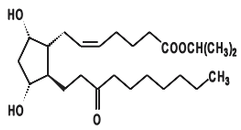
RESCULA®
(unoprostone isopropyl ophthalmic solution) 0.15%

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_{2a}. Its chemical name is 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:



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 absorbed 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.

(over)

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 AUC_{0-24} in male and female rats, respectively).

Under the conditions tested, unoprostone isopropyl and unoprostone free acid were neither mutagenic in an Ames assay nor clastogenic in a chromosome aberration assay in Chinese hamster lung-derived fibroblast cells. Under the conditions tested, unoprostone isopropyl was not genotoxic in a mouse lymphoma mutation assay or clastogenic in an *in vivo* chromosomal aberration test in mouse bone marrow.

Unoprostone isopropyl did not impair male or female fertility in rats at subcutaneous doses up to 50 mg/kg (approximately 10,000 fold the recommended human dose of 0.005 mg/kg/day).

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 for the 5 mL and 3.5 mg for the 2.5 mL filled product). Accidental ingestion of a bottle by a child will amount to 0.25 mg/kg in a child with a 30 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 2.5mL and 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).

Rx Only

NDC 58768-961-05 (5 mL)
NDC 58768-961-02 (2.5 mL)

Made in Canada by CIBA Vision Sterile Manufacturing for:
Novartis Ophthalmics, Duluth, GA 30097

NOVARTIS

I6084-C

May, 2001

NVO PART NO. I 6084-C

Approved	**Date**	**By**
Regulatory Affairs		
Packaging		
Marketing		
QA		