

1. PRODUCT NAME

Bimatoprost multichem 0.3 mg/mL eye drops

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains 0.3 mg bimatoprost.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Bimatoprost multichem eye drops are a clear, isotonic, colourless, sterile ophthalmic solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Bimatoprost multichem is indicated as monotherapy for the reduction of elevated intraocular pressure (IOP) in patients with chronic glaucoma or ocular hypertension; or as adjunctive therapy in patients not adequately controlled on other agents.

4.2 Dose and method of administration

Monotherapy

The recommended dose is one drop of Bimatoprost multichem in the affected eye(s) once daily, administered in the evening.

Adjunctive therapy

The recommended dose is one drop of Bimatoprost multichem 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 multichem eye drops.

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

Paediatric use

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

Use in elderly

No dosage adjustment in elderly patients is necessary.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

General

Bimatoprost multichem eye drops have 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 multichem should be used with caution in patients predisposed to low heart rate or low blood pressure.

Bimatoprost multichem 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 multichem 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 eye drops, 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. At 12 months, the incidence of iris pigmentation with bimatoprost was 1.5% and did not increase following 3 years of treatment. 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 multichem solution comes repeatedly in contact with the skin surface. Thus, it is important to apply Bimatoprost multichem 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 multichem 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 multichem 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 multichem has not been studied in patients with inflammatory ocular conditions, neovascular, inflammatory, angle-closure glaucoma, congenital glaucoma or narrow-angle

glaucoma.

Information for patients

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

There have been reports of bacterial keratitis associated with the use of multidose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent ocular disease. Patients with a disruption of the ocular epithelial surface are at greater risk of developing bacterial keratitis.

4.5 Interaction with other medicines and other forms of interaction

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 multichem.

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 antiglaucoma 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

Fertility

See section 5.3.

Pregnancy (Category B3)

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

See section 5.3 for additional information.

Lactation

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 multichem should stop breast feeding.

See section 5.3 for additional information.

4.7 Effects on ability to drive and use machines

Based on the pharmacodynamic profile, Bimatoprost multichem 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 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 were 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, 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 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

In addition to what has been observed in clinical trials, the following adverse reactions have been

identified during post-marketing use of bimatoprost. Because post-marketing reporting is voluntary and from a population of uncertain size, it is not possible to reliably estimate the frequency of these reactions:

Eye disorders

Periorbital and lid changes including deepening of the eyelid sulcus, erythema (periorbital), macular edema, ocular discomfort.

Skin and subcutaneous tissue disorders

Hair growth abnormal, skin discoloration

Gastrointestinal disorders

Nausea

Nervous system disorders

Dizziness

Immune system disorders

Hypersensitivity reaction including signs and symptoms of eye allergy and allergic dermatitis

Vascular disorders

Hypertension

Respiratory, thoracic and mediastinal disorders

Asthma, exacerbation of asthma, dyspnea

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

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 multichem 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 over 400 times higher than the accidental dose of one bottle (3 mL) of Bimatoprost multichem in a 10 kg child.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Antiglaucoma preparations; 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 humor 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 efficacy and safety

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 comparative 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.

Pooled efficacy data from the two clinical studies demonstrates that in the intent-to-treat population bimatoprost 0.03% ophthalmic solution, administered both once and twice daily as a monotherapy agent is superior to timolol 0.5% twice daily over a six month period at hours 0, 2 and 8 ($p \leq 0.05$). At the primary endpoint (hour 0 at month 6) mean decrease from baseline IOP in patients treated with bimatoprost once daily was -8.28 mmHg and was superior to that in patients treated with timolol (-6.44 mmHg, $p < 0.001$). At the primary endpoint (hour 0 at month 6) the mean decrease from baseline IOP in patients treated with bimatoprost once daily was -8.28 mmHg and was superior to that in patients treated with bimatoprost twice daily (-7.15 mmHg, $p < 0.001$). Therefore, twice daily dosing did not show any increased efficacy compared to once daily dosing. Mean IOP changes from baseline for bimatoprost once daily range from 7.01 mmHg to 8.75 mmHg from hours 0 to 8 over the six month period of evaluation. The similar range for timolol was 4.38 mmHg to 6.44 mmHg. Overall, bimatoprost once daily produced a reduction in IOP of 33%. Timolol twice daily produced a reduction of 23%.

In addition to mean change from baseline, a frequency analysis of the IOP recorded at hour 0 at each visit was performed. Consistently 50% 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 approximately 30% in the timolol group. In addition, those whose IOP was recorded

as over 22 mmHg were consistently less than 10% in the bimatoprost group compared to approximately 20% in the timolol group. These results provide positive clinical interpretation to the statistical superiority of the once daily regimen over timolol seen at all visits at hours 0, 2 and 8.

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. For the bimatoprost once daily/beta-blocker regimen hour 0, mean decreases from baseline were consistent over the three month period studied. The values ranged from 6.97 to 7.74 mmHg.

In the first study, bimatoprost 0.03% once or twice daily as an adjunct to beta-blocker therapy was compared with latanoprost 0.005% ophthalmic solution once daily, as an adjunct to betablocker therapy. At month 3, the mean decreases in IOP from baseline at hours 0, 2 and 8 in patients treated with bimatoprost once daily/beta-blocker in the intent to treat population 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. At the primary endpoint (hour 0 at month 3) mean decrease from baseline IOP in patients treated with bimatoprost once daily/beta-blocker was -7.95 mmHg and was non-inferior to that in patients treated with latanoprost/beta-blocker (-7.35 mmHg). At the primary endpoint (hour 0 at month 3) mean decrease from baseline IOP in patients treated with bimatoprost twice daily/betablocker was -7.26 mmHg and was non-inferior to that in patients treated with latanoprost/beta-blocker (-7.35 mmHg). Mean changes from baseline hour 0 IOP across all follow-up visits ranged from -7.23 to -7.95 mmHg with bimatoprost once daily/beta-blocker, and from -6.91 to -7.53 mmHg with latanoprost/beta-blocker. The decrease in IOP from baseline hour 0 was statistically significant within each treatment group at each follow-up visit ($p < 0.001$).

In the second study, bimatoprost 0.03% once or twice daily as an adjunct to beta-blocker therapy was compared with vehicle twice daily, as an adjunct to beta-blocker therapy. At month 3, the mean decreases in IOP from baseline at hours, 0, 2 and 8 in patients treated with bimatoprost once daily/beta-blocker in the intent to treat population 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 ($p < 0.001$). At the primary endpoint (hour 0 at month 3) mean decrease from baseline IOP in patients treated with bimatoprost once daily/beta-blocker was -7.38 mmHg and was superior to that in patients treated with vehicle/beta-blocker (-3.59 mmHg, $p < 0.001$). At the primary endpoint (hour 0 at month 3) mean decrease from baseline IOP in patients treated with bimatoprost twice daily/beta-blocker was -6.34 mmHg and was superior to that in patients treated with vehicle/beta-blocker (-3.59 mmHg, $p < 0.001$). Mean decreases from baseline hour 0 IOP across all follow-up visits ranged from 6.53 to 7.38 mmHg with bimatoprost once daily/beta-blocker, and from 2.04 to 3.59 mmHg with vehicle/beta-blocker. Mean decreases from baseline IOP at hours 0, 2 and 8 were superior to those seen in the vehicle/beta-blocker group at each time point at each follow-up visit ($p < 0.001$ in the bimatoprost once daily/beta-blocker group; $p \leq 0.003$ in the bimatoprost twice daily/beta-blocker group).

In a pooled analysis of both studies, at the primary endpoint (hour 0 at month 3) the mean

decrease from baseline IOP in patients treated with bimatoprost once daily/beta-blocker was – 7.74 mmHg and was superior to that in patients treated with bimatoprost twice daily/betablocker (-6.89 mmHg, $p = 0.017$).

5.2 Pharmacokinetic properties

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 radiolabelled 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.

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.

Carcinogenicity

The carcinogenic potential of orally administered (gavage) bimatoprost was evaluated in mice given 0.3, 1.0 or 2.0 mg/kg/day and in rats given 0.1, 0.3 or 1.0 mg/kg/day for 104 weeks. There was no evidence of tumorigenic potential at any of the administered dosages in either species. In the rat carcinogenicity study, a dose-related increase in vacuolated corpora lutea was observed. The ovarian effects in rats is believed to be species specific.

Mutagenicity

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

Impairment of fertility

Bimatoprost did not affect fertility in male or female rats at oral doses up to 0.6 mg/kg/day (approximately 103 times the intended human exposure).

Pregnancy category B3

In embryofoetal development studies in pregnant mice and rats, abortion but no developmental effects were observed at doses that were at least 33 or 97 times higher, respectively, than the intended human exposure. In peri/postnatal studies in rats, reduced gestation time, foetal death and decreased pup body weights were observed in dams given ≥ 0.3 mg/kg/day (a rodent-specific pharmacological effect; systemic exposure estimated to be at least 41 times the intended human exposure). This maternal toxicity likely resulted in decreased mating performance and gestational body weight gain in the offspring, but neurobehavioural functions were not affected.

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 41 times the expected human exposure.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- benzalkonium chloride (preservative)
- sodium phosphate dibasic
- citric acid monohydrate
- sodium chloride
- water -purified
- Hydrochloric acid and/or sodium hydroxide may be added to adjust pH.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Shelf life: 2 years

Discard contents 4 weeks after opening the bottle.

6.4 Special precautions for storage

To avoid contamination of the solution, keep container tightly closed. Do not touch dropper tip to any surface. Contents are sterile if seal is intact.

Storage: Store below 25°C

6.5 Nature and contents of container

Bimatoprost multichem 0.3mg/mL eye drops are supplied in plastic dropper bottles with a plastic screw cap. Each bottle has a fill volume of 3mL.

6.6 Special precautions for disposal

Not applicable.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Multichem NZ Limited
Private Bag 93527
Takapuna
AUCKLAND 0740
Telephone: (09) 488 0330

9. DATE OF FIRST APPROVAL

10 December 2015

10. DATE OF REVISION OF THE TEXT

19 November 2019

SUMMARY TABLE OF CHANGES

Section	Change
3	Description of the Bimatoprost powder deleted
4.2	Information for patients moved to section 4.4

NEW ZEALAND DATA SHEET

BIMATOPROST MULTICHEM

multichem

4.4	Addition of a precaution under the sub-heading "Information for patients" relating to potential bacterial contamination with the use of multidose preparations.
4.6	Editorial changes.
4.8	Additional Post-marketing Adverse Events have been included under the sub-headings "Eye disorders" and "Skin and subcutaneous tissue disorders"
5.1	Minor amendment of Pharmacotherapeutic group
5.2	Sub-headers added
5.3	Editorial changes
6.1	Excipients bullet-pointed