8 USE IN SPECIFIC POPULATIONS

5 WARNINGS AND PRECAUTIONS

5.2 Contact Lens Wear

BEPREVE should not be instilled while wearing contact lenses. Patient should remove contact lenses prior to instillation of BEPREVE. (5.2)

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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 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.

17 PATIENT COUNSELING INFORMATION

17.4 Persistent Dry Eye

Perseverative 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/m2 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.

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacokinetics

17.5 Breastfeeding

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.
Animal Data
Following a single 3 mg/kg oral dose (16 times the maximum RHOD, on a g/m² 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 BEPREVE (bepotastine besilate ophthalmic solution) 1.5% have not been established in pediatric patients under 2 years of age. Efficacy in pediatric patients under 15 years of age was extrapolated from clinical trials conducted in pediatric patients greater than 15 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
BEPREVE (bepotastine besilate ophthalmic solution) 1.5% is a sterile, isotonic aqueous solution containing the active ingredient bepotastine besilate as (S)-(+)-4-[[(S)-3-chloro-alpha-2-pyridylbenzoyl](-)1-propionamide butyric acid monobenzenesulfonate. The chemical structure for bepotastine besilate is:

\[
\text{COOH} \quad \text{Cl} \quad \text{OH} \quad \text{CH}_3
\]

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

Each mL of BEPREVE contains 15 mg bepotastine besilate. Bepotastine besilate is designated chemically as (S)-(+)-4-[[[(S)-3-chloro-alpha-2-pyridylbenzoyl](-)1-propionamide butyric acid monobenzenesulfonate. The chemical structure for bepotastine besilate is:

Absorption: The extent of systemic exposure to bepotastine besilate 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 (8 drops) 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 besilate is approximately 55% and independent of bepotastine besilate concentration.

Metabolism: In vitro metabolism studies with human liver microsomes demonstrated that bepotastine is minimally metabolized by CYP3A4 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 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 in 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.

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 1800 mg/kg/day (4800 times higher than the maximum RHOD, on a g/m² 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 3200 times higher than that anticipated in humans at the RHOD).

13.2 Clinical Studies
Clinical trials were conducted in two conjunctival allergen challenge (CAC) studies (127 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 of BEPREVE. 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 size:

5 mL (NDC 24208-629-02)
10 mL (NDC 24208-629-61)

STORAGE
Store at 15°C to 25°C (59°F to 77°F).

17 Patient Counseling Information
Stability 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 a contact lens if their eye is red and 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, which may be reinstated after 10 minutes following administration.

Distributed by:
Bausch + Lomb, a division of Valeant Pharmaceuticals North America LLC
Bridgewater, NJ 08807 USA
Under license from:
Senju Pharmaceutical Co., Ltd.
Osaka, Japan 541-0046

Bepreve is a trademark of Bausch & Lomb Incorporated or its affiliates. ©Bausch & Lomb Incorporated