

Alcon PACKAGING

FILE NAME: **AAA2224 L BMTPT 2_5ML**

ARTIST: (b) (4) SIGNATURE: _____ REV: C DATE: 02/02/13

COLORS: **BLACK** (b) (4) **COATING NOTATIONS -DIE VINYL**

DIMENSIONS / DRAWING NUMBER: _____ SPECIAL INSTRUCTIONS: _____

Alcon PROOFREADING REPORT

Docuproof System
 Proofreading
 Text Verification System (TVS)
 SRS Compare

TYPE OF INSPECTION: _____ SETTINGS: _____ INSPECTION RESULTS: _____
 # of Errors: _____

Electronic / Electronic
 Hardcopy / Hardcopy
 # of Images _____

Dimmer: _____
 Aperture: _____
 Zoom: _____
 Focus: _____

APPROVALS:
 Approved
 Correct & Return

SIGNATURE: _____ DATE: _____

Alcon (b) (4)

8:54 am, Mar 14, 2013

1. TEXT, COLOR & COATING AREA.
2. COLOR & COATING AREA, NO TEXT ALLOWED.
3. DWG. NO AND CONTROL DATE LOCATION.
4. QUIET AREA - NO TEXT, COLOR OR COATING ALLOWED, EXCEPT AS INDICATED.
5. PREPRINTED "LOT:" LOCATION.
6. PREPRINTED "EXP.:" LOCATION.

A00975--

L.B.L.P.S., SAMPLE BOTTLE

PKG. ENG. USE ONLY	
A00975--	
04/08/98	
(b) (4)	
APPROVAL: _____	
Z00100B	(b) (4) 4/09/98
PKG/DATE:	(4)
(b) (4)	
PKG/DATE:	(4) 4/09/98



SCALE: 2X



Alcon PACKAGING

FILE NAME: **AAA2225 L BMTPT 5ML**

ARTIST: (b) (4) SIGNATURE: _____ REV: E DATE: 02/01/13

DIMENSIONS / DRAWING NUMBER: _____
SPECIAL INSTRUCTIONS: _____

Alcon (b) (4)

COATING NOTATIONS
-DIE VINYL

5:22 pm, Feb 01, 2013

Alcon PROOFREADING REPORT

Docuproof System
 Proofreading
 Text Verification System (TVS)
 SRS Compare

TYPE OF INSPECTION: Electronic / Electronic
 Hardcopy / Hardcopy

SETTINGS: Dimmer: _____ Aperture: _____ Zoom: _____ Focus: _____

INSPECTION RESULTS: # of Errors: _____

APPROVALS:
 Approved
 Correct & Return

SIGNATURE: _____ DATE: _____

LBLPS, LINES 15/16, 5ML

PKG. ENG. USE ONLY	
L00858BD	
12/13/98	"BLACK INK" WAS
"BLACK OR HIGH CONTRAST"	

UNLESS OTHERWISE SPECIFIED:
TOLERANCE: ±1/32"

(b) (4)

APPROVAL: _____

Z00100A- (b) (4) 12/14/98

PKG/DATE: _____

PKG/DATE: _____ 12/18/98



Alcon PACKAGING

FILE NAME: AAA2226 L BMTPTST 7_5ML

ARTIST: (b) (4) SIGNATURE: _____ REV: F DATE: 02/05/13

COLORS: BLACK (b) (4) COATING NOTATIONS -DIE VINYL

DIMENSIONS / DRAWING NUMBER: _____ SPECIAL INSTRUCTIONS: _____

Alcon PROOFREADING REPORT

Docuproof System
 Proofreading
 Text Verification System (TVS)
 SRS Compare

TYPE OF INSPECTION: Electronic / Electronic Hardcopy / Hardcopy
 # of Images: _____

SETTINGS: Dimmer: _____ Aperture: _____ Zoom: _____ Focus: _____

INSPECTION RESULTS: # of Errors: _____

APPROVALS:
 Approved
 Correct & Return

SIGNATURE: _____ DATE: _____

LBLPS, LINES 15/16, 10ML

PKG, ENG, USE ONLY	
A00859-C	200308-
04/06/95	
CODE AREA INCREASED BY 1/16"	

(b) (4)

APPROVAL: _____

200100- _____

PKG/DATE: (b) (4) 4/06/95

PKG/DATE: (b) (4) 4/06/95

1. TEXT, COLOR & COATING AREA.
2. COLOR & COATING AREA, NO TEXT ALLOWED.
3. DWG, NO., & CONTROL DATE LOCATION.
4. QUIET AREA - NO TEXT, COLOR OR COATING ALLOWED, EXCEPT AS INDICATED.
5. PREPRINTED 'LOT:' LOCATION.
6. PREPRINTED 'EXP:' LOCATION.

Alcon (b) (4)

1:34 pm, Feb 05, 2013

A00859-C

DRAWING NUMBER AND CONTROL DATE TO BE UNDERLINED. SEE SPECIFICATION FOR DETAILS.



SCALE: 2X



SCALE: 1X

Alcon PACKAGING

FILE NAME: AAA2227 C BMT PST 2_5ML

ARTIST: (b) (4) SIGNATURE: _____ REV: G DATE: 02/14/13

COLORS: RI ACK (b) (4) COATING NOTATIONS -DIE VINYL

DIMENSIONS / DRAWING NUMBER: _____

SPECIAL INSTRUCTIONS: _____

Alcon PROOFREADING REPORT

Docuproof System
 Proofreading
 Text Verification System (TVS)
 SRS Compare

TYPE OF INSPECTION:
 Electronic / Electronic
 Hardcopy / Hardcopy
 _____ # of Images

SETTINGS:
 Dimmer: _____
 Aperture: _____
 Zoom: _____
 Focus: _____

INSPECTION RESULTS:
 # of Errors: _____

APPROVALS:
 Approved
 Correct & Return

SIGNATURE: _____

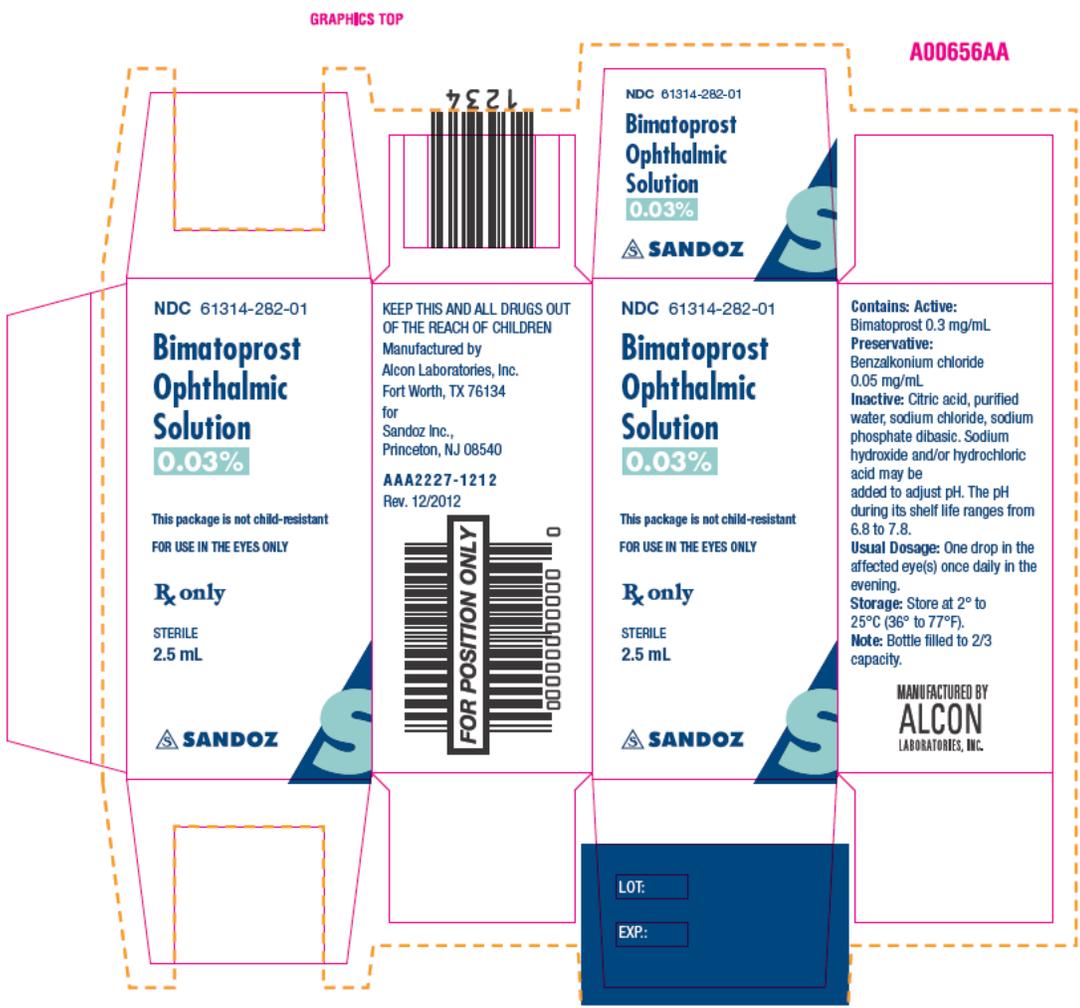
DATE: _____

1. GLUE AREA - NO TEXT, COLOR OR COATING.
2. CODE AREA - NO TEXT OTHER THAN LOT & EXPIRES, COATING AND COLOR ARE ACCEPTABLE.
3. BAR CODE AREA - FINISHED CODE TO BE CENTERED LEFT TO RIGHT.
4. QUIET AREA - NO TEXT OR COLOR ALLOWED.
5. PREPRINTED "LOT:" LOCATION.
6. PREPRINTED "EXP.:" LOCATION.



CTN/INS, SML

PKG, ENG, USE ONLY	
ADD56AA	
02/04/98	UPDATED TO NEW
FORMAT	
(b) (4)	
APPROVAL:	
Z001006-	(b) (4)
PKG/DATE:	13/05/98
PKG/DATE:	03/06/98



Alcon PACKAGING

FILE NAME: **AAA2228 C BMTBST 5ML**

ARTIST: (b) (4) SIGNATURE: _____ REV: H DATE: 03/05/13

DIMENSIONS / DRAWING NUMBER: _____
SPECIAL INSTRUCTIONS: _____

COLORS: RI Δ CK (b) (4) COATING NOTATIONS -DIE VINYL

Alcon (b) (4)

1:16 pm, Mar 05, 2013

Alcon PROOFREADING REPORT

Docuproof System
 Proofreading
 Text Verification System (TVS)
 SRS Compare

TYPE OF INSPECTION:
 Electronic / Electronic
 Hardcopy / Hardcopy
of Images: _____

SETTINGS:
Dimmer: _____
Aperture: _____
Zoom: _____
Focus: _____

INSPECTION RESULTS:
of Errors: _____

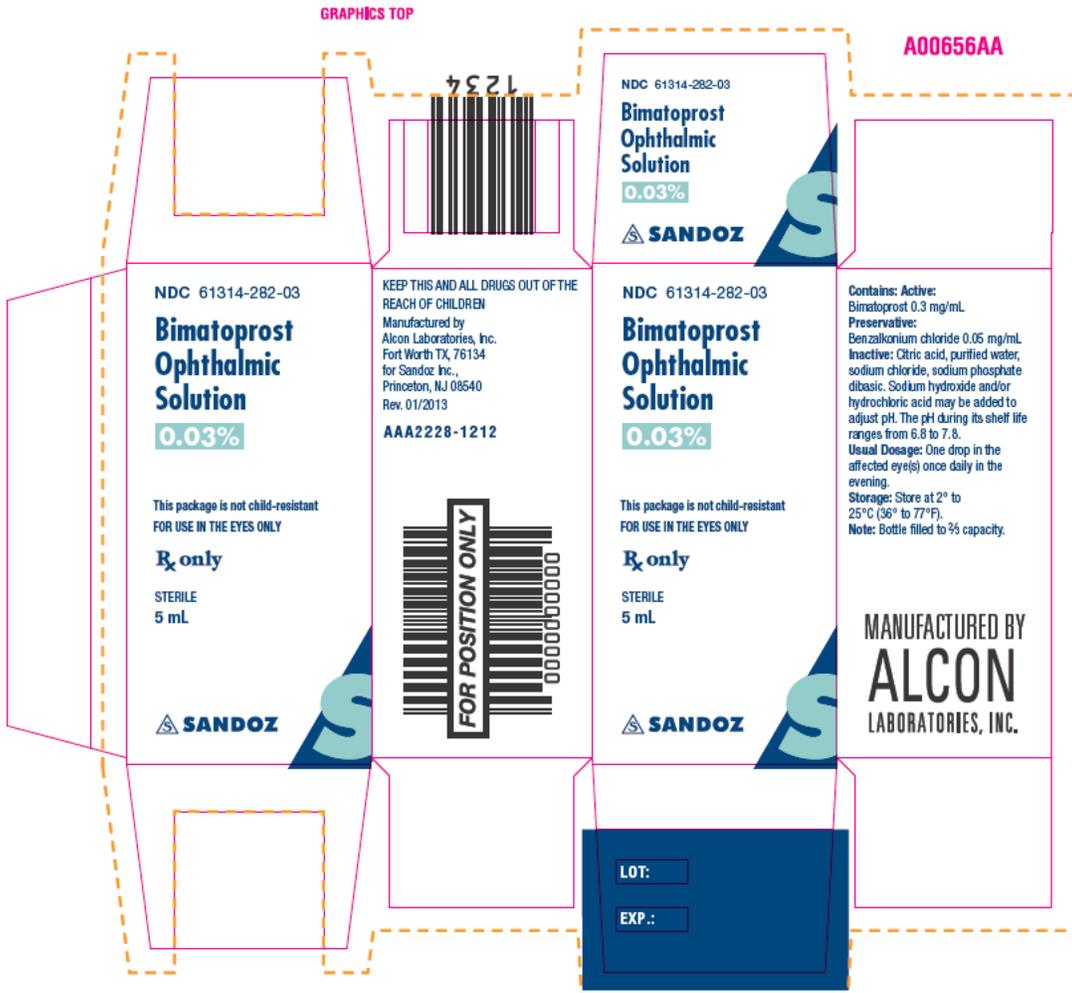
APPROVALS:
 Approved
 Correct & Return

SIGNATURE: _____
DATE: _____

1. GLUE AREA - NO TEXT, COLOR OR COATING.
2. CODE AREA - NO TEXT OTHER THAN LOT & EXPIRES. COATING AND COLOR ARE ACCEPTABLE.
3. BAR CODE AREA - FINISHED CODE TO BE CENTERED LEFT TO RIGHT.
4. QUIET AREA - NO TEXT OR COLOR ALLOWED.
5. PREPRINTED "LOT:" LOCATION.
6. PREPRINTED "EXP.:" LOCATION.

CTN/NS, SML

PKG. ENG. USE ONLY	
A00656AA	
02/04/98	UPDATED TO NEW
FORMAT (b) (4)	
APPROVAL: (b) (4)	
2081000-	
PKG/DATE:	03/05/98
PKG/DATE:	03/06/98



Alcon PACKAGING

FILE NAME: **AAA2229 C BMTPT 7_5ML**

ARTIST: (b) (4) SIGNATURE: _____ REV: **G** DATE: **02/14/13**

COLORS: **RI ACK (b) (4)** **COATING NOTATIONS - DIE VINYL**

DIMENSIONS / DRAWING NUMBER: _____
SPECIAL INSTRUCTIONS: _____

Alcon PROOFREADING REPORT

Docuproof System
 Proofreading
 Text Verification System (TVS)
 SRS Compare

TYPE OF INSPECTION:
 Electronic / Electronic
 Hardcopy / Hardcopy
of Images: _____

SETTINGS:
Dimmer: _____
Aperture: _____
Zoom: _____
Focus: _____

INSPECTION RESULTS:
of Errors: _____

APPROVALS:
 Approved
 Correct & Return

SIGNATURE: _____
DATE: _____

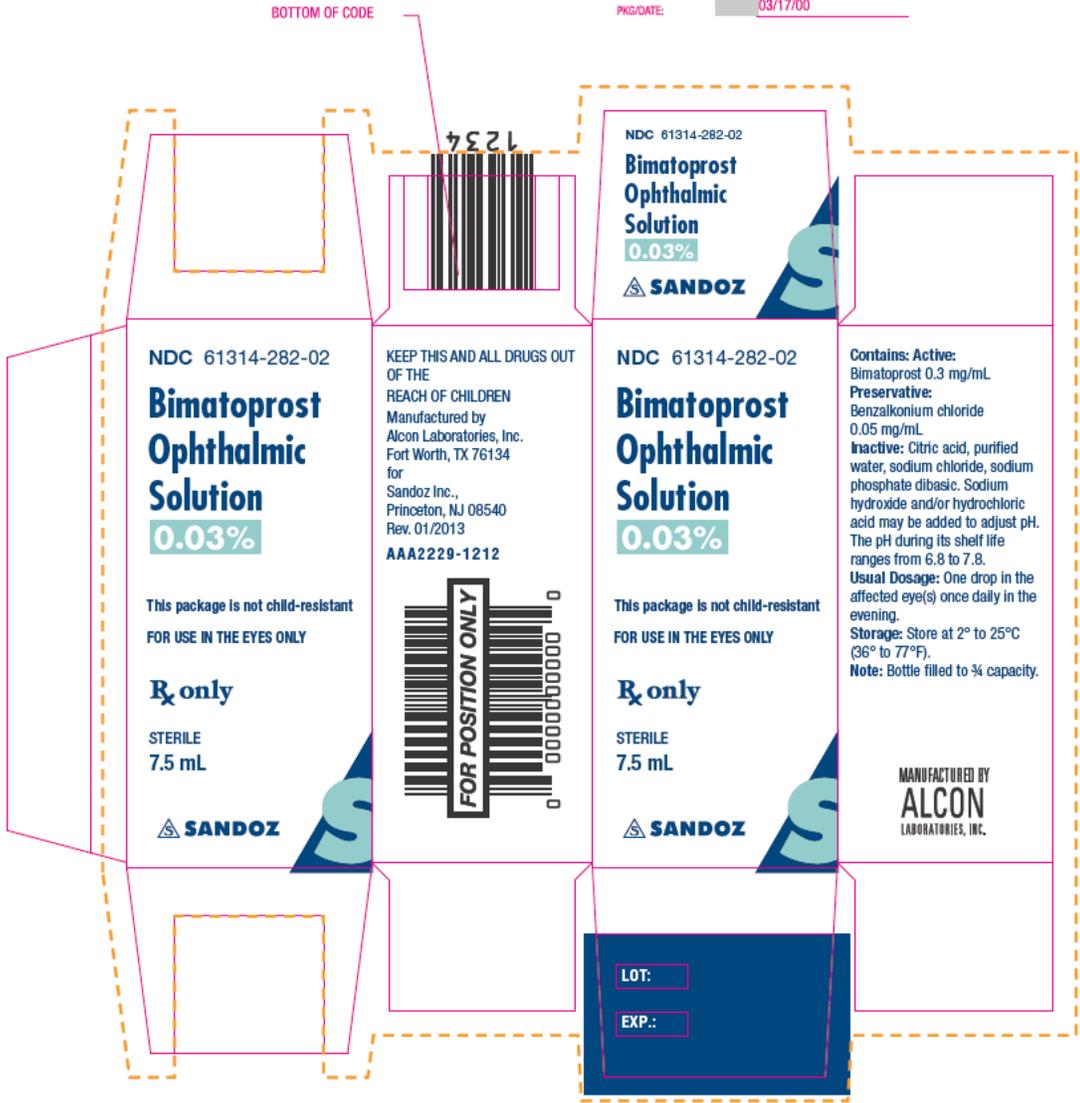
Alcon (b) (4)

10:55 am, Feb 14, 2013

CTNJNS - 10ML

PKG. ENG. USE ONLY	
A0680AA	
03/17/00	REVISED TO CURRENT
FORMAT	
(b) (4)	
APPROVAL: _____	
Z00108-	(b) (4)
PKG. DATE:	03/17/00
PKG. DATE:	03/17/00

1. GLUE AREA - NO TEXT, COLOR OR COATING.
2. CODE AREA - NO TEXT OTHER THAN LOT & EXPIRES. COLOR & COATING ARE ACCEPTABLE.
3. BAR CODE AREA - FINISHED CODE TO BE CENTERED LEFT TO RIGHT.
4. QUIET AREA - NO TEXT OR COLOR ALLOWED. COATING IS ACCEPTABLE.
5. PREPRINTED "LOT:" LOCATION.
6. PREPRINTED "EXP.:" LOCATION.



Alcon (b) (4)

10:30 am, Jan 20, 2015

DRAWING INFORMATION		
DWG NUMBER:	L00846B	REV: 0
DWG DESC.:	INSROLL, 10"X5" FOLD TO 5"X1.125"	
DWG DATE:	10/22/2012	
REV DESC.:		
DRAWN BY:	(b) (4)	
UNLESS OTHERWISE SPECIFIED: TOLERANCE: +/-1/32"		

LEGEND

- FOLD
- _____ CUT

- 2 ALCON DWG. NO. & CONTROL DATE - DIRECTION DETERMINED BY COPY.
- 3 NO TEXT, COLOR OR COATING
- 4 RESERVED FOR BAR CODE

HIGHLIGHTS OF PRESCRIBING INFORMATION
 These highlights do not include all the information needed to use Brimtoprost Ophthalmic Solution, 0.03% safely and effectively. See all prescribing information for Brimtoprost Ophthalmic Solution, 0.03%.

RECENT MAJOR CHANGES
 Warnings and Precautions, Intraocular Inflammation (5.3) 06/2014

INDICATIONS AND USAGE
 Brimtoprost 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)

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

ADVERSE REACTIONS AND DRUG INTERACTIONS
 Solution containing 0.3 mg/mL Brimtoprost. (2)

CONTRAINDICATIONS
 None. (4)

WARNINGS AND PRECAUTIONS
 - Pigmentation: Pigmentation of the iris, peripheral iris (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)
 - Use in Specific Populations: Use in pediatric patients below the age of 16 years is not recommended because of potential safety concerns related to bromocriptine following long-term chronic use. (8.4)

OVERDOSAGE
 11 DESCRIPTION
 12 CLINICAL PHARMACOLOGY
 12.1 Mechanism of Action
 12.3 Pharmacokinetics
 13 NONCLINICAL TOXICOLOGY
 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
 14 CLINICAL STUDIES
 16 HOW SUPPLIED/STORAGE AND HANDLING
 17 PATIENT COUNSELING INFORMATION
 17.1 Potential for Pigmentation
 17.2 Potential for Eyelash Changes
 17.3 Hand Lag the Contact Lens
 17.4 When to Seek Physician Advice
 17.5 Use with Contact Lenses
 17.6 Use with Other Ophthalmic Drugs

6.1 Clinical Studies Experience
 Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of another drug may not reflect the rates observed in practice. In clinical trials, the most frequent events associated with the use of Brimtoprost 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 periorbital skin, eyelid/iris, cilium, superficial punctate keratitis, periorbital/eyelid/iris, 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, a foreign body in the eye, conjunctival redness, increased tearing, pigmentation, and conjunctival edema. In less than 1% of patients, intraocular inflammation was reported as 0.1%. 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 headache, abnormal menstruation, sinusitis, and dizziness. 6.2 Postmarketing Experience The following reactions have been identified during postmarketing use of Brimtoprost Ophthalmic Solution, 0.03% in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of the frequency cannot be made. The reactions, which have been observed, are included due to either their seriousness, frequency of reporting, or a suspected causal connection to Brimtoprost Ophthalmic Solution, 0.03% or a combination of these factors. Include abnormal menstruation, dizziness, eyelid edema, hypertension, nausea, and periorbital and iris changes associated with a deepening of the eyelid sulcus.

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 or lowering 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 γ -glutamyl transaminase at baseline, bimatoprost 0.03% had no adverse effect on liver function over 48 months.

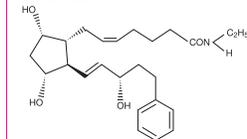
10 OVERDOSAGE

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 (2S,7S)-18,26,36,55)-3,5-Dihydroxy-2-[(1E,3S)-3-hydroxy-5-phenyl-1-pentenyl]cyclopentyl]-5-N-ethylphenylamide, and its molecular weight is 415.58. Its molecular formula is C₂₉H₃₇NDO₄. 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 mOsm/kg.

Bimatoprost Ophthalmic Solution, 0.03% contains **Active:** bimatoprost 0.3 mg/mL. **Preservative:** benzalkonium chloride 0.05 mg/mL. **Inactives:** citric acid, sodium chloride, sodium phosphate dibasic, and purified water. Sodium hydroxide and/or hydrochloric acid may be added to adjust pH. The pH during its shelf life ranges from 6.8 to 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_{0-24h} 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.

8009254 0115

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 4 times of 0.6 mg/kg/day (at least 180 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 base line IOP of 26 mmHg, the IOP-lowering effect of Bimatoprost Ophthalmic Solution, 0.03% once daily (in the evening) was 7 to 8 mmHg.

16 HOW SUPPLIED/STORAGE AND HANDLING

Bimatoprost Ophthalmic Solution, 0.03% is supplied sterile, in a white LDPE plastic DRÖP-TAINER® bottle with a natural LDPE dropper tip and a tan opaque polypropylene cap in the following sizes:

2.5 mL, 6.1 in 4 mL container	NDC 61314-282-01
5 mL, 6.1 in 8 mL container	NDC 61314-282-03
7.5 mL, 6.1 in 10 mL container	NDC 61314-282-02

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

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.

Rev 10 2014

Rx only

SANDOZ

Manufactured by Alcon Laboratories Inc
 Fort Worth, TX 76134
 for Sandoz Inc
 Princeton, NJ 08540

* DRÖP-TAINER is a registered trademark of Alcon Research, Ltd.