

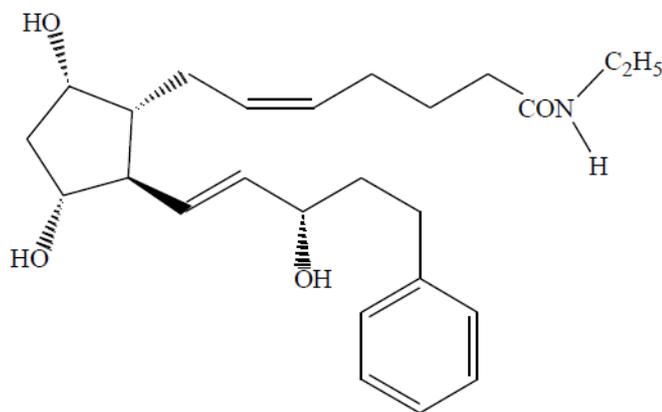
PRODUCT INFORMATION

BIMATOPROST® SANDOZ 300µg/mL EYE DROPS SOLUTION

NAME OF THE MEDICINE

Generic name: Bimatoprost

Chemical structure:



Chemical name:

(Z)-7-[(1R,2R,3R,5S)-3,5-Dihydroxy-2-[(1E,3S)-3-hydroxy-5-phenyl-1-pentenyl]cyclopentyl]-5-N-ethylheptenamide

Molecular weight: 415.58

Empirical formula: C₂₅H₃₇NO₄

CAS No.: 155206-00-1

DESCRIPTION

Bimatoprost is a prostamide with potent ocular hypotensive activity. Bimatoprost is a white or almost white crystalline 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 260 to 330 mOsmol/kg.

Bimatoprost Sandoz 300µg/mL is a sterile ophthalmic solution. Each mL of Bimatoprost Sandoz solution contains active ingredient bimatoprost 0.3 mg, preservative: benzalkonium chloride 0.05 mg and inactive ingredient sodium phosphate dibasic; citric acid monohydrate; sodium chloride; and water - purified. Hydrochloric acid and/or sodium hydroxide may be added to adjust pH.

PHARMACOLOGY

Pharmacotherapeutic group: ophthalmologicals; prostaglandin analogues; ATC code: S01EE03

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 biosynthesized 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 in man 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.

Pharmacokinetics

Absorption

Bimatoprost penetrates the human cornea and sclera *in vitro*. After once daily ocular administration of one drop of 0.03% bimatoprost to both eyes of 15 healthy subjects 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 bimatoprost C_{max} values were similar on days 7 and 14 at 0.0721 and 0.0822 ng/mL respectively. The mean AUC_{0-24hr} values were also similar on days 7 and 14 at 0.0742 and 0.096ng.hr/mL respectively, indicating that a steady systemic exposure to bimatoprost was reached during the first week of ocular dosing. The systemic exposure of bimatoprost is very low with no accumulation over time.

Distribution

Bimatoprost is moderately distributed into body tissues with a steady state systemic volume of distribution in humans of 0.67 L/kg. In human blood, bimatoprost resides mainly in the plasma. The plasma protein binding of bimatoprost is approximately 90%.

Data from *in vitro* studies showed that the overall extent of melanin binding was not dependent on concentration and the binding was reversible.

Metabolism

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

Excretion

Bimatoprost is eliminated primarily by renal excretion. Up to 67% of an intravenous dose of radiolabeled bimatoprost administered to healthy volunteers was excreted in the urine, 25% of the dose was excreted via the faeces. The elimination half-life, determined after intravenous administration, was approximately 45 minutes; the total blood clearance of unchanged bimatoprost was 1.5 L/hr/kg.

After twice daily dosing, the mean AUC_{0-24hr} value of 0.0634 ng.hr/mL for bimatoprost in the elderly (subjects 65 years or older) was statistically significantly higher than that of 0.0218 ng.hr/mL in young healthy adults, suggesting the existence of an age effect. However, this finding is not clinically relevant as systemic exposure for elderly and young subjects remained very low from ocular dosing. There was no accumulation of bimatoprost in the blood over time and the safety profile was similar in elderly and young patients.

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±4.18	23.16±3.88	23.73±3.79	23.44±3.76	23.30±3.86
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)	Latanopro st/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 3	-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 3	-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 3	-6.03 ^b ±4.15	-4.64±4.25	-5.89±3.91	-6.39 ^a ±3.77	-4.45 ^a ±4.23	-2.62±3.64

^a Bimatoprost superior to vehicle/timolol ($p \leq 0.001$); ^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.

INDICATIONS

Bimatoprost eye drops is indicated for the reduction of elevated intraocular pressure, or open angle glaucoma, as first line therapy or monotherapy or as adjunctive therapy to topical beta-blockers.

CONTRAINDICATIONS

Bimatoprost eye drops are contraindicated in patients with hypersensitivity to bimatoprost or to any component of the medication.

PRECAUTIONS

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.

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

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. Neither naevi nor freckles of the iris appear to be affected by treatment. 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. Periorbital tissue pigmentation has been reported to be reversible in some patients.

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.

Preclinical Findings:

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.

Effects of 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.

Paediatric Use:

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

Use in the elderly:

No dosage adjustment in elderly patients is necessary.

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.

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.

Other Information for patients:

Bimatoprost eye drops contain the preservative benzalkonium chloride, which may be absorbed by and cause discolouration of soft (hydrophilic) contact lenses. Patients wearing soft contact lenses should be instructed to remove their contact lenses prior to instillation of bimatoprost and wait at least 15 minutes following administration before reinserting the contact lenses. 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 eye injury and contamination of the solution.

INTERACTIONS WITH OTHER MEDICINES

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.

ADVERSE EFFECTS

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

In the two pivotal monotherapy trials (715 patients) the most frequently reported treatment-related adverse events were: conjunctival hyperemia in up to 42%, growth of eyelashes in up to 36% and ocular pruritus in up to 14% of patients. The incidence of conjunctival hyperemia 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 hyperemia 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 hyperemia, 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, lacrimation increased, ocular burning, ocular dryness, ocular irritation, photophobia, pigmentation of periocular skin, superficial punctate keratitis, tearing, visual disturbance/blurred vision and worsening of visual acuity.

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

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

Respiratory, thoracic and mediastinal disorders:

Asthma, exacerbation of asthma, dyspnea

DOSAGE AND ADMINISTRATION

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

Adjunctive Therapy: The recommended dose is one drop of bimatoprost eye drops 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 of bimatoprost eye drops, 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.

OVERDOSAGE

Contact the Poisons Information Centre on telephone 13 11 26 for advice on management of overdose.

In case of overdose treatment should be supportive and symptomatic.

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 (7.5mL) of bimatoprost in a 10 kg child.

PRESENTATION AND STORAGE CONDITIONS:

Bimatoprost Sandoz 300µg/mL eye drops sterile solution is packed in plastic dropper bottles with a plastic tamper-proof screw cap. Each bottle has a fill volume of 3 mL.

Store below 25°C.

Discard contents 4 weeks after opening the bottle.

SPONSOR NAME AND ADDRESS

Sandoz Pty Ltd
ABN 60 075 449 553
54 Waterloo Road,
North Ryde, NSW 2113, AUSTRALIA

Tel: 1800 634 500

POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription Only Medicine

Date of first inclusion in the Australian Register of Therapeutic Goods (ARTG):
3 November 2016