BEPOTASTINE BESILATE- bepotastine besilate solution/ drops
Mylan Pharmaceuticals Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BEPOTASTINE BESILATE OPHTHALMIC SOLUTION safely and effectively. See full prescribing information for BEPOTASTINE BESILATE OPHTHALMIC SOLUTION.

BEPOTASTINE BESILATE ophthalmic solution, for topical application in the eye
Initial U.S. Approval: 2009

INDICATIONS AND USAGE

Bepotastine besilate ophthalmic solution is a histamine H_1 receptor antagonist indicated for the treatment of itching associated with allergic conjunctivitis. (1)

DOSAGE AND ADMINISTRATION

Instill one drop into the affected eye(s) twice a day. (2)
Remove contact lenses prior to instillation of bepotastine besilate ophthalmic solution. (2)

DOSAGE FORMS AND STRENGTHS

Ophthalmic solution containing bepotastine besilate, 15 mg/mL (1.5%). (3)

CONTRAINDICATIONS

Hypersensitivity to any component of this product. (4)

WARNINGS AND PRECAUTIONS

- Contamination of Solution: Do not touch dropper tip to any surface. Keep bottle tightly closed when not in use. (5.1)
- Contact Lens Wear: Bepotastine besilate ophthalmic solution should not be used to treat contact lens-related irritation. (5.2)

ADVERSE REACTIONS

The most common adverse reaction occurring in approximately 25% of patients was a mild taste following instillation. Other adverse reactions which occurred in 2-5% of subjects were eye irritation, headache, and nasopharyngitis. (6.1)
To report SUSPECTED ADVERSE REACTIONS, contact Mylan Pharmaceuticals Inc. at 1-877-446-3679 (1-877-4-INFO-RX) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.
See 17 for PATIENT COUNSELING INFORMATION.

Revised: 3/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Bepotastine besilate ophthalmic solution, 1.5% is a histamine H_1 receptor antagonist indicated for the treatment of itching associated with signs and symptoms of allergic conjunctivitis.

2 DOSAGE AND ADMINISTRATION

Instill one drop of bepotastine besilate ophthalmic solution into the affected eye(s) twice a day.

Remove contact lenses prior to instillation of bepotastine besilate ophthalmic solution.

3 DOSAGE FORMS AND STRENGTHS

Ophthalmic solution containing bepotastine besilate 15 mg/mL (1.5%).

4 CONTRAINDICATIONS

Bepotastine besilate ophthalmic solution is contraindicated in patients with a history of hypersensitivity reactions to bepotastine or any of the other ingredients *[see Adverse Reactions (6.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Contamination of Tip and Solution

To minimize contaminating the dropper tip and solution, advise the patient not to touch the eyelids or surrounding areas with the dropper tip of the bottle and to keep the bottle

tightly closed when not in use.

5.2 Contact Lens Wear

Bepotastine besilate ophthalmic solution should not be used to treat contact lens-related irritation.

Bepotastine besilate ophthalmic solution should not be instilled while wearing contact lenses. Patient should remove contact lenses prior to instillation of bepotastine besilate ophthalmic solution, because benzalkonium chloride may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of bepotastine besilate ophthalmic solution.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

The most common reported adverse reaction occurring in approximately 25% of subjects was a mild taste following instillation. Other adverse reactions occurring in 2-5% of subjects were eye irritation, headache, and nasopharyngitis.

6.2 Post-Marketing Experience

Hypersensitivity reactions have been reported rarely during the post-marketing use of bepotastine besilate ophthalmic solution. Because these reactions are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The hypersensitivity reactions may include itching, body rash, and swelling of lips, tongue and/or throat.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available human data for the use of bepotastine besilate ophthalmic solution during pregnancy to inform any drug-associated risks.

Oral administration of bepotastine besilate to pregnant rats or rabbits during organogenesis or during the pre/postnatal period did not produce adverse embryofetal or offspring effects at clinically relevant systemic exposures. Maternal toxicity was observed in the rabbits at the lowest dose administered, 20 mg/kg/day (215 times the maximum recommended human ophthalmic dose, RHOD, on a mg/m^2 basis) *[see Data]*.

The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2 to 4%, and of miscarriage is 15 to 20%, of clinically recognized pregnancies.

Data

Animal Data

In embryofetal development studies, oral administration of bepotastine besilate to pregnant rabbits throughout organogenesis did not produce teratogenic effects at maternal doses up to 500 mg/kg/day (approximately 5400 times the maximum RHOD, on a mg/m^2 basis). A maternal no observed adverse effect level (NOAEL) was not identified in this study due to spontaneous abortion observed at the lowest dose tested, 20 mg/kg/day (approximately 215 times higher than the maximum RHOD, on a mg/m^2 basis). Oral administration of bepotastine besilate to pregnant rats throughout organogenesis produced skeletal anomalies at 1000 mg/kg/day (5400 times higher than the maximum RHOD, on a mg/m^2 basis), a dose that also produced maternal toxicity and lethality. No teratogenic effects were observed in rats at maternal doses up to 200 mg/kg/day (corresponding to an estimated blood plasma concentration 3300 times higher than that anticipated in humans at the maximum RHOD). A maternal NOAEL was observed at 10 mg/kg/day (54 times higher than the maximum RHOD, on a mg/m^2 basis). Following a single 3 mg/kg oral dose in rats (16 times higher than the maximum RHOD, on a mg/m^2 basis), the concentration of radio-labeled bepotastine besilate was similar in fetal liver and maternal blood plasma. The concentration in other fetal tissues was one-third to one-tenth the concentration in maternal blood plasma.

In a pre/postnatal development study, oral administration of bepotastine besilate to rats during the perinatal and lactation periods produced an increase in stillbirths and decreased growth and development in offspring at a maternal dose of 1000 mg/kg/day (5400 times higher than the maximum RHOD, on a mg/m^2 basis). There were no observed adverse effects on offspring of rats treated with 100 mg/kg/day (540 times higher than the maximum RHOD, on a mg/m^2 basis). Effects on parturition and maternal lethality were observed at 100 mg/kg/day and 1000 mg/kg/day, respectively. A maternal NOAEL was observed at 10 mg/kg/day (54 times higher than the maximum RHOD, on a mg/m^2 basis).

8.2 Lactation

Risk Summary

There are no data on the presence of bepotastine besilate in human milk, the effects on the breastfed infant or the effects on milk production.

The developmental and health benefits of breastfeeding should be considered, along with the mother’s clinical need for bepotastine besilate ophthalmic solution, and any potential adverse effects on the breastfed infant from bepotastine besilate ophthalmic solution.

Animal Data

Following a single 3 mg/kg oral dose (16 times the maximum RHOD, on a mg/m^2 basis) of radiolabeled bepotastine besilate to nursing rats 11 days after delivery, the maximum concentration of radioactivity in milk was 0.40 mcg-eq/mL 1 hour after administration; at 48 hours after administration, the radioactivity concentration was below detection limits. The milk radioactivity concentration was higher than the maternal blood plasma radioactivity concentration at each time of measurement. It is not known whether

bepotastine besilate would be present in maternal milk following topical ocular administration.

8.4 Pediatric Use

Safety and efficacy of bepotastine besilate ophthalmic solution, 1.5% have not been established in pediatric patients under 2 years of age. Efficacy in pediatric patients under 10 years of age was extrapolated from clinical trials conducted in pediatric patients greater than 10 years of age and from adults.

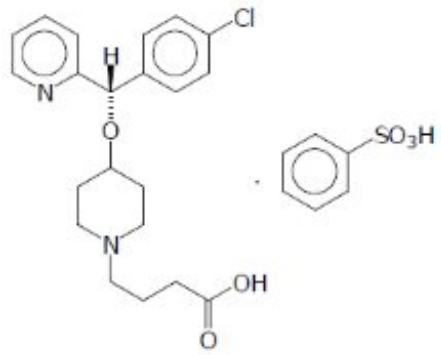
8.5 Geriatric Use

No overall differences in safety or effectiveness have been observed between elderly and younger patients.

11 DESCRIPTION

Bepotastine besilate ophthalmic solution, 1.5% is a sterile, topically administered drug for ophthalmic use. Each mL of bepotastine besilate ophthalmic solution contains 15 mg bepotastine besilate.

Bepotastine besilate is designated chemically as 4-[(S)-(4-Chlorophenyl)-2-pyridinylmethoxy]-1-piperidinebutanoic acid, benzenesulfonate salt. The chemical structure for bepotastine besilate is:



Bepotastine besilate is a white or creamish white crystalline powder. The molecular weight of bepotastine besilate is 547.06 daltons. Bepotastine besilate ophthalmic solution is supplied as a sterile, aqueous 1.5% solution, with a pH of 6.8.

The osmolality of bepotastine besilate ophthalmic solution, 1.5% is approximately 290 mOsm/kg.

Each mL of bepotastine besilate ophthalmic solution, 1.5% contains:

- Active: bepotastine besilate 15 mg (equivalent to 10.7 mg bepotastine)
- Preservative: benzalkonium chloride 0.005%
- Inactives: monobasic sodium phosphate dihydrate, sodium chloride, sodium hydroxide to adjust pH, and water for injection.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Bepotastine is a topically active, direct H_1-receptor antagonist and an inhibitor of the release of histamine from mast cells.

12.3 Pharmacokinetics

Absorption

The extent of systemic exposure to bepotastine following topical ophthalmic administration of bepotastine besilate 1% and 1.5% ophthalmic solutions was evaluated in 12 healthy adults. Following one drop of 1% or 1.5% bepotastine besilate ophthalmic solution to both eyes four times daily (QID) for 7 days, bepotastine plasma concentrations peaked at approximately 1 to 2 hours post-instillation. Maximum plasma concentrations for the 1% and 1.5% strengths were 5.1 ± 2.5 ng/mL and 7.3 ± 1.9 ng/mL, respectively. Plasma concentrations at 24 hours post-instillation were below the quantifiable limit (2 ng/mL) in 11/12 subjects in the two dose groups.

Distribution

The extent of protein binding of bepotastine is approximately 55% and independent of bepotastine concentration.

Metabolism

In vitro metabolism studies with human liver microsomes demonstrated that bepotastine is minimally metabolized by CYP450 isozymes.

In vitro studies demonstrated that bepotastine besilate does not inhibit the metabolism of various cytochrome P450 substrates via inhibition of CYP3A4, CYP2C9 and CYP2C19. The effect of bepotastine besilate on the metabolism of substrates of CYP1A2, CYP2C8 and CYP2D6 was not studied. Bepotastine besilate has a low potential for drug interaction via inhibition of CYP3A4, CYP2C9 and CYP2C19.

Excretion

The main route of elimination of bepotastine besilate is urinary excretion (with approximately 75-90% excreted unchanged in urine).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term dietary studies in mice and rats were conducted to evaluate the carcinogenic potential of bepotastine besilate. Bepotastine besilate did not significantly induce neoplasms in mice receiving a nominal dose of up to 200 mg/kg/day for 21 months, or rats receiving a nominal dose of up to 97 mg/kg/day for 24 months. These dose levels correspond to systemic exposures approximately 350 and 200 times higher than that

achieved at the RHOD, respectively.

The no observable adverse effect level for bepotastine besilate based on nominal dose levels in carcinogenicity tests were 18.7 to 19.9 mg/kg/day in mice and 9.6 to 9.8 mg/kg/day in rats (corresponding to systemic exposures approximately 60 and 20 times higher than that anticipated in humans at RHOD, respectively).

Mutagenesis

There was no evidence of genotoxicity in the Ames test (mutagenicity), in CHO cells (chromosome aberration), in mouse hepatocytes (unscheduled DNA synthesis), or in the mouse micronucleus test.

Impairment of Fertility

Oral administration of bepotastine to male and female rats at doses up to 1000 mg/kg/day (5400 times higher than the maximum RHOD, on a mg/m^2 basis) resulted in reduction in fertility index and surviving fetuses. Oral administration of bepotastine besilate produced no observed adverse effects on fertility or reproduction in rats at oral doses up to 200 mg/kg/day (corresponding to an estimated blood plasma concentration 3300 times higher than that anticipated in humans at the RHOD).

14 CLINICAL STUDIES

Clinical efficacy was evaluated in two conjunctival allergen challenge (CAC) studies (237 patients). Bepotastine besilate ophthalmic solution, 1.5% was more effective than its vehicle for relieving ocular itching induced by an ocular allergen challenge, both at a CAC 15 minutes post-dosing and a CAC 8 hours post-dosing of bepotastine besilate ophthalmic solution.

The safety of bepotastine besilate ophthalmic solution was evaluated in a randomized clinical study of 861 subjects over a period of 6 weeks.

16 HOW SUPPLIED/STORAGE AND HANDLING

Bepotastine Besilate Ophthalmic Solution, 1.5% is a sterile, clear colorless to pale yellow solution practically free from particles. Each mL of bepotastine besilate ophthalmic solution contains 15 mg bepotastine besilate equivalent to 10.7 mg bepotastine.

Bepotastine besilate ophthalmic solution, 1.5% is supplied as a 5 mL or 10 mL solution in a 5 mL or 10 mL three piece container, respectively, each consisting of a white opaque low density polyethylene container with a white opaque open nozzle and a white high density polyethylene cap.

5 mL fill
NDC 0378-7055-35
carton of one bottle

10 mL fill
NDC 0378-7055-67
carton of one bottle

Store at 15° to 25°C (59° to 77°F).

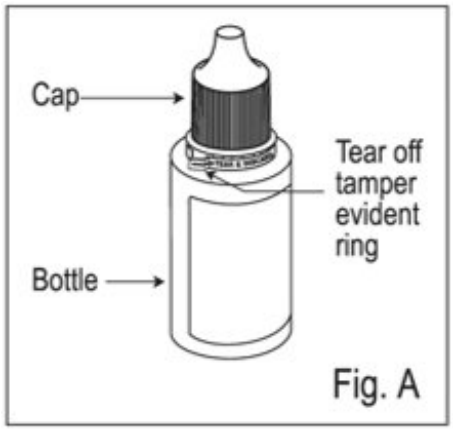
17 PATIENT COUNSELING INFORMATION

- Sterility of Dropper Tip: Advise patients not to touch the dropper tip to any surface, as this may contaminate the solution and to keep the bottle tightly closed when not in use.
- Concomitant Use of Contact Lenses: Advise patients not to wear contact lens if their eye is red and that bepotastine besilate ophthalmic solution should not be used to treat contact lens-related irritation. Patients should also be advised to remove contact lenses prior to instillation of bepotastine besilate ophthalmic solution, which may be reinserted after 10 minutes following administration.

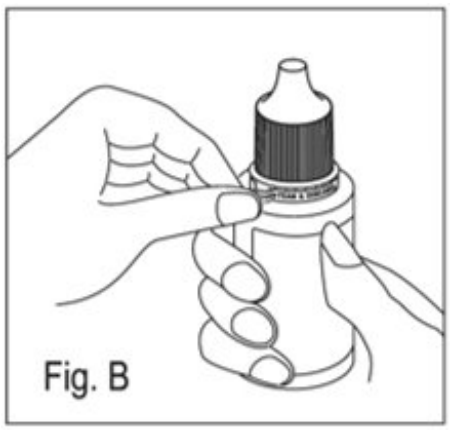
INSTRUCTIONS FOR USE:

Before you use Bepotastine Besilate Ophthalmic Solution, 1.5% for the first time:

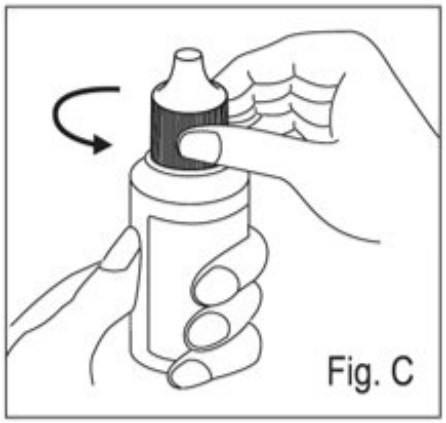
1. Check to make sure that the tamper evident ring between the bottle and the cap is not broken (**See Figure A**). If the tamper evident ring is broken or missing, contact your pharmacist.



2. Tear off the tamper evident ring (**See Figure B**).



3. To open the bottle, remove the cap by turning it in the counterclockwise direction (**See Figure C**).



This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured for:
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

Manufactured by:
Micro Labs Limited
Bangalore – 560 099, INDIA
M.L. No.: KTK/28/357/2006

Revised: 3/2018
MCR:BEPO:R4

PRINCIPAL DISPLAY PANEL – 1.5%

NDC 0378-7055-35

Bepotastine
Besilate
Ophthalmic
Solution
1.5%

For Topical Application
in the Eye.

Rx only 5 mL

Each mL contains:
Active: bepotastine besilate
15 mg equivalent to 10.7 mg
bepotastine.

Preservative: benzalkonium

chloride 0.005%

Inactives: monobasic sodium phosphate dihydrate, sodium chloride, sodium hydroxide to adjust pH, and water for injection.

Usual Dosage: Instill one drop into the affected eye(s) twice a day. See accompanying prescribing information.

This product is sterile when manufactured and should be dispensed in the original unopened container. Instruct patient on precautions to avoid contamination.

Keep this and all medication out of the reach of children.

Store at 15° to 25°C (59° to 77°F).

Manufactured for:
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

Made in India

MCR:705535:1C:R1

Mylan.com

M.L. No.: KTK/28/357/2006

BEPOTASTINE BESILATE

bepotastine besilate solution/ drops

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0378-7055
Route of Administration	OPHTHALMIC		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
BEPOTASTINE BESILATE (UNII: 6W18MO1QR3) (BEPOTASTINE - UNII:HYD2U48IAS)	BEPOTASTINE BESILATE	15 mg in 1 mL

Inactive Ingredients

Ingredient Name	Strength
BENZALKONIUM CHLORIDE (UNII: F5UM2KM3W7)	
SODIUM PHOSPHATE, MONOBASIC, DIHYDRATE (UNII: 5QWK665956)	
SODIUM CHLORIDE (UNII: 451W47IQ8X)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	
WATER (UNII: 059QF0KO0R)	

Product Characteristics

Color	YELLOW (clear colorless to pale yellow)	**Score**	
Shape		**Size**	
Flavor		**Imprint Code**	
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0378-7055-35	1 in 1 CARTON	05/28/2021	
1		5 mL in 1 BOTTLE, DROPPER; Type 0: Not a Combination Product		
2	NDC:0378-7055-67	1 in 1 CARTON	05/28/2021	
2		10 mL in 1 BOTTLE, DROPPER; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA206220	05/28/2021	

Labeler - Mylan Pharmaceuticals Inc. (059295980)

Revised: 3/2018 Mylan Pharmaceuticals Inc.