PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr ZIMED® PF

Bimatoprost Ophthalmic Solution

Solution , 0.03% w/v, Ophthalmic

(preservative-free, supplied in multi-dose container)

Elevated Intraocular Pressure Therapy

Prostamide Analogue

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Cambridge, Ontario, Canada
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Date of Initial Authorization:
DEC 14, 2022

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MAR 12, 2026

Submission Control Number: 305342

RECENT MAJOR LABEL CHANGES

None	

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

ZIMED® PF (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

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

No overall clinical differences in safety or effectiveness have been observed between elderly (> 65 years of age) and other adult patients. Use as for adult patients.

2 CONTRAINDICATIONS

ZIMED® PF is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see section 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Patients with a history of contact hypersensitivity to silver should not use this product as dispensed drops may contain traces of silver (see 2 CONTRAINDICATIONS).

4.2 Recommended Dose and Dosage Adjustment

The recommended dosage is one drop in the affected eye(s) once daily in the evening. The dosage of ZIMED® PF should not exceed once daily since it has been shown that more frequent administration of bimatoprost ophthalmic solution may lessen the intraocular pressure lowering effect and increase the frequency and severity of adverse events. (see 7 WARNINGS and PRECAUTIONS, Ophthalmologic).

Health Canada has not authorized an indication for pediatric use (see 1 INDICATIONS, 1.1 Pediatrics (< 18 years of age)).

Hepatic Impairment: ZIMED® PF has not been studied in patients with moderate to severe hepatic impairment and should therefore be used with caution in such patients (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).

Renal Impairment: ZIMED® PF has not been studied in patients with renal impairment and should therefore be used with caution in such patients (see 7 WARNINGS AND PRECAUTIONS, Renal).

4.4 Administration

If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

Contact lenses should be removed prior to instillation of ZIMED® PF and may be reinserted 15 minutes following its administration.

4.5 Missed Dose

Patients should be instructed to apply a single drop as soon as they remember, and then to return to their regular routine.

5 OVERDOSAGE

No information is available on overdosage in humans. If overdose with ZIMED® PF occurs, treatment should be symptomatic.

In short-term 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 100 times higher than the amount of bimatoprost to which a 10 kg child would be exposed were it to ingest the entire contents of a bottle of ZIMED® PF.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/ Composition	Non-medicinal Ingredients
Ophthalmic	solution, 0.03% w/v	Citric acid monohydrate, disodium hydrogen phosphate heptahydrate, water, sodium chloride. Sodium hydroxide and/or hydrochloric acid may be added to adjust pH.

ZIMED® PF is a sterile preservative-free ophthalmic solution. Each mL of ZIMED® PF contains bimatoprost 0.3 mg.

ZIMED® PF is supplied sterile in a 5 mL bottle manufactured from LDPE, equipped with the Novelia® one-way valve and PureFlow® technology system. The cap and top are impregnated

with silver ions to prevent bacterial growth. Each bottle of 3 mL sufficient for 4 week's treatment.

7 WARNINGS AND PRECAUTIONS

General

Bimatoprost ophthalmic solutions have been reported to cause changes to pigmented tissue. The changes include increased pigmentation and growth of eyelashes and increased pigmentation of the iris and periorbital tissue (eyelid). The increased pigmentation may be permanent.

ZIMED® PF may gradually change eye colour, 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 area of the eye are currently unknown.** The change in iris colour occurs slowly and may not be noticeable for several months to years. Pigmentation is expected to increase as long as bimatoprost ophthalmic solution is administered. Noticeable darkening of the iris has been reported in 1.5% of patients treated for 12 months with bimatoprost ophthalmic solution 0.03% (with benzalkonium chloride 0.05 mg/mL as preservative) at the proposed dose of one drop once daily in each affected eye (1.1% of patients treated for 6 months).

Patients should be informed of the possibility of iris colour change. In addition, 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 be advised of the potential for a disparity between the eyes in length, thickness, and/or number of eyelashes.

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 colour change is likely to be permanent. Neither nevi nor freckles of the iris are expected to be affected by treatment.

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.

Patients with a history of contact hypersensitivity to silver should not use this product as dispensed drops may contain traces of silver.

Carcinogenesis and Mutagenesis

See 16 NON-CLINICAL TOXICOLOGY.

Driving and Operating Machinery

Based on the pharmacodynamic profile, bimatoprost is not expected to influence a patient's ability to drive or operate machinery. 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.

Hepatic/Biliary/Pancreatic

ZIMED® PF has not been studied in patients with 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 alanine aminotransferase (ALT), aspartate aminotransferase (AST) and/or bilirubin at baseline, bimatoprost 0.03% (with benzalkonium chloride 0.05 mg/mL as preservative) had no adverse effect on liver function over 48 months.

Ophthalmologic

ZIMED® PF should be used with caution in patients with active intraocular inflammation (e.g., uveitis) because the inflammation may be exacerbated.

Macular edema, including cystoid macular edema, has been reported during treatment with bimatoprost ophthalmic solution 0.03% (with benzalkonium chloride 0.05 mg/mL as preservative). ZIMED® PF 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 (e.g., intraocular surgery, retinal vein occlusions, ocular inflammatory disease and diabetic retinopathy).

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

Limited experience is available with the use in patients with open-angle glaucoma with pseudoexfoliative and pigmentary glaucoma, and chronic angle-closure glaucoma with patent iridotomy.

In bimatoprost 0.03% 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 intraocular pressure (IOP)-lowering effect. There is a potential for the IOP- lowering effect of prostaglandin analogues (e.g., ZIMED® PF) to be reduced in patients with glaucoma or ocular hypertension when used with other prostaglandin analogues. Patients using ZIMED® PF with other prostaglandin analogues should be monitored for changes to their intraocular pressure.

Bimatoprost has not been studied in patients wearing contact lenses. Contact lenses should be removed prior to instillation of ZIMED® PF and may be reinserted 15 minutes following its administration.

Cases of corneal calcification have been reported very rarely in association with the use of phosphate containing eye drops in some patients with significantly damaged corneas.

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.

Renal

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

Reproductive Health - Fertility

Bimatoprost did not impair fertility in male or female rats at doses of up to 0.6 mg/kg/day (approximately 103 times the human exposure based on blood AUC levels obtained in subjects administered bimatoprost ophthalmic solution 0.03% (with benzalkonium chloride 0.05 mg/mL as preservative), one drop/day in both eyes for 14 days).

7.1 Special Populations

7.1.1 Pregnant Women

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, ZIMED® PF should be administered during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In embryo/fetal developmental studies in pregnant mice and rats, abortion was observed at oral doses of bimatoprost which were at least 33 or 97 times, respectively, the intended human exposure as measured by blood AUC levels obtained in subjects administered bimatoprost ophthalmic solution 0.03% (with benzalkonium chloride 0.05 mg/mL as preservative), one drop/day in both eyes for 14 days.

Maternal toxicity, evidenced by reduced gestation length, late resorptions, fetal death, postnatal mortality and reduced pup body weights were observed when female rats received oral doses which were at least 41 times the intended human exposure (based on blood AUC levels obtained in subjects administered bimatoprost ophthalmic solution 0.03% (with benzalkonium chloride 0.05 mg/mL as preservative), one drop/day in both eyes for 14 days). Cohabitation times in the offspring were increased but neurobehavioral functions were not affected.

7.1.2 Breast-feeding

It is not known whether bimatoprost is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ZIMED® PF is administered to a nursing woman.

7.1.3 Pediatrics (< 18 years of age)

Health Canada has not authorized an indication for pediatric use (see 1 INDICATIONS, 1.1 Pediatrics (< 18 years of age)).

7.1.4 Geriatrics

No overall clinical differences in safety or effectiveness have been observed between elderly and other adult patients. Use as for adult patients.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

A multicenter, double-masked, parallel-group, active-controlled study designed to compare the efficacy and safety of bimatoprost 0.03% (without benzalkonium chloride) with bimatoprost 0.03% (with benzalkonium chloride) once-daily for 12 weeks demonstrated that the two formulations had similar safety profiles. The most frequently reported adverse event was conjunctival hyperaemia (23.9% of patients treated).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The data presented below are taken from a randomized, multicenter, double-masked, parallel-group clinical study, of 12 weeks duration, which was conducted in 597 patients with glaucoma or ocular hypertension. A summary of the most common ocular adverse events observed in this study (incidence ≥ 1.0%), regardless of causality, is presented in Table 2.

Table 2 Number (%) of Patients with Ocular Adverse Events, Regardless of Causality, Reported by ≥ 1% of Patients in Any Treatment Group

System Organ Class Preferred Term	Bimatoprost 0.03% Preservative-Free N = 301	Bimatoprost 0.03% N = 295
Eye Disorders		
Conjunctival hyperemia	72 (23.9%)	77 (26.1%)
Eye pruritus	12 (4.0%)	12 (4.1%)
Punctate keratitis	9 (3.0%)	9 (3.1%)
Foreign body sensation in eyes	7 (2.3%)	2 (0.7%)
Dry eye	5 (1.7%)	9 (3.1%)
Growth of eyelashes	5 (1.7%)	1 (0.3%)
Eye pain	4 (1.3%)	3 (1.0%)
Eye irritation	3 (1.0%)	4 (1.4%)
Erythema of eyelid	3 (1.0%)	1 (0.3%)
Skin and Subcutaneous Tissue Disorders		
Skin hyperpigmentation	3 (1.0%)	2 (0.7%)

In this study, one or more adverse events, regardless of causality, were reported by a numerically lower proportion of patients in the bimatoprost preservative-free group (40.5%) compared with bimatoprost (44.1%). The most frequent treatment-related adverse events were conjunctival hyperaemia, eye pruritus, and punctate keratitis. The majority of cases of hyperaemia were graded as trace to mild on macroscopic evaluation. No safety concerns were noted from other ocular assessments.

Overall, 5 patients discontinued treatment due to adverse events: 0.7% (2/301) of patients in the bimatoprost preservative-free group and 1.0% (3/295) in the bimatoprost group.

8.3 Less Common Clinical Trial Adverse Reactions

The following adverse events were observed with an incidence rate < 1% for bimatoprost preservative-free:

Eye Disorders: vision blurred, hair growth abnormal, iris hyperpigmentation, lacrimation increased, conjunctival edema, asthenopia, eyelids pruritus, eyelid edema, photophobia

Nervous System Disorders: Headache

8.5 Post-Market Adverse Reactions

The following adverse reactions have been identified during post-marketing use of bimatoprost preservative-free. 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: Eye discharge, ocular discomfort, macular edema, erythema (periorbital) , blepharitis, eye swelling, eyelid irritation, eyelid pain, blepharal pigmentation, eye edema, periorbital and lid changes associated with periorbital fat atrophy and skin tightness resulting in deepening of the eyelid sulcus, eyelid ptosis, enophthalmos and eyelid retraction, prostaglandin analogue periorbitopathy, conjunctival disorder.

Gastrointestinal disorders: nausea

General disorders and administration site conditions: instillation site irritation

Immune System Disorders: Hypersensitivity reaction including signs and symptoms of eye allergy and allergic dermatitis

Nervous System Disorders: Dizziness

Respiratory, Thoracic and Mediastinal Disorders: Asthma, exacerbation of asthma, dyspnea, COPD exacerbation

Skin and subcutaneous tissue disorders: hair growth abnormal, burning sensation (eyelid), madarosis (temporary loss of a few eyelashes to loss of sections of eyelashes), rash (including macular, erythematous, and pruritic limited to the eyelids and periorbital region), trichorrhexis (temporary eyelash breakage), dry skin of the eyelid and/or periolar area, hordeolum, trichiasis, hypertrichosis, eyelid margin crusting, skin discoloration (periocular).

Vascular Disorders: Hypertension

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

No specific drug interaction studies have been conducted. However, no drug-drug interactions are anticipated in humans since systemic drug concentrations of bimatoprost are extremely low (less than 0.2 ng/mL) following repeated ocular dosing with bimatoprost ophthalmic solution 0.03% (with benzalkonium chloride 0.05 mg/mL as preservative) and as metabolism and excretion involves multiple pathways.

In clinical studies, bimatoprost 0.03% (with benzalkonium chloride) 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.

There is a potential for the intra-ocular pressure (IOP)-lowering effect of prostaglandin analogues (e.g., ZIMED® PF) to be reduced in patients with glaucoma or ocular hypertension when used with other prostaglandin analogues (see 7 WARNINGS AND PRECAUTIONS, Ophthalmologic).

9.4 Drug-Drug Interactions

Interactions with other drugs have not been established.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Bimatoprost is a synthetic prostamide analogue and is structurally related to prostaglandin F2α in that the carboxylic acid group is replaced with an electronically neutral substituent. Its mechanism of action resembles that of prostamide F2α, a naturally occurring substance.

Bimatoprost exhibits no meaningful pharmacological activity at known prostaglandin receptors as well as no uterotonic or mitogenic activity. Studies suggest that it lowers intraocular pressure (IOP) by increasing uveoscleral and trabecular meshwork outflow, with no significant effect on aqueous humor inflow. Pharmacodynamic studies in humans demonstrated a significant 30-35% decrease in outflow resistance compared to vehicle treated eyes based on tonographic data and calculated values of apparent outflow resistance. The ocular hypotensive effect does not involve a COX-dependent mechanism.

10.2 Pharmacodynamics

Dosage Determination Studies for Treatment of Elevated IOP

Four Phase 2 dose-ranging studies were conducted in patients with open-angle glaucoma or ocular hypertension. A dose-response study in 60 patients with twice-daily dosing for 5 ± 2 days showed significant reductions from baseline IOP with bimatoprost 0.01% w/v and 0.03% formulations as well as with timolol 0.5%, compared to vehicle. Among the bimatoprost concentrations evaluated, 0.03% had the best ratio of safety to efficacy, and the 24-hour post-dose results suggested the potential for efficacy with once-daily dosing.

The effects of 0.003%, 0.01% and 0.03% bimatoprost (non-preserved formulations) and of twice-daily versus once-daily (evening) dosing were compared to timolol 0.5% and vehicle in 100 patients treated for one month. Although 0.01% and 0.03% had similar safety profiles, 0.03% had significantly better efficacy. There was no significant difference in efficacy between twice-daily and once-daily dosing.

A study in 106 patients evaluated once-daily evening dosing for 28 days with bimatoprost 0.03% (preserved and non-preserved formulations), AGN 192151 0.06% (a congener of bimatoprost), latanoprost 0.005%, and vehicle. Although the sample size was small, bimatoprost and latanoprost appeared to exhibit comparable safety profiles. The profiles were similar with the preserved and non-preserved formulations of bimatoprost 0.03%.

The mean reductions in IOP are shown in Table 3.

Table 3 Mean Reduction in Intraocular Pressure (mmHg) from Baseline to Day 29

Bimatoprost 0.03% Non-preserved N = 21	Bimatoprost 0.03% Preserved N = 21	Latanoprost N = 22	Vehicle Non-preserved N = 21
8.9 ± 0.7	8.0 ± 0.9	7.6 ± 0.5	1.7 ± 1.2

A study in 32 patients evaluated once-daily morning dosing for 28 days with bimatoprost 0.03% or vehicle. The ocular hypotensive effect of bimatoprost 0.03% with once-daily morning dosing was similar to that observed with once-daily evening dosing.

In the Phase 2 dose-response studies, bimatoprost 0.03% provided greater lowering of IOP than 0.003%, 0.01%, or 0.1%, with similar number of treatment-related adverse events as the 0.01% concentration. Thus the 0.03% concentration was selected for evaluation in Phase 3 studies. Significant IOP-lowering effects were shown for this concentration with once- daily dosing.

The effect of bimatoprost ophthalmic solution 0.03% (with benzalkonium chloride 0.05 mg/mL as preservative) within the first 12 hours of dosing was evaluated in two studies. When dosed in the morning, bimatoprost began to take effect within 4 hours after initial instillation and was followed by continued decreases in IOP through 12 hours. The effect of bimatoprost 0.03% ophthalmic solution (with benzalkonium chloride 0.05 mg/mL as preservative) between

12 and 24 hours post-instillation also was evaluated. Mean IOP at 12 hours post-dosing was 17.7 mmHg and 16.9 mmHg 24 hours after the last dose. Based on this information, once-daily evening dosing is recommended so that the time of anticipated maximal efficacy of the drug coincides with the morning hours (08:00 to 11:00 AM) when untreated IOP is usually highest.

10.3 Pharmacokinetics

Bimatoprost penetrates the human cornea and sclera well in vitro. The mean corneal permeability coefficient was 3.24×10^{-6} cm/sec. Bimatoprost penetrated human scleral tissue better than corneal tissue with a mean scleral permeability coefficient of 14.5×10^{-6} cm/sec.

After one drop of bimatoprost ophthalmic solution 0.03% (with benzalkonium chloride 0.05 mg/mL as preservative) was administered once daily to both eyes of 15 healthy subjects, blood bimatoprost 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.

Systemic exposure after repeated ocular application is low. Steady state was achieved after one week of once daily dosing with one drop of bimatoprost ophthalmic solution 0.03% (with benzalkonium chloride 0.05 mg/mL as preservative) to both eyes, with mean C_{max} values of 0.07 and 0.08 ng/mL on day 7 and 14, respectively, and mean $AUC_{0\text{-}24h}$ of 0.074 and 0.096 ng•hr/mL on day 7 and 14, respectively.

The blood concentrations of bimatoprost from patients with open angle glaucoma or ocular hypertension in two Phase 3 safety and efficacy studies were measured (N=88 on once-daily treatment and N=89 on twice-daily treatment). The samples were collected at approximately 5 minutes after the evening dose over a 3-month treatment period. Bimatoprost blood concentrations were similar to those observed in normal, healthy subjects and there was no significant systemic drug accumulation over time. The C-1 acid metabolite (AGN 191522) was typically not measurable in blood samples from these studies.

Therapeutic drug monitoring in the Phase 3 studies showed that in one study that the elderly group had a higher concentration in the blood; however, this was not observed in the second Phase 3 study.

There was no significant systemic drug accumulation over time with the once daily dosing regimen. Mean blood concentration was around 0.08 ng/mL after 12 months of QD or BID dosing with bimatoprost ophthalmic solution 0.03% (with benzalkonium chloride 0.05 mg/mL as preservative). The once daily regimen corresponded to a total exposure of 6.13 mg (one 28 µL drop in each eye once a day for 12 months) or 0.00028 mg/kg/day for a 60 kg individual over 12 months.

Absorption

Bimatoprost is rapidly absorbed across the human cornea and sclera, with scleral penetration being more efficient. Animal studies show that it is well distributed into ocular tissues following ocular administration, where only minimal metabolism occurs in humans.

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. The in vitro binding of bimatoprost to synthetic melanin was ~20% at concentrations of 0.2 - 100 µg/mL. 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. Bimatoprost then undergoes oxidation, N-deethylation and glucuronidation to form a diverse variety of metabolites. Studies using human liver microsomes and recombinant human P450 isozymes identified CYP 3A4 as one of the enzymes involved in the metabolism of bimatoprost in humans. However, since multiple enzymes and pathways are involved in the biotransformation of bimatoprost, no significant drug- drug interactions are anticipated.

Bimatoprost is only minimally metabolized in ocular tissues in humans, and is active in its intact form, without metabolic modification.

Elimination

Following an intravenous dose of radiolabelled 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. Both urinary and fecal routes are important pathways for elimination of the parent compound and its metabolites, following intravenous administration. Sixty-seven percent of the administered dose of bimatoprost was excreted in the urine with only a small fraction excreted as unchanged drug. Twenty-five percent of the dose was recovered in feces of which 15-40% was eliminated as unchanged drug.

Special Populations and Conditions

- **Geriatrics:** Elderly individuals (> 65 years) exhibited higher systemic levels but this was not considered to be clinically relevant since no overall clinical differences in safety or effectiveness have been observed between elderly and other adult patients.

11 STORAGE, STABILITY AND DISPOSAL

ZIMED® PF should be stored in the original bottle, between 15 °C and 25 °C. Keep the bottle in the outer carton in order to protect from light. Keep in a safe place out of the reach of children. Do not freeze.

Once the multi-dose container has been opened, the bottle should be used within 28 days.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

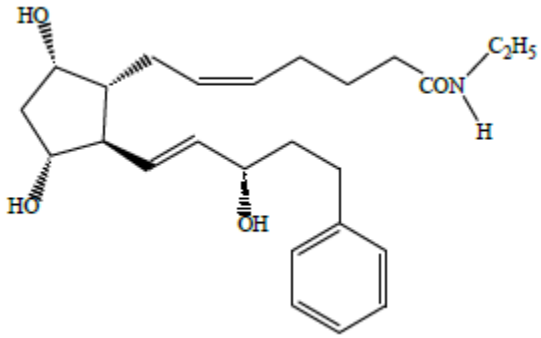
Drug Substance

Proper name: bimatoprost

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 formula and molecular mass: $C_{25}H_{37}NO_4$; 415.58

Structural formula:



Physicochemical properties: Bimatoprost is a white to off-white powder, which is soluble in ethyl alcohol and methyl alcohol and slightly soluble in water.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Adult Patients with Open Angle Glaucoma or Ocular Hypertension

A double-masked, randomized, parallel group study compared the efficacy and safety of once-daily (evening) administration of bimatoprost preservative-free (without benzalkonium chloride) with bimatoprost (with benzalkonium chloride) for 12 weeks in patients with glaucoma or ocular hypertension. Of the 597 patients randomized, 302 received bimatoprost preservative-free and 295 patients received bimatoprost.

Table 4 Summary of Patient Demographics for Study Comparing Bimatoprost Preservative-Free and Bimatoprost

Study Design	Dosage, Route of Administration and Duration	Study Subjects (n)	Mean Age (Range)	Sex
Phase 3 double-masked, randomized, active-controlled, parallel group	Bimatoprost preservative-free Bimatoprost; one drop every evening for 12 weeks	Bimatoprost preservative-free (n = 302) Bimatoprost (n = 295)	64.8 years (29 - 92 years)	M: 246 F: 351

Of the 597 enrolled patients (ITT population), 98.0% (585/597) completed the study. The mean age of patients was 64.8 years (range 29 to 92 years). The majority of patients were female (58.8%, 351/597) and Caucasian (71.2%, 425/597).

The primary population for the efficacy analyses was the per-protocol (PP) population. The primary efficacy variable was derived from the IOP measurements. The primary efficacy analysis was the change from baseline (follow-up minus baseline) in worse eye IOP at each hour evaluated (hours 0, 2, and 8) at week 12 using the PP population. The treatments were compared using the ANCOVA model with treatment and investigator as the main effects and baseline worse-eye IOP as the covariate. A 2-sided 95% confidence interval (CI) for the treatment difference (bimatoprost preservative-free minus bimatoprost) was constructed from the ANCOVA model for each timepoint analyzed.

The hypothesis was that bimatoprost preservative-free is non-inferior to bimatoprost at the week 12 visit. Non-inferiority would be declared if bimatoprost preservative-free was non-inferior to bimatoprost at each hour evaluated (hours 0, 2, and 8) at week 12. Bimatoprost preservative-free was considered to be non-inferior to bimatoprost at the time point if the upper limit of the 95% confidence interval (CI) did not exceed 1.5 mmHg.

For the primary analysis, bimatoprost preservative-free was considered to be non-inferior to bimatoprost at each hour evaluated (hours 0, 2 and 8) during the week 12 visit for worse eye IOP change from baseline: upper limit of the 95% CI for between-treatment difference (bimatoprost preservative-free minus bimatoprost) did not exceed 1.5 mmHg (as well as not exceeding 1.0 mmHg) in the PP population. In fact, the upper limit did not exceed 0.75 mmHg at any week 12 timepoint. Non-inferiority was also demonstrated for the ITT population. Both treatments studied showed statistically and clinically significant mean decreases from baseline in worse eye IOP at all follow-up timepoints of 2, 6 and 12 weeks ($p < 0.001$).

The mean changes from baseline in worse eye IOP for the PP population are summarized in Table 5.

Table 5 Mean Change from Baseline in Worse Eye IOP (mmHg) (PP Population)

Visit	Timepoint	Statistic	Bimatoprost Preservative-free N = 295	Bimatoprost N = 291	Bimatoprost Preservative-free – Bimatoprost Difference, (95% CI[a])
Week 2	Hour 0	N	283	281	0.37 (–0.05, 0.78)
		Mean	–7.22	–7.55	
		SD	2.845	2.968	
	Hour 2	N	282	279	0.31 (–0.10, 0.72)
		Mean	–6.85	–7.17	
		SD	3.217	2.922	
	Hour 8	N	283	280	0.25 (–0.15, 0.64)
		Mean	–6.03	–6.27	
		SD	3.160	3.399	
Week 6	Hour 0	N	276	277	0.14 (–0.30, 0.58)
		Mean	–7.43	–7.58	
		SD	2.783	3.089	
	Hour 2	N	275	276	0.10 (–0.33, 0.52)
		Mean	–7.01	–7.14	
		SD	3.059	3.122	
	Hour 8	N	276	277	0.26 (–0.15, 0.68)
		Mean	–6.02	–6.34	
		SD	3.291	3.407	
Week 12	Hour 0	N	281	274	0.32 (–0.12, 0.75)
		Mean	–7.49	–7.77	
		SD	2.900	3.029	
	Hour 2	N	279	272	0.02 (–0.42, 0.45)
		Mean	–7.06	–7.11	
		SD	3.333	3.192	
	Hour 8	N	279	272	0.13 (–0.29, 0.55)
		Mean	–5.93	–6.06	
		SD	3.432	3.602	

CI = confidence interval; SD = standard deviation.

[a] CIs are based on the ANCOVA model with treatment and investigator as main effects and baseline worse eye IOP as the covariate. Estimated difference (bimatoprost preservative-free minus bimatoprost) was based on the least-squares means from the ANCOVA model.

Both treatments studied showed statistically and clinically significant mean decreases from baseline in worse eye IOP at all follow-up timepoints ($p < 0.001$). Mean changes from baseline IOP ranged from −7.49 to −5.93 mmHg for bimatoprost preservative-free, and from −7.77 to −6.06 mmHg for bimatoprost across the study as measured on weeks 2, 6, and 12 (hours 0, 2, and 8) in the PP population (Table 5).

15 MICROBIOLOGY

No microbiological information is required for this sterile drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology: The acute toxicity of bimatoprost was evaluated in single intraperitoneal and intravenous (IV) dose studies in mice and rats. A dose of 96 mg/kg administered intraperitoneally to mice, and up to 3 mg/kg IV administered to rats produced no adverse effects.

Long-term Toxicity

No treatment-related ocular or systemic effects were produced in Dutch belted rabbits when 0.03% or 0.1% bimatoprost ophthalmic formulation was instilled to the eye once or twice daily for 6 months. The highest dose (0.1% twice daily) produced 53 times the systemic drug exposure seen in humans treated with 1 drop in each eye of bimatoprost ophthalmic solution 0.03% once daily for 2 weeks.

No treatment-related systemic effects were observed in cynomolgus monkeys when 0.03% or 0.1% bimatoprost ophthalmic formulation was instilled to the eye once or twice daily for 1 year. An increase in iris pigmentation was noted in some animals in all treated groups. 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. Reversible dose-related periocular effects characterized by a prominent upper and/or lower sulcus and widening of the palpebral fissure of the treated eye was also observed. No functional or microscopic change related to the periocular change was observed. The highest dose (0.1% twice daily) produced at least 65 times the systemic drug exposure seen in humans treated with 1 drop into each eye of bimatoprost ophthalmic solution 0.03% once daily for 2 weeks. (Human dose calculated as 21 µg in a 35 µL drop dosed once daily in both eyes - not based on the 28 µL drop size as used in the bimatoprost Phase 3 studies).

No effects were observed in mice given 4 mg/kg/day bimatoprost orally for 3 months. This dose achieved systemic exposure that was 149 times higher than that observed in humans treated with bimatoprost ophthalmic solution 0.03% with 0.05 mg/mL benzalkonium chloride, one drop/day in both eyes for 14 days. Female mice given oral doses of 8 mg/kg/day showed a reversible thymic lymphoid proliferation. This effect was observed only in mice and at a dose

460-fold higher than that observed in humans given bimatoprost ophthalmic solution 0.03% with 0.05 mg/mL benzalkonium chloride, one drop/day in both eyes for 14 days.

Increased aspartate aminotransferase (AST) and alanine aminotransferase (ALT)(2- to 5-fold in males) was observed in rats given 8 or 16 mg/kg/day orally for 13 weeks. These changes were reversible after 4 weeks without treatment and no microscopic correlate was observed. In addition, increased ovarian weight and increased number of prominent, vacuolated corpora lutea were observed with these doses and with the dose of 4 mg/kg/day. Ovarian changes were also reversible at 4 weeks. The effects on the ovaries could be related to the pharmacological effect of this class drug in rats since these changes were not observed in other species. A dose of 4 mg/kg/day achieved systemic exposure that was 1538 times higher than that observed in humans treated with 1 drop into each eye of bimatoprost ophthalmic solution 0.03% once daily for 2 weeks.

A slight, reversible increase in ALT and AST was observed in rats given 0.1 mg/kg/day orally for 1 year. There were no associated microscopic liver findings. A dose-related, reversible cellular vacuolation of corpora lutea at 0.3 mg/kg/day in female rats was observed. The lowest effect dose of 0.1 mg/kg/day achieved systemic exposure (C_{max}) that was 8 times higher than that observed in humans treated with bimatoprost ophthalmic solution 0.03% with 0.05 mg/mL benzalkonium chloride, one drop/day in both eyes for 14 days. Hepatic and ovarian effects in rats were considered species-specific since these changes have not been observed in mice and monkeys at systemic exposures up to 2,800-to-14,000-fold higher, respectively, than those in humans given bimatoprost ophthalmic solution 0.03% with 0.05 mg/mL benzalkonium chloride, one drop/day in both eyes for 14 days.

No treatment related systemic effects were produced when monkeys were intravenously administered from 0.01 to 1.0 mg/kg/day bimatoprost for 17 weeks. An increase in the prominence of the periocular sulci and widening of the palpebral fissure of both eyes were observed in all treated monkeys. This finding was reversible at 12 weeks after cessation of treatment. A dose of 0.01 mg/kg/day achieved systemic exposure that was 235 times greater than that observed in humans treated with 1 drop into each eye of bimatoprost ophthalmic solution 0.03% once daily for 2 weeks.

Carcinogenicity: Bimatoprost was not carcinogenic when administered once daily orally (by gavage) at doses of 0.3, 1.0 and 2.0 mg/kg/day to mice and 0.1, 0.3 and 1.0 mg/kg/day to rats (192 or 291 times the human exposure based on blood AUC levels from subjects given bimatoprost ophthalmic solution 0.03% with 0.05 mg/mL benzalkonium chloride, one drop/day in both eyes for 14 days) for 104 weeks.

Mutagenicity: Bimatoprost was not mutagenic or clastogenic in a series of in vitro and in vivo studies (Ames test, mouse lymphoma and micronucleus tests).

Reproductive and Developmental Toxicology:

Impairment of Fertility

No impairment of fertility occurred in rats when males were treated for 70 days prior to cohabitation and females were treated for 15 days prior to mating. Treatment was continued in males until copulation was observed and in females through gestation day 7. The highest dose (0.6 mg/kg/day) achieved systemic exposure that was 103 times that observed in humans treated with 1 drop of bimatoprost ophthalmic solution 0.03% in each eye once daily for 2 weeks.

Pregnancy/Teratogenic Effects

Bimatoprost given orally at doses up to 0.3 or 0.6 mg/kg/day to pregnant rats during gestation day 7 through 17 caused abortion but no drug-related developmental effects. This effect was also seen in mice receiving 0.3 mg/kg/day during gestation day 6 through 15. The maternal no-observable-adverse-effect level (NOAEL) of bimatoprost was 0.1 or 0.3 mg/kg/day for mice or rats, respectively. Abortion was expected as a rodent-specific pharmacological effect. The lowest effect dose of 0.3 mg/kg in mice and rats achieved systemic exposure (AUC) that was at least 33 or 97 times higher respectively, than that observed in humans treated with bimatoprost ophthalmic solution 0.03% with 0.05 mg/mL benzalkonium chloride, one drop/day in both eyes for 14 days.

Perinatal and Postnatal

Treatment of F0 female rats given 0.3 mg/kg/day (at systemic exposure estimated at 41 times that observed in humans treated with bimatoprost ophthalmic solution 0.03% with 0.05 mg/mL benzalkonium chloride, one drop/day in both eyes for 14 days) or greater caused maternal toxicity as evidenced by reduced gestation length, increased late resorption, fetal death, and postnatal mortality and reduced pup body weight (a rodent-specific pharmacological effect). No effects on postnatal development and mating performance of the F1 offspring were observed in groups treated with dosages as high as 0.1 mg/kg/day. Neurobehavioral function, Caesarean- sectioning parameters, and litter parameters in F1 rats were unaffected by doses as high as 1.3 mg/kg/day.

Animal Lactation

In animal studies, bimatoprost has been shown to be excreted in breast milk.

Special Toxicology: Bimatoprost did not possess antigenic, cutaneous or systemic anaphylactic potential, or produce dermal contact hypersensitivity responses when administered topically, intradermally or systemically in rodents and guinea pigs.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]ZIMED® PF
bimatoprost ophthalmic solution (preservative-free)

Read this carefully before you start taking ZIMED® PF and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about ZIMED® PF.

What is ZIMED® PF used for?

ZIMED® PF eye drops are used to reduce high pressure in the eye in patients with conditions called "open angle glaucoma" or "ocular hypertension". If the high pressure is not reduced, it could damage your eye sight.

ZIMED® PF does not contain a preservative, so it may be used in patients who could benefit from preservative-free drops.

How does ZIMED® PF work?

ZIMED® PF is an antiglaucoma medicine. It belongs to a group of medicines called prostamides. Your eye contains a clear, watery liquid that feeds the inside of the eye. Liquid is constantly being drained out of the eye and new liquid is made to replace this. If the liquid cannot drain out quickly enough, the pressure inside the eye builds up.

ZIMED® PF works by increasing the flow of liquid that is drained. This reduces the pressure inside the eye.

What are the ingredients in ZIMED® PF?

Medicinal ingredient: Bimatoprost

Non-medicinal ingredients: Citric acid monohydrate, disodium hydrogen phosphate heptahydrate, water, sodium chloride. Small amounts of sodium hydroxide and/or hydrochloric acid may be added to adjust pH.

ZIMED® PF comes in the following dosage forms:

Ophthalmic solution, 0.03% w/v.

Do not use ZIMED®® PF if:

- if you are allergic to bimatoprost, to any of the other ingredients, or to any of the parts of the container (see **What are the ingredients in ZIMED® PF)**.

- If you are allergic to silver. The cap and top of the ZIMED® PF bottle contain silver to prevent bacterial growth. ZIMED® PF may contain traces of silver in the dispensed drops.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ZIMED® PF. Talk about any health conditions or problems you may have, including if you:

- are taking or have recently taken any other medicines.
- are pregnant or breastfeeding a baby. Talk to your healthcare professional before taking any medicine.
- have an active eye infection or any other eye condition.
- develop another eye condition (an injury or an infection).
- need to have eye surgery.

Other warnings you should know about:

Driving and Using Machinery:
Your sight may become blurred for a short period of time just after using ZIMED® PF. Do NOT drive or use machines until your sight is clear again.

Skin and Eyelashes:
ZIMED® PF may cause your eyelashes to darken, thicken, and grow, and cause the skin around the eyelid to darken too. Avoid having it running onto the cheek or other skin areas.

Eye Colour:
The colour of your iris (eye) may also go darker over time. These changes may be permanent. The change may be more noticeable if you are only treating one eye. The long-term effects on the eye colour are unknown.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

No drug interaction studies have been done with ZIMED® PF.

Your healthcare professional needs to know about other medicines (including eye drops) that you are using or plan to use. This includes medicines obtained without a prescription.

Use of ZIMED® PF with other eye products should be discussed with your healthcare professional beforehand.

How to take ZIMED® PF:
The recommended dose is 1 drop in the affected eye(s) once daily in the evening.

Do NOT use if the tamper-proof seal on the bottle neck is broken before you first use ZIMED® PF.

Do NOT use ZIMED® PF while you wear contact lenses. If you wear contact lenses, take your lenses out before using ZIMED® PF. Wait 15 minutes after using the drops before you put your lenses back in.

If you use ZIMED® PF with another eye drop, wait at least 5 minutes between putting in ZIMED® PF and then the other drops.

1. Before putting a drop in the eye, release the first drop away from the eye to check the force needed to get only one drop out of the bottle.

2. Wash your hands. Tilt your head back and look at the ceiling.

3. Gently pull down the lower eyelid until there is a small pocket.

4. Turn the bottle upside down and squeeze it to release one drop into each eye that needs treatment.

5. Let go of the lower lid and close your eye for 30 seconds.

6. Wipe off any excess that runs down the cheek or other skin areas.
   If a drop misses your eye, try again.

Before putting the cap back on, shake the bottle once in a downwards direction, without touching the dropper tip. This is to remove any liquid on the tip. To avoid infections and eye injury, do not let the tip of the bottle touch your eye or anything else. Put the cap back on and close the bottle right after you have used it.

Usual Dose:
1 drop in the affected eye(s) once daily in the evening.

Overdose:

If you think you, or a person you are caring for, has taken too much ZIMED® PF or in case of accidental swallowing, immediately contact your healthcare professional, regional poison control centre or hospital emergency department, even if there are no symptoms.

Missed Dose:
If you forget to take ZIMED® PF, use a single drop as soon as you remember, and then go back to your regular dosing schedule. Do not take two doses in the same day to make up for the one that you missed.

Talk to your healthcare professional before stopping this treatment. If you stop using ZIMED® PF, the pressure inside your eye may go up.

What are possible side effects from using ZIMED® PF?
These are not all the possible side effects you may have when taking ZIMED® PF. If you experience any of the side effects not listed here, tell your healthcare professional.

- A feeling that something is in your eye
- Blurred vision
- Darker iris colour
- Darker skin colour around the eye
- Dryness
- Eye redness
- Hair growth around the eye
- Headaches
- Irritation
- Itchy and swollen eyelids
- Itchy eyes
- Longer eyelashes
- Pain
- Red eyelids
- Sensitivity to light
- Small breaks in the surface of the eye (with or without inflammation).
- Swelling of the cornea
- Tears
- Tired eyes

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional."

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting www.healthcanada.gc.ca/medeffect for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store ZIMED® PF between 15 °C and 25 °C.

Store in the original bottle and keep the bottle in the outer carton in order to protect from light.

Do not use the drops after the expiry date stated on the bottle label and carton. The expiry date refers to the last day of that month.

Once the bottle is opened, it should be used within 28 days, even if there are still some drops left. This will prevent infections. To help you remember, write down the date you opened it.

Ask your healthcare professional how to dispose of medicines you no longer use.

Keep out of reach and sight of children.

If you want more information about ZIMED® PF:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drugproduct-database.html; the manufacturer's website https://www.luvomedical.com, or by calling 1-833-542-2633

This leaflet was prepared by Luvo Medical Technologies Inc.

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