125 mm

260 mm

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory

OLOPATADINE HYDROCHLORIDE OPHTHALMIC SOLUTION USP 0.2 %

ALERCHEK 0.2%

COMPOSITION

Each ml Contains :
Active:Olopatadine Hydrochloride USP 2.22mg,
equivalent to Olopatadine 2mg.
Preservative: Benzalkonium Chloride NF 0.01%
Inactives: Povidone, Dibasic Sodium Phosphate, Sodium Chloride, Edetate Disodium, Hydrochloric acid and / Sodium Hydroxide (adjust pH) and Water for Injection.

DOSAGE FORM

Ophthalmic Solution

PHARMACOLOGY

Pharmacodynamics

Pharmacotherapeutic group: ophthalmologicals; decongestant and antiallergics; other antiallergics
ATC code: S01GX09
Olopatadine is a potent selective antiallergic/antihistaminic agent that exerts its effects through multiple distinct mechanisms of actions. It antagonizes histamine (the primary mediator of allergic response in humans) and prevents histamine induced inflammatory cytokine production by human conjunctival epithelial cells. Olopatadine is devoid of effects on alpha-adrenergic, dopaminergic and muscarinic type 1 and 2 receptors. Data from in vitro studies suggest that it may act on human conjunctival mast cells to inhibit the release of pro-inflammatory mediators. In patients with patent nasolacrimal ducts, topical ocular administration of Olopatadine Eye Drops, Solution was suggested to reduce the nasal signs and symptoms that frequently accompany seasonal allergic conjunctivitis. It does not produce a clinically significant change in pupil diameter.

Pharmacokinetics

Absorption
Olopatadine was absorbed into the eye and reached maximal levels (C_{max}) within 30 minutes to 2 hours (T_{max}) in ocular tissues following bilateral single topical ocular instillation of 1 drop of increasing dose strengths of Olopatadine (0.15%, 0.2% and 0.7%) in Male New Zealand White (NZW) Rabbits. Plasma levels of Olopatadine were low (C_{max} < 20 ng/mL) following bilateral topical ocular administration of 0.15%/0.2%/0.7% Olopatadine ophthalmic solution to rabbits.

In the humans, plasma levels following topical ocular administration (2 drops of 0.1% in both eyes, four times-daily, 4 days; 2 drops of 0.15% in both eyes, twice daily, 14 days; 2 drops of 0.2% in both eyes, twice daily, 7 days; 1 drop of 0.77% in each eye for 7 days) and oral administration (20 mg, twice daily, 13.5 days) are shown in below Table. Compared with the oral administration exposure on Day 12, the mean exposure estimates show Olopatadine C_{max} (1.64 ng/mL) and AUC_{0-12} (9.68 ng*h/mL) after multiple 0.77% topical ocular doses was 184-fold and 102-fold lower than the C_{max} (302 ng/mL) and AUC_{0-12} (987 ng*h/mL) after multiple 20 mg oral doses of Olopatadine. These data indicate that topical ocular doses of 0.77% Olopatadine hydrochloride ophthalmic solution has a wide margin of safety since it resulted in a systemic exposure that is much lower than that after oral doses of 20 mg Olopatadine hydrochloride.

Comparison of Olopatadine plasma concentration after topical ocular dosing and oral dosing

Route of administration	Dosage	C_{max} (ng/mL) Mean ± SD	AUC (ng*hr/mL) Mean ± SD
Topical ocular	1 drop of 0.77% in both eyes once daily, 6.5 days	1.64 ± 0.889	9.68 ± 4.42
	2 drops of 0.1% in both eyes, 4 times-daily, 4 days	0.565 ± 0.463	1.95 ± 1.28*1
	2 drops of 0.15% in both eyes, twice-daily, 14 days	0.76 ± 0.31	-*2
	2 drops of 0.2% in both eyes, twice-daily, 7 days	0.736 ± 0.327	3.63 ± 1.70*3
Oral	20 mg tablet, twice-daily, 13.5 days	302 ± 53	987 ± 146*3

*1: AUC_{0-6} *2: Not calculated because of insufficiency of samples *3: AUC_{0-12} mean estimates from Day 12

Distribution

Studies in rabbits show ocular tissues associated with the site of dosing i.e., conjunctiva and cornea, had the highest concentrations of Olopatadine after bilateral single topical ocular instillation of 1 drop of increasing dose strengths of Olopatadine (0.15%, 0.2% and 0.7%) in Male New Zealand White (NZW) Rabbits. Olopatadine concentrations in aqueous humor, choroids, ICB and lens increases with increasing concentrations of Olopatadine. Studies conducted in pigmented Dutch belted rabbits indicated a low degree of binding to melanin pigmented tissues.

Biotransformation/Metabolism

Studies have not been conducted to investigate the metabolism of Olopatadine in ocular tissues since toxicology and clinical studies have shown it to be safe and effective. The major metabolites of Olopatadine following oral administration in humans are N-desmethyl Olopatadine (M1) and Olopatadine N-oxide (M3). N-desmethyl Olopatadine (M1) is almost exclusively demethylated by the cytochrome P-450 isozyme 3A4 (CYP3A4). Olopatadine was not an inhibitor of cytochrome P-450 isozymes and therefore drug-drug interactions due to metabolic interactions were not expected.

In the humans after topical ocular administration, N-desmethyl metabolite of Olopatadine (M1) was not quantifiable (≤ 0.050 ng/mL) in plasma sample in all subjects.

Excretion/Elimination

Studies have not been conducted to investigate the excretion of Olopatadine in the urine or feces after topical ocular instillation. In rats after ^{14}C oral administration, Olopatadine was rapidly eliminated from the body primarily by urinary excretion and biotransformation (metabolism). In humans, urinary excretion of unchanged drug was the major route of elimination.

Studies conducted to investigate the elimination of Olopatadine in rabbits showed concentrations of Olopatadine in various ocular tissues (aqueous humor, choroid, conjunctiva, cornea, and ICB) over the dose strengths (0.1 to 0.7% ophthalmic solution) declined with a half-life of less than 4.65 hours.

In humans, the systemic plasma half-life was less than 3 hours.

Linearity/Non-Linearity
In a single dose study, Olopatadine showed a dose proportional increasing in exposure (C_{max} and AUC) in ocular tissues after topical ocular instillation.

Preclinical Safety Data

Non-clinical data reveal no special hazard for humans treated with Olopatadine Hydrochloride Eye Drops, Solution at concentrations up to and including 0.7% based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential.

Effects in non-clinical reproductive and developmental toxicity studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

Oral doses of up to 400 mg/kg/day (~ 40,000-fold higher than the prescribed dose in a 50 kg adult treated with the highest concentration of Olopatadine commercially available, 0.7%) resulted in some general toxicity, but had no effect on fertility and general reproductive parameters when either males or females were treated prior to and through mating. No effects were observed on embryo-fetal development in rats or rabbits treated with Olopatadine orally, by gavage, at doses of up to 600 mg/kg/day and 400 mg/kg/day, respectively. Peri- and postnatal toxicity studies in rats demonstrated maternal toxicity, and reduced pup survival and weights at the highest dose of 600 mg/kg/day (~ 60,000- fold higher than the prescribed dose in a 50 kg adult treated with the highest concentration of Olopatadine commercially available, 0.7%), administered to the dam during late gestation and the lactation period. Pup viability and weight gain were also reduced at dose levels of 60 and 200 mg/kg/day. Olopatadine has been detected in the milk of nursing rats following oral administration.

INDICATIONS

Treatment of ocular itching associated with allergic conjunctivitis.
Results from clinical studies up to 12 weeks duration demonstrate that ALERCHEK 0.2% solution when dosed once a day is effective in the treatment of the ocular signs and symptoms of allergic conjunctivitis and rhinoconjunctivitis, and the nasal symptoms of allergic rhinoconjunctivitis. Conjunctival allergen challenge studies demonstrated that ALERCHEK 0.2% solution is significantly more effective than its vehicle within 3 minutes after antigen challenge and up to 24 hours after dosing.

Pharmacode

5 mm

10 mm

5 mm

70 mm

125 mm

260 mm

DOSAGE AND ADMINISTRATION

Dosage
Adults : One drop in each affected eye once daily.
Elderly : No dosage adjustment in elderly patients is necessary.

Pediatric population
Safety and effectiveness in pediatric patients below the age of 3 years have not been established.

Special populations

- Olopatadine Eye Drops, Solution has not been studied in patients with renal or hepatic disease. However, no dosage adjustment is expected to be necessary in hepatic or renal impairment.

Method of administration

- For topical ocular use only. Not for injection or oral use.
- After the bottle cap is removed, if the tamper evident snap collar is loose, remove before using the product.
- To prevent contamination of the dropper tip and solution, care must be taken not to touch the eyelids, surrounding areas, or other surfaces with the dropper tip of the bottle.
- Keep the bottle tightly closed when not in use.
- In case of concomitant therapy with other topical ocular medicines, an interval of 5 minutes should be allowed between successive applications. Eye ointments should be administered last.
- Patients should be advised not to wear a contact lens if their eye is red.
- ALERCHEK Eye Drops, Solution 0.2% should not be used to treat contact lens related irritation.

CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

ALERCHEK Eye Drops, Solution contains benzalkonium chloride which may cause eye irritation and is known to discolour soft contact lenses. Avoid contact with soft contact lenses.
Patients who wear soft contact lenses and whose eyes are not red, should be instructed to wait at least ten minutes after instilling ALERCHEK Olopatadine Ophthalmic Solution 0.2% before they insert their contact lenses.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

No clinically relevant interactions have been described.

FERTILITY, PREGNANCY AND LACTATION

Fertility

Studies have not been performed to evaluate the effect of administration of Olopatadine on human fertility. Effects in non-clinical fertility studies in male and female animals were observed only at dosages considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.
No effects on human fertility are anticipated since systemic exposure to Olopatadine is negligible by the topical ocular route (AUC_{0-6} of 9.7 ng*hr/mL in humans administered 1 drop of 0.77% Olopatadine in both eyes once daily for 6.5 days).
Olopatadine can be used by women of childbearing potential.

Pregnancy:

Teratogenic effect: Pregnancy Category C
There are no or limited amount of data from the use of Olopatadine in pregnant women. Effects in non-clinical reproduction and developmental toxicity studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.
No effects during pregnancy are anticipated since systemic exposure to Olopatadine is negligible by the topical ocular route (AUC_{0-6} of 9.7 ng*hr/mL in humans administered 1 drop of 0.77% Olopatadine in both eyes once daily for 6.5 days).
Before prescribing Olopatadine to a pregnant woman, a physician should weigh the benefit of administration to the woman to the risk of the fetus.

Breast-feeding

Available pharmacodynamic/toxicological data in animals have shown excretion of Olopatadine/ metabolites in milk following high dose systemic Olopatadine administration (See Section Preclinical Safety Data). Radioactivity has been identified in the milk of nursing rats at concentrations of 0.33 to 4.28 times that of plasma concentrations (1,184 ng*hr/mL AUC_{0-24} in lactating rat plasma) following a 1 mg/kg oral administration of ^{14}C-Olopatadine.
Based upon the low level of Olopatadine present in human plasma following topical ocular administration (AUC_{0-6} of 9.7 ng*hr/mL in humans administered 1 drop of 0.77% Olopatadine in both eyes once daily for 6.5 days), the concentration of Olopatadine potentially present in breast milk is expected to be negligible. However, as there is no data available on the concentration of Olopatadine/metabolites in human milk following topical ocular administration, a risk to the suckling child cannot be excluded.
Patients should be informed that antihistamines may affect the milk production of a nursing mother. Before prescribing Olopatadine to a nursing mother, a physician should weigh the benefit of administration to the mother to the risk of the breastfeeding child.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Olopatadine is a non-sedating anti-histamine. Temporary blurred vision after drop use, or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs after instillation, the patient must wait until the vision clears before driving or using machinery.

UNDESIRABLE EFFECTS

Clinical Studies
The following adverse reactions have been reported during clinical studies with Olopatadine hydrochloride ophthalmic solution, 0.1% and 0.2% and are classified according to the subsequent convention: very common (≥ 1/10), common (≥ 1/100 to <1/10), uncommon (≥ 1/1,000 to <1/100), rare (≥ 1/10,000 to <1/1,000) and very rare (<1/10,000). Within each frequency-grouping, adverse reactions are presented in order of decreasing seriousness.

System Organ Classification	MedDRA Preferred Term (v. 17.0)
Nervous system disorders	Uncommon: headache, dysgeusia Rare: dizziness
Eye disorders	Uncommon: punctate keratitis, keratitis, eye pain, dry eye, eyelid oedema, eye pruritus, eye discharge, ocular hyperaemia, eyelid margin crusting, ocular discomfort Rare: photophobia, vision blurred, erythema of eyelid
Respiratory, thoracic and mediastinal disorders	Uncommon: nasal dryness
Gastrointestinal disorders	Rare: dry mouth
Skin and subcutaneous tissue disorders	Rare: dermatitis contact
General disorders and administration site conditions	Uncommon: fatigue

The following adverse experiences have been reported in 5% or less of patients:

Non-ocular: back pain, flu syndrome, increased cough, infection, nausea, rhinitis, and sinusitis.
Cold syndrome and pharyngitis were reported at an incidence of 7 to 11%.
Some of these events were similar to the underlying disease being studied.

Post-Marketing Surveillance

Additional adverse reactions identified from post-marketing surveillance include the following. Frequencies cannot be estimated from the available data.

System Organ Classification	MedDRA Preferred Term (v.17.0)
Immune system disorders	hypersensitivity
Eye disorders	lacrimation increased
Gastrointestinal disorders	nausea

OVERDOSE

Due to the characteristics of this preparation, no toxic effects are to be expected with an ocular overdose of this product, nor in the event of accidental ingestion of the contents of one bottle.

STORAGE AND HANDLING INSTRUCTIONS

Store under normal storage conditions below 30°C. Protect from light.

SHELF-LIFE 24 Months.

Use the Solution within one month after opening the container.

PACKAGING INFORMATION

ALERCHEK 0.2 % Eye Drops: Fill volume of 2.5 ml in 5 ml LDPE bottle with LDPE Nozzle and HDPE cap.

XXXXXXXXX

Manufactured by:
INDOCO REMEDIES LTD.
Plant II, L-32, 33, 34 Verna Industrial Area, Verna, Goa 403 722, INDIA.
Regd. Office: 166, C.S.T. Road, Mumbai 400 098, INDIA.

SIN15526P

INDOCO REMEDIES LTD.
Packaging Development Department
Packaging Material Specification

Item: Leaflet
A/W Code No.: xxxxxxxxxxx
Open Size: 125 x 260 mm
Folding Pattern: H-Unfolded: 260 mm Folded: 22 mm
W-Unfolded: 125 mm Folded: 125 mm
GSM/Paper: 54 Gsm Maplitho Paper
Colour: Pantone 286U
Pharma code: F- 892 std. B- 893 std.
Approved by:
PDD: _____ HOD: _____
Reason for Preparation: New Development for Singapore

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olopatadine 0.2% Leaflet xxxxxxxxxxxx.cdr
28.02.18/ 7.03.18/ 15.03.18 / 18.05.18 / 11.05.2022