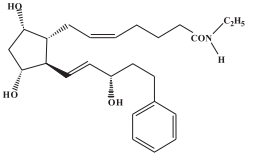
BAUSCH+LOMB

Imatoflo™
(Bimatoprost Ophthalmic Solution 0.03% w/v)

GENERIC NAME
Bimatoprost 0.03% w/v

DOSAGE FORM
Ophthalmic solution

DESCRIPTION
Bimatoprost Ophthalmic Solution is a synthetic prostamide analog with ocular hypotensive activity. Its chemical name is (Z)-7-[(1R,2R,3R,5S)-3,5-Dihydroxy-2-[(1E,3S)-3-hydroxy-5-phenyl-1-pentenyl]cyclopentyl]-5-N-ethylheptenamide, and its molecular weight is 415.58. Its molecular formula is C25H37NO4. Its chemical structure is:



Bimatoprost is a powder, which is very soluble in ethyl alcohol and methyl alcohol and slightly soluble in water. Bimatoprost Ophthalmic Solution is a clear, isotonic, colorless, sterile ophthalmic solution with an osmolality of approximately 290 mOsmol/kg.

COMPOSITION
Active: Bimatoprost 0.03% w/v
Inactive Ingredients: Sodium chloride, Disodium hydrogen phosphate, Heptahydrate, Citric acid, Monohydrate, Sodium hydroxide, hydrochloride acid
Preservative Added: Benzalkonium chloride solution 0.02% v/v

INDICATIONS
Imatoflo™ (Bimatoprost Ophthalmic Solution 0.03% w/v) is indicated for the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension.

DOSAGE AND ADMINISTRATION
The recommended dosage is one drop in the affected eye(s) once daily in the evening. Each drop of Imatoflo™ (Bimatoprost Ophthalmic Solution 0.03% w/v) provides 30 micro liters of drug volume. Imatoflo™ should not be administered more than once daily since it has been shown that more frequent administration of prostaglandin analogs 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.

USE IN SPECIAL POPULATIONS
Pregnancy:
Teratogenic Effects: Pregnancy Category C. In embryo/foetal developmental studies in pregnant mice and rats, abortion has been reported at oral doses of bimatoprost which achieved at least 33 or 97 times respectively, the maximum intended human exposure based on blood AUC levels. There are no adequate and well-controlled studies of Bimatoprost Ophthalmic Solution administration in pregnant women. Because animal reproductive studies are not always predictive of human response therefore this drug should be administered during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Non-Teratogenic Effects
No adequate studies have been reported on non-teratogenic effects of Bimatoprost Ophthalmic Solution

Nursing Mothers
It is not known whether Bimatoprost Ophthalmic Solution is excreted in human milk, although in animal studies, bimatoprost has been shown to be excreted in breast milk. Many drugs are excreted in human milk therefore caution should be exercised when Bimatoprost Ophthalmic Solution is administered to a nursing woman.

Pediatric Use
Use in paediatric patients below the age of 16 years is not recommended because of potential safety concerns related to increased pigmentation following long-term chronic use.

Geriatric Use
No overall clinical differences in safety or effectiveness have been observed between patients 65 years of age and older compared to younger adult patients.

Hepatic Impairment
In patients with a history of liver disease or abnormal ALT, AST and/or bilirubin at baseline, Bimatoprost Ophthalmic Solution had no adverse effect on liver function over 48 months.

CONTRAINDICATIONS
Bimatoprost ophthalmic solution is contraindicated in patients with known hypersensitivity to any ingredient in the formulation.

WARNINGS AND PRECAUTIONS

FOR EXTERNAL USE ONLY. NOT FOR INJECTION

Pigmentation
Bimatoprost Ophthalmic Solution has been reported to cause changes to pigmented tissues. The most frequently reported changes were increased pigmentation of the iris, periorbital tissue (eyelid) and eyelashes. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. After discontinuation of Bimatoprost Ophthalmic Solution, pigmentation of the iris is likely to be permanent, while pigmentation of the periorbital tissue and eyelash changes have been reported to be reversible in some patients. The long term effects of increased pigmentation are not known. Iris color change 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. While treatment with Bimatoprost Ophthalmic Solution can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly. (see INFORMATION FOR PATIENT).

Eyelash Changes
Bimatoprost Ophthalmic Solution may gradually change eyelashes and vellus hair in the treated eye. These changes include increased length, thickness, and number of lashes. Eyelash changes are usually reversible upon discontinuation of treatment.

Intraocular Inflammation
Bimatoprost Ophthalmic Solution is advised to be used with caution in patients with active intraocular inflammation (e.g., uveitis) because the inflammation may be exacerbated.

Macular Edema
Macular oedema, including cystoid macular oedema, has been reported during treatment with bimatoprost. Bimatoprost Ophthalmic Solution 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 oedema.

Angle-closure, Inflammatory or Neovascular Glaucoma
Bimatoprost Ophthalmic Solution has not been evaluated for the treatment of angle-closure, inflammatory or neovascular glaucoma.

Bacterial Keratitis
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 PATIENT).

DRUG INTERACTIONS
Bimatoprost Ophthalmic Solution 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 five minutes apart.Contact lenses should be removed prior to instillation of Bimatoprost Ophthalmic Solution and may be reinserted 15 minutes following its administration.

UNDESIRABLE EFFECTS
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 with Bimatoprost Ophthalmic Solution the most common adverse event was conjunctival hyperemia (range 25% – 45%). Approximately 0.5% to 3% of patients discontinued therapy due to conjunctival hyperemia with 0.01% or 0.03% bimatoprost ophthalmic solutions. Other common events (>10%) included growth of eyelashes, and ocular pruritus. Additional ocular adverse events (reported in 1 to 10% of patients) with bimatoprost ophthalmic solutions included ocular dryness, visual disturbance, ocular burning, foreign body sensation, eye pain, pigmentation of the periocular skin, blepharitis, cataract, superficial punctate keratitis, eyelid erythema, ocular irritation, eyelash darkening, eye discharge, tearing, photophobia, allergic conjunctivitis, asthenopia, increases in iris pigmentation, conjunctival oedema, conjunctival hemorrhage, and abnormal hair growth. Intraocular inflammation, reported as iritis was reported in less than 1% of patients. Systemic adverse events reported in approximately 10% of patients with Bimatoprost Ophthalmic Solution were infections (primarily colds and upper respiratory tract infections). Other systemic adverse events (reported in 1 to 5% of patients) included headaches, abnormal liver function and asthenia.

PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTIES

Pharmacodynamics
Bimatoprost, a prostaglandin analog, is a synthetic structural analog of prostaglandin with ocular hypotensive activity. It 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

Absorption: After one drop of Bimatoprost was administered once daily to both eyes of 15 healthy subjects for two weeks, blood concentrations peaked within 10 minutes after dosing and were below the lower limit of detection (0.025 ng/mL) in most subjects within 1.5 hours after dosing. Mean Cmax and AUC 0-24hr values were similar on days 7 and 14 at approximately 0.08 ng/mL and 0.09 nghr/mL, respectively, indicating that steady state was reached during the first week of ocular dosing. There was no significant systemic drug accumulation over time.
Distribution: Bimatoprost is moderately distributed into body tissues with a steady-state volume of distribution of 0.67 L/kg. In human blood, bimatoprost resides mainly in the plasma. Approximately 12% of bimatoprost remains unbound in human plasma.
Metabolism: 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.
Elimination: Following an intravenous dose of radiolabeled bimatoprost (3.12 µg/kg) to six 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. Up to 67% of the administered dose was excreted in the urine while 25% of the dose was recovered in the faeces.

CLINICAL STUDIES
In clinical studies of patients with open angle glaucoma or ocular hypertension with a mean baseline IOP of 26 mmHg, the IOP-lowering effect of Bimatoprost ophthalmic solution 0.03% once daily (in the evening) was 7-8 mmHg.In a 3 month clinical study of patients with open angle glaucoma or ocular hypertension with an average baseline IOP of 23.5 mmHg, the IOP-lowering effect of Bimatoprost ophthalmic solution 0.01% once daily (in the evening) was up to 7.5 mmHg and was approximately 0.5 mmHg less effective than Bimatoprost ophthalmic solution 0.03%. In this same study, Bimatoprost ophthalmic solution 0.01% also had a similar overall safety profile compared with Bimatoprost ophthalmic solution 0.03%. After 2 months of treatment, discontinuations were 8.1% for Bimatoprost ophthalmic solution 0.01% and 13.4% for Bimatoprost ophthalmic solution 0.03%.

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
Bimatoprost was not found to be carcinogenic in either mice or rats when administered by oral gavage at doses of up to 2 mg/kg/day and 1 mg/kg/day respectively (at least 192 and 291 times the recommended human exposure based on blood AUC levels respectively) for 104 weeks.
Bimatoprost was not mutagenic or clastogenic in the Ames test, in

the mouse lymphoma test, or in the in vivo mouse micronucleus tests.Bimatoprost did not impair fertility in male or female rats up to doses of 0.6 mg/kg/day (at least 103 times the recommended human exposure based on blood AUC levels).

OVERDOSE
No information is available on overdosage in humans. If overdose with Bimatoprost Ophthalmic Solution occurs, treatment should be symptomatic.

INFORMATION FOR PATIENTS:

- Bimatoprost Ophthalmic Solution has potential for increased brown pigmentation of the iris, which may be permanent. There is also a possibility of eyelid skin darkening, which may be reversible after discontinuation of Bimatoprost Ophthalmic Solution.
- There is a possibility of eyelash and vellus hair changes in the treated eye during treatment with Bimatoprost Ophthalmic Solution. These changes may result in a disparity between eyes in length, thickness, pigmentation, number of eyelashes or vellus hairs, and/or direction of eyelash growth. Eyelash changes are usually reversible upon discontinuation of treatment.
- Imatoflo™ is sterile when packed. Patient are advised not to allow the dropper tip/ dispensing tip to touch any surface, as this may contaminate the solution.
- If there is a development of intercurrent ocular condition (e.g., trauma or infection) have ocular surgery, or develop any ocular reactions, particularly conjunctivitis and eyelid reactions, immediately seek physician's advice.
- Imatoflo™ contains benzalkonium chloride, which may be absorbed by soft contact lenses therefore contact lenses should be removed prior to instillation of this drug and be reinserted 15 minutes following its administration.
- If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes between applications.
- The preferred method for eye drop self-instillation includes holding the head horizontal with punctual occlusion and eyelid closure for three minutes. (DOUBLE DOT: Digital occlusion of Tear Duct and Don't Open Technique) as systemic absorption can be reduced (by up to 70%) with this technique.
- Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye, surrounding structure, fingers, or any other surface in order to avoid contamination of the solution by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

INCOMPATIBILITIES
Not reported

SHELF LIFE
Please see Mfg. Date/ Expiry Date printed on pack. Do not use the product after the expiry date which is stated on the packaging. The expiry date refers to the last day of that month.

PACKAGING INFORMATION

Imatoflo™ (Bimatoprost Ophthalmic Solution 0.03% w/v) is supplied in a 3 ml plastic bottle with a white cap.

STORAGE AND HANDLING INSTRUCTIONS

Keep in a cool place. Protect from light.

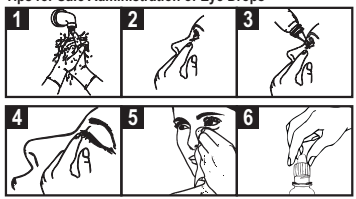
Use the solution within one month after opening the container.

KEEP ALL MEDICINES OUT OF REACH OF CHILDREN

REFERENCES:

Using Prescribing Information Lumigan®, Allergan, Inc., Irvine, CA 92612
Information compiled in December 2011

Tips for Safe Administration of Eye Drops#



1. Wash your hands thoroughly before administration.
2. Bend your head backwards and gently pull your lower eyelid down.
3. Turn the bottle upside down and squeeze it to release one drop into each eye that needs treatment.
4. Let go of the lower lid, and close your eye for 30 seconds.
5. Wipe away any liquid that falls onto your cheek with a tissue.
6. Close the cap immediately after use.

Take Care of your eye drops:

- Do not let the dropper or dispensing tips touch your eye, finger, or any other surface.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If more than one type of Eye Drops are used, wait for at least five minutes before administering the second medication to avoid washout of the previous drug.
- Consult your physician if eye symptoms become worse after using eye drops.

#*Read this entire leaflet carefully before you start using this medicine. Keep this leaflet. You may need to read it again. If you have any further questions, ask your Physician.*

Marketed by:
BAUSCH & LOMB EYECARE (I) PVT. LTD.
R-13 & 14, Ansal Chambers–II,
6 Bhikaji Cama Place,
New Delhi 110066

Manufactured in India by:
Micro Labs Limited
Plot No: 113 to 116, 4th Phase;
K.I.A.D.B., Bommasandra Industrial Area,
Bangalore-560099