

**INDICATIONS AND USAGE**

BEPREVE® is a histamine H₁ receptor antagonist indicated for the treatment of itching associated with signs and symptoms of allergic conjunctivitis.

**DOSE AND ADMINISTRATION**

Instill one drop of BEPREVE into the affected eye(s) twice a day (BID). (2)

**CONTRAINdications**

Hyper-sensitivity to any component of this product. (4)

**DOSE FORMS AND STRENGTHS**

Solution containing bepotastine besilate, 1.5%. (3)

**ADVERSE REACTIONS**

The most commonly reported adverse reactions occurring in approximately 25% of patients were eye irritation, headache, and nasopharyngitis. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Bausch + Lomb, a division of Valeant Pharmaceuticals North America LLC, at 1-800-321-4576, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

**USAGE IN SPECIFIC POPULATIONS**

8.5 Geriatric Use

8.4 Pediatric Use

8.3 Nursing Mothers

8.1 Pregnancy

A single 3 mg/kg oral dose. The concentration in other fetal tissues was one-third to one-tenth the systemic concentration approximately 3,300 times the topical ocular use in humans), however, no evidence of infertility was observed in rats given oral bepotastine besilate 1,000 mg/kg/day; however, no evidence of infertility was observed in rats given oral bepotastine besilate 1,000 mg/kg/day (approximately 3,300 times the topical ocular use in humans). The concentration of radio-labeled bepotastine besilate was similar in fetal liver and maternal blood plasma following a single 3 mg/kg oral dose. The concentration in other fetal tissues was one-third to one-tenth the concentration in maternal blood plasma...

An incipient in utero growth retardation and development were observed in pups born from rats given oral bepotastine besilate 1,000 mg/kg/day (representing a systemic concentration approximately 3,300 times that anticipated for topical ocular use in humans), but did show some potential for causing skeletal abnormalities at 1,000 mg/kg/day. There were no teratogenic effects seen in rats at oral doses up to 100 mg/kg/day during organogenesis and fetal development the doses given to the conceptus were approximately 3,300 times the anticipated for topical ocular use in humans). Bepotastine besilate was not found to be teratogenic in rats during organogenesis and fetal development at oral doses up to 200 mg/kg/day (representing a systemic concentration approximately 3,300 times the anticipated for topical ocular use in humans).

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8.3 Nursing Mothers
Following a single 3 mg/kg oral dose of radio-labeled bepotastine besilate to nursing rats, the maximum concentration of radioactivity in milk was 0.40 mcg-eq/mL 1 hour after administration; at 48 hours after administration the concentration was below detection limits. The milk concentration was higher than the maternal blood plasma concentration at each time of measurement.

It is not known if bepotastine besilate is excreted in human milk. Caution should be exercised when BEPREVE (bepotastine besilate ophthalmic solution) 1.5% is administered to a nursing woman.

8.4 Pediatric Use
Safety and efficacy of BEPREVE (bepotastine besilate ophthalmic solution) 1.5% have not been established in pediatric patients under 2 years of age. The safety and 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 adult studies.

8.5 Geriatric Use
No overall difference in safety or effectiveness has been observed between elderly and younger patients.

11 DESCRIPTION
BEPREVE (bepotastine besilate ophthalmic solution) 1.5% is a sterile, topically administered drug for opthalmic use. Each mL of BEPREVE contains 15 mg bepotastine besilate. Bepotastine besilate is designated chemically as (+)-4-[[S-(p-chloro-alpha -2-pyridylbenzoyl)]-1-piperidine butyric acid monobenzensulfonate. The chemical structure for bepotastine besilate is:

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\text{Bepotastine besilate is a white or pale yellowish crystalline powder. The molecular weight of bepotastine besilate is 547.06 daltons. BEPREVE® (bepotastine besilate ophthalmic solution) supplied as a sterile, aqueous 1.5% solution, with a pH of 6.8. The osmolality of BEPREVE (bepotastine besilate ophthalmic solution) 1.5% is approximately 290 mmOsm/L. Each mL of BEPREVE® (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, USP.}

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Bepotastine is a topically active, direct H₁-receptor antagonist and an inhibitor of the release of histamine from mast cells.

12.2 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 seven days, bepotastine plasma concentrations peaked at approximately one to two hours post-installation. 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 concentration at 24 hours post-installation were below the quantifiable limit (2 ng/mL) in 1/12 subjects in the two dose groups.

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

Metabolism: In vitro metabolism studies with human liver microsomes demonstrated that bepotastine besilate is minimally metabolized by CYP450 enzymes. In vitro studies demonstrated that bepotastine does not inhibit the metabolism of various cytochrome P450 substrate 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, CYP2C8, and CYP2C19.

Excretion: The main route of elimination of bepotastine besilate is urinary excretion (with approximately 70% unmetabolized unchanged in urine).

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
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 an oral dose of 18.7 to 19.9 mg/kg/day in mice and 9.8 to 9.8 mg/kg/day in rats (representing exposure margins of approximately 60 and 20 times the systemic exposure anticipated for topical ocular use in humans).

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

When oral bepotastine was administered to male and female rats at doses up to 1,000 mg/kg/day, there was a slight reduction in fertility index and the litter size. Male fertility was not seen in rats given 200 mg/kg/day oral bepotastine besilate (approximately 3,300 times the systemic concentration anticipated for topical ocular use in humans).

14 CLINICAL STUDIES
Clinical efficacy was evaluated in 2 conjunctival allergen challenge (CAC) studies (237 patients). BEPREVE (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. The safety of BEPREVE was evaluated in a randomized clinical study of 861 subjects over a period of 6 weeks.

16 HOW SUPPLIED/STORAGE AND HANDLING
BEPREVE (bepotastine besilate ophthalmic solution) 1.5% is supplied in a white low density polyethylene plastic squeeze bottle with a white controlled dropper tip and a white polypropylene cap in the following strengths:

5 mL (NDC 24208-629-02) 10 mL (NDC 24208-629-01)

STORAGE Store at 15º - 25ºC (59º - 77ºF).

17 PATIENT COUNSELING INFORMATION
Topical Ophthalmic Use Only
For topical ophthalmic administration only. Sterility of Dropper Tip
Patients should be advised to not touch dropper tip to any surface, as this may contaminate the contents.

Concomitant Use of Contact Lenses
Patients should be advised not to wear a contact lens if their eye is red. Patients should be advised that BEPREVE should not be used to treat contact lens-related irritation.

Patients should also be advised to remove contact lenses prior to instillation of BEPREVE.

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Patients should be advised to also remove contact lenses prior to instillation of BEPREVE. The preservative in BEPREVE, benzalkonium chloride, may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of BEPREVE.

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