

PRODUCT MONOGRAPH

Pr ALOMIDE®

Lodoxamide Tromethamine
Ophthalmic Solution 0.1% (as lodoxamide)

Anti-Allergy Agent

ALCON CANADA INC
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PRODUCT MONOGRAPH

NAME OF DRUG:

Pr ALOMIDE®

Lodoxamide Tromethamine Ophthalmic Solution 0.1%
(as lodoxamide)

THERAPEUTIC CLASSIFICATION:

Anti-Allergy Agent

CLINICAL PHARMACOLOGY

Lodoxamide, a mast cell stabilizer inhibits the *in vivo* type I immediate hypersensitivity reaction in animals and man.

In vitro studies have demonstrated the ability of lodoxamide to stabilize mast cells and prevent the antigen specific induced release of histamine. In addition, lodoxamide prevents the release of other mast cell inflammatory mediators (i.e. SRS-A, slow reacting substances of anaphylaxis also known as the peptido-leukotrienes) and appears to inhibit eosinophil chemotaxis. Lodoxamide inhibits histamine release *in vitro* by preventing the movement of calcium into the mast cell after stimulation.

INDICATIONS

Treatment of the ocular signs and symptoms associated with vernal keratoconjunctivitis, giant papillary conjunctivitis, and allergic/atopic conjunctivitis.

CONTRAINDICATIONS

Hypersensitivity to any component of this product.

PRECAUTIONS

General:

As with all ophthalmic medications containing benzalkonium chloride, patients should be advised to remove their contact lenses to instill ALOMIDE (Lodoxamide Tromethamine Ophthalmic Solution) and wait at least 15 minutes before reinserting the lenses.

Use in Pregnancy:

Reproduction studies with lodoxamide tromethamine administered orally to rats and rabbits have not shown any effect of the product on fertility or reproductive performance, or any evidence of embryotoxicity or pre-and postnatal toxicity. However, there are no adequate and well controlled studies in pregnant women. Since animal reproduction studies are not always predictive of human response, ALOMIDE (Lodoxamide tromethamine ophthalmic solution) should be used during pregnancy only if clearly needed.

PRECAUTIONS (cont)

Nursing Mothers:

It is not known whether lodoxamide is excreted in human milk. Caution should be exercised when ALOMIDE ophthalmic solution is given to a nursing mother.

Usage in Children:

The safety and effectiveness of ALOMIDE ophthalmic solution in children below the age of four years have not been established.

ADVERSE REACTIONS

ALOMIDE (Lodoxamide tromethamine ophthalmic solution) has been generally well tolerated. In controlled clinical studies the most common side effect reported was mild and transient discomfort upon instillation (8.7% of patients) expressed as burning, stinging, itching or tearing.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Overdosage in the use of topical ophthalmic preparations is a remote possibility. Discontinue medication when heavy or protracted use is suspected.

DOSAGE AND ADMINISTRATION

The dose for adults and children is one or two drops in each eye four times a day at regular intervals.

Patients should be advised that the effect of therapy with ALOMIDE ophthalmic solution is dependent upon its administration at regular intervals, as directed.

The safety and effectiveness of ALOMIDE ophthalmic solution in children below the age of four years have not been established.

Improvements in signs and symptoms in response to therapy with ALOMIDE solution (decreased discomfort, itching, foreign body sensation, photophobia, acute ocular pain, tearing, discharge, erythema/swelling, bulbar conjunctivae, limbus, epithelial disease, ptosis) are usually evident within a few days, but longer treatment for up to four weeks is sometimes required. Once symptomatic improvement has been established, therapy should be continued for as long as needed to sustain improvement.

PHARMACEUTICAL INFORMATION

Drug Substance:

Proper Name: Lodoxamide Tromethamine

Chemical Name: N, N'-(2-chloro-5-cyano-m-phenylene) dioxamic acid tromethamine salt.

Structural Formula:

Empirical Formula: $C_{19}H_{28}ClN_5O_{12}$

Molecular Weight: 553.91

Physical Form: White to off white powder or crystals

Composition:

ALOMIDE (Lodoxamide Tromethamine Ophthalmic Solution) is a sterile isotonic solution containing lodoxamide 0.1% (as 0.178% lodoxamide tromethamine), and benzalkonium chloride 0.007% as preservative, with mannitol, hydroxypropyl methylcellulose, sodium citrate, tyloxapol, citric acid, edetate disodium, and purified water.

DOSAGE FORM

Availability: Pr ALOMIDE solution is supplied in natural plastic ophthalmic DROPTAINER® dispensers containing 10 mL or in natural plastic unit dose containers each containing 0.4 mL. Lodoxamide tromethamine is a Schedule F (prescription) drug.

Storage: Store at room temperature (2 - 30°C).

Special Instructions: Patients should be instructed to avoid contamination of the dropper tip.

INFORMATION TO PATIENT

Indications: Your doctor has prescribed ALOMIDE solution for you to treat the symptoms of allergy (itching, discomfort, tearing etc) in your eyes. Regular use of this product is essential to obtain relief from your allergic symptoms.

Precautions:

- 1) Remove your contact lenses before using ALOMIDE solution.
- 2) Wait at least 15 minutes after using ALOMIDE solution before inserting your lenses.
- 3) Do not touch the dropper tip to any surface to avoid contamination.

Instructions: Put one drop into each eye, four times per day at regular intervals (about every 4 hours) while awake. It is necessary to use ALOMIDE solution regularly to obtain relief from your allergic eyes.

PHARMACOLOGY

Lodoxamide, a mast cell stabilizer, inhibits the *in vivo* type I immediate hypersensitivity reaction in animals and man. Allergen-induced bronchospasms and reduced pulmonary function in monkeys are prevented with lodoxamide treatment. A cutaneous vascular permeability increase associated with reagin or IgE and antigen mediated reactions in rats, monkeys and humans are inhibited with lodoxamide therapy. A similar vascular reaction in the palpebral conjunctiva of rats has been inhibited with topical ocular administration of lodoxamide. Therefore, it is anticipated that lodoxamide will be useful in the treatment of ocular diseases where type I immediate hypersensitivity plays a major role in the pathogenesis.

In vitro studies have demonstrated the ability of lodoxamide to stabilize mast cells and prevent the antigen specific induced release of histamine. In addition, lodoxamide prevents the release of other mast cell inflammatory mediators (i.e. SRS-A, slow reacting substances of anaphylaxis, also known as the peptido-leukotrienes) and appears to inhibit eosinophil chemotaxis. Lodoxamide inhibits histamine release *in vitro* by preventing the movement of calcium into the mast cell after stimulation.

PHARMACOLOGY (cont)

In a multi-centre double-masked study (9 centres), 0.1% lodoxamide was more effective than 2% sodium cromoglycate in the treatment of the signs and symptoms of conjunctivitis of an allergic nature (vernal, giant papillary, atopic/allergic types). Ocular signs and symptoms were generally controlled in fourteen to twenty-one days of therapy (q.i.d. dosing), and improvement continued with further therapy. Based upon physician and patient judgements, a therapeutic effect was observed within seven days of the initiation of treatment. In a similar single centre study, 0.1% lodoxamide was judged more effective than 2% sodium cromoglycate, but the difference was not statistically significant.

Lodoxamide has no intrinsic vasoconstrictor, antihistaminic, cyclooxygenase inhibition or other anti-inflammatory activity.

The disposition of ^{14}C -lodoxamide was studied in six healthy adult volunteers receiving a 3 mg (50 μCi) oral dose of lodoxamide. Urinary excretion was the major route of elimination. The elimination half-life of ^{14}C -lodoxamide was 8.5 hours in urine. In a study conducted in twelve healthy adult volunteers, topical administration of ALOMIDE ophthalmic solution, one drop in each eye four times per day for ten days, did not result in any measurable lodoxamide plasma levels at a detection limit of 2.5 ng/ml.

TOXICOLOGY**Acute Toxicity**

Species/Route	LD ₅₀ (mg/kg)	Signs of Toxicity
Mouse, i.p	4,000 - 5,000	Depression, laboured breathing, partially closed eyes.
Mouse, i .p	3634	Depression, prostration, coma.
Mouse, p.o	>5,000	None
Rat, p.o	>4,000	None
Rat, p.o.	>5,000	None
Rat, i.p	5,019	Altered gait, thirstiness, prostration, coma.
Rat, i.p.	>5,000	Slight amount of blood tinged abdominal fluid.

Chronic Toxicity

Species/Route	Daily Dosage (mg/kg)	Signs of Toxicity
Mouse, p.o 14 days	0, 500, 1600, 5,000	None
Dog, p.o. One month	10, 30, 100	None
Mouse, p.o 3 months	0, 500, 1600, 5,000	None
Rat, p.o 1, 3 months	10, 30, 100	Decreases in erythrocyte parameters in females
Rat, p.o 1 year	10, 30, 100	Dose related decrease in body weights in males. Small renal calculi (relationship questionable).
Monkey, p.o 1 year	10, 30, 100	No overt effects
Rat, p.o 2 year (carcinogenicity)	10, 30, 100	Comparable to controls.

Mutagenicity

Test System	Result
Ames (Salmonella) (3 strains) with and without activation	Negative up to 2,000 ug/plate
Ames (Salmonella) (2 additional strains) with and without metabolic activation	Negative 250-2,000 ug/plate

Reproduction and Teratology

Species/Route	Dosage (mg/kg/day)	Findings
Rat, p.o Segment 1	30 - Male 10, 30 - Female	No adverse effects.
Rat, p.o Segment 1	10, 30, 100	Possible decrease in proportion of litter surviving.
Rat, p.o Segment 2	10, 30	No adverse effects.
Rat, p.o Segment 2	10, 30, 100	Not teratogenic.
Rat, p.o Segment 3	10, 30	No adverse effects.
Rat, p.o Segment 3	10, 30, 100	No adverse effects.
Rabbit, p.o Segment 2	10, 30, 100	No adverse effects.
Rabbit, p.o Segment 2	10, 30	No adverse effects.

Ocular Studies

Species	Dosage (mg/kg)	Signs of Toxicity
Rabbit Ocular Irritation 14 days	0.1%, 1% both eyes BID	Reddening of eyelids- comparable to control
Rabbit Ocular Irritation Every 30 mins. for 12 doses (1 day)	0.25% 0.5% 1% right eye	Minimal-moderate conjunctival congestion and discharge; minimal fluorescein staining. Comparable to controls.
Rabbit Ocular Irritation 1, 3 months	with HPMC-0.25% 0.5, 1% w.o HPMC-0.5% right eye; QID	Minimal-moderate conjunctival congestion and discharge. Sporadic and transient instances of superficial corneal epithelium, irregularities (not dose related) in product and vehicle with HPMC.
Monkey Ocular Irritation 3 months	0.25, 0.5, 1% right eye; QID	None

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