

266 mm
133 mm

26 mm



265779

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BIMATOPROST Ophthalmic Solution, 0.03%

safely and effectively. See full prescribing information for BIMATOPROST Ophthalmic Solution, 0.03%.

BIMATOPROST Ophthalmic Solution, 0.03%

For topical ophthalmic use
Initial U.S. Approval: 2001

-----RECENT MAJOR CHANGES-----
Warnings and Precautions, Intraocular Inflammation (5.3)
09/2014

-----INDICATIONS AND USAGE-----
Bimatoprost Ophthalmic Solution, 0.03% is a prostaglandin analog indicated for the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension. (1)

-----DOSAGE AND ADMINISTRATION-----
One drop in the affected eye(s) once daily in the evening. (2)

-----DOSAGE FORMS AND STRENGTHS-----
Solution containing 0.3 mg/mL bimatoprost. (3)

FULL PRESCRIBING INFORMATION: CONTENTS*

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- 2 DOSAGE AND ADMINISTRATION
- 3 DOSAGE FORMS AND STRENGTHS
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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Bimatoprost Ophthalmic Solution, 0.03% is indicated for the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension.

-----CONTRAINDICATIONS-----
None. (4)

-----WARNINGS AND PRECAUTIONS-----

- Pigmentation.
Pigmentation of the iris, periorbital tissue (eyelid) and eyelashes can occur. Iris pigmentation is likely to be permanent (5.1).
- Eyelash Changes.
Gradual change to eyelashes including increased length, thickness and number of lashes. Usually reversible. (5.2)

-----ADVERSE REACTIONS-----
Most common adverse reaction is conjunctival hyperemia (45%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Apotex Corp. at 1-800-667-4708 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----USE IN SPECIFIC POPULATIONS-----
Use in pediatric patients below the age of 16 years is not recommended because of potential safety concerns related to increased pigmentation following long-term chronic use. (8.4)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 06/2015

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 - 17.6 Use with Other Ophthalmic Drugs

*Sections or subsections omitted from the full prescribing information are not listed.

2 DOSAGE AND ADMINISTRATION

The recommended dosage is one drop in the affected eye(s) once daily in the evening. Bimatoprost ophthalmic solution, 0.03% should not be administered more than once daily since it has been shown that more frequent administration of prostaglandin analogs may decrease the intraocular pressure lowering effect.

Reduction of the intraocular pressure starts approximately 4 hours after the first administration with maximum effect reached within approximately 8 to 12 hours.

Bimatoprost ophthalmic solution, 0.03% may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

3 DOSAGE FORMS AND STRENGTHS
Ophthalmic solution containing bimatoprost 0.3 mg/mL.

4 CONTRAINDICATIONS
None

5 WARNINGS AND PRECAUTIONS

5.1 Pigmentation
Bimatoprost ophthalmic solution has been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris, periorbital tissue (eyelid) and eyelashes. Pigmentation is expected to increase as long as bimatoprost is administered. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. After discontinuation of bimatoprost, pigmentation of the iris is likely to be permanent, while pigmentation of the periorbital tissue and eyelash changes have been reported to be reversible in some patients. Patients who receive treatment should be informed of the possibility of increased pigmentation. The long term effects of increased pigmentation are not known.

Iris color change may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts of the iris become more brownish. Neither nevi nor freckles of the iris appear to be affected by treatment. While treatment with bimatoprost ophthalmic solution, 0.03% can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly [see PATIENT COUNSELING INFORMATION (17.1)].

5.2 Eyelash Changes
Bimatoprost ophthalmic solution, 0.03% may gradually change eyelashes and vellus hair in the treated eye. These changes include increased length, thickness, and number of lashes. Eyelash changes are usually reversible upon discontinuation of treatment.

5.3 Intraocular Inflammation
Prostaglandin analogs, including bimatoprost, have been reported to cause intraocular inflammation. In addition, because these products may exacerbate inflammation, caution should be used in patients with active intraocular inflammation (e.g., uveitis).

5.4 Macular Edema
Macular edema, including cystoid macular edema, has been reported during treatment with bimatoprost ophthalmic solution. Bimatoprost ophthalmic solution, 0.03% 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.

5.5 Bacterial Keratitis
There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface [see PATIENT COUNSELING INFORMATION (17.3)].

5.6 Use with Contact Lenses
Contact lenses should be removed prior to instillation of bimatoprost ophthalmic solution, 0.03% and may be reinserted 15 minutes following its administration.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience
Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

In clinical trials, the most frequent events associated with bimatoprost ophthalmic solution, 0.03% occurring in approximately 15% to 45% of patients, in descending order of incidence, included conjunctival hyperemia, growth of eyelashes, and ocular pruritus. Approximately 3% of patients discontinued therapy due to conjunctival hyperemia.

Ocular adverse events occurring in approximately 3 to 10% of patients, in descending order of incidence, included ocular dryness, visual disturbance, ocular burning, foreign body sensation, eye pain, pigmentation of the periocular skin, blepharitis, cataract, superficial punctate keratitis, periorbital erythema, ocular irritation, and eyelash darkening. The following ocular adverse events reported in approximately 1 to 3% of patients, in descending order of incidence, included: eye discharge, tearing, photophobia, allergic conjunctivitis, asthenopia, increases in iris pigmentation, and conjunctival edema. In less than 1% of patients, intraocular inflammation was reported as iritis.

Systemic adverse events reported in approximately 10% of patients were infections (primarily colds and upper respiratory tract infections). The following systemic adverse events reported in approximately 1 to 5% of patients, in descending order of incidence included headaches, abnormal liver function tests, asthenia, and hirsutism.

6.2 Postmarketing Experience
The following reactions have been identified during postmarketing use of bimatoprost ophthalmic solution in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The reactions, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to bimatoprost ophthalmic solution, or a combination of these factors, include: abnormal hair growth, dizziness, eyelid edema, hypertension, nausea, and periorbital and lid changes associated with a deepening of the eyelid sulcus.

133 mm

266 mm

26 mm

200 mm

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy Pregnancy Category C

Teratogenic effects

In embryo/fetal developmental studies in pregnant mice and rats, abortion was observed at oral doses of bimatoprost which achieved at least 33 or 97 times, respectively, the maximum intended human exposure based on blood AUC levels.

At doses at least 41 times the maximum intended human exposure based on blood AUC levels, the gestation length was reduced in the dams, the incidence of dead fetuses, late resorptions, peri- and postnatal pup mortality was increased, and pup body weights were reduced.

There are no adequate and well-controlled studies of bimatoprost ophthalmic solution, 0.03% administration in pregnant women. Because animal reproductive studies are not always predictive of human response bimatoprost ophthalmic solution, 0.03% should be administered during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers

It is not known whether bimatoprost ophthalmic solution, 0.03% 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 should be exercised when bimatoprost ophthalmic solution, 0.03% is administered to a nursing woman.

8.4 Pediatric Use

Use in pediatric patients below the age of 16 years is not recommended because of potential safety concerns related to increased pigmentation following long-term chronic use.

8.5 Geriatric Use

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

8.6 Hepatic Impairment

In patients with a history of liver disease or abnormal ALT, AST and/or bilirubin at baseline, bimatoprost 0.03% had no adverse effect on liver function over 48 months.

10 OVERDOSAGE

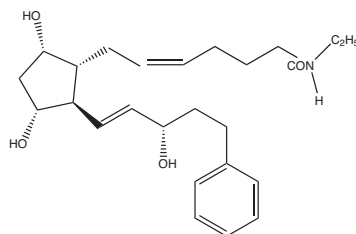
No information is available on overdosage in humans. If overdose with bimatoprost ophthalmic solution, 0.03% occurs, treatment should be symptomatic.

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/m² is at least 70 times higher than the accidental dose of one bottle of bimatoprost ophthalmic solution, 0.03% for a 10 kg child.

11 DESCRIPTION

Bimatoprost ophthalmic solution, 0.03% is a synthetic prostamide analog with ocular hypotensive activity. Its chemical name is (Z)-7-[(1R,2R,3R,5S)-3,5-Dihydroxy-2-[(1E,3S)-3-hydroxy-5-phenyl-1-pentenyl]cyclopentyl]-5-N-ethylheptenamide, and its molecular weight is 415.58.

Its molecular formula is C₂₅H₃₇NO₄. Its chemical structure is:



Bimatoprost is a powder, which is very soluble in ethyl alcohol and methyl alcohol and slightly soluble in water. Bimatoprost ophthalmic solution, 0.03% is a clear, isotonic, colorless, sterile ophthalmic solution with an osmolality of approximately 290 mOsmol/kg.

Bimatoprost Ophthalmic Solution, 0.03% contains **Active:** bimatoprost 0.3 mg/mL; **Inactives:** benzalkonium chloride 0.05 mg/mL; citric acid; sodium chloride; sodium phosphate dibasic; and water for injection. Sodium hydroxide and/or hydrochloric acid may be added to adjust pH. The pH during its shelf life ranges from 6.8-7.8.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Bimatoprost, a prostaglandin analog, is a synthetic structural analog of prostaglandin with ocular hypotensive activity. It selectively mimics the effects of naturally occurring substances, prostamides. Bimatoprost is believed to lower intraocular pressure (IOP) in humans by increasing outflow of aqueous humor through both the trabecular meshwork and uveoscleral routes. Elevated IOP presents a major risk factor for glaucomatous field loss. The higher the level of IOP, the greater the likelihood of optic nerve damage and visual field loss.

12.3 Pharmacokinetics

Absorption

After one drop of bimatoprost ophthalmic solution, 0.03% was administered once daily to both eyes of 15 healthy subjects for two weeks, blood 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. Mean C_{max} and AUC_{0-24hr} values were similar on days 7 and 14 at approximately 0.08 ng/mL and 0.09 ng•hr/mL, respectively, indicating that steady state was reached during the first week of ocular dosing. There was no significant systemic drug accumulation over time.

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.

Elimination

Following an intravenous dose of radiolabeled 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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Bimatoprost was not carcinogenic in either mice or rats when administered by oral gavage at doses of up to 2 mg/kg/day and 1 mg/kg/day respectively (at least 192 and 291 times the recommended human exposure based on blood AUC levels respectively) for 104 weeks.

Bimatoprost was not mutagenic or clastogenic in the Ames test, in the mouse lymphoma test, or in the *in vivo* mouse micronucleus tests.

Bimatoprost did not impair fertility in male or female rats up to doses of 0.6 mg/kg/day (at least 103 times the recommended human exposure based on blood AUC levels).

14 CLINICAL STUDIES

In clinical studies of patients with open angle glaucoma or ocular hypertension with a mean baseline IOP of 26 mmHg, the IOP-lowering effect of bimatoprost ophthalmic solution, 0.03% once daily (in the evening) was 7-8 mmHg.

16 HOW SUPPLIED/STORAGE AND HANDLING

Bimatoprost Ophthalmic Solution, 0.03% is supplied sterile in white opaque polypropylene bottles with translucent polypropylene droppers and turquoise opaque polypropylene caps in the following sizes:

2.5 mL fill in 5 mL container	- NDC 60505-0583-4
5 mL fill in 5 mL container	- NDC 60505-0583-1
7.5 mL fill in 10 mL container	- NDC 60505-0583-5

Storage: Store at 2° to 25°C (36° to 77°F).

Handling: After initial opening, remove the turquoise colored tamper evident ring from the bottle prior to replacing the cap.

17 PATIENT COUNSELING INFORMATION

17.1 Potential for Pigmentation

Advise patients about the potential for increased brown pigmentation of the iris, which may be permanent. Also inform patients about the possibility of eyelid skin darkening, which may be reversible after discontinuation of bimatoprost ophthalmic solution, 0.03%.

17.2 Potential for Eyelash Changes

Inform patients of the possibility of eyelash and vellus hair changes in the treated eye during treatment with bimatoprost ophthalmic solution, 0.03%. These changes may result in a

disparity between eyes in length, thickness, pigmentation, number of eyelashes or vellus hairs, and/or direction of eyelash growth. Eyelash changes are usually reversible upon discontinuation of treatment.

17.3 Handling the Container

Instruct patients to avoid allowing the tip of the dispensing container to contact the eye, surrounding structures, fingers, or any other surface in order to avoid contamination of the solution by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

17.4 When to Seek Physician Advice

Advise patients that if they develop an intercurrent ocular condition (e.g., trauma or infection), have ocular surgery, or develop any ocular reactions, particularly conjunctivitis and eyelid reactions, they should immediately seek their physician's advice concerning the continued use of bimatoprost ophthalmic solution, 0.03%.

17.5 Use with Contact Lenses

Advise patients that bimatoprost ophthalmic solution, 0.03% contains benzalkonium chloride, which may be absorbed by soft contact lenses. Contact lenses should be removed prior to instillation of bimatoprost ophthalmic solution, 0.03% and may be reinserted 15 minutes following its administration.

17.6 Use with Other Ophthalmic Drugs

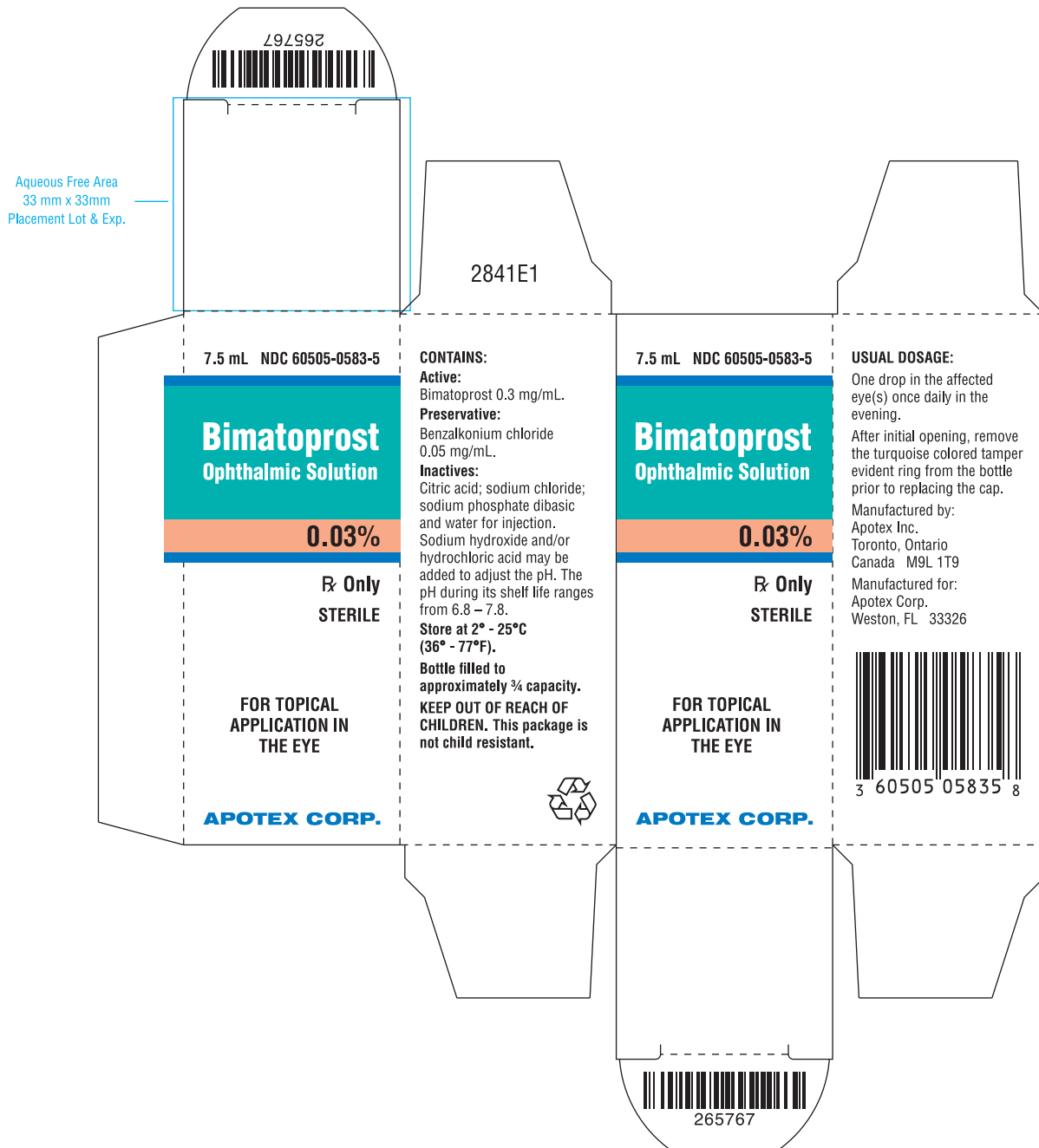
Advise patients that if more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes between applications.

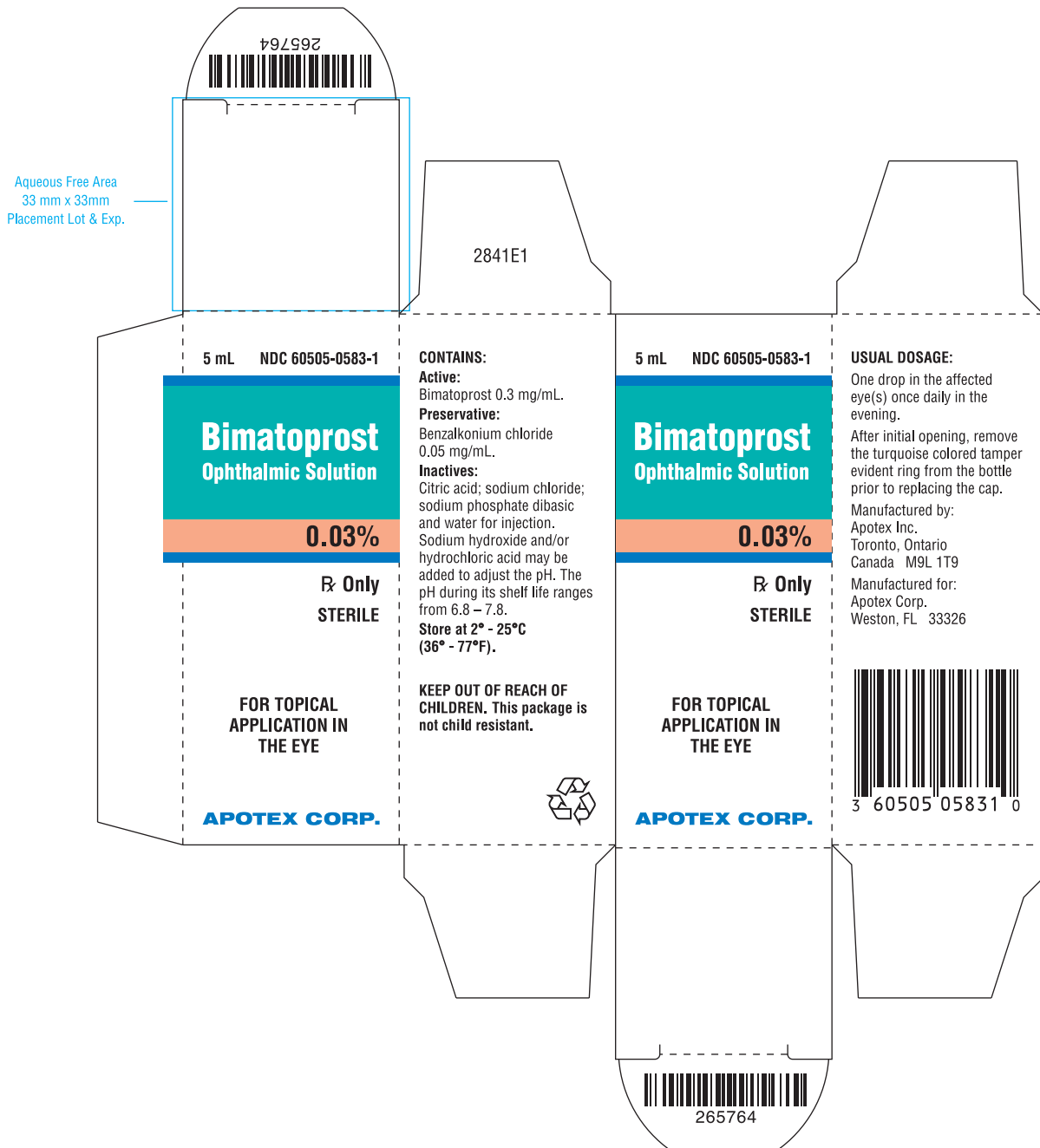
Manufactured by:
Apotex Inc.
Toronto, Ontario
Canada M9L 1T9

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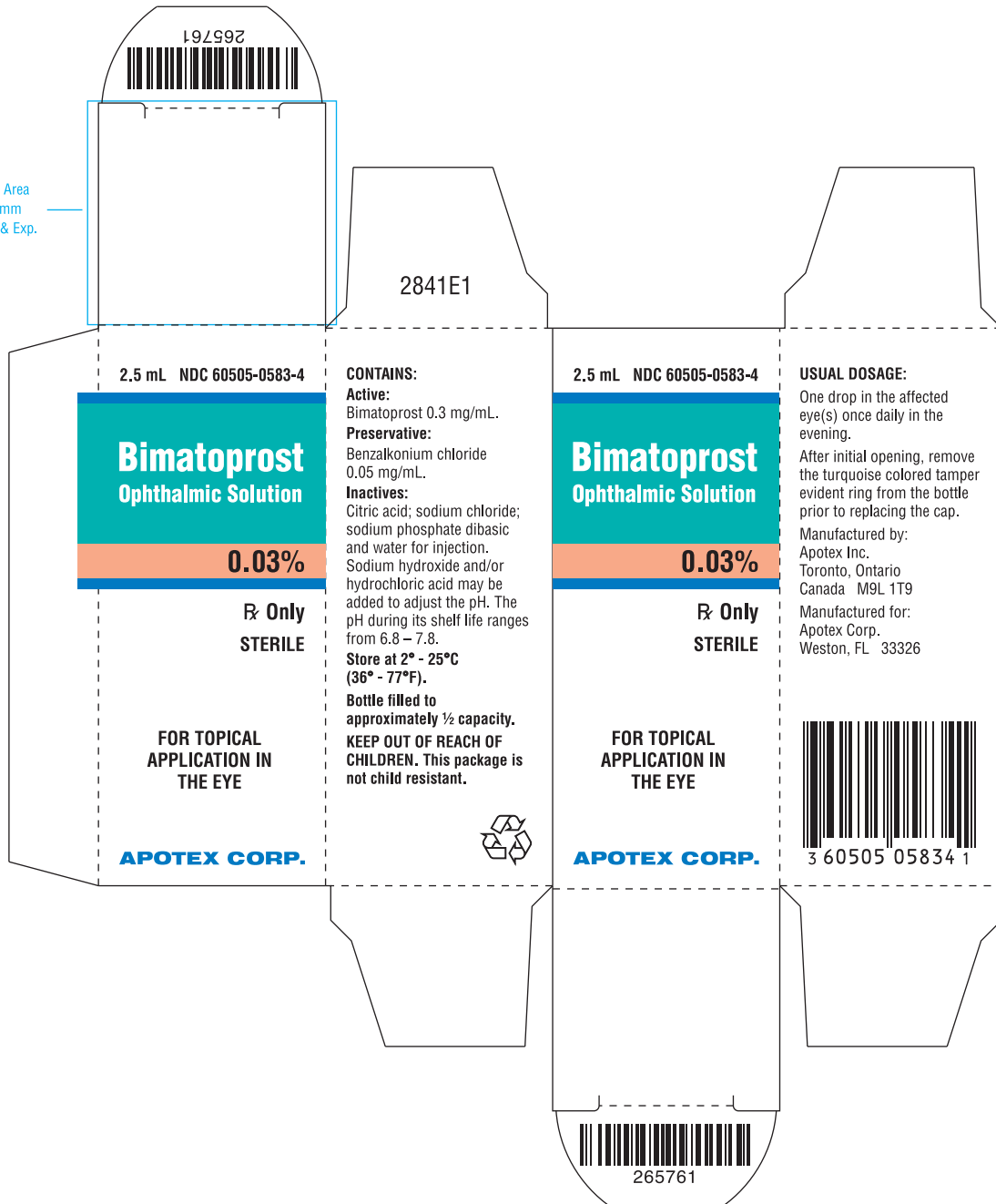
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Apotex Corp.
Weston, FL
33326

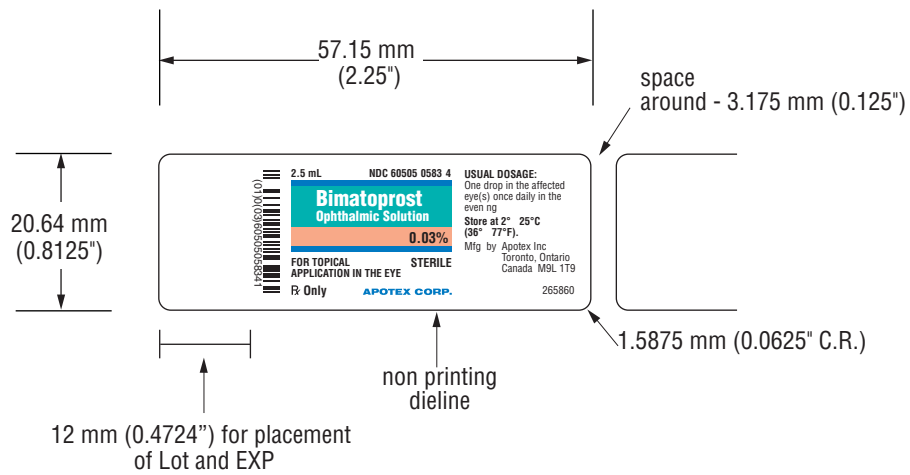
June 2015



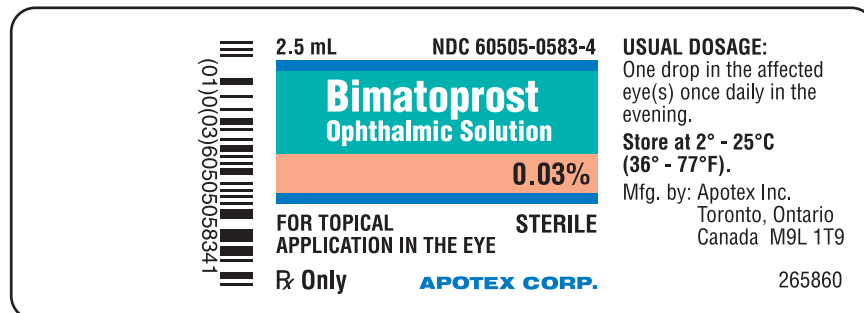


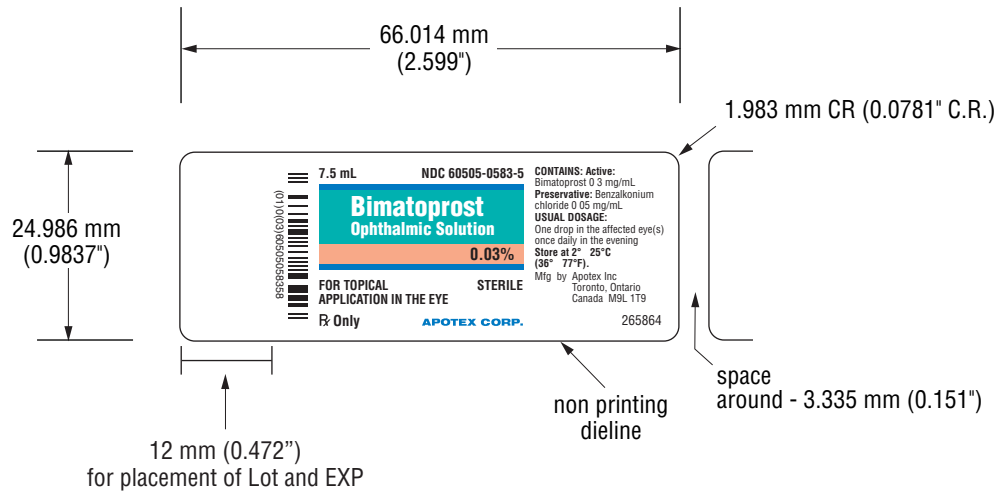
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33 mm x 33mm
Placement Lot & Exp.



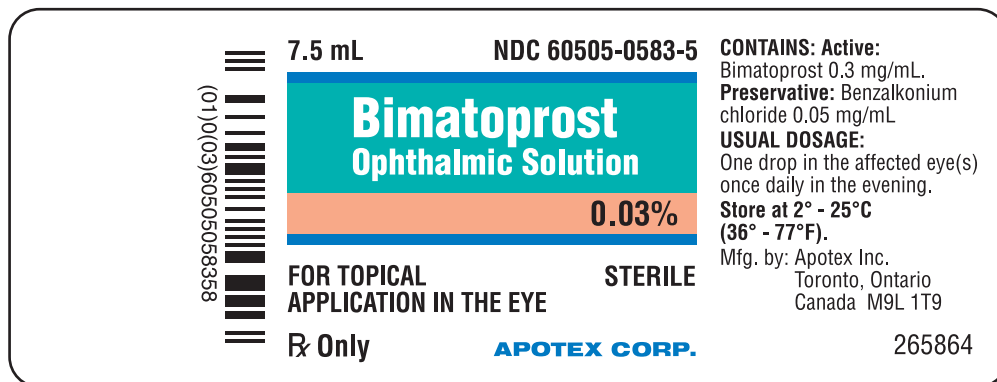


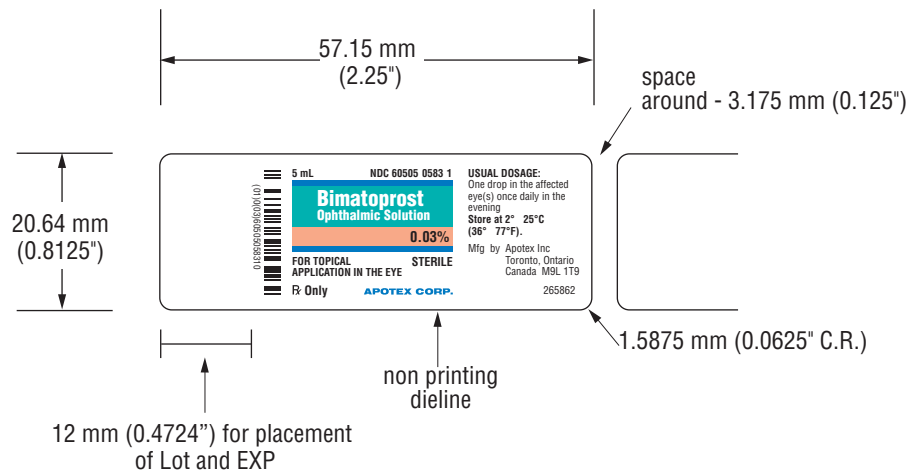
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