**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**

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**FULL PRESCRIBING INFORMATION: CONTENTS***

**1 INDICATIONS AND USAGE**
**2 DOSAGE AND ADMINISTRATION**
**3 DOSAGE FORMS AND STRENGTHS**
**4 CONTRAINDICATIONS**
**5 WARNINGS AND PRECAUTIONS**
5.1 Iris Pigmentation
5.2 Lid Pigmentation
5.3 Intraocular Inflammation
5.4 Macular Edema
5.5 Contamination of Tip and Solution
5.6 Use with Contact Lenses
**6 ADVERSE REACTIONS**
6.1 Clinical Studies Experience
6.2 Postmarketing Experience
**8 USE IN SPECIFIC POPULATIONS**
8.1 Pregnancy
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
**11 DESCRIPTION**
**12 CLINICAL PHARMACOLOGY**
12.1 Mechanism of Action
12.3 Pharmacokinetics
**13 NONCLINICAL TOXICOLOGY**
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
**14 CLINICAL STUDIES**
**16 HOW SUPPLIED/STORAGE AND HANDLING**
**17 PATIENT COUNSELING INFORMATION**
17.1 Handling the Bottle
17.2 Potential for Iris Darkening
17.3 Potential for Eyelid Skin Darkening
17.4 Use with Contact Lenses
17.5 Multiple Therapies

*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.

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### 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,

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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.

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### 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

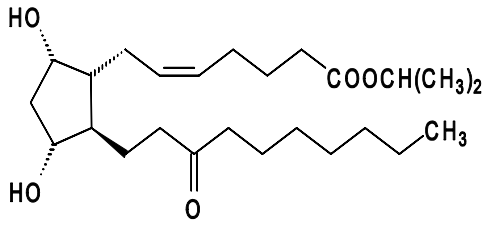
Safety and effectiveness in pediatric patients have not been established.

### 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.

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