Heart Rate Change from Baseline in UIOS 0.15% subjects and Placebo subjects were not statistically significantly different at any timepoint.

Blood Pressure

Drug treatment was not associated with a consistent or clinically meaningful effect on blood pressure.

At all timepoints, the mean change from baseline systolic blood pressure was not statistically significant, and at only one timepoint (Recovery 15 Minutes) was there as statistically significant change from baseline diastolic blood pressure occurring with TMOS 0.5% treatment ($P = 0.022$).

Adverse Events

There were no deaths or other serious adverse events reported. Only one subject (#119) was discontinued for an adverse event (blurred vision) after treatment with UIOS in Period 1 and after TMOS in Period 2.

The most frequent ocular adverse events in subjects treated with UIOS 0.15% were burning and stinging upon instillation (66%, $n=19$), dry eye (10%, $n=3$), and irritation (7%, $n=2$).

The non-ocular adverse events reported in subjects treated with UIOS 0.15% were gastrointestinal disorder, vaginitis, and pharyngitis (3% each, $n=1$ each).

8.1.4 Reviewer's Summary of Efficacy and Safety

Subjects treated with TMOS 0.5% demonstrated statistically significantly different Heart Rate Changes from Baseline (i.e. Heart Rate was lower) during exercise and recovery compared to subjects treated with UIOS 0.15%.

Drug treatment was not associated with a consistent or clinically meaningful effect on blood pressure.

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8.1.5 Study #5 Protocol C98-UIOS-013

Title: The Effect of a Single Dose of Topical Unoprostone Isopropyl 0.15% Ophthalmic Solution on Pulmonary Function in Subjects with Stable Mild-to-Moderate Asthma

Test Drug Schedule: Subjects received a single drop of UIOS 0.15% into each eye on the study day (Visit 2 and 3) that they were assigned to receive the test product.

| Investigator Number | Investigator | Number Randomized |
|---------------------|---|-------------------|
| 01 | Kulasiri A Gunawardena, M.D. Bucks, SL2 4 EG, United Kingdom | 17 |

8.1.5 Study Design

This was a prospective, randomized, double-masked, two-period cross-over, placebo-controlled comparison of UIOS 0.15% given as a single dose with a 3-day wash-out period between the 2 study days.

The study consisted of 3 visits: a screening visit (Visit 1), two study visits (Visits 2 & 3) separated by a wash-out period of 3 days, and a follow-up telephone call. Even though subjects were allowed to continue their usual therapy for reactive airway disease, they were requested to withhold their treatment of inhaled bronchodilators (6 hours for short-acting inhaled bronchodilators and at least 24 hours for long-acting bronchodilators) prior to the morning of their visits (Visit 1, 2, and 3).

The screening visit (Visit 1) was conducted within 4 weeks prior to Visit 2 to obtain subject's consent to participate in the study and to review the inclusion/exclusion criteria, medical history and demographics, vital signs (heart rate, blood pressure) and pulmonary functions, as well as pregnancy test, subjective pulmonary symptoms, and ocular signs and symptoms.

The first study day visit (Visit 2) was scheduled in the morning at 0900 ± 1.5 hours. Medical history and demographics, subjective pulmonary symptoms, and ocular signs and symptoms were re-checked, and the subjects had two baseline evaluations at -30 and -5 minutes. These evaluations included their clinical status, heart rate, brachial blood pressure and spirometry, i.e., Forced Expiratory Volume in one second (FEV₁), Forced Vital Capacity (FVC) and Peak Expiratory Flow Rate (PEFR). Once all the baseline evaluations were completed and the subject was considered eligible to be randomized, one drop of the study medication (either UIOS 0.15% or vehicle placebo) was instilled into each eye (0 minute).

Following the instillation of the eye drops, spirometry was performed over a 4-hour observation period at time-points 15, 30, 45, 60, 120, 180, and 240 minutes post-dose. Blood pressure and heart rate were recorded. Five minutes after the 240-measurement, the subject inhaled 2 puffs of [redacted] (albuterol sulfate) via a metered dose inhaler (MDI), and spirometry was repeated after 20 minutes to assess the bronchodilator response.

After the 4-hour observation period and after bronchodilation, any adverse events, subjective pulmonary symptoms, and ocular signs and symptoms that occurred during these time periods and afterwards were recorded. During the 4-hour examination period, if subjects experienced an acute distress of asthma symptoms or a fall in $FEV_1 \geq 20\%$ of that visit's baseline value, they were to be dosed immediately with inhaled [redacted] and were to be followed until they returned to baseline clinical status.

After a washout period of 3 days, subjects returned for Visit 3 at about the same time of the day as at Visit 2 (0900 \pm 1.5 hours). Baseline evaluations were performed again. Average baseline FEV_1 value within a subject was not to vary by more than 15% between Visit 2 and Visit 3. If the baseline average of the -30 and -5 minute measurements of FEV_1 was $< 45\%$ of the predicted value the subject was to be withdrawn from the study. Otherwise, the subjects were crossed over to receive the alternative medication (placebo or UIOS 0.15%) and the post-dosing assessments were done as on the first study day (Visit 2).

A follow-up telephone call was made 7 days (\pm 2 days) after Visit 3 to assess any adverse events which had occurred after the end of the second study day (Visit 3).

Reviewer's Comments:

The study design for this protocol is fundamentally flawed – this should be taken into consideration when interpreting its results.

The Sponsor did not deem the inclusion of a positive control treatment arm appropriate since the pulmonary effects of timolol maleate were well documented and were felt to represent an ethical concern.

Without the inclusion of a positive control arm, conclusions should not be made regarding the pulmonary effects of timolol maleate versus unoprostone isopropyl ophthalmic solutions based on this study.

Efficacy and Safety Variables

No efficacy data were collected in this study. The protocol defined primary safety endpoint was a 4-hour post-dose weighted mean FEV_1 . Additional safety endpoints were a 4-hour post-dose weighted means for $P_{\text{-FR}}$ and FVC, peak change in FEV_1 from baseline, maximum percentage change in FEV_1 compared with the pre-dose baseline, and the change in FEV_1 after bronchodilator [redacted] challenge.

Also recorded were blood pressure, heart rate, subjective pulmonary symptoms, changes in vital signs, and reported adverse events. Ocular safety variables were redness, burning/stinging of the eyes and other signs of ocular irritation.

Reviewer's Comments:

The agency did not agree with the assessment of a 4-hour post-dose weighted mean FEV₁ as the primary efficacy variable as stated in the protocol. The agency also did not agree with the assessment of 4-hour post-dose weighted mean FVC or PEVR as secondary efficacy variables.

The primary efficacy variable utilized in the review of this NDA was the assessment of mean FEV₁ at each individual time point.

Study Population

Subjects 18 to 70 years of age with:

- 1) a history of reversible airway obstruction with an increase in FEV₁ or PEFR at least 15% after inhaling a short-acting bronchodilator, documented within the last six months, and
- 2) mild-to-moderate airway obstruction, defined by an initial FEV₁ of at least 65% of the predicted value.

Subject Disposition and Demographics

Seventeen subjects were randomized, nine to Sequence 1 (UIOS 0.15% on Study Day 1 and vehicle placebo on Study Day 2), and eight to Sequence 2 (vehicle placebo on Study Day 1 and UIOS 0.15% on Study Day 2). One randomized subject in Sequence 2 (#110) could not come for the second study day and was withdrawn from the study. Sixteen subjects completed the study as per protocol.

Table C98-UIOS-013-01 – Subject Disposition

| Number of Subjects | Sequence 1* | Sequence 2* | Total |
|---|-------------|-------------|-------|
| • Screened | | | 19 |
| • Randomized (Intent-to-treat) | 9 | 8 | 17 |
| • Completed (Per protocol) | 9 | 7 | 16 |
| • Premature Discontinuation Protocol violation | | 1 | 1 |

*Sequence 1 = UIOS → placebo; Sequence 2 = placebo → UIOS

Demographic and baseline characteristics are summarized below.

Table C98-UIOS-013-02 – Demographic and Baseline Characteristics

| Variable | | Per protocol (n=16) | Intent-to-treat (n=17) |
|---------------------------|--------------|------------------------|---------------------------|
| Age (years) | mean (range) | 43 (21 – 61) | 44 (21 – 62) |
| Age group (years) | 18-29 | 4 | 4 |
| | 30-39 | 2 | 2 |
| | 40-49 | 4 | 4 |
| | 50-59 | 4 | 4 |
| | 60-70 | 2 | 3 |
| Gender | male | 10 | 10 |
| | female | 6 | 7 |
| Ethnic Origin | Caucasian | 100% | 100% |
| FEV ₁ (litres) | mean (SD) | 2.67 (0.58) | 2.62 (0.59) |
| PEFR (l/min) | mean (SD) | 396.56 (94.61) | 388.74 (97.12) |
| FVC (litres) | mean (SD) | 3.69 (1.00) | 3.64 (0.99) |

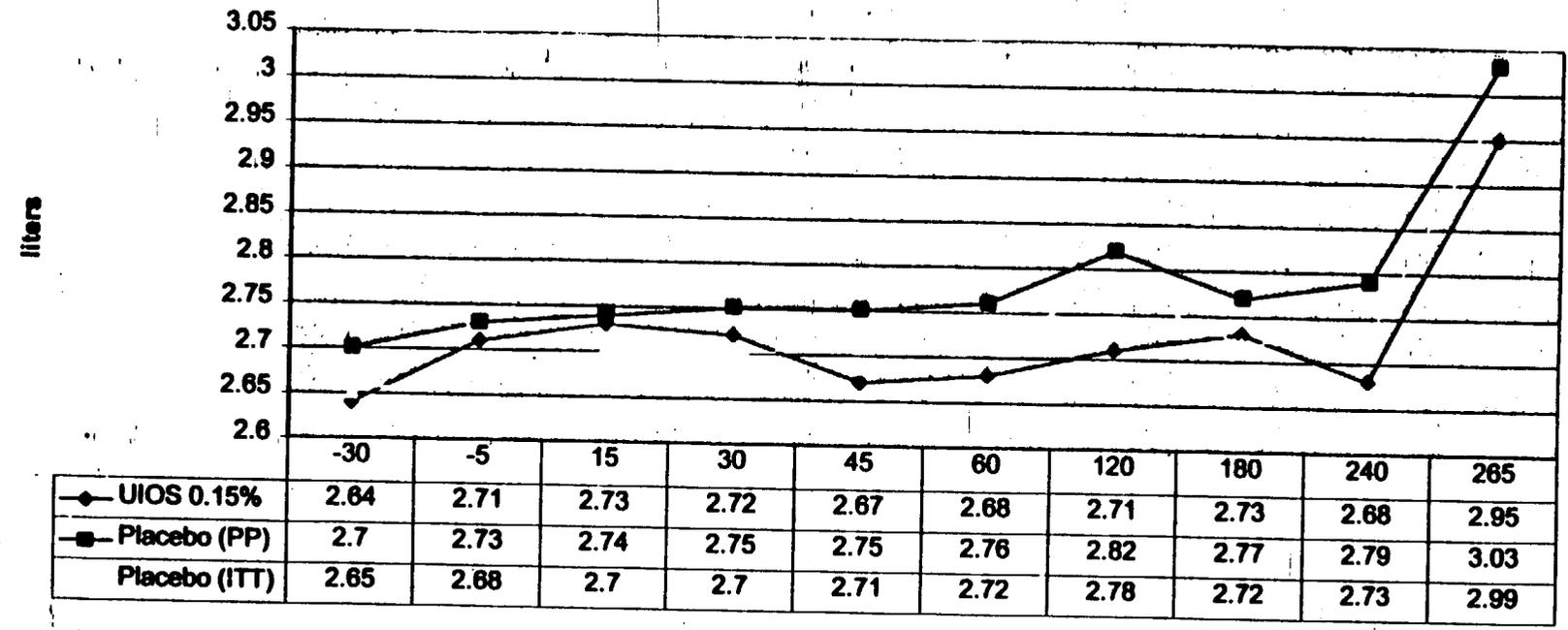
Reviewer's Comments:

There were no statistically significant differences in the treatment sequences for any demographic variable recorded.

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Safety – Protocol C98-UIOS-013

Mean FEV1 per Timepoint



Time = 0 minutes: Study Drug Administration Time = 240 minutes: Bronchodilator Administration

Reviewer's Comments: *UIOS 0.15% does not reduce the FEV₁ by more than 0.11 liters compared to Placebo (PP and ITT analyses) at any timepoint. 0.11 liters correspond to approximately 4% of the Baseline FEV₁.*

The differences found in mean FEV₁ between UIOS 0.15% and Placebo are not clinically relevant.

Other Pulmonary Function Variables

No other pulmonary function variables measured [Peak Expiratory Flow Rate (liters/min), Forced Vital Capacity (liters), Peak Change in FEV₁ vs. Baseline (liters), Maximum Change in FEV₁ vs. Baseline (%), and Change in FEV₁ after Bronchodilator Challenge (liters)] demonstrated clinically significant differences between treatment arms.

Vital Signs

There were no clinically significant differences in heart rate or systolic and diastolic blood pressures between treatment groups.

Adverse Events

There were no deaths and no significant adverse events other than death.

There were 5 treatment-emergent AE: 2 case of headaches, 1 case of each of exacerbation of asthma, tearing and rhinitis. Of the two subjects who reported headaches, one was treated with UIOS and one was treated with placebo. One subject reported an exacerbation of asthma the evening after treatment with placebo, but the subject required no corrective treatment. One subject experienced tearing from the left eye on the same day as he was treated with UIOS 0.15%. Tearing lasted under an hour. One subject experienced rhinitis after treatment with UIOS 0.15%.

8.1.5 Reviewer's Summary of Efficacy and Safety

The differences found in mean FEV₁ between UIOS 0.15% and Placebo were not clinically relevant. However, the study design for this protocol is fundamentally flawed – this should be taken into consideration when interpreting its results.

Without the inclusion of a positive control arm, conclusions should not be made regarding the pulmonary effects of timolol maleate versus unoprostone isopropyl ophthalmic solutions based on this study.

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8.1.6 Synopsis of Additional Submitted Studies

Protocol C97-UIOS-010

A Four-Week Comparison of the Efficacy and Safety of Unoprostone Isopropyl 0.15% Ophthalmic Solution (UIOS) BID versus Placebo BID versus Latanoprost 0.005% Ophthalmic Solution (LOS) QD in Adjunctive Therapy with Timolol Maleate 0.5% Ophthalmic Solution (TMOS) BID in Subjects diagnosed with Primary Open Angle Glaucoma or Ocular Hypertension

Reviewer's Comments:

An analysis of the change from baseline IOP at the morning (pre-dose), mid-morning (+2 hours), early (+6 hours) and late (+8 hours) afternoon assessments revealed that the difference between TMOS + UIOS and TMOS + placebo increased during the day in favor of TMOS + UIOS. This difference was statistically significant at each timepoint.

At all time points, the combination TMOS + LOS demonstrated statistically significantly lower IOPs than the combination TMOS + UIOS.

Protocol C97-UIOS-006

An Evaluation of the Effect of 0.15% Unoprostone Isopropyl Ophthalmic Solution on Ocular Hemodynamics in Patients with Primary Open-Angle Glaucoma

Reviewer's Comments:

The results of this study suggested that UIOS 0.15% provided a statistically significant decrease from baseline in mean morning IOP vs. placebo, but did not increase or decrease blood flow in retinal capillaries of subjects with primary open-angle glaucoma.

Protocol C97-UIOS-007

An Evaluation of Unoprostone Isopropyl 0.15% Ophthalmic Solution on Aqueous Humor Dynamics in Subjects Diagnosed with Ocular Hypertension

Reviewer's Comments:

The study results demonstrated a statistically significant mean IOP reduction from baseline (2 mmHg) in the UIOS treatment group.

However, there were no significant changes in any variable of aqueous humor dynamics for either treatment group. UIOS had no measurable impact on fluorophotometric outflow facility, uveoscleral outflow facility or tonographic outflow facility.

The applicant asserts that if a 2 mmHg mean drop in IOP (as observed in the UIOS-treated eyes of this study) was due solely to a decrease in aqueous humor flow, then an average decrease in flow of 0.44 μ L/min. should have also been observed. No such change in aqueous humor flow (inflow) was noted in this study.

It remains a possibility that some component of the decrease in IOP was due to a statistically undetectable change in aqueous humor flow. The applicant suggests that UIOS 0.15% lowers IOP by mechanisms other than a significant suppression of aqueous humor flow (inflow).

Periodic Safety Update Report on Rescula 0.12% (Japan)

Reviewer's Comments:

The report is obviously translated from the original Japanese and is difficult to follow in the English translation. It summarizes postmarketing safety surveys over a five-year period in a cohort of more than subjects.

Eight (8) cases of iris pigmentation and two (2) cases of eyelid pigmentation were reported. Iris color before Rescula administration was unknown in all ten (10) cases. Reporting was also concentrated at certain institutions with 7/10 reported cases submitted by a single physician.

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9 Overview of Efficacy

Twice-daily-dosed UIOS 0.15% does not demonstrate equivalence in the ability to lower IOP compared to twice-daily-dosed TMOS 0.5%. There is also greater variation in the IOP during the day with UIOS 0.15%.

Twice-daily-dosed UIOS 0.15% lowers intraocular pressure by approximately 3-4 mmHg.

10 Overview of Safety

Iris color and eyelash changes have been observed. The frequency of these changes cannot be accurately determined at this time.

The percentage of patients successfully completing the principle studies was lower in the UIOS 0.15% treatment group than in other treatment groups.

A single study (Protocol C97-UIOS-010) reporting the intraocular pressure lowering effect of UIOS 0.15% as adjunctive therapy with a β -blocker was available for review in this NDA submission. Although there were no safety findings that would suggest a significant hazard or undue risk associated with the adjunctive use of UIOS 0.15% with a β -blocker, a second study (C98-UIOS-011) of 12-weeks duration is not available for review in this submission.

10.2.1 ADR Incidence Tables for the Double-Masked Periods

Incidence of All Ocular and Non-Ocular Adverse Events ($\geq 1\%$)

| Ocular Adverse Events | Unoprostone Isopropyl | | | Timolol Maleate | | | P-value (Pooled Data) |
|--|-----------------------|---------------|-------------------|-----------------|---------------|-------------------|-----------------------------|
| | C4 (N=379) | C5 (N=278) | Pooled (N=657) | C4 (N=192) | C5 (N=138) | Pooled (N=330) | |
| Burning/Stinging | 25.3 | 18.3 | 22.4 | 14.6 | 12.3 | 13.6 | 0.001 |
| Burning/stinging upon drug instillation | 27.2 | 6.8 | 18.6 | 19.8 | 2.9 | 12.7 | 0.023 |
| Itching | 16.4 | 9.0 | 13.2 | 13.5 | 2.9 | 9.1 | 0.060 |
| Injection | 10.8 | 12.6 | 11.6 | 14.6 | 5.8 | 10.9 | 0.832 |
| Dry eyes | 16.1 | 3.2 | 10.7 | 12.0 | 0.7 | 7.3 | 0.107 |
| Foreign Body Sensation | 12.7 | 4.0 | 9.0 | 14.6 | 2.9 | 9.7 | 0.727 |
| Abnormal Vision | 10.6 | 5.0 | 8.2 | 10.4 | 7.2 | 9.1 | 0.631 |
| Lacrimation Disorder | 9.0 | 2.5 | 6.2 | 9.9 | 2.2 | 6.7 | 0.784 |
| Eyelid disorder | 4.7 | 7.2 | 5.8 | 4.2 | 5.1 | 4.5 | 0.458 |
| Photophobia | 5.5 | 3.6 | 4.7 | 4.2 | 2.9 | 3.6 | 0.510 |
| Conjunctivitis | 2.9 | 3.6 | 3.2 | 1.6 | 6.5 | 3.6 | 0.710 |
| Blepharitis | 2.1 | 3.2 | 2.6 | 1.6 | 0.7 | 1.2 | 0.241 |
| Cataract Specified | 2.6 | 2.2 | 2.4 | 3.1 | 1.4 | 2.4 | 1.000 |
| Corneal Lesion | 1.3 | 3.6 | 2.3 | 3.1 | 2.9 | 3.0 | 0.522 |
| Discharge | 3.2 | 1.1 | 2.3 | 2.6 | 0 | 1.5 | 0.483 |
| Keratitis | 3.4 | 0.4 | 2.1 | 2.1 | 0 | 1.2 | 0.450 |
| Irritation | 2.4 | 0.4 | 1.5 | 2.6 | 0 | 1.5 | 1.000 |
| Eye Pain | 2.4 | 0 | 1.4 | 1.6 | 2.2 | 1.8 | 0.589 |
| Vitreous Disorder | 1.3 | 1.4 | 1.4 | 1.0 | 0 | 0.6 | 0.353 |
| Eye Disorder | 1.3 | 1.1 | 1.2 | 1.6 | 1.4 | 1.5 | 0.769 |

| Non-Ocular Adverse Events | Unoprostone Isopropyl | | | Timolol Maleate | | | P-value (Pooled Data) |
|------------------------------|-----------------------|---------------|-------------------|-----------------|---------------|-------------------|-----------------------------|
| | C4 (N=379) | C5 (N=278) | Pooled (N=657) | C4 (N=192) | C5 (N=138) | Pooled (N=330) | |
| Flu syndrome | 7.1 | 4.0 | 5.8 | 5.2 | 4.3 | 4.8 | 0.657 |
| Headache | 4.5 | 4.7 | 4.6 | 5.7 | 5.8 | 5.8 | 0.439 |
| Rhinitis | 2.6 | 6.8 | 4.4 | 1.0 | 9.4 | 4.5 | 1.000 |
| Hypertension | 4.0 | 2.5 | 3.3 | 4.7 | 1.4 | 3.3 | 1.000 |
| Pharyngitis | 4.7 | 1.1 | 3.2 | 4.7 | 2.9 | 3.0 | 1.000 |
| Sinusitis | 4.0 | 0.4 | 2.4 | 7.3 | 0 | 4.2 | 0.121 |
| Pain | 3.2 | 1.4 | 2.4 | 2.6 | 0.7 | 1.8 | 0.651 |
| Dizziness | 1.6 | 1.8 | 1.7 | 1.6 | 2.9 | 2.1 | 0.620 |
| Accidental injury | 1.8 | 1.4 | 1.7 | 2.1 | 0.7 | 1.5 | 1.000 |
| Allergic reaction | 1.6 | 1.8 | 1.7 | 1.0 | 0 | 0.6 | 0.239 |
| Back pain | 1.6 | 1.4 | 1.5 | 2.1 | 0 | 1.2 | 0.784 |
| Rash | 1.8 | 0.7 | 1.4 | 1.0 | 1.4 | 1.2 | 1.000 |
| Bronchitis | 1.6 | 0.7 | 1.2 | 2.1 | 1.4 | 1.8 | 0.569 |
| Cough increased | 1.8 | 0.4 | 1.2 | 2.6 | 0.7 | 1.8 | 0.569 |
| Diabetes mellitus | 1.3 | 1.1 | 1.2 | 0.5 | 0 | 0.3 | 0.286 |
| Insomnia | 1.1 | 1.1 | 1.1 | 1.6 | 0.7 | 1.2 | 1.000 |

Statistical significance was determined using Fisher's exact test.

11 Labeling Review

Reviewer's Comments:

Recommended additions are shown by underlining: recommended deletions are shown by strikethrough lines.

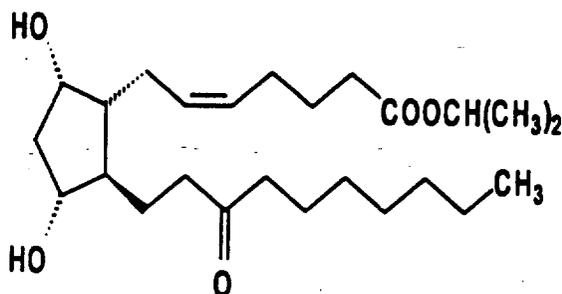
RESCULA®

Rx Only

(unoprostone isopropyl ophthalmic solution) 0.15%

DESCRIPTION

Unoprostone Isopropyl is [redacted] a docosanoid [redacted] analogue of an inactive biosynthetic cyclic derivative of arachidonic acid, 13, 14-dihydro-15-keto-prostaglandin F_{2α}. Its chemical name is [redacted] isopropyl (+)-(Z)-7-[(1R, 2R, 3R, 5S)-3,5-dihydroxy-2-(3-oxodecyl) cyclopentyl] -5-heptenoate. Its molecular formula is C₂₅H₄₄O₅ and its chemical structure is:



MW 424.62

Unoprostone isopropyl is a clear, colorless viscous liquid [redacted] 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 [redacted] 5.0 - 6.5, and an osmolality of 235 - 300 mOsmol/kg.

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

CLINICAL PHARMACOLOGY

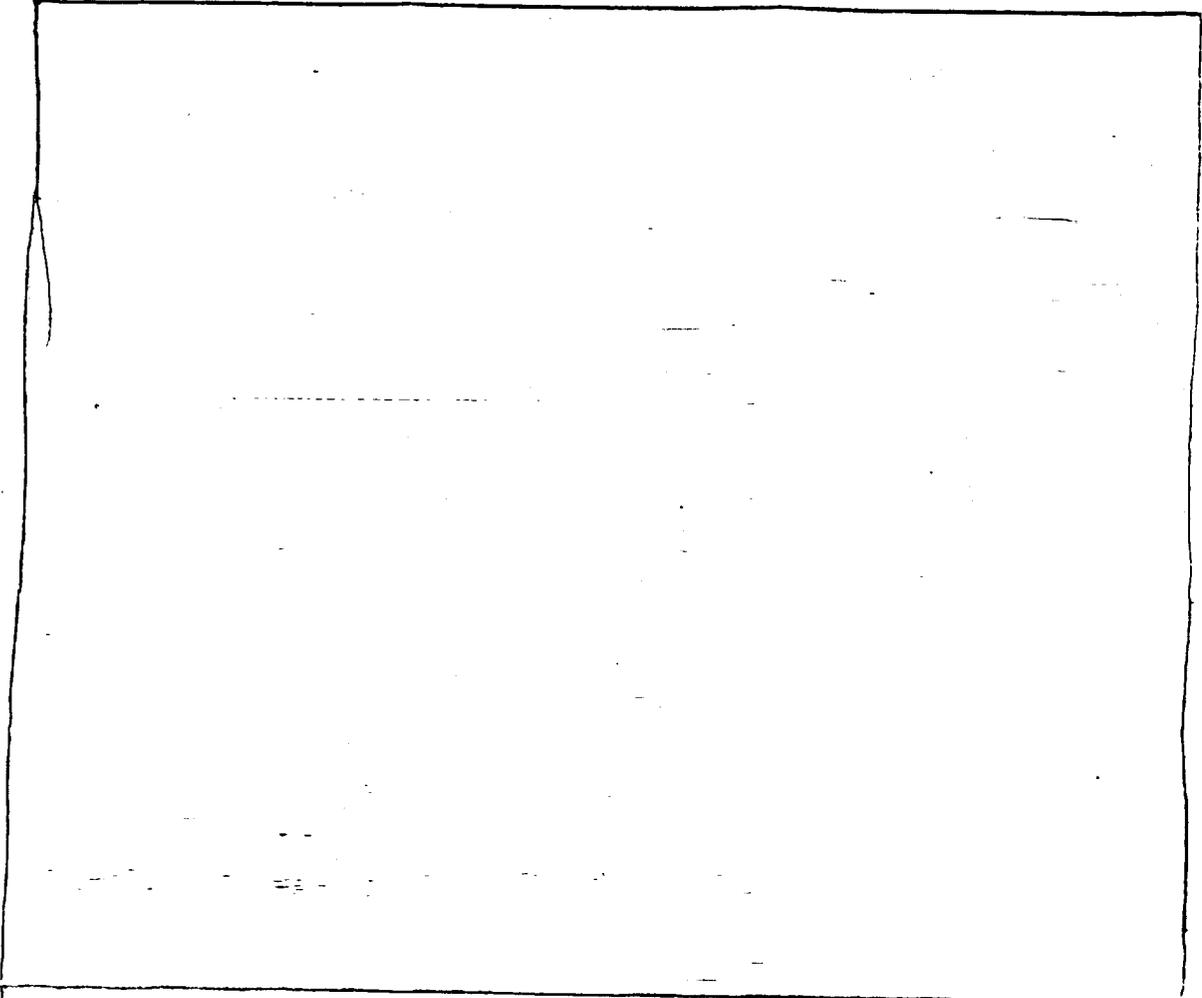
Mechanism of Action

When instilled in the eye, RESCULA® is believed to reduce elevated intraocular pressure (IOP), by increasing the outflow of aqueous humor, but the exact mechanism is unknown at this time.

Pharmacokinetics / Pharmacodynamics:

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.

Elimination: Elimination of unoprostone free acid from human plasma is rapid, with a half-life of 14 minutes. Plasma levels [redacted] hours following ocular instillation. The metabolites are excreted predominantly in urine.

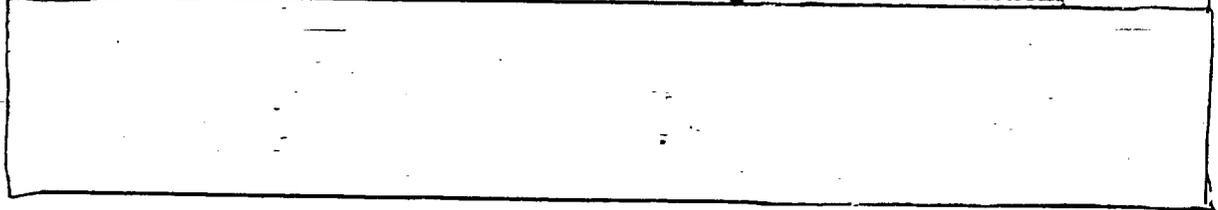


Clinical Studies

[redacted] Clinical studies showed that in patients with mean baseline IOP of 23 mm Hg, RESCULA[®] lowers intraocular pressure by approximately 3- 4 mm Hg.



[redacted] RESCULA[®]
lowers intraocular pressure without affecting cardiovascular function. [redacted]



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 who are intolerant of other intraocular pressure lowering medications or insufficiently responsive (failed to achieve target IOP determined after multiple measurements over time) to another intraocular pressure lowering medication.

CONTRAINDICATIONS

Known hypersensitivity to unoprostone isopropyl, benzalkonium chloride or any other ingredients in this product.

WARNINGS

Rescula has been reported to cause changes to pigmented tissue. These changes may be permanent.

Rescula may gradually change eye color, increasing the amount of brown pigment in the iris. The long-term effects and the consequences of potential injury to the eye are currently unknown. The change in iris color occurs slowly and may not be noticeable for months to several years. Patients should be informed of the possibility of iris color change.

PRECAUTIONS

General: There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface (see Information for Patients).

RESCULA[®] should be used with caution in patients with active intraocular inflammation (e.g., uveitis).

RESCULA[®] has not been evaluated for the treatment of angle closure, inflammatory or neovascular glaucoma [REDACTED]

RESCULA[®] has not been studied in patients with renal or hepatic impairment and should [REDACTED] be used with caution in such patients.

RESCULA[®] should not be administered while wearing contact lenses.

Patients should also be advised that RESCULA[®] contains benzalkonium chloride which may be adsorbed by contact lenses. Contact lenses should be removed prior to administration of the solution. Lenses may be reinserted 15 minutes following administration of RESCULA[®].

Information for Patients: Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures because this could cause the tip to become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

Patients should also be advised that if they develop an intercurrent ocular condition (e.g., trauma or infection) or have ocular surgery, they should immediately seek their physician's advice concerning the continued use of the multidose container.

Patients should be advised that if they develop any ocular reactions, particularly conjunctivitis and eyelid reactions, they should immediately seek their physician's advice.

If more than one topical ophthalmic drug is being used the drugs should be administered at least five minutes apart.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Rescula® 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 AUC₀₋₂₄ 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).

Pregnancy: Teratogenic Effects: Pregnancy Category C.

There were no teratogenic effects observed in rats and rabbits up to 5 and 0.3 mg/kg/day (approximately 1000 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 2.0 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 ≥ 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 [redacted] no adequate and [redacted] well-controlled studies in pregnant women. Because animal studies are not always predictive of human response, [redacted] RESCULA should be used during pregnancy only if [redacted] the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Unoprostone isopropyl has been identified in breast milk in rats following intravenous administration. It is not known whether topical ocular administration could result in sufficient systemic absorption to produce detectable quantities in breast milk. Nevertheless, caution should be exercised when RESCULA® is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

In [redacted] clinical studies, the most common ocular adverse events, [redacted] were burning/stinging, burning/stinging upon drug instillation, dry eyes, itching, and injection; [redacted] These were reported in approximately 10-25% of patients. [redacted]

Ocular adverse events occurring in approximately 5% to 910% of patients were [redacted] abnormal vision, eyelid disorder, foreign body sensation, and lacrimation disorder. [redacted]

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

Other ocular adverse events 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, iris hyperpigmentation, iritis, optic atrophy, ptosis, retinal hemorrhage, and visual field defect [redacted]

The most frequently reported nonocular adverse event associated with the use of Rescula in the clinical trials was flu syndrome that was observed in approximately 6% of patients.

Nonocular adverse events reported in the 1% to 5% of patients were accidental injury, allergic reaction, back pain, bronchitis, cough increased, diabetes mellitus, dizziness, headache, hypertension, insomnia, pharyngitis, pain, rhinitis, and sinusitis.

OVERDOSAGE

There [redacted] is no published information available regarding overdose with -RESCULA 0.15% [redacted]. The risk of adverse effects due to accidental oral ingestion is very low since the amount of active ingredient in each bottle is [redacted] limited (7.5 mg in a 5 mL vial). Accidental ingestion of a vial by a child with 30 kg body weight will amount to 0.25 mg/kg body weight. [redacted]

If overdose does occur, treatment should be symptomatic.

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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 minutes apart.

HOW SUPPLIED

RESCULA® (unoprostone isopropyl ophthalmic solution) 0.15% is a clear, isotonic, buffered, preserved colorless solution of unoprostone isopropyl 0.15% (1.5 mg/mL). RESCULA® 0.15% is supplied as 5 mL solution in a 7.5 mL polypropylene bottles with a natural polypropylene dropper tip and a

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

NDC 58768-691-05

Made in Canada by CIBA Vision Sterile Manufacturing for:
CIBA Vision®, A Novartis Company
Duluth, GA 30097

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ON ORIGINAL

Conclusions

Rescula (unoprostone isopropyl ophthalmic solution) 0.15% lowers intraocular pressure to a small degree (3-4 mmHg in patients with baseline IOP \geq 22 mm Hg). The amount of IOP reduction is significantly less than that observed with timolol maleate 0.5%.

The potential benefit outweighs the potential risks in this application only if safety information and efficacy information are properly labeled. Indications and usage in the labeling should specify the use of unoprostone isopropyl ophthalmic solution 0.15% as second line therapy for the reduction of intraocular pressure.

A significant change in iris color may signal the ability of the unoprostone isopropyl to increase the number of melanosomes (pigment granules) in melanocytes. The long-term effects on the melanocytes and the consequences of potential injury to the melanocytes and/or disposition of pigment granules to other areas of the eye are currently unknown.

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MAY 1991

13 Recommendations

- 1) *Following resolution of any chemistry/manufacturing issues and labeling issues, NDA 21-214 is recommended for approval for lowering intraocular pressure in patients with chronic open-angle glaucoma or ocular hypertension who are intolerant of other IOP-lowering medications or insufficiently responsive to another IOP-lowering medication.*
- 2) *The applicant should submit revised labeling consistent with the recommendations in this review.*
- 3) *The applicant should also propose a post-marketing plan to adequately address concerns raised by the report of increased iris pigmentation and the potential for changes in eyelash length and density over time.*

/S/

William M. Boyd, M.D. 
Medical Officer

NDA 21-214
HFD-550/Div Files
HFD-550/MO/Boyd
HFD-550/Dep Director/Chambers
HFD-550/Div Dir/Midthun
HFD-880/Biopharm/Tandon
HFD-725/Biostats/Li
HFD-550/Chem/Fenselau
HFD-550/PharmTox/Wilson
HFD-550/PM/Rodriguez
HFD-340/Carreras

/S/7/6/6

**Medical Officer's Review of NDA 21-214
120-Day Safety Update**

NDA 21-214
Medical Officer's Review

Submission: 6/16/00
Review Completed: 6/23/00

Proposed Tradename: Rescula

Generic Name: unoprostone isopropyl ophthalmic solution 0.15%

Sponsor: CIBA Vision
11460 Johns Creek Parkway
Duluth, GA 30097

Pharmacologic Category: prostaglandin analogue
(docosanoid analogue of a PGF_{2α} metabolite)

Proposed Indication: Lowering of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension

Dosage Form and Route of Administration: Ophthalmic solution for topical ocular administration

Submitted: Pooled 120-Day Safety Information for Protocols C97-UIOS-004 and C97-UIOS-005

Reviewer's Comments and Conclusions:

No trends emerged from the pooling of data from the second six months of treatment in Studies -004 and -005.

After 12 months of dosing in 659 subjects (Studies -004 and -005), only one case of iris color change has been documented photographically, giving a one-year incidence of 0.12%. This case was documented in a Safety Supplement in the original NDA submission.

There were three AEs reported for increased eyelash length. Two were confirmed by image analysis. One subject (#2104) was treated with UIOS and had increases of 20-75%. The other subject (#2408) was treated with betaxolol and had lower eyelash lengthening of about 20%. Subject #2104 is currently the only confirmed case of increase in eyelash length after UIOS treatment.

Two subjects reported increased eyelash density as AEs, and one was confirmed by image analysis. This subject (#2709) was treated with TMOS and density of the lower lid increased about 20%.

One death, previously unreported, occurred during the second six months of therapy. Subject #1614 (Study -005) was a 63-year-old male who died from cranioencephalic trauma.

A comparison of the 12-month AE incidences show an incremental increased incidence in most AE categories for both UIOS 0.15% and TMOS 0.5%. The overall safety profile remains similar to data from the original NDA submission. See Tables 1 and 2.

Table 1 – Incidence of All Ocular Adverse Events (≥ 1%)

| Ocular Adverse Events | Unoprostone Isopropyl | | Timolol Maleate | | P-value |
|---|-----------------------|---------------------|--------------------|---------------------|---------|
| | 6 Month (N=657) | 12 Month (N=659) | 6 Month (N=330) | 12 Month (N=331) | |
| Burning/Stinging | 22.4 | 24.9 | 13.6 | 17.2 | .006 |
| Burning/stinging upon drug instillation | 18.6 | 18.8 | 12.7 | 12.7 | .014 |
| Itching | 13.2 | 15.5 | 9.1 | 14.2 | .638 |
| Injection | 11.6 | 14.1 | 10.9 | 12.7 | .558 |
| Dry eyes | 10.7 | 12.6 | 7.3 | 9.4 | .141 |
| Abnormal Vision | 8.2 | 12.3 | 9.1 | 11.2 | .678 |
| Foreign Body Sensation | 9.0 | 11.5 | 9.7 | 11.2 | .916 |
| Lacrimation Disorder | 6.2 | 8.8 | 6.7 | 9.4 | .814 |
| Eyelid disorder | 5.8 | 8.0 | 4.5 | 7.9 | 1.00 |
| Photophobia | 4.7 | 5.8 | 3.6 | 4.2 | .366 |
| Cataract Specified | 2.4 | 5.6 | 2.4 | 4.8 | .656 |
| Conjunctivitis | 3.2 | 4.1 | 3.6 | 5.4 | .336 |
| Blepharitis | 2.6 | 3.3 | 1.2 | 2.1 | .324 |
| Corneal Lesion | 2.3 | 3.3 | 3.0 | 3.9 | .716 |
| Discharge | 2.3 | 3.0 | 1.5 | 1.8 | .299 |
| Keratitis | 2.1 | 3.0 | 1.2 | 1.5 | .198 |
| Visual field defect | 0.9 | 2.4 | 0.6 | 1.5 | .484 |
| Vitreous Disorder | 1.4 | 2.3 | 0.6 | 1.2 | .329 |
| Eye Pain | 1.4 | 2.1 | 1.8 | 2.4 | .820 |
| Irritation | 1.5 | 1.5 | 1.5 | 1.8 | .791 |
| Eye hemorrhage | 0.9 | 1.5 | 1.8 | 1.8 | .791 |
| Retinal disorder | 0.5 | 1.4 | 0.6 | 1.5 | 1.00 |
| Eye Disorder | 1.2 | 1.2 | 1.5 | 1.8 | .569 |
| Optic atrophy | 0.2 | 1.2 | 0.3 | 1.8 | .569 |

P-value compares 12-month data for UIOS to TMOS. Statistical significance determined using Fisher's exact test.

Table 2 – Incidence of All Non-Ocular Adverse Events (≥ 1%)

| Non-Ocular Adverse Events | Unoprostone Isopropyl | | Timolol Maleate | | P-value |
|---------------------------|-----------------------|----------|-----------------|----------|---------|
| | 6 Month | 12 Month | 6 Month | 12 Month | |
| | (N=657) | (N=659) | (N=330) | (N=331) | |
| Flu syndrome | 5.8 | 7.9 | 4.8 | 6.6 | .524 |
| Hypertension | 3.3 | 6.2 | 3.3 | 6.0 | 1.00 |
| Headache | 4.6 | 5.3 | 5.8 | 6.6 | .389 |
| Rhinitis | 4.4 | 4.9 | 4.5 | 5.7 | .546 |
| Pharyngitis | 3.2 | 4.4 | 3.0 | 4.8 | .749 |
| Pain | 2.4 | 3.3 | 1.8 | 2.4 | .556 |
| Sinusitis | 2.4 | 2.9 | 4.2 | 4.8 | .144 |
| Back pain | 1.5 | 2.6 | 1.2 | 2.1 | .827 |
| Hypercholesteremia | 0.9 | 2.4 | 1.8 | 3.3 | .414 |
| Accidental Injury | 1.7 | 2.4 | 1.5 | 3.3 | .414 |
| Rash | 1.4 | 2.0 | 1.2 | 1.8 | 1.00 |
| Allergic reaction | 1.7 | 2.0 | 0.6 | 0.9 | .288 |
| Dizziness | 1.7 | 1.8 | 2.1 | 3.0 | .255 |
| Bronchitis | 1.2 | 1.7 | 1.8 | 2.1 | .621 |
| Diabetes mellitus | 1.2 | 1.7 | 0.3 | 0.3 | .071 |
| Cough increased | 1.2 | 1.4 | 1.8 | 2.1 | .426 |
| Arthritis | 0.6 | 1.4 | 0.9 | 1.2 | 1.00 |
| Urinary tract infection | 0.9 | 1.4 | 0.3 | 0.3 | .178 |
| Abdominal pain | 0.9 | 1.1 | 0.6 | 1.2 | 1.00 |
| Insomnia | 1.1 | 1.1 | 1.2 | 1.2 | 1.00 |
| Infection | 0.5 | 1.1 | 0.0 | 0.9 | 1.00 |

P-value compares 12-month data for UIOS to TMOS. Statistical significance determined using Fisher's exact test.

There are no clinically significant differences in the treatment groups at Month 12 for the ocular safety measurements: visual acuity, manifest refraction, dilated ophthalmoscopy, slit lamp biomicroscopy, specular microscopy, or visual fields.

Clinical lab testing was again performed on 150 subjects in Study-004 (U.S.) for chemistry and hematology parameters. There were no clinically significant differences found between the treatment groups.

There were no statistically or clinically significant changes from baseline for any vital sign variable for the UIOS 0.15% treatment group any visit for both studies.

- 1) *Information contained in this safety update is comparable to previous safety information reviewed for the original NDA.*
- 2) *Original conclusions regarding the safety of unoprostone isopropyl ophthalmic solution 0.15% for the lowering of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension are not altered.*

/S/

William M. Boyd, M.D.
Medical Officer

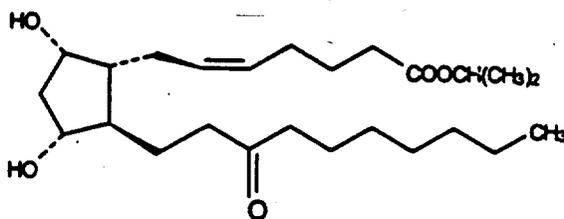
NDA 21-214
HFD-550/Div Files
HFD-550/MO/Boyd
HFD-550/Dep Director/Chambers /S/1/7/00
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HFD-880/Biopharm/Tandon
HFD-725/Biostats/Li
HFD-550/Chem/Fenselau
HFD-550/PharmTox/Wilson
HFD-550/PM/Rodriguez
HFD-340/Carreras

Medical Officer's Review of NDA 21-214

NDA 21-214
Medical Officer's Review #2

Submission: 7/25/00
Review Completed: 7/25/00

Proposed Tradename: Rescula
Generic Name: unoprostone isopropyl ophthalmic solution 0.15%
Chemical Name:



Rescula C₂₅H₄₄O₅

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

Sponsor: CIBA Vision
11460 Johns Creek Parkway
Duluth, GA 30097

Pharmacologic Category: prostaglandin analogue
(docosanoid analogue of a PGF_{2α} metabolite)

Proposed Indication: Lowering of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension

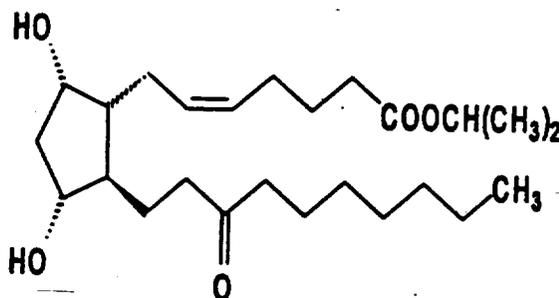
Submitted: Revised labeling based on previous review and discussion with the sponsor.

RESCULA®
(unoprostone isopropyl ophthalmic solution) 0.15%

Rx Only

DESCRIPTION

Unoprostone Isopropyl is a docosanoid, a structural analogue of an inactive biosynthetic cyclic derivative of arachidonic acid, 13, 14-dihydro-15-keto-prostaglandin F_{2α}. Its chemical name is isopropyl (+)-(Z)-7-[(1R, 2R, 3R, 5S)-3,5-dihydroxy-2-(3-oxodecyl)cyclopentyl]-5-heptenoate. Its molecular formula is C₂₃H₄₄O₅ and its chemical structure is:



MW 424.62

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.

CLINICAL PHARMACOLOGY

Mechanism of Action

When instilled in the eye, RESCULA® is believed to reduce elevated intraocular pressure (IOP), by increasing the outflow of aqueous humor, but the exact mechanism is unknown at this time.

Pharmacokinetics / Pharmacodynamics:

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.

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.

Clinical Studies

Clinical studies showed that in patients with mean baseline IOP of 23 mm Hg, RESCULA[®] lowers intraocular pressure by approximately 3-4 mm Hg throughout the day. RESCULA[®] appears to lower intraocular pressure without affecting cardiovascular or pulmonary function.

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 who are intolerant of other intraocular pressure lowering medications or insufficiently responsive (failed to achieve target IOP determined after multiple measurements over time) to another intraocular pressure lowering medication.

CONTRAINDICATIONS

Known hypersensitivity to unoprostone isopropyl, benzalkonium chloride or any other ingredients in this product.

WARNINGS

Rescula has been reported to cause changes to pigmented tissue. These changes may be permanent.

Rescula may gradually change eye color, increasing the amount of brown pigment in the iris. The long-term effects and the consequences of potential injury to the eye are currently unknown. The change in iris color occurs slowly and may not be noticeable for months to several years. Patients should be informed of the possibility of iris color change.

PRECAUTIONS

General: There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface (see Information for Patients).

RESCULA® should be used with caution in patients with active intraocular inflammation (e.g., uveitis).

RESCULA® has not been evaluated for the treatment of angle closure, inflammatory or neovascular glaucoma.

RESCULA® has not been studied in patients with renal or hepatic impairment and should be used with caution in such patients.

RESCULA® should not be administered while wearing contact lenses.

Patients should also be advised that RESCULA® contains benzalkonium chloride which may be adsorbed by contact lenses. Contact lenses should be removed prior to administration of the solution. Lenses may be reinserted 15 minutes following administration of RESCULA®.

Information for Patients: Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures because this could cause the tip to become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

Patients should also be advised that if they develop an intercurrent ocular condition (e.g., trauma or infection) or have ocular surgery, they should immediately seek their physician's advice concerning the continued use of the multidose container.

Patients should be advised that if they develop any ocular reactions, particularly conjunctivitis and eyelid reactions, they should immediately seek their physician's advice.

If more than one topical ophthalmic drug is being used the drugs should be administered at least five minutes apart.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Rescula® 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 AUC₀₋₂₄ 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).

Pregnancy: Teratogenic Effects: Pregnancy Category C.

There were no teratogenic effects observed in rats and rabbits up to 5 and 0.3 mg/kg/day (approximately 1000 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 2.0 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 ≥ 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.

Nursing Mothers: Unoprostone isopropyl has been identified in breast milk in rats following intravenous administration. It is not known whether topical ocular administration could result in sufficient systemic absorption to produce detectable quantities in breast milk. Nevertheless, caution should be exercised when RESCULA[®] is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

In clinical studies, the most common ocular adverse events 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 events occurring in approximately 5% to 10% of patients were abnormal vision, eyelid disorder, foreign body sensation, and lacrimation disorder.

Ocular adverse events occurring in approximately 1% to 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 events 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 event associated with the use of Rescula in the clinical trials was flu syndrome that was observed in approximately 6% of patients. Nonocular adverse events reported in the 1% to 5% of patients were accidental injury, allergic reaction, back pain, bronchitis, cough increased, diabetes mellitus, dizziness, headache, hypertension, insomnia, pharyngitis, pain, rhinitis, and sinusitis.

OVERDOSAGE

There is no published information available regarding overdose with RESCULA 0.15%. The risk of adverse effects due to accidental oral ingestion is very low since the amount of active ingredient in each bottle is limited (7.5 mg in a 5 mL vial). Accidental ingestion of a vial by a child with 30 kg body weight will amount to 0.25 mg/kg body weight.

If overdose does occur, treatment should be symptomatic.

ANIMAL TOXICOLOGY

In cynomolgus monkeys administered Rescula for twelve months at 150 µg/eye/day (equal to the human dose), one of ten animals exhibited increased pigmentation of the iris. The incidence did not change when the administered dose was increased to 300 µg/eye/day (twice the human dose) for an additional six months.

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 minutes apart.

HOW SUPPLIED

RESCULA® (unoprostone isopropyl ophthalmic solution) 0.15% is a clear, isotonic, buffered, preserved colorless solution of unoprostone isopropyl 0.15% (1.5 mg/mL). RESCULA® 0.15% is supplied as 5 mL solution in a 7.5 mL natural polypropylene bottle with a natural polypropylene dropper tip, a turquoise polypropylene closure and a clear tamper-evident shrinkband.

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

NDC 58768-961-05

Made in Canada by CIBA Vision Sterile Manufacturing for:
CIBA Vision®, A Novartis Company
Duluth, GA 30097

APPEARS THIS WAY
ON ORIGINAL

Recommendations:

NDA 21-214, Rescula (unoprostone isopropyl ophthalmic solution) 0.15%, is recommended for approval for lowering intraocular pressure in patients with chronic open-angle glaucoma or ocular hypertension who are intolerant of other IOP-lowering medications or insufficiently responsive to another IOP-lowering medication.

/S/

William M. Boyd, M.D.
Medical Officer

NDA 21-214

HFD-550/Div Files

HFD-550/MO/Boyd

HFD-550/Dep Director/Chambers /S/ 7/24/00

HFD-550/Div Dir/Midthun

HFD-880/Biopharm/Tandon

HFD-725/Biostats/Li

HFD-550/Chem/Fenselau

HFD-550/PharmTox/Wilson

HFD-550/PM/Rodriguez

HFD-340/Carreras

Medical Officer's Review #2

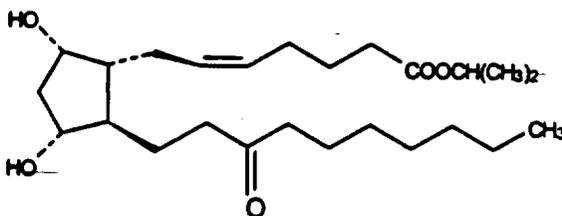
NDA 21-214 Rescula (unoprostone isopropyl ophthalmic solution) 0.15%

Medical Officer's Review of NDA 21-214

NDA 21-214
Medical Officer's Review #3

Submission: 7/27/00
Review Completed: 7/27/00

Proposed Tradename: Rescula
Generic Name: unoprostone isopropyl ophthalmic solution 0.15%
Chemical Name:



Rescula C₂₅H₄₄O₃

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

Sponsor: CIBA Vision
11460 Johns Creek Parkway
Duluth, GA 30097

Pharmacologic Category: prostaglandin analogue
(docosanoid analogue of a PGF_{2α} metabolite)

Proposed Indication: Lowering of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension

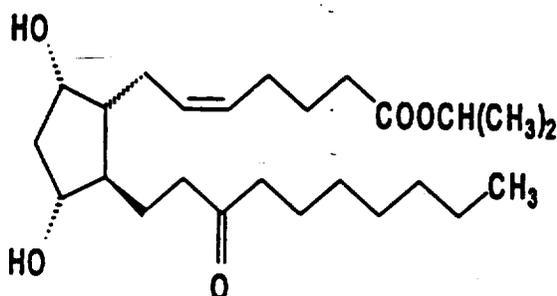
Submitted: Revised labeling based on previous review and discussion with the sponsor.

RESCULA[®]
(unoprostone isopropyl ophthalmic solution) 0.15%

Rx Only

DESCRIPTION

Unoprostone Isopropyl is a docosanoid, a structural analogue of an inactive biosynthetic cyclic derivative of arachidonic acid, 13, 14-dihydro-15-keto-prostaglandin F_{2α}. Its chemical name is isopropyl (+)-(Z)-7-[(1R, 2R, 3R, 5S)-3,5-dihydroxy-2-(3-oxodecyl)cyclopentyl]-5-heptenoate. Its molecular formula is C₂₅H₄₄O₅ and its chemical structure is:



MW 424.62

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.

CLINICAL PHARMACOLOGY

Mechanism of Action

When instilled in the eye, RESCULA[®] is believed to reduce elevated intraocular pressure (IOP), by increasing the outflow of aqueous humor, but the exact mechanism is unknown at this time.

Pharmacokinetics / Pharmacodynamics:

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.

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.

Clinical Studies

Clinical studies showed that in patients with mean baseline IOP of 23 mm Hg, RESCULA® lowers intraocular pressure by approximately 3-4 mm Hg throughout the day. RESCULA® appears to lower intraocular pressure without affecting cardiovascular or pulmonary function.

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 who are intolerant of other intraocular pressure lowering medications or insufficiently responsive (failed to achieve target IOP determined after multiple measurements over time) to another intraocular pressure lowering medication.

CONTRAINDICATIONS

Known hypersensitivity to unoprostone isopropyl, benzalkonium chloride or any other ingredients in this product.

WARNINGS

Rescula has been reported to cause changes to pigmented tissue. These changes may be permanent.

Rescula may gradually change eye color, increasing the amount of brown pigment in the iris. The long-term effects and the consequences of potential injury to the eye are currently unknown. The change in iris color occurs slowly and may not be noticeable for months to several years. Patients should be informed of the possibility of iris color change.

PRECAUTIONS

General: There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface (see Information for Patients).

RESCULA® should be used with caution in patients with active intraocular inflammation (e.g., uveitis).

RESCULA® has not been evaluated for the treatment of angle closure, inflammatory or neovascular glaucoma.

RESCULA® has not been studied in patients with renal or hepatic impairment and should be used with caution in such patients.

RESCULA® should not be administered while wearing contact lenses.

Patients should also be advised that RESCULA® contains benzalkonium chloride which may be adsorbed by contact lenses. Contact lenses should be removed prior to administration of the solution. Lenses may be reinserted 15 minutes following administration of RESCULA®.

Information for Patients: Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures because this could cause the tip to become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

Patients should also be advised that if they develop an intercurrent ocular condition (e.g., trauma or infection) or have ocular surgery, they should immediately seek their physician's advice concerning the continued use of the multidose container.

Patients should be advised that if they develop any ocular reactions, particularly conjunctivitis and eyelid reactions, they should immediately seek their physician's advice.

If more than one topical ophthalmic drug is being used the drugs should be administered at least five minutes apart.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Rescula® 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 AUC₀₋₂₄ 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).

Pregnancy: Teratogenic Effects: Pregnancy Category C.

There were no teratogenic effects observed in rats and rabbits up to 5 and 0.3 mg/kg/day (approximately 1000 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 2.0 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 ≥ 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.

Nursing Mothers: Unoprostone isopropyl has been identified in breast milk in rats following intravenous administration. It is not known whether topical ocular administration could result in sufficient systemic absorption to produce detectable quantities in breast milk. Nevertheless, caution should be exercised when RESCULA[®] is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

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

ADVERSE REACTIONS

In clinical studies, the most common ocular adverse events 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 events occurring in approximately 5% to 10% of patients were abnormal vision, eyelid disorder, foreign body sensation, and lacrimation disorder.

Ocular adverse events occurring in approximately 1% to 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 events 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 event associated with the use of Rescula in the clinical trials was flu syndrome that was observed in approximately 6% of patients. Nonocular adverse events reported in the 1% to 5% of patients were accidental injury, allergic reaction, back pain, bronchitis, cough increased, diabetes mellitus, dizziness, headache, hypertension, insomnia, pharyngitis, pain, rhinitis, and sinusitis.

OVERDOSAGE

There is no published information available regarding overdosage with RESCULA 0.15%. The risk of adverse effects due to accidental oral ingestion is very low since the amount of active ingredient in each bottle is limited (7.5 mg in a 5 mL vial). Accidental ingestion of a vial by a child with 30 kg body weight will amount to 0.25 mg/kg body weight.

If overdosage does occur, treatment should be symptomatic.

ANIMAL TOXICOLOGY

In cynomolgus monkeys administered Rescula for twelve months at 150 µg/eye/day (equal to the human dose), one of ten animals exhibited increased pigmentation of the iris. The incidence did not change when the administered dose was increased to 300 µg/eye/day (twice the human dose) for an additional six months.

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 minutes apart.

HOW SUPPLIED

RESCULA® (unoprostone isopropyl ophthalmic solution) 0.15% is a clear, isotonic, buffered, preserved colorless solution of unoprostone isopropyl 0.15% (1.5 mg/mL). RESCULA® 0.15% is supplied as 5 mL solution in a 7.5 mL natural polypropylene bottle with a natural polypropylene dropper tip, a turquoise polypropylene closure and a clear tamper-evident shrinkband.

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

NDC 58768-961-05

**Made in Canada by CIBA Vision Sterile Manufacturing for:
CIBA Vision®, A Novartis Company
Duluth, GA 30097**

**APPEARS THIS WAY
ON ORIGINAL**

Recommendations:

NDA 21-214, Rescula (unoprostone isopropyl ophthalmic solution) 0.15%, is recommended for approval for lowering intraocular pressure in patients with chronic open-angle glaucoma or ocular hypertension who are intolerant of other IOP-lowering medications or insufficiently responsive to another IOP-lowering medication.

/S/

William M. Boyd, M.D.
Medical Officer

NDA 21-214
HFD-550/Div Files
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/S/ 7/27/00