Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

Betoact 1.5% w/v
(Bepotastine Besilate 1.5% w/v)

2. Qualitative and quantitative composition

Bepotastine Besilate 15mg/mL

This product contains benzalkonium chloride as a preservative
For a full list of excipients, see section 6.1

3. Pharmaceutical form

Ophthalmic solution
Colourless to pale yellow, clear solution, free from visible particles.

4. Clinical particulars

4.1 Therapeutic indications

Bepotastine ophthalmic solution 1.5% is a histamine H1 receptor antagonist indicated for the treatment of itching associated with signs and symptoms of allergic conjunctivitis.

4.2 Posology and method of administration

Bepotastine ophthalmic solution 1.5% is a histamine H1 receptor antagonist indicated for the treatment of itching associated with signs and symptoms of allergic conjunctivitis.

4.3 Contraindications

Bepotastine is contraindicated in patients with a history of hypersensitivity reactions to bepotastine or any of the other ingredients.

4.4 Special warnings and precautions for use

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.

Contact Lens Wear

Bepotastine should not be used to treat contact lens-related irritation. Bepotastine should not be instilled while wearing contact lenses.
Patient should remove contact lenses prior to instillation of Bepotastine, because benzalkonium chloride may be absorbed by soft contact lenses.
Lenses may be reinserted after 10 minutes following administration of Bepotastine.

4.5 Interaction with other medicinal products and other forms of interaction

No information provided

4.6 Pregnancy and Lactation

Risk Summary

There are no available human data for the use of BEPREVE 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.

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).

Lactation

Risk Summary

There are no data on the presence of BEPREVE 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 BEPREVE, and any potential adverse effects on the breastfed infant from BEPREVE.

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.

4.7 Effects on ability to drive and use machines

Patients should be cautioned against engaging in activities requiring complete mental alertness, and motor coordination such as operating machinery until their response to Bepostatine is known.

4.8 Undesirable effects

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

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.

Post-Marketing Experience

Hypersensitivity reactions have been reported rarely during the post-marketing use of bepotastine. 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.

4.9 Overdose

No Information Provided.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmic antihistamines and decongestants.
ATC Code:

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

5.2 Pharmacokinetic properties

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).

5.3 Preclinical safety data

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.
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).

6. Pharmaceutical Particulars

6.1 List of Excipients
Benzalkonium chloride
Sodium Chloride
Sodium dihydrogen phosphate dehydrate
Sodium hydroxide
Water for injection

6.2 Incompatibilities
Not applicable

6.3 Shelf-Life
24 months

6.4 Special Precautions for storage
Store below 30°C

6.5 Nature and Content of container
5mL solution filled in a LDPE vial, a carton containing one such vial and a package insert.

6.6 Special precautions for disposal and other handling
Not Applicable

7. Marketing Authorization Holder
Marketing Authorization holder
Ajanta Pharma Limited
Ajanta House
Charkop, Kandivili (West)
Mumbai- 400 067
India

Manufacturing Site Address
Ajanta Pharma Limited
Mirza, Palashabari Road, Vill-Kokjhar, Kamrup, Assam
India

8. Marketing Authorization Number
CTD10078

9. Date of first authorization/renewal of the authorization
24/12/2022

10. Date of revision of the text
13/09/2023

11. Dosimetry
Not Applicable

12. Instructions for preparation of Radiopharmaceuticals
Not Applicable