INDICATIONS AND USAGE

BEPREVE® (bepotastine besilate ophthalmic solution) 1.5%, is a histamine H1 receptor antagonist indicated for the treatment of itching associated with allergic conjunctivitis.

Dosage and Administration

Instill one drop into the affected eye(s) twice a day.

Contraindications

Hypersensitivity to any component of this product.

WARNINGS AND PRECAUTIONS

Contamination of Tip and Solution

Do not touch the dropper tip or any surface. Keep bottle tightly closed when not in use.

Dosage Forms and Strengths

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

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 patients included: conjunctivitis, nasopharyngitis, and eye irritation.

6.2 Post-Marketing 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 patients included: conjunctivitis, nasopharyngitis, and eye irritation.

INFORMATION FOR BEPREVE

8.1 Pregnancy

In embryofetal development studies, oral administration of bepotastine besilate to rats during the peri- and postnatal periods did not produce adverse embryofetal or offspring effects at clinically relevant systemic exposures. Maternal toxicity was observed in the rats at the lowest dose tested, 20 mg/kg/day (415 times higher than the maximum recommended human ophthalmic dose, RHOD, on a mg/m² basis). See Data. No teratogenic effects were noted at clinically relevant systemic exposures. Maternal and developmental toxicity was observed at 500 mg/kg/day (approximately 10,000 times higher than the maximum RHOD, on a mg/m² 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 3,000 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/m² basis). Following a single 3 mg/kg oral dose in rats (16 times higher than the maximum RHOD), on a mg/m² basis), no evidence of any reproductive effects at 50 mg/kg/day was noted. At 50 mg/kg/day, the concentration of radio-labeled bepotastine besilate was similar in fetal liver and maternal blood plasma. The concentration in other fetal tissues was approximately 25 times higher than that in maternal blood plasma.

In a pre/postnatal development study, oral administration of bepotastine besilate to rats during the peri- and postnatal periods produced an increase in stillbirths and decreased survival of offspring. The maternal no observed adverse effect level (NOAEL) was 20 mg/kg/day (415 times higher than the maximum RHOD, on a mg/m² basis), a dose that also produced maternal toxicity and lethality. No teratogenic effects were noted at maternal doses up to 200 mg/kg/day (corresponding to an estimated blood plasma concentration 3,000 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/m² basis). Following a single 3 mg/kg oral dose in rats (16 times higher than the maximum RHOD, on a mg/m² basis), no evidence of any reproductive effects at 50 mg/kg/day was noted. At 50 mg/kg/day, the concentration of radio-labeled bepotastine besilate was similar in fetal liver and maternal blood plasma. The concentration in other fetal tissues was approximately 25 times higher than that in maternal blood plasma.

In a perinatal development study, oral administration of bepotastine besilate to rats during the period of organogenesis and lactation periods did not produce adverse embryofetal or offspring effects at clinically relevant systemic exposures. Maternal toxicity was observed in the rats at the lowest dose tested, 20 mg/kg/day (415 times higher than the maximum recommended human ophthalmic dose, RHOD, on a mg/m² basis). See Data.

In a perinatal development study, oral administration of bepotastine besilate to rats during the period of organogenesis and lactation periods did not produce adverse embryofetal or offspring effects at clinically relevant systemic exposures. Maternal toxicity was observed in the rats at the lowest dose tested, 20 mg/kg/day (415 times higher than 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.

Data

Animal Data

In embryofetal development studies, oral administration of bepotastine besilate to pregnant rabbits throughout organogenesis did not produce teratogenic effects at clinically relevant systemic exposures. Maternal toxicity was observed at the lowest dose tested, 20 mg/kg/day (415 times higher than the maximum RHOD, on a mg/m² basis). Oral administration of bepotastine besilate to pregnant rats throughout organogenesis did not produce skeletal anomalies at 1000 mg/kg/day (5400 times higher than the maximum RHOD, on a mg/m² basis), a dose that also produced maternal toxicity and lethality. No teratogenic effects were noted at maternal doses up to 500 mg/kg/day (approximately 10,000 times higher than the maximum RHOD, on a mg/m² basis), a dose that also produced maternal toxicity and lethality. No teratogenic effects were noted at maternal doses up to 200 mg/kg/day (corresponding to an estimated blood plasma concentration 3,000 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/m² basis). Following a single 3 mg/kg oral dose in rats (16 times higher than the maximum RHOD, on a mg/m² basis), no evidence of any reproductive effects at 50 mg/kg/day was noted. At 50 mg/kg/day, the concentration of radio-labeled bepotastine besilate was similar in fetal liver and maternal blood plasma. The concentration in other fetal tissues was approximately 25 times higher than that in maternal blood plasma.

In a pre/postnatal development study, oral administration of bepotastine besilate to rats during the period of organogenesis and lactation periods produced an increase in stillbirths and decreased survival of offspring. The maternal no observed adverse effect level (NOAEL) was 20 mg/kg/day (415 times higher than the maximum RHOD, on a mg/m² basis), a dose that also produced maternal toxicity and lethality. No teratogenic effects were noted at maternal doses up to 200 mg/kg/day (corresponding to an estimated blood plasma concentration 3,000 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/m² basis). Following a single 3 mg/kg oral dose in rats (16 times higher than the maximum RHOD, on a mg/m² basis), no evidence of any reproductive effects at 50 mg/kg/day was noted. At 50 mg/kg/day, the concentration of radio-labeled bepotastine besilate was similar in fetal liver and maternal blood plasma. The concentration in other fetal tissues was approximately 25 times higher than that in maternal blood plasma.

In a perinatal development study, oral administration of bepotastine besilate to rats during the period of organogenesis and lactation periods did not produce adverse embryofetal or offspring effects at clinically relevant systemic exposures. Maternal toxicity was observed in the rats at the lowest dose tested, 20 mg/kg/day (415 times higher than the maximum recommended human ophthalmic dose, RHOD, on a mg/m² basis). See Data.

In a perinatal development study, oral administration of bepotastine besilate to rats during the period of organogenesis and lactation periods did not produce adverse embryofetal or offspring effects at clinically relevant systemic exposures. Maternal toxicity was observed in the rats at the lowest dose tested, 20 mg/kg/day (415 times higher than 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.

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of fertility

14 CLINICAL STUDIES

15 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

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

This is an abstract of information contained in the BEPREVE prescribing information. Please refer to the original prescribing information for complete information.
Bepotastine besilate is a white to pale yellowish-white crystalline powder. The molecular weight of bepotastine besilate is 547.06 daltons. BEPREVE ophthalmic solution is supplied as a sterile, topically administered drug for ophthalmic use. BEPREVE (bepotastine besilate ophthalmic solution) 1.5% contains 15 mg bepotastine besilate. Bepotastine besilate is designated chemically as (+) -4-[(S)-p-chloro-alpha -2-pyridylbenzyl]oxy-1-piperidine butyric acid monobenzenesulfonate. The chemical structure for bepotastine besilate is:

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

Bepotastine besilate is a steroidal drug for ophthalmic use. It is supplied as a 1% and 1.5% solution, with an approximate pH of 6.8. The osmolality of BEPREVE (bepotastine besilate ophthalmic solution) 1.5% is approximately 295 mOsm/kg. The osmolality of BEPREVE (bepotastine besilate ophthalmic solution) 1.5% contains:

- Actives: monobasic sodium phosphate dihydrate, sodium chloride, sodium hydroxide to adjust pH, and water for injection, USP.
- Preservative: benzalkonium chloride 0.005%.

The no observable adverse effect level for bepotastine besilate on nominal dose levels in carcinogenicity tests were 18.7 to 19.3 mg/kg/day in mice and 9.8 to 9.8 mg/kg/day in rats (corresponding to systemic exposures approximately 60 and 20 times higher than that anticipated in humans at the RDDO, respectively).

14 CLINICAL STUDIES

Clinical efficacy was evaluated in two conjunctival allergen challenge (CACC) studies. 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 bottle with a sterile linear low density polyethylene controlled dropper tip and a white polypropylene cap in the following sizes:

- NDC 24208-629-02 5 mL Bottle
- NDC 24208-629-01 10 mL Bottle

Storage: 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 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 reinserted after 10 minutes following administration.

Distributed by:

- Bausch & Lomb, a division of Bausch Health US, LLC
  - Bridgewater, NJ 08807 USA

Manufactured by:

- Bausch & Lomb Incorporated
  - Tampa, FL 33637 USA

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  - Osaka, Japan 541-0046
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