# AUSTRALIAN PRODUCT INFORMATION
# APO- BIMATOPROST (BIMATOPROST) EYE DROPS

## 1 NAME OF THE MEDICINE

Bimatoprost

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Bimatoprost 0.3 mg/mL.

For the full list of excipients see section **6.1 List of Excipients**

## 3 PHARMACEUTICAL FORM

APO-Bimatoprost, 0.3 mg/mL eye drops are a sterile, clear, colourless solution supplied in a plastic dropper bottle with a plastic screw cap.

## 4 CLINICAL PARTICULARS

### 4.1 THERAPEUTIC INDICATIONS

The reduction of elevated intraocular pressure, or open angle glaucoma, as first line therapy or monotherapy or as adjunctive therapy to topical beta-blockers.

### 4.2 DOSE AND METHOD OF ADMINISTRATION

APO-Bimatoprost, is **not** intended for oral administration and is for individual patient use only.

**Dosage**

Monotherapy: The recommended dose is one drop in the affected eye(s) once daily, administered in the evening.

Adjunctive Therapy: The recommended dose is one drop in the affected eye(s) once daily, administered in the evening.

More frequent administration has not been shown to provide increased efficacy.

If more than one topical ophthalmic medication is to be used, the other medication should not be used within 5 minutes of using bimatoprost eye drops.

In order to minimise systemic absorption, patients should be instructed to apply pressure to the tear duct immediately following administration of the drug.

To avoid contamination of the solution, keep container tightly closed. Do not touch dropper tip to any surface. Discard contents 4 weeks after opening the bottle. Contents are sterile if seal is intact.

### 4.3 CONTRAINDICATIONS

Patients with known hypersensitivity to bimatoprost or any of the excipients of the medication.

## 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

### General

Bimatoprost has not been studied in patients with heart block more severe than first degree or uncontrolled congestive heart failure. There have been a limited number of spontaneous reports of bradycardia or hypotension with bimatoprost eye drops. Bimatoprost should be used with caution in patients predisposed to low heart rate or low blood pressure.

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.

During treatment with bimatoprost, darkening of the eyelid skin and gradual increased eyelash growth (lengthening, darkening and thickening) with no consequent untoward ocular effects have been observed. Increased iris pigmentation has also been reported. The change in iris pigmentation occurs slowly and may not be noticeable for several months to years. The effect has been seen in up to 2% of patients treated with bimatoprost for up to 6 months. The long term effects of increased iris pigmentation are not known. Before treatment is initiated, patients should be informed of the possibility of eyelash growth, darkening of the eyelid skin and increased iris pigmentation. Some of these changes may be permanent and may lead to differences in appearance between the eyes when only one eye is treated.

There is the potential for hair growth to occur in areas where bimatoprost solution comes repeatedly in contact with the skin surface. Thus, it is important to apply bimatoprost as instructed and to avoid it running onto the cheek or other skin areas.

In bimatoprost studies in patients with glaucoma or ocular hypertension, it has been shown that more frequent exposure of the eye to more than one dose of bimatoprost daily may decrease the IOP-lowering effect. Patients using bimatoprost with other prostaglandin analogues should be monitored for changes to their intraocular pressure.

Bimatoprost should be used with caution in patients with active intraocular inflammations (e.g. uveitis) because the inflammation may be exacerbated.

Macular oedema, including cystoid macular oedema, has been reported during treatment with bimatoprost 0.03% ophthalmic solution for elevated IOP. 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 oedema (e.g. intraocular surgery, retinal vein occlusions, ocular inflammatory disease and diabetic retinopathy).

Bimatoprost has not been studied in patients with inflammatory ocular conditions, neovascular, inflammatory, angle-closure glaucoma, congenital glaucoma or narrow-angle glaucoma.

### Information for patients

Bimatoprost eye drops contain the preservative benzalkonium chloride, which may be absorbed by soft contact lenses. Contact lenses should be removed prior to instillation of bimatoprost and may be reinserted 15 minutes following administration. Bimatoprost should not be administered while wearing contact lenses.

The tip of the bottle should not be allowed to contact the eye, surrounding structures, fingers or any other surface in order to avoid contamination of the solution.

### Use in renal impairment

Bimatoprost has not been studied in patients with renal impairment and should therefore be used with caution in such patients.

### Use in hepatic impairment

Bimatoprost has not been studied in patients with r hepatic impairment and should therefore be used with caution in such patients.

### Use in the elderly

No dosage adjustment in elderly patients is necessary.

### Paediatric use

Safety and effectiveness in patients below 18 years of age have not been established.

### Effects on laboratory tests

No data available.

## 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No interaction studies have been performed.

No drug-drug interactions are anticipated in humans since systemic concentrations of bimatoprost are extremely low (less than 0.2 ng/mL) following ocular dosing. No effects on hepatic drug metabolising enzymes were observed in pre-clinical 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 drug interactions.

Concomitant use of bimatoprost and anti-glaucoma agents other than topical beta-blockers has not been evaluated during adjunctive glaucoma therapy.

There is a potential for the IOP-lowering effect of prostaglandin analogues to be reduced in patients with glaucoma or ocular hypertension when used with other prostaglandin analogues.

## 4.6 FERTILITY, PREGNANCY AND LACTATION

### Effects on fertility

Bimatoprost did not affect fertility in male or female rats at oral doses up to 0.6 mg/kg/day corresponding to 30 - 50 times the expected human exposure (based on blood AUC calculated from total blood concentration).

### Use in pregnancy

Category B3

Bimatoprost and/or its metabolites crossed the placenta in rats. In embryo/foetal developmental studies in pregnant mice and rats, abortion was observed at oral doses of bimatoprost of 0.3 and 0.6 mg/kg/day, respectively, resulting in exposures 15 and 34 times the expected human exposure (based on blood AUC calculated from total blood concentration). Bimatoprost was not teratogenic at up to 0.6 mg/kg/day in mice or rats. At doses of ≥ 0.3 mg/kg/day PO in rats, approximately 20 times the expected human exposure, the gestation length was reduced, embryofoetal losses and peri- and postnatal pup mortality were increased, and pup body weights were reduced.

There are no adequate and well-controlled studies in pregnant women. Bimatoprost should not be used during pregnancy unless clearly necessary.

**Use in lactation**

Bimatoprost was excreted in rat milk following PO administration. Increased pup mortality and depressed pup growth occurred when dams were treated PO with bimatoprost from gestation day 7 to lactation day 20 at ≥0.3 mg/kg/day, corresponding to exposures approximately 20 times the expected human exposure (based on blood AUC calculated from total blood concentration).

There are no data on the excretion of bimatoprost into human milk or on the safety of bimatoprost exposure in infants. Because many drugs are excreted in human milk, nursing women who use bimatoprost should stop breast feeding.

## 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Based on the pharmacodynamic profile, bimatoprost is not expected to affect the ability to drive and use machines. As with any ocular medication, if transient blurred vision occurs at instillation, the patient should wait until the vision clears before driving or using machinery.

## 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

In clinical studies, over 1,700 patients have been treated with bimatoprost.

In the two pivotal monotherapy trials (715 patients) the most frequently reported treatment-related adverse events were: conjunctival hyperaemia in up to 42%, growth of eyelashes in up to 36% and ocular pruritus in up to 14% of patients. The incidence of conjunctival hyperaemia at baseline was 25.1% and 17.8% in patients allocated to treatment with bimatoprost once daily and timolol twice daily, respectively. At 6 months, the incidence of patients with a greater than mild increase in conjunctival hyperaemia was 6.2% and 0.4% in patients treated with bimatoprost once daily and timolol twice daily, respectively. Less than 7% of patients discontinued due to any adverse event.

The following undesirable effects definitely, probably or possibly related to treatment were reported during clinical trials with bimatoprost. Most were ocular, mild to moderate, and none was serious:

**Eye disorders:**

Very common (>10%): conjunctival hyperaemia, growth of eyelashes, ocular pruritus.

Common (<10%): allergic conjunctivitis, asthenopia, blepharitis, blepheral pigmentation, conjunctival oedema, corneal erosion, eye discharge, eyelash darkening, eyelid erythema, eyelid pruritus, eye pain, foreign body sensation, increased iris pigmentation, ocular burning, ocular dryness, ocular irritation, photophobia, pigmentation of periocular skin, superficial punctate keratitis, tearing, visual disturbance and worsening of visual acuity.

Uncommon (<1%): blepharospasm, eyelid oedema, eyelid retraction, iritis, retinal haemorrhage.

**Nervous system disorders:**

Common (<10%): headache

Uncommon (<1%): depression, vertigo

**Musculoskeletal and connective tissue disorders:**

Common (<10%): asthenia

**Respiratory, thoracic and mediastinal disorders:**

Uncommon (<1%): infection (primarily colds and upper respiratory tract infections)

**Skin and subcutaneous tissue disorders:**

Common (<10%): skin hyperpigmentation

Uncommon (<1%): hirsutism

**Post-marketing Experiences:**

**Eye disorders:**

Deepened lid sulcus (enophthalmos), erythema (periorbital), macular oedema

**Skin and subcutaneous tissue disorders:**

Hair growth abnormal

**Gastrointestinal disorders:**

Nausea

**Nervous system disorders:**

Dizziness

**Vascular disorders:**

Hypertension

**Reporting suspected adverse effects**

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems and contact Apotex Medical Information Enquiries/Adverse Drug Reaction Reporting on 1800 195 055

## 4.9 OVERDOSE

If overdosage occurs, treatment should be symptomatic and supportive.

Ophthalmic overdose: No case of overdose has been reported, and is unlikely to occur after ocular administration.

Systemic overdose resulting from accidental ingestion: If bimatoprost is accidentally ingested, the following information may be useful: in two-week oral rat and mouse studies, doses up to 250 mg/kg/day did not produce any toxicity. This dose expressed as mg/kg is 1,100 times higher than the accidental dose of one bottle (7.5 mL) of bimatoprost in a 10kg child.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 PHARMACODYNAMIC PROPERTIES

### Mechanism of action

Bimatoprost is a novel synthetic prostamide analogue with potent ocular hypotensive activity. It selectively mimics the effects of a newly discovered naturally occurring substance, prostamide. Prostamide is biosynthesised from anandamide by a pathway involving COX-2 but not COX-1, suggesting a new pathway that leads to the synthesis of endogenous lipid amides that lower intraocular pressure (IOP). Bimatoprost and prostamides differ from prostaglandins (PGs) in that prostamides are biosynthesised from a different precursor, anandamide; bimatoprost does not stimulate any previously described prostanoid receptor; it is not mitogenic; it does not contract the human uterus; and it is electrochemically neutral.

Bimatoprost reduces intraocular pressure by increasing aqueous humour outflow through the trabecular meshwork and enhancing uveoscleral outflow. Reduction of the intraocular pressure starts approximately 4 hours after the first administration and maximum effect is reached within approximately 8 to 12 hours. The duration of effect is maintained for at least 24 hours.

Clinical studies have shown mean intraocular pressure decreases of up to 9 mmHg.

### Clinical trials

Elevated IOP presents a major risk factor in the pathogenesis of glaucomatous visual field loss. The higher the level of intraocular pressure, the greater the likelihood of optic nerve damage and glaucomatous visual field loss. Bimatoprost has the action of lowering intraocular pressure with no clinically relevant effects on heart rate and blood pressure observed in clinical trials.

### Monotherapy

The efficacy of bimatoprost eye drops was demonstrated in two multi-centre studies compared with timolol 0.5% after 6 months treatment in subjects with chronic glaucoma or ocular hypertension. In each, both once daily and twice daily bimatoprost was compared to twice daily timolol 0.5%. A total of 1198 patients were enrolled in the two studies with 474 receiving bimatoprost once daily, 483 receiving bimatoprost twice daily and 241 receiving timolol.

**Table 1: Intraocular Pressure (mm Hg) ± SD in Individual Phase 3 Monotherapy Studies: Mean Baseline and Mean Changes from Baseline at Month 6**

| Timepoint Visit | Study 1 | | | Study 2 | | |
|---|---|---|---|---|---|---|
| | Bimatoprost QD (n = 240) | Bimatoprost BID (n = 240) | Timolol (n = 122) | Bimatoprost QD (n = 234) | Bimatoprost BID (n = 243) | Timolol (n = 119) |
| **Hour 0** | | | | | | |
| Baseline | 25.85 ± 3.18 | 26.10 ± 3.06 | 25.82 ± 2.94 | 26.05 ± 3.28 | 25.59 ± 3.15 | 25.71 ± 3.31 |
| Month 6 | -7.88[a] ± 3.69 | -7.00[b] ± 3.85 | -6.27 ± 3.48 | -8.69[a] ± 3.96 | -7.30[b] ± 3.71 | -6.63 ± 3.65 |
| **Hour 2** | | | | | | |
| Baseline | 24.64 ± 3.86 | 24.80 ± 3.95 | 24.01 ± 3.64 | 24.70 ± 3.51 | 24.39 ± 3.49 | 24.11 ± 3.44 |
| Month 6 | -7.59[a] ± 4.47 | 6.00[b] ± 4.36 | -5.29 ± 3.93 | -8.59[a] ± 3.60 | -6.64[b] ± 3.88 | -5.96 ± 3.78 |
| **Hour 8** | | | | | | |
| Baseline | 23.87 ± 3.99 | 23.92 ± 4.48 | 23.16 ± 3.88 | 23.73 ± 3.79 | 23.44 ± 3.76 | 23.30 ± 3.86 |

| Timepoint Visit | Study 1 | | | Study 2 | | |
|---|---|---|---|---|---|---|
| | Bimatoprost QD (n = 240) | Bimatoprost BID (n = 240) | Timolol (n = 122) | Bimatoprost QD (n = 234) | Bimatoprost BID (n = 243) | Timolol (n = 119) |
| Month 6 | -6.88[a] ± 4.28 | -5.55[a] ± 4.46 | -4.17 ± 3.96 | -7.14[a] ± 3.94 | -6.14[a] ± 3.77 | -4.96 ± 3.80 |

a Bimatoprost superior to timolol (p ≤ 0.05); b Bimatoprost non-inferior to timolol.; N = number of patients at baseline

Bimatoprost eye drops administered once daily as monotherapy, have consistently shown clinically and statistically superior IOP reduction vs timolol 0.5% twice daily over a six month period. Mean IOP changes from baseline for bimatoprost once daily ranged from 6.88 to 7.88 mmHg in study 1 and 7.14 to 8.69 mmHg in study 2. These were superior to the decreases seen in the timolol group (4.17 to 6.27 mmHg and 4.96 to 6.63 mmHg respectively). Twice daily dosing did not show any increased efficacy compared to once daily dosing.

In addition to mean change from baseline, a frequency analysis of the IOP recorded at hour 0 at each visit was performed. In the two studies 46% and 52.5% of patients achieved an IOP of 17 mmHg or less (a commonly agreed 'target IOP') with bimatoprost once daily over the time period studied, compared to 25.4% and 29% in the timolol group. These results corroborate the statistical and clinical superiority of the once daily regimen over timolol seen at all visits.

**Adjunctive Therapy**

The ability of bimatoprost 0.03% eye drops to lower IOP when used as adjunctive therapy to topical beta-blocker monotherapy has been evaluated in two large scale multi-centre, randomised 3 month studies, involving 722 patients of which 489 received bimatoprost. The numbers and proportions of the different topical beta-blocking agents used in the studies were representative of clinical practice.

**Table 2: Intraocular Pressure (mm Hg) ± SD in Individual Phase 3 Adjunctive Studies: Mean Baseline and Mean Changes from Baseline at Month 3**

| Timepoint Visit | Study 1 | | | Study 2 | | |
|---|---|---|---|---|---|---|
| | Bimatoprost QD / BB (n = 153) | Bimatoprost BID / BB (n = 146) | Latanoprost / BB (n = 138) | Bimatoprost QD / BB (n = 93) | Bimatoprost BID / BB (n = 97) | Vehicle / BB (n = 95) |
| **Hour 0** | | | | | | |
| Baseline | 25.02 ± 2.95 | 24.99 ± 2.51 | 25.17 ± 2.97 | 24.51 ± 2.50 | 24.64 ± 2.76 | 24.40 ± 2.90 |
| Month 6 | -7.95[b] ± 3.81 | -7.26[b] ± 3.48 | -7.35 ± 3.74 | -7.38[a] ± 4.72 | -6.34[a] ± 3.86 | -3.59 ± 3.46 |
| **Hour 2** | | | | | | |
| Baseline | 23.18 ± 3.68 | 23.11 ± 3.62 | 23.32 ± 3.34 | 22.22 ± 3.35 | 22.25 ± 3.86 | 21.54 ± 3.46 |
| Month 6 | -7.03[b] ± 3.99 | -5.33 ± 4.09 | -6.39 ± 3.92 | -6.45[a] ± 4.20 | -4.73[a] ± 4.07 | -2.29 ± 3.65 |
| **Hour 8** | | | | | | |
| Baseline | 22.42 ± 3.90 | 22.36 ± 4.03 | 23.05 ± 3.67 | 21.96 ± 3.04 | 22.15 ± 3.99 | 21.44 ± 3.48 |
| Month 6 | -6.03[b] ± 4.15 | -4.64 ± 4.25 | -5.89 ± 3.91 | -6.36[a] ± 3.77 | -4.45[a] ± 4.23 | -2.62 ± 3.64 |

a Bimatoprost superior to vehicle/timolol (p ≤ 0.001); b Bimatoprost non-inferior to latanoprost/BB.; N = number of patients at baseline; BB = beta-blocker

Overall at month 3 in study 1, the mean decreases from baseline IOP at hours 0, 2 and 8 in patients treated with bimatoprost once daily/beta-blocker ranged from 6.03 to 7.95 mmHg. These were non-inferior to the decreases seen in the latanoprost/beta-blocker group (5.89 to 7.35 mmHg) at all time points.

Overall at month 3 in study 2, the mean decreases from baseline IOP at hours 0, 2 and 8 in patients treated with bimatoprost once daily/beta-blocker ranged from 6.39 to 7.38 mmHg. These were superior to the decreases seen in the vehicle/beta-blocker group (2.62 to 3.59 mmHg) at all time points. Bimatoprost once daily/beta-blocker showed superiority to vehicle/beta-blocker at all time points at all visits.

## 5.2 PHARMACOKINETIC PROPERTIES

## 5.3 PRECLINICAL SAFETY DATA

Ocular administration of bimatoprost in monkeys at concentrations of 0.03% or 0.1% once or twice daily for 1 year caused an increase in iris pigmentation and reversible dose-related periocular effects characterised by a prominent upper and/or lower sulcus and widening of the palpebral fissure. No associated increase in melanocyte number was observed with the pigmentation. It appears that the mechanism of increased iris pigmentation is due to increased stimulation of melanin production in melanocytes and not to an increase in melanocyte number.

Periocular effects were also observed in an intravenous toxicity study at systemic exposures at least 235-fold higher than that observed in humans after ocular administration. No functional or microscopic changes related to the periocular effects were observed. The mechanism of action for the observed periocular changes is unknown.

**Genotoxicity**

Bimatoprost was not mutagenic or clastogenic in a bacterial mutation assay, in a mouse lymphoma test *in vitro* or in a mouse micronucleus test.

**Carcinogenicity**

Long-term studies in mice and rats revealed no evidence of carcinogenicity following oral (by gavage) administration of bimatoprost at doses up to 2 and 1 mg/kg/day, respectively. These doses resulted in systemic bimatoprost levels 85 - 95 times the maximum anticipated human exposure (based on blood AUC). In the rat carcinogenicity study, a dose-related increase in vacuolated corpora lutea was observed. The clinical relevance of this ovarian effect is unclear.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 LIST OF EXCIPIENTS

- Benzalkonium chloride
- anhydrous citric acid
- sodium chloride
- dibasic anhydrous sodium phosphate
- purified water
- with sodium hydroxide or hydrochloric acid for pH adjustment

## 6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

## 6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

## 6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Discard contents 4 weeks after opening the bottle.

## 6.5 NATURE AND CONTENTS OF CONTAINER

APO-Bimatoprost Eye Drops

Bottle containing 3 mL of solution: AUST R 204398

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Contents are sterile if seal is intact.

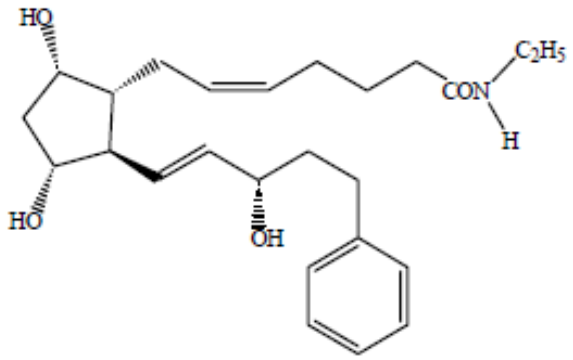
## 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

## 6.7 PHYSICOCHEMICAL PROPERTIES

Bimatoprost is a prostamide with potent ocular hypotensive activity. It is a white to off-white powder and is very soluble in ethyl alcohol and methyl alcohol and slightly soluble in water. Bimatoprost is a clear, isotonic, colourless, sterile ophthalmic solution with an osmolality of approximately 300 mOsmol/kg.

**Chemical structure**




Chemical Name: (*Z*)-7-[(1*R*,2*R*,3*R*,5*S*)-3,5-Dihydroxy-2-[(1*E*,3*S*)-3-hydroxy-5-phenylpent-1- enyl]cyclopentyl]-*N*-ethylhept-5-enamide

Molecular Formula: $C_{25}H_{37}NO_4$

Molecular Weight: 415.58

**CAS number**

155206-00-1

# 7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

# 8 SPONSOR

Apotex Pty Ltd
16 Giffnock Avenue
Macquarie Park NSW 2113
Australia

Tel: (02) 8877 8333
Web: www1.apotex.com/au

# 9 DATE OF FIRST APPROVAL

14 March 2014

# 10 DATE OF REVISION

24 October 2018

**Summary table of changes**

| Section Changed | Summary of new information |
|---|---|
| All | Reformatted product information, minor editorial changes |
| | |
| | |