

**PRODUCT MONOGRAPH**

**Pr SANDOZ BIMATOPROST TOPICAL**

Bimatoprost Topical Solution 0.03% w/v

Eyelash Growth Enhancer

Prostamide Analogue

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Bimatoprost Topical Solution 0.03% w/v

**PART I: HEALTH PROFESSIONAL INFORMATION**

**SUMMARY PRODUCT INFORMATION**

<b>Route of Administration</b>	<b>Dosage Form / Strength</b>	<b>All Nonmedicinal Ingredients</b>
Intended for Dermal Topical Application to the Upper Eyelid Margin	Sterile Solution/ 0.03% w/v	Benzalkonium chloride (0.05 mg/mL), as preservative; sodium chloride, sodium phosphate dibasic, citric acid monohydrate, and purified water. Sodium hydroxide and/or hydrochloric acid may be added to adjust pH.

**INDICATIONS AND CLINICAL USE**

**Sandoz Bimatoprost Topical** (bimatoprost topical solution 0.03% w/v) is indicated to treat hypotrichosis of the eyelashes by increasing their growth including length, thickness and darkness.

Patients without visible eyelashes were not studied.

**Geriatrics (>65 years of age):**

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

**Pediatrics (<18 years of age):**

Not recommended for pediatric use. Safety and effectiveness in pediatric patients have not been established.

**CONTRAINDICATIONS**

Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.

## **WARNINGS AND PRECAUTIONS**

Patients who receive treatment with Sandoz Bimatoprost Topical should be informed of the possibility of increased iris pigmentation (IP).

### **Iris Pigmentation**

Bimatoprost-containing products, including bimatoprost ophthalmic solution and topic, have been associated with iris pigmentation (IP) (see Post-market Adverse Drug Reactions section). 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 Post-Market Adverse Drug Reactions section).

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 postmarketing cases of bimatoprost (see Post-Market Adverse Drug Reactions section). Bimatoprost-induced IP is most likely permanent. Treatment with Sandoz Bimatoprost Topical 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 use than anticipated. Because improper use may play a role in increasing the risk of IP with bimatoprost, it is important to emphasize the correct use of the product and advise patients to use Sandoz Bimatoprost Topical according to the specialized administration procedure (see DOSAGE AND ADMINISTRATION – Administration).

### **Contamination of Sandoz Bimatoprost Topical or Applicators**

The tip of the Sandoz Bimatoprost Topical 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 Sandoz Bimatoprost Topical 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).

### **Hair Growth Outside the Treatment Area**

There is the potential for hair growth to occur in areas where Sandoz Bimatoprost Topical comes in repeated contact with the skin surface. It is important to apply Sandoz Bimatoprost Topical 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 Sandoz Bimatoprost Topical 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 0.03% w/v during clinical trials were periorbital, whereas these changes reported during clinical trials with the use of bimatoprost topical solution 0.03% w/v were limited to the targeted applied area (upper eyelid), and occurred less frequently.

### **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 0.03% w/v 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 intraocular pressure lowering effect. In patients using bimatoprost ophthalmic solution or other prostaglandin analogs for the treatment of elevated intraocular pressure, the concomitant use of Sandoz Bimatoprost Topical may interfere with the desired reduction in IOP. Patients using prostaglandin analogs including bimatoprost ophthalmic solution for IOP reduction should only use Sandoz Bimatoprost Topical after consulting with their physician and should be monitored for changes to their intraocular pressure.

### **Intraocular Inflammation**

Sandoz Bimatoprost Topical 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 ophthalmic solution 0.03% w/v for elevated IOP. Sandoz Bimatoprost Topical 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 Sandoz Bimatoprost Topical and may be reinserted 15 minutes following its administration. Patients should be advised that Sandoz Bimatoprost Topical contains benzalkonium chloride, which may be absorbed by soft contact lenses.

### **Effects on ability to drive and use machines**

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.

### **Patients with no visible eyelashes-alopecia**

The efficacy and safety of Sandoz Bimatoprost Topical 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 Sandoz Bimatoprost Topical.

### **Renal**

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

### **Hepatic/Biliary/Pancreatic**

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

### **Sexual Function/Reproduction**

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

### **Carinogenesis and Mutagenesis**

Bimatoprost was neither carcinogenic nor mutagenic in animals and *in vitro* studies (see TOXICOLOGY).

### **Special Populations**

**Pregnant Women:** 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 after ocular administration of bimatoprost ophthalmic solution as measured by area-under-the curve blood levels.

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 after ocular administration of bimatoprost ophthalmic solution. Cohabitation times in the offspring were increased but neurobehavioural functions were not affected.

As the clinical dose of Sandoz Bimatoprost Topical 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 Sandoz Bimatoprost Topical.

There are no adequate and well-controlled studies of Sandoz Bimatoprost Topical administration in pregnant women. Because animal reproductive studies are not always predictive of human response, Sandoz Bimatoprost Topical should be administered during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nursing Women:** 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 Sandoz Bimatoprost Topical is administered to a nursing woman.

## **ADVERSE REACTIONS**

### **Adverse Drug 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 Sandoz Bimatoprost Topical 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 1).

### **Clinical Trial Adverse Drug Reactions**

*Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

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 1.

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

	Number of patients (%)	
MedDRA preferred term	Bimatoprost topical solution 0.03% w/v N=137	Vehicle N=141
<b>Eye Disorders</b>		
Eye pruritus	5 (3.6)	1 (0.7)
Conjunctival hyperemia <sup>a</sup>	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)
<b>Immune System Disorders</b>		
Seasonal allergy	2 (1.5)	0 (0.0)
<b>Infections And Infestations</b>		
Sinusitis	2 (1.5)	2 (1.4)
Influenza	2 (1.5)	0 (0.0)
<b>Benign And Malignant Neoplasms</b>		
Blepharal papilloma	2 (1.5)	0 (0.0)
<b>Skin And Subcutaneous Tissue Disorders</b>		
Skin hyperpigmentation	4 (2.9)	1 (0.7)
Dermatitis contact	2 (1.5)	0 (0.0)

<sup>a</sup> 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, dizziness, nausea, asthenia, eye pruritus, eyelid pruritus, irritation eye, erythema eyelid, blepharal pigmentation.

#### **Less Common Clinical Trial Adverse Drug Reactions (<1%)**

Clinical studies have shown increased iris pigmentation (IP) in glaucoma patients treated with bimatoprost ophthalmic products. In clinical trials, the incidence of IP associated with bimatoprost ophthalmic products 0.03% and 0.01% 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 0.03% w/v therapy is only about 5% of that in bimatoprost ophthalmic solution 0.03%, the risk of bimatoprost topical solution 0.03% w/v-associated IP is expected to be very low. However, during the postmarketing phase, there have been reports of IP associated with the use of bimatoprost (see Post-Market Adverse Drug Reaction).

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.

#### **Post-Market Adverse Drug Reactions**

Bimatoprost - In addition to what has been observed in clinical trials, the following adverse reactions have been identified during post marketing use of bimatoprost 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, vision blurred, enophthalmos (deepened eyelid sulcus), eye discharge, eye pain, eye swelling, eyelid irritation, eyelid edema, eyelid pain, eyelids pruritus, iris hyperpigmentation, increased lacrimation, foreign body sensation in eyes.

It is clear that bimatoprost exposure levels with bimatoprost 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 use. In addition, the post-marketing reporting rate of IP with bimatoprost topical solution 0.03% w/v is higher than that observed with bimatoprost ophthalmic solution 0.03% w/v. While the exact reason for the observed differences is not clear, improper administration and excessive doses of bimatoprost topical solution 0.03% w/v may result in increased reports of IP (see DOSAGE AND ADMINISTRATION - Administration).

**Immune system disorder:** Hypersensitivity (systemic allergic reaction), Hypersensitivity (local allergic reaction).

**Nervous system disorder:** Headache

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

## **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 Sandoz Bimatoprost Topical 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 intraocular pressure lowering effect. In patients using bimatoprost ophthalmic solution or other prostaglandin analogs for the treatment of elevated intraocular pressure, the concomitant use of Sandoz Bimatoprost Topical may interfere with the desired reduction in IOP. Patients using prostaglandin analogs including bimatoprost ophthalmic solution for IOP reduction should only use Sandoz Bimatoprost Topical after consulting with their physician and should be monitored for changes to their intraocular pressure (see WARNINGS AND PRECAUTIONS).

### **Drug-Food Interactions**

Interactions with food have not been established.

### **Drug-Herb Interactions**

Interactions with herbal products have not been established.

### **Drug-Laboratory Interactions**

Interactions with laboratory tests have not been established.

## **DOSAGE AND ADMINISTRATION**

### **Recommended Dose and Dosage Adjustment**

Special device and administration procedure are recommended for delivering proper dose of Sandoz Bimatoprost Topical (bimatoprost topical solution 0.03% w/v) 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 the Administration subsection). 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 Administration Section).

Additional applications of Sandoz Bimatoprost Topical will not increase the growth of eyelashes and may increase the risk of adverse reactions (see Post-Market Adverse Drug Reactions section).

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

### **Missed Dose**

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

### **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 Sandoz Bimatoprost Topical 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 Sandoz Bimatoprost Topical.

**See Patient Medication Information, section title How to Use Sandoz Bimatoprost Topical.**

### **OVERDOSAGE**

For management of a suspected drug overdose, particularly by accidental oral ingestion, contact your regional Poison Control Centre.
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No information is available on overdosage in humans. If overdose with Sandoz Bimatoprost Topical occurs, treatment should be symptomatic. If Sandoz Bimatoprost Topical 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<sup>2</sup>, 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 Sandoz Bimatoprost Topical.

## **ACTION AND CLINICAL PHARMACOLOGY**

### **Mechanism of Action**

Bimatoprost is a synthetic prostamide analogue and is structurally related to prostaglandin F<sub>2α</sub> (PGF<sub>2α</sub>) in that the carboxylic acid group is replaced with an electronically neutral substituent. Its mechanism of action resembles that of prostamide F<sub>2α</sub>, a naturally occurring substance. Sandoz Bimatoprost Topical 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).

### **Pharmacokinetics**

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, with mean C<sub>max</sub> values of 0.07 and 0.08 ng/mL on day 7 and 14, respectively, and mean AUC<sub>0-24h</sub> of 0.074 and 0.096 ng•hr/mL on day 7 and 14, respectively.

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 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.

**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.

**Excretion:** 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.

### **STORAGE AND STABILITY**

Sandoz Bimatoprost Topical should be stored in the original container at 2°C - 25°C. Discard unused solution at the end of treatment. Keep in a safe place out of the reach of children.

### **In-use Condition**

Keep the product between 2°C and 25°C, for a period of 30 days for the 3 mL bottle and 70 days for the 5 mL bottles after the first opening of the bottles. “Discard the unused portion 30 days after opening the 3 mL bottle. Discard the unused portion 70 days after opening the 5 mL bottle.”

## **DOSAGE FORMS, COMPOSITION AND PACKAGING**

Sandoz Bimatoprost Topical is supplied in opaque white low density polyethylene dispenser bottles and tips with turquoise polystyrene caps in the following configurations: 3.0 mL sterile solution in 4 mL bottle accompanied by 70 disposable applicators and 5.0 mL sterile solution in 8 mL bottle accompanied by 140 disposable applicators.

Sandoz Bimatoprost Topical is a clear, isotonic, buffered, preserved, colourless, sterile solution with a pH of  $7.3 \pm 0.5$ , and an osmolality of approximately 303 mOsmol/kg.

Each mL of Sandoz Bimatoprost Topical contains bimatoprost 0.3 mg with the following non-medicinal ingredients: benzalkonium chloride 0.05 mg as preservative, sodium chloride, sodium phosphate dibasic, citric acid monohydrate, and purified water. Sodium hydroxide and/or hydrochloric acid may be added to adjust pH.

Sandoz Bimatoprost Topical (bimatoprost topical solution 0.03% w/v) is available in the following packaging formats:

- 3 mL sterile solution bottle, accompanied by 70 sterile disposable applicators packaged in a separate blister format.
- 5 mL sterile solution bottle, accompanied by 140 sterile disposable applicators packaged in a separate blister format.

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

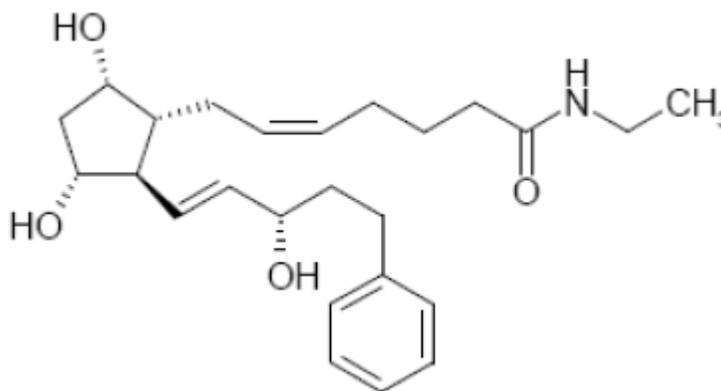
#### Drug Substance

Proper name: bimatoprost

Chemical name: (5z)-7-[(1R,2R,3R,5S)-3,5-Dihydroxy-2-[(1E,3S)-3-hydroxy-5-phenyl-1-pentenyl]cyclopentyl]-N-ethyl-5-heptenamide

Molecular formula and molecular mass: C<sub>25</sub>H<sub>37</sub>NO<sub>4</sub>; 415.5 g/mol

Structural formula:



Physicochemical properties: Bimatoprost is a white to off-white powder, which is very soluble in ethanol and methanol and slightly soluble in water.

## CLINICAL TRIALS

### Study demographics and trial design

**Table 2 - Summary of patient demographics for the clinical trial 192024-032 (ITT Population)**

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
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 runoff 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 WARNING AND PRECAUTIONS).

#### Study results:

Bimatoprost topical solution 0.03% w/v 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 0.03% w/v 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  $\geq 1$  GEA grade was statistically significantly different from vehicle from 8 weeks of treatment to end of treatment (Week 16, endpoint) see Table 3.

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

Visit <sup>a</sup>	Bimatoprost topical solution 0.03% w/v N=137 N (%)	Vehicle N=141 N (%)	p-value <sup>b</sup>
Week 1	7 (5.1%)	3 (2.1%)	0.2124 <sup>c</sup>
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)	<b>107 (78.1%)</b>	<b>26 (18.4%)</b>	<b>&lt; 0.0001</b>
Week 20 (Post-treatment phase)	103 (78.6%)	27 (21/4)	< 0.0001

<sup>a</sup> LOCF was performed on weeks 1 to 16 and week 20 analysis was based only on observed cases.

<sup>b</sup> 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.

<sup>c</sup> Fisher’s exact test was performed.

In this study, patients were also evaluated for the effect of bimatoprost topical solution 0.03% w/v 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 4.

**Table 4 - 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 0.03% w/v	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 <sup>2</sup> ; % 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 0.03% w/v 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 5 - 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 <sup>a</sup>	Bimatoprost topical solution 0.03% (N = 137)	Vehicle (N = 141)	P-value <sup>b</sup>
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)	0.1164c
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

Source: Table 14.5-21, CSR 192024-032

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.

<sup>a</sup> LOCF was performed for weeks 1 through 16; week 20 analysis was based only on observed cases.

<sup>b</sup> 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.

<sup>c</sup> Fisher's exact test was performed.

## DETAILED PHARMACOLOGY

### Animal Pharmacology

#### *Ocular Studies*

Studies in ocular normotensive and laser-induced ocular hypertensive cynomolgus monkeys indicated that bimatoprost potently reduces intraocular pressure. 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.

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.

#### Metabolism and Pharmacokinetics

##### *Ocular Pharmacokinetics*

Following a single ocular instillation of <sup>3</sup>H-bimatoprost to rabbits and single and multiple ocular instillations to monkeys, bimatoprost was absorbed rapidly and was well distributed in the eye. The absorbed radioactivity was found mainly in the anterior segment of the eye and the highest concentrations of radioactivity were found in the conjunctiva, cornea, sclera, iris, and ciliary body in both rabbit and monkey eyes. Maximal concentrations in these tissues were reached within 0.5 to 2 hours post-dose. Twenty-four hours after the last dose in monkeys, bimatoprost concentrations in the ciliary body (the purported site of action) were still over 5-fold higher than the *in vitro* EC<sub>50</sub> value of 14 ng/mL required for pharmacological effect.

##### *Systemic Absorption Following Ocular and Oral Administration*

Bimatoprost was systemically absorbed after ophthalmic administration to rabbits and monkeys. The C<sub>max</sub> in plasma was 3.23 ng-eq/mL in monkeys following twice-daily ocular administration of 0.1% bimatoprost for 10 days and 6.28 ng-eq/mL in rabbits following a single administration of 0.1%. The oral bioavailability of bimatoprost was 40%, 29% and 3% in mice, rats and monkeys, respectively. The low oral bioavailability in monkeys was attributed to extensive first-pass metabolism.

### *Systemic Disposition after Intravenous Administration*

Following intravenous administration to mice, rats and monkeys bimatoprost had a moderate apparent volume of distribution at steady state ranging from 2.1 to 6.0 L/kg. Bimatoprost had a mean residence time of 0.28 hr in mice, 0.42 hr in rats and 0.93 hr in monkeys, indicating that bimatoprost was rapidly eliminated in all three species. The mean blood clearance was 12, 9.5 and 2.4 L/hr/kg, respectively. In mice and rats, total blood clearance appeared to be greater than liver blood flow, indicating the involvement of extrahepatic metabolism.

### *Systemic Tissue Distribution*

The unbound fraction of bimatoprost in mouse, rat, rabbit and monkey plasma ranged from 28 to 37% *in vitro*. The *in vitro* binding of bimatoprost to synthetic melanin was not extensive at approximately 20%, and was reversible. Following intravenous administration of <sup>3</sup>H-bimatoprost to rats, either as a single dose or after daily injections for 21 days, radioactivity was rapidly distributed to all tissues and organs examined. The highest concentrations of radioactivity were seen in the gastrointestinal tract, liver, kidney and urinary bladder. The blood-to-plasma ratio of radioactivity was 0.75, indicating that bimatoprost remained in the plasma portion of the blood. By 168 hours postdose, all radioactivity in the body was accounted for by tritiated water, and not by bimatoprost or its metabolites. Following a single intravenous administration of <sup>3</sup>H-bimatoprost to pregnant rats, there was a low, but quantifiable, amount of drug transfer into the placenta, amniotic fluid and fetus. Following intravenous administration of <sup>3</sup>H-bimatoprost to lactating rats, the concentrations of radioactivity found in milk were similar to those seen in plasma. Therefore the amount of drug related material transferred into milk at the clinical dose level is expected to be extremely low.

### *Ocular Metabolism*

After ophthalmic administration, bimatoprost was extensively metabolized in all of the ocular tissues in the rabbit eye. In contrast, bimatoprost, at exaggerated doses, was only minimally metabolized in the monkey eye following ophthalmic administration.

### *Systemic Metabolism*

Following a single 3,000 mcg/kg or 1,000 mcg/kg intravenous administration (~3,300 to ~8,500 fold human dose) to rats and monkeys, bimatoprost was extensively metabolized by glucuronidation, hydroxylation, deamidation and N-deethylation, with glucuronidated metabolites accounting for the majority of the drug-related material in the blood, urine and faeces of both species. In pregnant rats, at least 22 metabolites were detected in the maternal tissues following a single intravenous administration of <sup>3</sup>H-bimatoprost. The C1-acid metabolite of bimatoprost was the major species detected in the uterus and ovaries (about 45% of total radioactivity), while bimatoprost was the major species detected in the fetus (about 50% of total radioactivity). The C-1 acid is the major metabolite in rats and rabbits, but not in dogs, monkeys, or humans. Following one month of daily intravenous administration to rats and monkeys, bimatoprost was found to have no clinically significant effect on any of the hepatic drug metabolizing enzymes tested. In studies using recombinant human P450 enzymes, CYP3A4/5 were identified as the most important Cytochrome P450 enzymes involved in the hydroxylation of bimatoprost.

### *Excretion*

Both the urinary and fecal routes are important pathways for excretion of bimatoprost and its metabolites in rats and monkeys. Following a single intravenous administration of <sup>3</sup>H-bimatoprost to rats, the urinary excretion of radioactivity was 42% of the dose in females and 27% in males, while the fecal excretion of radioactivity was 49% in females and 69% in males. Following a single intravenous administration of <sup>3</sup>H-bimatoprost in monkeys, male and females excreted 58 and 64% of the dose into the urine and 24 and 31% into the faeces, respectively. The mean total recovery of radioactivity was >90% for both genders.

### Human Pharmacology

#### **Mechanism of Action**

Bimatoprost is a synthetic prostamide analogue and is structurally related to prostaglandin F<sub>2α</sub> in that the carboxylic acid group is replaced with an electronically neutral substituent. Its mechanism of action resembles that of prostamide F<sub>2α</sub>, a naturally occurring substance. Bimatoprost 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 the pigment (melanin) formation in the hair follicles. The overall effect is increased length, thickness and darkness of eyelashes (prominence).

#### Pharmacokinetics

##### *Absorption and Systemic Drug Exposure*

Bimatoprost penetrates the human cornea and sclera well *in vitro*. The mean corneal permeability coefficient was 3.24 x 10<sup>-6</sup> cm/sec. Bimatoprost penetrated human scleral tissue better than corneal tissue with a mean scleral permeability coefficient of 14.5 x 10<sup>-6</sup> cm/sec. After one drop of 0.03% ophthalmic solution was administered once daily to both eyes of 15 healthy subjects for two weeks, blood bimatoprost concentrations were below the lower limit of detection (0.025 ng/mL) in most subjects within 1 to 1.5 hours after dosing. Mean bimatoprost C<sub>max</sub> values were similar on days 7 and 14 at 0.0721, and 0.0822 ng/mL, respectively. The mean AUC<sub>0-24 hr</sub> values were also similar on days 7 and 14 at 0.0742, and 0.096 ng•hr/mL, respectively, indicating that a steady systemic exposure to bimatoprost had been reached during the first week of ocular dosing.

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 (18-44 years, mean = 28.5) or elderly patients (65-80 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  $AUC_{0-24 \text{ hr}}$  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 remain 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.

#### *Elimination*

Following an intravenous dose of radiolabelled bimatoprost (3.12 mcg/kg) to six healthy subjects, the maximum blood concentration of unchanged bimatoprost was 12.2 ng/mL and declined rapidly with an elimination half-life of 0.771 hour (approximately 45 minutes). Blood concentrations of AGN 191522, the C-1 acid metabolite, were much lower than those of bimatoprost as peak concentration was 0.12 ng/mL. The total blood clearance (Cl<sub>b</sub>) of unchanged bimatoprost was 1.50 L/hr/kg.

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.

## **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 aminoglutarate 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  $\geq 0.1$  mg/kg/day orally for 1 year. There were no associated microscopic liver findings. A dose-related, reversible cellular vacuolation of corpora lutea at  $\geq 0.3$  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.

#### *Mutagenicity*

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.

#### *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 blood AUC levels) for 104 weeks.

## *Reproduction and Teratology*

### *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 Toxicity Studies*

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.

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**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE****PATIENT MEDICATION INFORMATION****PrSandoz® Bimatoprost Topical  
Bimatoprost Topical Solution 0.03% w/v  
Sterile**

**Read this carefully before you start using Sandoz Bimatoprost Topical 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 Sandoz Bimatoprost Topical.**

**What is Sandoz Bimatoprost Topical used for:**

Sandoz Bimatoprost Topical is used to treat hypotrichosis (less than normal hair) of the eyelash to increase the length, thickness and darkness of eyelashes.

**How does Sandoz Bimatoprost Topical work:**

Sandoz Bimatoprost Topical 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 Sandoz Bimatoprost Topical:**

Medicinal ingredients: Bimatoprost

Non-medicinal ingredients: Benzalkonium chloride (0.05 mg/mL) as preservative, sodium chloride, sodium phosphate dibasic, citric acid monohydrate, and purified water. Sodium hydroxide and/or hydrochloric acid may be added to adjust pH.

**Sandoz Bimatoprost Topical comes in the following dosage forms:**

Sandoz Bimatoprost Topical (Bimatoprost Topical Solution 0.03% w/v) is available in the following packaging formats:

- 3 mL sterile solution bottle with 70 accompanying sterile, disposable applicators.
- 5 mL sterile solution bottle with 140 accompanying sterile, disposable applicators.

**Do not use Sandoz Bimatoprost Topical 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).

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you use Sandoz Bimatoprost Topical. 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 Sandoz Bimatoprost Topical 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 Sandoz Bimatoprost Topical.
- 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

Sandoz Bimatoprost Topical 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 Sandoz Bimatoprost Topical.

Using too much Sandoz Bimatoprost Topical (overdose) may contribute to iris pigmentation.

Sandoz Bimatoprost Topical use may also cause darkening of the eyelid skin which may be reversible in most patients.

#### Hair growth

It is possible for hair growth to occur in other areas of your skin that Sandoz Bimatoprost Topical 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 Sandoz Bimatoprost Topical.

#### Changes in vision

Application of Sandoz Bimatoprost Topical 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 IOP, you should only use Sandoz Bimatoprost Topical under the close supervision of your physician.

#### **The following may interact with Sandoz Bimatoprost Topical:**

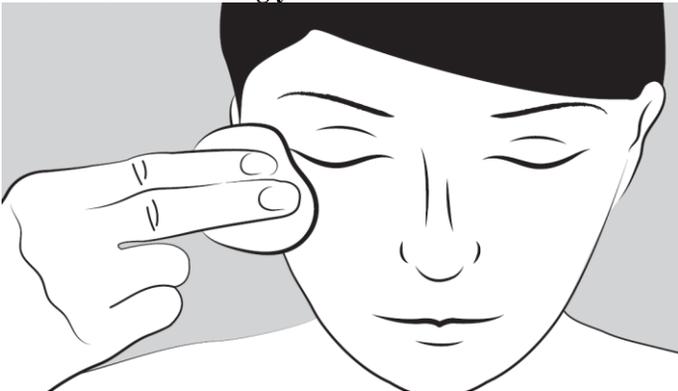
No specific drug interaction studies have been done with this medication.

#### **How to use Sandoz Bimatoprost Topical:**

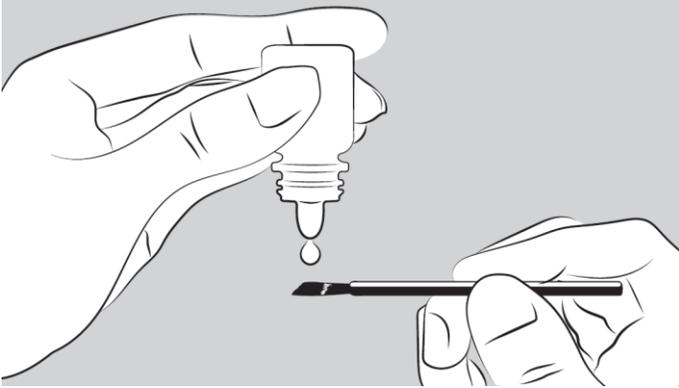
- Clean your face and ensure that makeup and contact lenses are removed (see Illustration 1).
- Remove an applicator from its tray. Then, holding the sterile applicator horizontally, place **ONLY** one drop of Sandoz Bimatoprost Topical on the area of the applicator closest to the tip but not on the 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**



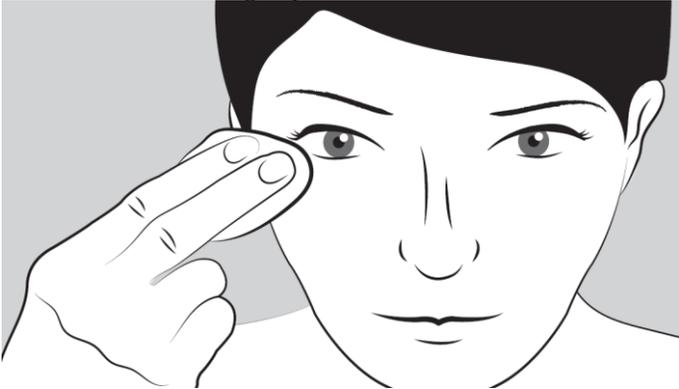
**Illustration 2: Properly applying the drop to the unmodified applicator**

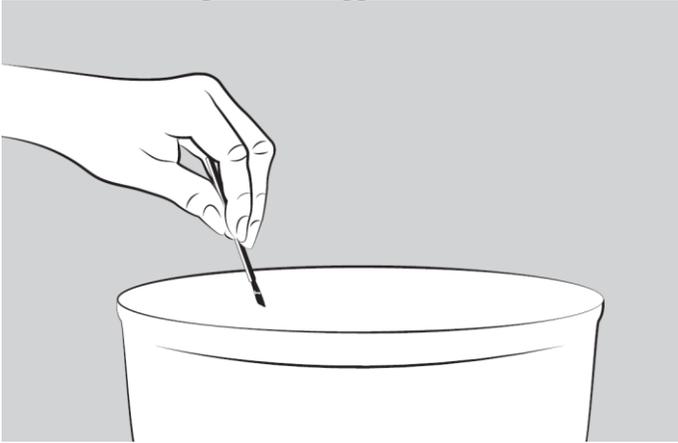


**Illustration 3: Applying Sandoz Bimatoprost Topical to the upper eyelid margin using the unmodified applicator provided**



**Illustration 4: Blotting any excess of solution**



**Illustration 5: Dispose of the applicator**

**DO NOT APPLY in your eye or to the lower lid.** ONLY use the sterile applicators supplied with Sandoz Bimatoprost Topical to apply the product. **Do not reuse or modify applicators and do not use any other brush/applicator to apply Sandoz Bimatoprost Topical.** Fifty percent of patients treated with bimatoprost in a clinical study saw significant improvement by 2 months after starting treatment.

If Sandoz Bimatoprost Topical 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.

Sandoz Bimatoprost Topical 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 Sandoz Bimatoprost Topical. They may be reinserted 15 minutes after Sandoz Bimatoprost Topical application. Always use Sandoz Bimatoprost Topical exactly as your doctor has instructed you.

**Usual adult 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 Sandoz Bimatoprost Topical 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 Sandoz Bimatoprost Topical solution from a single dose gets into your eyes, **it is not expected to cause harm.**

In case of drug overdose, particularly accidental oral ingestion, contact a healthcare professional (e.g. doctor), hospital emergency department or regional Poison Control Center, even if there are no symptoms.

**Missed Dose:**

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

**What are possible side effects from using Sandoz Bimatoprost Topical?**

These are not all the possible side effects you may feel when taking Sandoz Bimatoprost Topical. If you experience any side effects not listed here, contact your healthcare professional.

Like all medicines, Sandoz Bimatoprost Topical can have side effects. Most of the side effects are not serious.

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

**Serious side effects and what to do about them**

Symptom/effect	Talk to your healthcare professional		Stop using drug and get immediate medical help
	Only if severe	In all cases	
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, talk to 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:**

Sandoz Bimatoprost Topical should be stored in the original container at 2°C to 25°C.

Discard the unused portion 30 days after opening the 3 mL bottle. Discard the unused portion 70 days after opening the 5 mL bottle.

Do not use the drops after the expiry date (marked “EXP:”) on the bottle and the box.

Keep out of reach and sight of children.

**If you want more information about Sandoz Bimatoprost Topical:**

- 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.html>) the manufacturer’s website [sandoz.ca](http://sandoz.ca), or by calling 1-800-361-3062

or by written request at:  
 110 Rue de Lauzon  
 Boucherville, Québec, Canada  
 J4B 1E6

Or by e-mail at:  
[medinfo@sandoz.com](mailto:medinfo@sandoz.com)

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