PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrAPO-BIMATOPROST

Bimatoprost Topical Solution

Solution, 0.03% w/v, Topical

Prostamide Analogue

APOTEX INC. 150 Signet Drive Toronto Ontario M9L 1T9	Date of Initial Authorization: SEP 10, 2013 Date of Revision: OCT 13, 2022

Submission Control Number.: 263284

RECENT MAJOR LABEL CHANGES

N/A

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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

APO-BIMATOPROST (bimatoprost topical solution, 0.03% w/v) is indicated for:

- treatment of hypotrichosis of the eyelashes by increasing their growth including length, thickness and darkness.

Patients without visible eyelashes were not studied.

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 and other adult patients. Use as for adult patients.

2 CONTRAINDICATIONS

- APO-BIMATOPROST 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 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Not applicable.

4.2 Recommended Dose and Dosage Adjustment

- Special device and administration procedure are recommended for delivering proper dose of APO-BIMATOPROST once nightly. This is done by adding ONLY ONE drop of the drug solution on a special applicator with which the medication is applied to the upper eyelid margin of one eye following a specified administration procedure. See 4.4 Administration. As a result, only a small fraction of the solution applied to the applicator/device is actually administered on the dermal part of the upper eye lid margin of each eye per day. The recommended administration procedure should be closely followed to ensure the recommended dose is properly applied. See 4.4 Administration.
- Additional applications of APO-BIMATOPROST will not increase the growth of eyelashes and may increase the risk of adverse reactions. See 8.5 Post-Market Adverse Reactions.
- Upon discontinuation of treatment, eyelash growth is expected to gradually return to its pre-treatment level.

Health Canada has not authorized an indication for pediatric use.

4.3 Reconstitution

Not applicable.

4.4 Administration

Intended for dermal topical application to the upper eyelid margin.

The following administration procedure should be closely followed to ensure that recommended dose is administered.

Ensure the face is clean, makeup and contact lenses are removed. Once nightly, place ONLY one drop of APO-BIMATOPROST solution on the disposable sterile applicator supplied with the package and apply evenly along the skin of the upper eyelid margin at the base of the eyelashes. The upper lid margin in the area of lash growth should feel lightly moist without runoff. Blot any excess solution runoff outside the upper eyelid margin with a tissue or other absorbent cloth. Dispose of the applicator after one use. Repeat for the opposite eyelid margin using a NEW sterile applicator.

- Do not apply directly in the eye.
- Do not add more than one drop to an applicator.
- Blot any excess solution outside the upper eyelid margin with a tissue or other absorbent material.
- Do not administer the medication more than once daily.
- Do not apply to the lower eyelash line.
- Do not use the same applicator for more than one eye.
- Do not reuse applicators.
- Do not alter the applicator in any form.
- Do not use any other brush/applicator to apply APO-BIMATOPROST.

See PATIENT MEDICATION INFORMATION, How to take APO-BIMATOPROST section.

4.5 Missed Dose

If a dose is missed, patients should be instructed to return to their regular routine the following day.

5 OVERDOSAGE

No information is available on overdosage in humans. If overdose with APO-BIMATOPROST occurs, treatment should be symptomatic. If bimatoprost topical solution is accidentally ingested, the following information may be useful: in 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 165 times higher than the amount of bimatoprost to which a 10 kg child would be exposed were it to accidentally ingest one 3 mL bottle of bimatoprost topical solution.

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
Topical	Solution / 0.03% w/v	benzalkonium chloride 0.05 mg/mL as preservative, citric acid anhydrous, sodium chloride, sodium phosphate dibasic anhydrous, and water for injection. hydrochloric acid and/or sodium hydroxide may be added to adjust pH.

APO-BIMATOPROST Topical Solution, 0.03% w/v is supplied in white opaque polypropylene bottles with translucent polypropylene droppers and turquoise opaque polypropylene caps in the following configuration: 3 mL sterile solution in a 5 mL bottle accompanied by 60 disposable applicators.

APO-BIMATOPROST Topical Solution, 0.03% w/v is a clear, isotonic, buffered, preserved, colorless, sterile solution with a pH of 7.3 ± 0.5, and an osmolality of approximately 290 mOsmol/kg.

APO-BIMATOPROST Topical Solution, 0.03% w/v is packaged as follows:

- 3 mL bottle of sterile solution, accompanied by 60 sterile disposable applicators packaged in a separate blister format. These 2 components, solution and applicators, are combined in a carton.

7 WARNINGS AND PRECAUTIONS

General

Patients who receive treatment with APO-BIMATOPROST should be informed of the possibility of increased iris pigmentation (IP).

Carcinogenesis and Mutagenesis

Bimatoprost was neither carcinogenic nor mutagenic in animals and *in vitro* studies. See 16 NON-CLINICAL TOXICOLOGY.

Driving and Operating Machinery

As with any ocular medication, if transient blurred vision occurs after application to the upper eyelashes, the patient should wait until the vision clears before driving or using machinery.

Hepatic/Biliary/Pancreatic

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

Ophthalmologic

Iris Pigmentation:

Bimatoprost-containing products, including bimatoprost ophthalmic solution and bimatoprost topical solution, have been associated with IP. See 8.5 Post-market Adverse Reactions. Based on clinical experience with bimatoprost-containing products, iris color changes may not be noticeable for weeks to

several months or longer, although there are some reports associated with shorter duration of treatment. The related causes are not known. See 8.5 Post-Market Adverse Reactions.

Typically in bimatoprost-associated IP, increased brown pigmentation around the pupil spreads concentrically towards the periphery of the iris. This may affect the entire iris. The color change may not be symmetrical in the iris of an eye or between the irises of the two eyes. Darker or brown spots in iris were reported in some of the post-marketing cases of bimatoprost topical solution. See 8.5 Post-Market Adverse Drug Reactions. Bimatoprost-induced IP is most likely permanent. Treatment with APO-BIMATOPROST should be discontinued if IP is observed.

Because overall exposure to bimatoprost is considerably lower with bimatoprost topical solution than with bimatoprost ophthalmic solution, under approved conditions of use, it is expected that the risk of IP associated with bimatoprost topical solution would be very low compared to the risk associated with the use of bimatoprost ophthalmic solution. However, there have been higher numbers of reports of IP with bimatoprost topical solution use than anticipated. Because improper use may play a role in increasing the risk of IP with bimatoprost topical solution, it is important to emphasize the correct use of the product and advise patients to use bimatoprost topical solution according to the specialized administration procedure. See 4.4 Administration).

Contamination of Bimatoprost Topical Solution or Applicators

The tip of the APO-BIMATOPROST bottle should not be allowed to contact the eye, surrounding structures, fingers or any other surface in order to avoid eye injury or contamination of the solution. It is important to use APO-BIMATOPROST as instructed, by placing one drop on the single-use-per eye applicator. The accompanying sterile applicators should only be used on one eye and then discarded since reuse of applicators increases the potential for contamination and infections. There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. See PATIENT MEDICATION INFORMATION, How to take APO-BIMATOPROST section.

Effects on Intraocular Pressure:

Bimatoprost ophthalmic solution lowers intraocular pressure (IOP) when instilled directly to the eye in patients with elevated IOP. In clinical trials, in patients without elevated IOP, bimatoprost topical solution lowered IOP, however, the magnitude of the reduction was not cause for clinical concern.

In ocular hypertension studies with bimatoprost ophthalmic solution it has been shown that exposure of the eye to more than one dose of bimatoprost daily may decrease the IOP lowering effect. In patients using bimatoprost ophthalmic solution or other prostaglandin analogs for the treatment of elevated IOP, the concomitant use of bimatoprost topical solution may interfere with the desired reduction in IOP. Patients using prostaglandin analogs including bimatoprost ophthalmic solution for IOP reduction should only use APO-BIMATOPROST after consulting with their physician and should be monitored for changes to their IOP.

Intraocular Inflammation:

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

Macular Edema:

Macular edema, including cystoid macular edema, has been reported during treatment with bimatoprost 0.03% ophthalmic solution for elevated IOP. APO-BIMATORPOST 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.

Use with Contact Lenses:

Contact lenses should be removed prior to application of APO-BIMATOPROST and may be reinserted 15 minutes following its administration. Patients should be advised that APO-BIMATOPROST contains benzalkonium chloride, which may be absorbed by soft contact lenses.

Renal

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

Reproductive Health: Female and Male Potential

- **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 Area Under the Curve (AUC) levels after ocular administration).

Skin

Hair Growth Outside the Treatment Area:

There is the potential for hair growth to occur in areas where bimatoprost topical solution comes in repeated contact with the skin surface. It is important to apply APO-BIMATOPROST only to the skin of the upper eyelid margin at the base of the eyelashes using the accompanying sterile applicators, and to carefully blot any excess APO-BIMATOPROST from the eyelid margin to avoid it running onto the cheek or other skin areas.

Lid Pigmentation:

Bimatoprost has been reported to cause pigment changes (darkening) to periorbital pigmented tissues and eyelashes. The increased pigmentation is expected to be present as long as bimatoprost is administered but has been reported to be reversible upon discontinuation of bimatoprost in most patients.

Pigment changes (darkening) of lids observed with the use of bimatoprost ophthalmic solution during clinical trials were periorbital, whereas these changes reported during clinical trials with the use of bimatoprost topical solution were limited to the targeted applied area (upper eyelid), and occurred less frequently.

Patients with no visible eyelashes-alopecia:

The efficacy and safety of bimatoprost topical solution in patients with no visible eyelashes due to underlying systemic diseases or conditions (e.g., alopecia universalis, or trichotillomania) or drug-induced alopecia (e.g., cytotoxic antineoplastic agents) has not been studied. It is recommended that the underlying condition or systemic disease be managed appropriately prior to considering APO-BIMATOPROST.

7.1 Special Populations

7.1.1 Pregnant Women

There are no adequate and well-controlled studies of bimatoprost topical solution administration in pregnant women. Because animal reproductive studies are not always predictive of human response,

APO-BIMATOPROST 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 that were at least 33 or 97 times, respectively, the intended human exposure (AUC) after ocular administration of bimatoprost ophthalmic solution.

Maternal toxicity and reduced pup body weights were observed when female rats received oral doses that were at least 41 times the intended human exposure (AUC) after ocular administration of bimatoprost ophthalmic solution. See NON-CLINICAL TOXICOLOGY.

As the clinical dose of bimatoprost topical solution is a fraction of the bimatoprost ophthalmic solution dose, the above margins of safety for maternal and embryo/fetal effect are expected to be greater for bimatoprost topical solution.

7.1.2 Breast-feeding

It is not known whether bimatoprost is excreted in human milk, although in animal studies, bimatoprost has been shown to be excreted in breast milk. Because many drugs are excreted in human milk, caution, considering the benefit to risk ratio, should be exercised when APO-BIMATOPROST is administered to a nursing woman.

7.1.3 Pediatrics

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

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

In one multicentre, double-masked, randomized, vehicle-controlled, parallel study of 4 months duration (Study 192024-032), most adverse events detected were ocular, mild to moderate, and not serious.

The most frequently reported adverse events with the use of bimatoprost topical solution were eye pruritis, conjunctival hyperemia, skin hyperpigmentation, ocular irritation, dry eye symptoms, and erythema of the eyelid. These events occurred in less than 4% of patients (see **Table 2**).

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.

In the clinical study (192924-032) 278 subjects with hypotrichosis, otherwise healthy (without ocular or systemic diseases) were treated with bimatoprost topical solution for four months. Subjects (n=251) followed a post-treatment period that lasted 4 weeks.

Adverse reactions that were reported by greater than 1% of subjects enrolled in Study 192024-032 are presented in **Table 2.**

Table 2 Number (%) of Adverse Reactions Reported by Greater Than 1% of Subjects, Treatment and Post-treatment Periods Combined (Study 192024-032)

	Bimatoprost Topical Solution n = 137 (%)	**Vehicle n = 141 (%)**
Eye Disorders		
Eye pruritus	5 (3.6)	1 (0.7)
Conjunctival hyperemia[a]	5 (3.6)	0 (0.0)
Eye irritation	3 (2.2)	2 (1.4)
Dry eye	3 (2.2)	1 (0.7)
Erythema of eyelid	3 (2.2)	1 (0.7)
Immune System Disorders		
Seasonal allergy	2 (1.5)	0 (0.0)
Infections and Infestations		
Sinusitis	2 (1.5)	2 (1.4)
Influenza	2 (1.5)	0 (0.0)
Benign and Malignant Neoplasms		
Blepharal papilloma	2 (1.5)	0 (0.0)
Skin and Subcutaneous Tissue Disorders		
Skin hyperpigmentation	4 (2.9)	1 (0.7)
Dermatitis contact	2 (1.5)	0 (0.0)

[a] Conjunctival hyperaemia was the only preferred term that was reported by a statistically significantly higher percentage of subjects in the bimatoprost group compared with the vehicle group.

Overall for the study as a whole, 40.1% (55/137) of subjects in the bimatoprost group and 29.1% (41/141) of subjects in the vehicle group reported at least 1 adverse event (AE), a difference that was not statistically significant. Four subjects in each treatment group discontinued the study due to an adverse event. The adverse events that led to study discontinuation by the 4 subjects in the vehicle group were lymphoma, eyelid erythema, conjunctival hemorrhage (all mild or moderate severity), and low IOP (severe). The adverse events that led to study discontinuation by the 4 subjects in the bimatoprost group were eczema, dry eye, eye inflammation, and contact dermatitis, all of which were of mild or moderate severity. All were ongoing at the time of discontinuation, with the exception of contact dermatitis, which had resolved without sequelae. The adverse event of eye inflammation was considered by the investigator to be unrelated to treatment.

Adverse reactions reported with bimatoprost ophthalmic solution for the reduction of intraocular pressure include, ocular dryness, visual disturbance, ocular burning, foreign body sensation, eye pain, blepharitis, cataract, superficial punctate keratitis, eye discharge, tearing, photophobia, allergic conjunctivitis, asthenopia, increases in iris pigmentation, conjunctival edema, conjunctival hyperemia,

macular edema, eyelid edema, periorbital erythema, abnormal hair growth, iritis, deepened lid sulcus, enophthalmos, infections (primarily colds and upper respiratory tract infections), hypertension, headaches, dizzinesss, nausea, asthenia, eye pruritus, eyelid pruritus, irritation eye, erythema eyelid, blepharal pigmentation.

8.3 Less Common Clinical Trial Adverse Reactions

Clinical studies have shown increased IP in glaucoma patients treated with bimatoprost ophthalmic products. In clinical trials, the incidence of IP associated with bimatoprost ophthalmic solution, 0.03% w/v and bimatoprost ophthalmic solution, 0.01% w/v was 1.5% and 0.05%, respectively. Based on the dose-dependent nature of bimatoprost ophthalmic solution-associated IP and the fact that the daily administered bimatoprost dose in the bimatoprost topical solution therapy is only about 5% of that in bimatoprost ophthalmic solution, 0.03% w/v, the risk of bimatoprost topical solution-associated IP is expected to be very low. However, during the post-marketing phase, there have been reports of IP associated with the use of bimatoprost topical solution. See 8.5 Post-Market Adverse Reactions.

For bimatoprost ophthalmic solution the following ocular AEs (<1%) were blepharospasm, eyelid oedema, chalazion, eye oedema, hordeolum, conjunctival bleb, conjunctival folliculosis, eyelid pain, iritis (ocular inflammation), keratitis, visual field defect, vitreous floaters.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Not applicable.

8.5 Post-Market Adverse Reactions

In addition to what has been observed in clinical trials, the following adverse reactions have been identified during post marketing use of bimatoprost topical solution in clinical practice. 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: blepharitis, eye discharge, eye pain, eye swelling, eyelid edema, eyelid irritation, eyelid pain, eyelids pruritus, foreign body sensation in eyes, increased lacrimation, iris hyperpigmentation, periorbital and lid changes associated with periorbital fat atrophy and skin tightness resulting in deepening of eyelid sulcus and eyelid ptosis, skin exfoliation of the eyelid and/or periorbital area, vision blurred.

It is clear that bimatoprost exposure levels with bimatoprost topical solution are a fraction of that seen with bimatoprost ophthalmic solution use in glaucoma, if used according to recommended conditions; nevertheless, there have been reports of IP with bimatoprost topical solution use. In addition, the post-marketing reporting rate of IP with bimatoprost topical solution is higher than that observed with bimatoprost ophthalmic solution. While the exact reason for the observed differences is not clear, improper administration and excessive doses of bimatoprost topical solution may result in increased reports of IP. See 4.4 Administration.

Immune system disorder: hypersensitivity (systemic allergic reaction), hypersensitivity (local allergic reaction)

Nervous system disorder: headache

Skin and subcutaneous tissue disorders: burning sensation (eyelid), dry skin of the eyelid and/or periocular area, erythema periorbital, hair growth abnormal, hordeolum, 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), skin discoloration (periorbital), trichiasis, trichorrhexis (temporary eyelash breakage).

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 and as metabolism and excretion involves multiple pathways. Topical dermal administration of bimatoprost topical solution is expected to result in lower systemic drug concentrations than after topical ocular administration.

In ocular hypertension studies with bimatoprost ophthalmic solution, it has been shown that exposure of the eye to more than one dose of bimatoprost daily may decrease the IOP lowering effect. In patients using bimatoprost ophthalmic solution or other prostaglandin analogs for the treatment of elevated IOP, the concomitant use of bimatoprost topical solution may interfere with the desired reduction in IOP. Patients using prostaglandin analogs including bimatoprost ophthalmic solution for IOP reduction should only use APO-BIMATOPROST after consulting with their physician and should be monitored for changes to their IOP. See 7 WARNINGS AND PRECAUTIONS.

9.3 Drug-Behavioural Interactions

Not applicable.

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 $F_{2\alpha}$ ($PGF_{2\alpha}$) in that the carboxylic acid group is replaced with an electronically neutral substituent. Its mechanism of action resembles that of prostamide $F_{2\alpha}$, a naturally occurring substance. Bimatoprost topical solution exhibits no meaningful pharmacological activity at known prostaglandin receptors as well as no uterotonic or mitogenic activity.

Although the precise mechanism of action is not entirely understood, the growth of eyelashes is believed to occur by increasing the duration of the anagen or growth phase of the hair cycle: increased thickness/fullness is believed to result from extending the anagen phase and increase in darkness occurs by stimulation of pigment (melanin) formation in the hair follicles. The overall effect is increased length, thickness and darkness of eyelashes (prominence).

10.2 Pharmacodynamics

Daily administration (once a day) of bimatoprost ophthalmic solution 0.03% for 14 days to mouse eyes produced a significant increase in eyelash number with no signs of inflammation, hyperplasia, or other adverse effects. Bimatoprost ophthalmic solution 0.03% also increased the length and thickness of mouse eyelashes. Additional studies in ocular normotensive and laser-induced ocular hypertensive cynomolgus monkeys indicated that bimatoprost potently reduces intraocular pressure when applied to the eye. Five-day studies in ocular normotensive monkeys and one day studies in ocular hypotensive monkeys demonstrated that a 0.001% dose of bimatoprost could significantly lower intraocular pressure. Five day studies in ocular normotensive Beagle dogs confirmed bimatoprost as a potent ocular hypotensive over a dose range of 0.001% to 0.1% when given either once daily or twice daily.

Bimatoprost did not alter pupil diameter in monkeys at the 0.1% dose. This is in contrast to Beagle dog studies, where 0.001% to 0.1% doses produced miosis.

10.3 Pharmacokinetics

Table 3 – Summary of Mean Bimatoprost Pharmacokinetic Parameters Following Once-daily Ocular Administration of Bimatoprost 0.03% to Each Eye of Healthy Subjects for 2 Weeks

Collection Day	C_{max} (ng/mL)	T_{max} (hr)	AUC (ng•hr/mL)[a]
1	0.0864	0.105	0.1024
7	0.0721	0.131	0.0742
14	0.0822	0.107	0.0960

[a] AUC refers to $AUC_{0\text{-}inf}$ on Day 1 and $AUC_{0\text{-}24h}$ on Days 7 and 14.

After one drop of 0.03% bimatoprost ophthalmic solution 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 0.03% bimatoprost ophthalmic solution to both eyes.

In patients with glaucoma or ocular hypertension, bimatoprost blood concentrations were similar to those observed in normal healthy subjects.

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. The once daily regimen corresponded to a total exposure of 6.13 mg (one 28 mcL 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 penetrates the human cornea and sclera well *in vitro*. The mean corneal permeability coefficient was 3.24 x 10^{-6} cm/sec. Bimatoprost penetrated human scleral tissue better than corneal tissue with a mean scleral permeability coefficient of 14.5 x 10^{-6} cm/sec.

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 with bimatoprost ophthalmic solution 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 accumulation of bimatoprost following twice-daily dosing for 7 days in either young (18 to 44 years, mean = 28.5) or elderly patients (65 to 80 years, mean = 71.0). Bimatoprost appeared rapidly in the blood in both age groups, and was below the LLOQ by 1.5 hours in most patients. Systemic exposure was higher in the elderly than the young following both single and multiple dosing (124% and 213%, respectively). The mean AUC_{0-24} hr value of 0.0634 ng•hr/mL in elderly subjects was statistically significantly higher than that of 0.0218 ng•hr/mL in young subjects, suggesting the existence of an age effect. However, this finding is not considered clinically relevant as bimatoprost exhibits similar efficacy and safety profiles in both the young and elderly populations.

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 mcg/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 mcg/kg) to six healthy subjects, the maximum blood concentration of unchanged drug was 12.2 ng/mL and decreased rapidly with an elimination half-life of approximately 45 minutes. The total blood clearance of bimatoprost was 1.5 L/hr/kg. Up to 67% of the administered dose was excreted in the urine while 25% of the dose was recovered in the feces. Both urinary and fecal routes are important pathways for elimination of the parent compound and its metabolites, following intravenous administration.

Special Populations and Conditions

- **Geriatrics:** Elderly individuals (>65 years) exhibited higher systemic levels but this was not considered to be clinically relevant since bimatoprost had a similar efficacy and safety profile in both the young (<65 years of age) and elderly that participated in the clinical trials.

11 STORAGE, STABILITY AND DISPOSAL

APO-BIMATOPROST Topical Solution, 0.03% w/v should be stored in the original container at 2°C to 25°C.

Discard 28 days after opening.

Keep out of reach and sight of children.

12 SPECIAL HANDLING INSTRUCTIONS

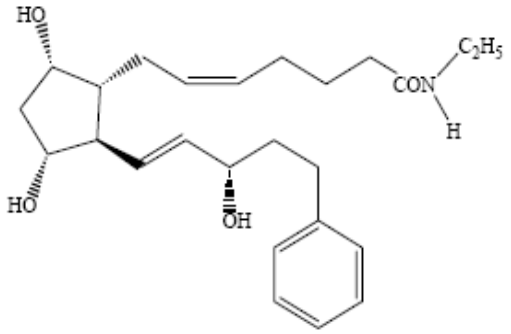
There are no special handling instructions.

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:	$C_{25}H_{37}NO_4$ and 415.58 g/mol
Structural Formula:	



Physicochemical properties:	Bimatoprost is a white to off-white powder, which is very soluble in ethyl alcohol and methyl alcohol and slightly soluble in water.
Melting Point:	68°C ± 2°C
Optical Rotation:	$[\alpha_D]$ +33 at 37°C
Solubility in pH 2-9:	0.04 mg/mL
pKa:	16.46 ± 0.46

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Treatment of Hypotrichosis of the Eyelashes

Table 4 - Summary of patient demographics for clinical trials in treatment of hypotrichosis of the eyelashes

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
192024-032	multicentre, double-masked, randomized, vehicle-controlled, parallel study	Bimatoprost 0.03% QD Vehicle QD One drop was applied to the special applicator and was applied over the upper eyelid margin once daily. Any run-off of the medication was to be blotted. 4 months	278 total: BIM: N=137 Vehicle: N=141	49.8 (22 - 78)	F=270 M= 8

The 2 treatment groups were comparable at baseline, with no statistically significant demographic differences. Overall, the mean age of the subjects was 49.8 years (range 22–78 years). The majority of the population were female (97.1%) and Caucasian (80.9%). The majority of subjects had light irides (60.1%). As per inclusion criteria, all enrolled subjects conformed to the Global Eyelash Assessment (GEA) scale at baseline with a score of 1 (20.1%) or 2 (79.9%), with a similar distribution of GEA scores in both treatment groups. No subjects in either treatment group had baseline GEA scores of 3 (marked) or 4 (very marked).

Patients with no visible eyelashes due to underlying systemic diseases or conditions (e.g., alopecia universalis, or trichotillomania) or drug-induced alopecia (e.g., cytotoxic antineoplastic agents) were excluded from the study. See 7 WARNING AND PRECAUTIONS.

Results of study in treatment of hypotrichosis of the eyelashes

Bimatoprost topical solution was evaluated for its effect on overall eyelash prominence in a multicentre, double-masked, randomized, vehicle-controlled, parallel study including 278 adult patients for four months of treatment. The primary efficacy endpoint in this study was the proportion of subjects achieving an increase in overall eyelash prominence as measured by at least a 1- grade increase on the 4-point Global Eyelash Assessment (GEA) scale, from baseline to the end of the treatment period (week 16). Bimatoprost topical solution was more effective than vehicle in improving the GEA score, with statistically significant differences seen at 8-week, 12-week, and 16-week (**primary endpoint**) treatment durations.

The proportion of subjects achieving ≥ 1 GEA grade was statistically significantly different from vehicle from 8 weeks of treatment to end of treatment (Week 16, endpoint) see **Table 5**.

The GEA is a 4-point scale with representative photos for each grade comprised of the scores “minimal, moderate, marked, and very marked.” GEA scale with a photonumeric (photography) guide provides the necessary photo guidance for clinicians in the assignment of 1 of these 4 scores in the assessment of

overall eyelash prominence. To use the tool, the investigator assesses the subjects' eyelashes across both eyes during a live evaluation and assigns a score based on a comparison between the subject's eyelashes and the photonumeric guide.

Table 5 - Number (%) of subjects with at least a 1-grade increase from baseline in Global Eyelash Assessment, Treatment and Post-treatment Periods (ITT Population)

Visit[a]	Bimatoprost Topical Solution N=137 N (%)	Vehicle N=141 N (%)	p-value[b]
Week 1	7 (5.1%)	3 (2.1%)	0.2124[c]
Week 4	20 (14.6%)	11 (7.8%)	0.0719
Week 8	69 (50.4%)	21 (14.9%)	< 0.0001
Week 12	95 (69.3%)	28 (19.9%)	< 0.0001
Week 16 (Primary Endpoint)	107 (78.1%)	26 (18.4%)	< 0.0001
Week 20 (Post-treatment phase)	103 (78.6%)	27 (21/4)	< 0.0001

[a] LOCF was performed on weeks 1 to 16 and week 20 analysis was based only on observed cases.

[b] P-values are based on Pearson's chi-square test or Fisher's exact test if at least 25% of the cells have expected cell sizes of < 5.

[c] Fisher's exact test was performed.

In this study, patients were also evaluated for the effect of bimatoprost topical solution on the length, thickness, and darkness of their eyelashes. Improvements from baseline in eyelash growth as measured by digital image analysis (number of pixels) assessing eyelash length, fullness/thickness, and darkness were statistically significantly more pronounced in the bimatoprost group at week 8.

Upon discontinuation of treatment, eyelash growth is expected to return to its pre-treatment level.

Secondary endpoints are presented in **Table 6**.

Table 6 - Improvements from baseline in eyelash growth as measured by digital image analysis assessing eyelash length, fullness/thickness, and darkness (ITT population)

Efficacy endpoint at Week 16 (mean change from baseline)	Bimatoprost Topical Solution	Vehicle	p-value
Eyelash length (mm; % increase; pixels*)	N=137 1.39; 25%; 51.63	N=141 0.11; 2%; 4.19	< 0.0001
Fullness/thickness (mm^2; % increase; pixels*)	N=136 0.71; 106%; 12.21	N=136 0.06; 12%; 1.10	< 0.0001
Eyelash darkness (intensity**; % increase in darkness)	N=135 -20.15; -18%	N=138 -3.57; -3%	< 0.0001

* 1 pixel is approximately 0.027 mm

** a negative value is representative of eyelash darkening

After the 16-week treatment period, a 4-week post-treatment period followed during which the effects of bimatoprost on increased eyelash prominence, length, thickness, and darkness were maintained to a

statistically significant degree ($p < 0.0001$ for all). Longer term effect of discontinuation has not been assessed. The effect on eyelash growth is likely reversible following longer term discontinuation.

When evaluating patients who achieved a 2-grade increase on the 4-point GEA scale from baseline to the end of the treatment period (week 16), bimatoprost topical solution was more effective than vehicle in the GEA score, with statistically significant differences seen at 12-week and 16-week (primary endpoint) treatment durations.

Table 7 - Number (%) of Subjects with at Least a 2-Grade Increase from Baseline in GEA Score on the 4-Point GEA Scale: Treatment and Post-treatment Periods (ITT Population)

Visit[a]	Bimatoprost 0.03% (N = 137)	Vehicle (N = 141)	P-value[b]
Week 1	0/137 (0.0)	0/141 (0.0)	N/A
Week 4	0/137 (0.0)	0/141 (0.0)	N/A
Week 8	5/137 (3.6)	1/141 (0.7)	0.1164[c]
Week 12	28/137 (20.4)	1/141 (0.7)	< 0.0001
Week 16	45/137 (32.8)	2/141 (1.4)	< 0.0001
Week 20	49/131 (37.4)	4/126 (3.2)	< 0.0001

N/A: not applicable

Note: Summaries of week 1 to 16 pertain to the ITT population in the treatment period and week 20 the post-treatment period.

[a] LOCF was performed for weeks 1 through 16; week 20 analysis was based only on observed cases.

[b] P-values are based on Pearson's chi-square test or Fisher's exact test if at least 25% of the cells have expected cell sizes of < 5.

[c] Fisher's exact test was performed.

15 MICROBIOLOGY

No microbiological information is required for this 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 0.03% bimatoprost 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 0.03% bimatoprost once daily for 2 weeks. (Human dose calculated as 21 mcg in a 35 mcL drop dosed once daily in both eyes - not based on the 28 mcL drop size as used in the bimatoprost ophthalmic solution Phase III studies.)

No effects were observed in mice given 4 mg/kg/day bimatoprost orally for 3 months. This dose achieved systemic exposure that was at least 149 times higher than that observed in humans after topical ocular administration. 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 far exceeding the intended human exposure after ocular administration (460-fold higher).

Increased serum aminoglutamate oxaloacetate and glutamate pyruvate transaminase (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 at least 1538 times higher than that observed in humans treated with 1 drop into each eye of 0.03% bimatoprost once daily for 2 weeks.

A slight, reversible increase in alanine aminotransferase and aspartate aminotransferase 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 the human clinical dose after topical ocular administration. 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 topical ocular doses of bimatoprost (1 drop into each eye of 0.03% bimatoprost once daily for 2 weeks).

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 0.03% bimatoprost once daily for 2 weeks.

Penetration into the eyelid skin by molecules of similar molecular weight and logP to bimatoprost is low, approximately 1.5%, therefore, the systemic exposure after dermal application of bimatoprost 0.03% on the upper eyelid margin is not expected to exceed that obtained after ocular dosing in humans. In addition, the amount of product, and therefore dose, delivered to the eyelid by topical dermal application is lower than the dose given to the eye by ocular administration.

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 (approximately 192 or 291 times the human exposure after ocular administration based on AUC levels) for 104 weeks.

Genotoxicity: Bimatoprost was not mutagenic or clastogenic in a series of *in vitro* and *in vivo* studies (Ames test, Mouse Lymphoma and Micronucleus tests).

Salmonella/Escherichia Coli Mutagenicity Assay:

Bimatoprost was tested in the bacterial reverse mutation assay (Ames assay) using *S. typhimurium* tester strains TA98, TA100, TA 1535, and TA1537 and E. coli tester strains WP2 uvrA (pKM101) and WP2

(pKM101) in the presence and absence of Aroclor-induced rat liver S9. No positive response was observed in the mutagenicity assay at concentrations of up to 5000 mcg per plate.

Mouse Lymphoma Mutagenesis Assay:

Bimatoprost was tested in the reduced volume L5178Y/TK+/- mouse lymphoma mutagenesis assay in the presence and absence of Aroclor-induced rat liver S9, and was negative when tested at concentrations up to 900 mcg/mL with or without S9.

In Vivo Mouse Micronucleus Assay:

Bimatoprost was assayed for clastogenic activity and potential to disrupt the mitotic apparatus by evaluating micronuclei in polychromatic erythrocyte (PCE) cells in mouse bone marrow. Bimatoprost is considered negative in the mouse bone marrow micronucleus test following 20 mg/kg/day in mice. The high dose was based on the limit of solubility.

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 0.03% bimatoprost 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 6 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 1 drop of 0.03% bimatoprost in each eye once daily for 2 weeks.

Perinatal and Postnatal:

Treatment of F0 female rats given 0.3 mg/kg/day (at systemic exposure estimated 41 times the intended clinical dose) 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 0.3 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.

17 SUPPORTING PRODUCT MONOGRAPHS

1) LATISSE® (bimatoprost) Topical Solution, 0.03% w/v, Control Number 266211, Product Monograph, AbbVie Corporation, August 25, 2022.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrAPO-BIMATOPROST

Bimatoprost Topical Solution

Read this carefully before you start taking **APO-BIMATOPROST** 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 **APO-BIMATOPROST**.

What is APO-BIMATOPROST used for?

APO-BIMATOPROST is used to treat hypotrichosis (less than normal hair) of the eyelash to increase the length, thickness and darkness of eyelashes.

How does APO-BIMATOPROST work?

APO-BIMATOPROST is believed to lengthen the growth period of your eyelashes and increasing the number of lashes involved in the growth phase. This results in longer, fuller and darker eyelashes.

What are the ingredients in APO-BIMATOPROST?

Medicinal ingredients: Bimatoprost

Non-medicinal ingredients: benzalkonium chloride as preservative, citric acid anhydrous, sodium chloride, sodium phosphate dibasic anhydrous, and water for injection. Hydrochloric acid and/or sodium hydroxide may be added to adjust pH.

APO-BIMATOPROST comes in the following dosage forms:

Topical solution 0.03%, w/v

Do not use APO-BIMATOPROST if:

- You are allergic to bimatoprost, to any of the other ingredients, or to any of the parts of the container (see section What are the ingredients in APO-BIMATOPROST?).

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

- have no visible eyelashes. Your doctor will consider any underlying conditions to determine whether this product is appropriate for you
- are taking, or have recently taken, any other medicines. Using APO-BIMATOPROST with other medicines or bimatoprost products may reduce their effectiveness.
- are pregnant or are planning to become pregnant
- are breastfeeding or planning to breastfeed. Ask your doctor about how to feed your baby while using APO-BIMATOPROST.
- have an active eye infection, inflammation (e.g. uveitis) or any other eye or eyelid condition
- need to have eye surgery

Other warnings you should know about:

Changes in eye and eyelid colour:

APO-BIMATOPROST use has been associated with iris pigmentation (change in the coloured part of the eye). This is likely to be permanent. To help avoid pigmentation, it is extremely important to strictly observe the following measures:

- Do not apply directly in the eye.
- Do not add more than one drop to an applicator.
- Blot any excess solution outside the upper eyelid margin with a tissue or other absorbent material.
- Do not administer the medication more than once daily.
- Do not apply to the lower eyelash line.
- Do not use the same applicator for more than one eye.
- Do not reuse applicators.
- Do not alter the applicator in any form.
- Do not use any other brush/applicator to apply APO-BIMATOPROST.

Using too much APO-BIMATOPROST may contribute to iris pigmentation. APO-BIMATOPROST use may also cause darkening of the eyelid skin which may be reversible in most patients. (see Overdose section).

Hair growth:

It is possible for hair growth to occur in other areas of your skin that APO-BIMATOPROST frequently touches. Any excess solution outside the upper eyelid margin should be blotted with a tissue or other absorbent material to reduce the chance of this from happening. It is also possible for a difference in eyelash length, thickness, fullness, pigmentation, number of eyelash hairs, and/or direction of eyelash growth to occur between eyes. These differences, should they occur, will usually go away if you stop using APO-BIMATOPROST.

Changes in vision:

Application of APO-BIMATOPROST may temporarily blur your vision. Do not drive or use machines until your vision has cleared.

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

If you are using bimatoprost ophthalmic solution or other products in the same class for elevated intraocular pressure (IOP), or if you have a history of abnormal IP, you should only use APO-BIMATOPROST under the close supervision of your doctor.

The following may interact with APO-BIMATOPROST:

No specific drug interaction studies have been done with this medication.

How to take APO-BIMATOPROST:

- DO NOT APPLY in your eye or to the lower lid. ONLY use the sterile applicators supplied with APO-BIMATOPROST to apply the product. Do not reuse or modify applicators and do not use any other

brush/applicator to apply APO-BIMATOPROST. Fifty percent of patients treated with bimatoprost topical solution in a clinical study saw significant improvement by 2 months after starting treatment.

- If APO-BIMATOPROST solution from a single dose gets into the eye, it is not expected to cause harm. Don't allow the tip of the bottle or applicator to contact surrounding structures, fingers, or any other unintended surface in order to avoid contamination by common bacteria known to cause infections.
- APO-BIMATOPROST contains a preservative called benzalkonium chloride which may discolour soft contact lenses if the eye is exposed. If you wear contact lenses, remove them before using APO-BIMATOPROST. They may be reinserted 15 minutes after APO-BIMATOPROST application.
- Always use APO-BIMATOPROST exactly as your doctor has instructed you.

Follow these steps to use APO-BIMATOPROST properly:

- Clean your face and ensure that makeup and contact lenses are removed ***(see Illustration 1)***.
- Remove an applicator from its tray. Then, holding the sterile applicator horizontally, place ONLY one drop of APO-BIMATOPROST on the area of the applicator closest to the tip but not on the tip ***(see Illustration 2)***.
- Immediately draw the applicator carefully across the skin of the upper eyelid margin at the base of the eyelashes (where the eyelashes meet the skin) going from the inner part of your lash line to the outer part ***(see Illustration 3)***.
- Blot any excess solution beyond the eyelid margin ***(see Illustration 4).***
- Dispose of the applicator after one use ***(see Illustration 5).***
- Repeat for the opposite upper eyelid margin using a NEW sterile applicator. This helps minimize any potential for contamination from one eyelid to another.

Illustration 1: Ensuring your face is clean

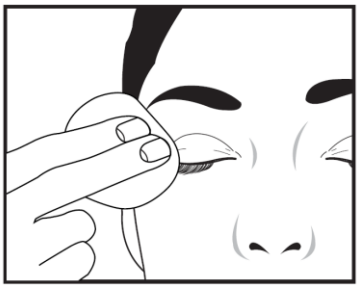


Illustration 2: Properly applying the drop to the unmodified applicator

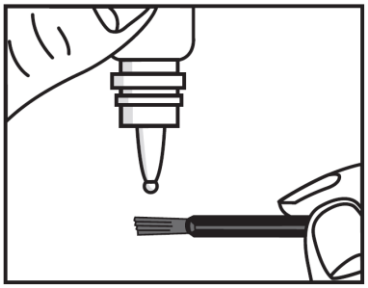
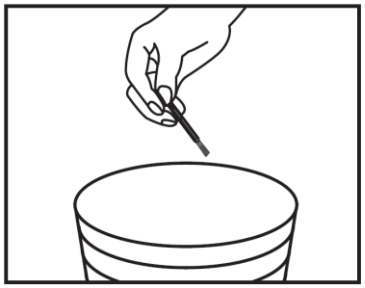


Illustration 3: Applying APO-BIMATOPROST to the upper eyelid margin using the unmodified applicator provided

Illustration 4: Blotting any excess solution

Illustration 5: Dispose of the applicator



Usual dose:

The recommended dosage is one application nightly to the skin of the upper eyelid margin of each eye at the base of the eyelashes only.

Use of APO-BIMATOPROST more than once a day is not expected to increase the growth of eyelashes more than use once a day.

Overdose:

Overdosing (putting more than one drop on the applicator) may result in an increased chance of iris pigmentation (IP). Any extra solution outside the upper lid margin should be blotted with a tissue. If APO-BIMATOPROST solution from a single dose gets into your eyes, it is not expected to cause harm.

If you think you, or a person you are caring for, have taken too much APO-BIMATOPROST, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms**.**

Missed Dose:

If you miss a dose, don't try to "catch up." Just apply APO-BIMATOPROST solution the next evening. Do not double dose.

What are possible side effects from using APO-BIMATOPROST?

These are not all the possible side effects you may have when taking APO-BIMATOPROST. If you experience any side effects not listed here, tell your healthcare professional.

Like all medicines, APO-BIMATOPROST can have side effects. Most of the side effects are not serious.

The most common side effects after using APO-BIMATOPROST solution are an itching sensation in the eyes and/or eye redness. This was reported in approximately 4% of patients. APO-BIMATOPROST solution may cause other less common side effects which typically occur on the skin close to where APO-BIMATOPROST is applied, or in the eyes. These include skin darkening, iris pigmentation, eye irritation, peeling of skin, deepening and drooping of the eyelid, dryness of the eyes and redness of the eyelids.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
UNKNOWN FREQUENCY			
New ocular condition (e.g., trauma or infection), experience a sudden decrease in visual acuity (vision), have ocular (eye) surgery, or develop any ocular reactions, particularly conjunctivitis (eyelid infection) and eyelid reactions		✓	

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 the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) 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:

APO-BIMATOPROST should be stored in the original container at 2°C to 25°C.

Discard 28 days after opening.

Keep out of reach and sight of children.

If you want more information about APO-BIMATOPROST:

- 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:

  (http://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); Find the Patient Medication Information on the manufacturer's website (http://www.apotex.ca/products), or by calling 1-800-667-4708.

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9.

Last revised: OCT 13, 2022