For the use of an Ophthalmologist or a Hospital or a Laboratory only.

Bimatoprost Ophthalmic Solution

Careprost®

PESPI0030

Composition:

Each ml contains:

Bimatoprost	0.3 mg
Benzalkonium Chloride Solution IP (As Preservative)	0.01% w/v
Aqueous Buffered Vehicle	q.s.

Clinical Pharmacology:

Bimatoprost is a prostamide, a synthetic structural analog of prostaglandin $F_{2\text{-alpha}}$ ($PGF_{2\text{-alpha}}$) with ocular hypotensive activity.

Mechanism of Action

Bimatoprost selectively mimics the effects of naturally occurring substances, prostamides. Bimatoprost is believed to lower intraocular pressure (IOP) in humans by increasing outflow of aqueous humor through both the trabecular meshwork and uveoscleral routes. Elevated IOP presents a major risk factor for glaucomatous field loss. The higher the level of IOP, the greater the likelihood of optic nerve damage and visual field loss.

Pharmacokinetics

Bimatoprost penetrates the human cornea and sclera well *in vitro*. After once daily ocular administration of one drop of 0.03% bimatoprost to both eyes for two weeks, blood concentrations peaked within 10 minutes after dosing and declined to below the lower limit of detection (0.025 ng/ml) within 1.5 hours after dosing. Mean C_{max} and $AUC_{0\text{-}24hr}$ values were similar on days 7 and 14 at approximately 0.08 ng/mL and 0.09 ng•hr/mL, respectively, indicating that steady state was reached during the first week of ocular dosing. After ocular administration, the systemic exposure of bimatoprost is very low with no accumulation over time.

Bimatoprost is moderately distributed into body tissues and the systemic volume of distribution in humans at steady state was 0.67 l/kg. In human blood, bimatoprost resides mainly in the plasma. The plasma protein binding of bimatoprost is approximately 88%. Approximately 12% of bimatoprost remains unbound in human plasma.

Bimatoprost is the major circulating species in the blood once it reaches the systemic circulation following ocular dosing. Bimatoprost then undergoes oxidation, N-deethylation and glucuronidation to form a diverse variety of metabolites.

Following an intravenous dose of radiolabeled bimatoprost (3.12 mcg/kg) to healthy subjects, the maximum blood concentration of unchanged drug was 12.2 ng/mL and decreased rapidly with an elimination half life of approximately 45 minutes. The total blood clearance of bimatoprost was 1.5 L/hr/kg. Bimatoprost is eliminated primarily by renal excretion; up to 67% of an intravenous dose was excreted in the urine while 25% of the dose was excreted via the feces.

Indications:

Careprost® is indicated for the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension.

Contra-indications:

Hypersensitivity to bimatoprost or any other ingredient of the formulation.

Warnings and Precautions:

FOR EXTERNAL USE ONLY. NOT FOR INJECTION.

Bimatoprost ophthalmic solution has been reported to cause changes to pigmented tissues. These reports include increased pigmentation and growth of eyelashes and increased pigmentation of the iris and periorbital tissue (eyelid). These changes may be permanent.

Bimatoprost may gradually change eye color, increasing the amount of brown pigment in the iris by increasing 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 deposition of pigment granules to other areas of the eye are currently unknown. The change in iris color occurs slowly and may not be noticeable for several months to years. Patients should be informed of the possibility of iris color change.

Bimatoprost ophthalmic solution contains the preservative benzalkonium chloride, which may be absorbed by soft contact lenses. Contact lenses should be removed prior to instillation and may be reinserted 15 minutes following administration.

Benzalkonium chloride, which is commonly used as a preservative in ophthalmic products, has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy. Since bimatoprost ophthalmic solution contains benzalkonium chloride, monitoring is required with frequent or prolonged use in dry eye patients or where the cornea is compromised.

Eyelid skin darkening has also been reported in association with the use of bimatoprost. Bimatoprost may gradually change eyelashes; these changes include increased length, thickness, pigmentation, and number of lashes.

Patients who are expected to receive treatment in only one eye should be informed about the potential for increased brown pigmentation of the iris, periorbital tissue, and eyelashes in the treated eye and thus, heterochromia between the eyes. They should also be advised of the potential for a disparity between the eyes in length, thickness, and/or number of eyelashes.

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.

Patients may slowly develop increased brown pigmentation of the iris. This change may not be noticeable for several months to years. Typically the brown pigmentation around the pupil is expected to spread concentrically towards the periphery in affected eyes, but the entire iris or parts of it may also become more brownish. Until more information about increased brown pigmentation is available, patients should be examined regularly and, depending on the clinical situation, treatment may be stopped if increased pigmentation ensues. The increase in brown iris pigment is not expected to progress further upon discontinuation of treatment, but the resultant color change may be permanent. Neither nevi nor freckles of the iris are expected to be affected by treatment.

Bimatoprost should be used with caution in patients with active intraocular inflammation (e.g., uveitis). Macular edema, including cystoid macular edema, has been reported during treatment with bimatoprost ophthalmic solution. Bimatoprost 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.

Bimatoprost has not been studied in patients with compromised respiratory function and should therefore be used with caution in

such patients. In clinical studies, in those patients with a history of a compromised respiratory function, no significant untoward respiratory effects have been seen. Bimatoprost has not been studied in patients with heart block more severe than first degree or uncontrolled congestive heart failure.
Bimatoprost has not been studied in patients with inflammatory ocular conditions, neovascular, inflammatory, angle-closure glaucoma, congenital glaucoma or narrow-angle glaucoma.
If irritation occurs, the use of this formulation should be discontinued.
Bimatoprost is not expected to affect the ability to drive and use machines. As with any ocular treatment, if transient blurred vision occurs at instillation, the patient should wait until the vision clears before driving or using machinery.

Pregnancy & Lactation
There are no adequate and well controlled studies of bimatoprost administration in pregnant women.
Because animal reproductive studies are not always predictive of human response, bimatoprost should be administered during pregnancy only if the potential benefit justifies the potential risk to the fetus.
It is not known whether bimatoprost is excreted in human milk, although in animal studies, bimatoprost has been shown to be excreted in breast milk. Because many drugs are excreted in human milk, caution should be exercised when bimatoprost is administered to a nursing woman.

Drug Interactions:
No interactions are anticipated in humans, since systemic concentrations of bimatoprost are extremely low (less than 0.2 ng/ml) following ocular dosing. Bimatoprost is biotransformed by any of multiple enzymes and pathways, and no effects on hepatic drug metabolising enzymes were observed in preclinical studies. Therefore, specific interaction studies with other medicinal products have not been performed with bimatoprost.
In clinical studies, bimatoprost was used concomitantly with a number of different ophthalmic beta-blocking agents without evidence of interactions. Concomitant use of bimatoprost and antiglaucomatous agents other than topical beta-blockers has not been evaluated during adjunctive glaucoma therapy.

Side effects:
The most commonly reported adverse effects with bimatoprost ophthalmic solution were conjunctival hyperemia, growth of eyelashes, ocular pruritus, ocular dryness, visual disturbance, worsening of visual acuity, ocular burning, foreign body sensation, eye pain, pigmentation of the periocular skin, blepharitis, cataract, superficial punctate keratitis, eyelid erythema, eyelid pruritus, ocular irritation, eyelash darkening, eye discharge, tearing, photophobia, allergic conjunctivitis, asthenopia, increases in iris pigmentation, conjunctival edema, corneal erosion, iritis, cystoid macular edema, eyelid retraction, retinal hemorrhage, and uveitis.
Systemic adverse events reported with bimatoprost were infections (primarily colds and upper respiratory tract infections), headache, abnormal liver function tests, hypertension, dizziness, peripheral edema, asthenia, and hirsutism.

Overdosage:
No information is available on overdosage in humans. If overdose with bimatoprost ophthalmic solution occurs, treatment should be symptomatic and supportive. In oral (by gavage) mouse and rat studies, doses up to 100 mg/kg/day did not produce any toxicity. This dose expressed as mg/m^2 is at least 70 times higher than the accidental dose of one bottle of bimatoprost for a 10 kg child.

Dosage and Administration:
The recommended dosage is one drop in the affected eye(s) once daily in the evening. The dosage of bimatoprost ophthalmic solution should not exceed once daily since it has been shown that more frequent administration may decrease the intraocular pressure lowering effect.
Reduction of the intraocular pressure starts approximately 4 hours after the first administration with maximum effect reached within approximately 8 to 12 hours.
Bimatoprost may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic drug is being used, the drugs should be administered at least 5 minutes apart.
The dropper tip should not be allowed to touch any surface since this may contaminate the solution.
Pediatric use: Bimatoprost has only been studied in adults and therefore its use is not recommended in children or adolescents.
Hepatic and Renal impairment: Bimatoprost has not been studied in patients with renal or moderate to severe hepatic impairment and should therefore be used with caution in such patients. In patients with a history of mild liver disease or abnormal ALT, AST and/or bilirubin at baseline, bimatoprost had no adverse effect on liver function over 24 months.

Storage:
Store at temperature not exceeding 25°C. Do not freeze. The solution should be used within one month after opening the container.

Presentation:
Careprost® is available as 3 ml in plastic bottles.

® Registered Trade Mark

For further details, please write to:

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