

1. NAME OF THE MEDICINAL PRODUCT

PATANOL*

Olopatadine hydrochloride ophthalmic solution, 0.1%

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of PATANOL* contains:

Active ingredients: 1.11 mg olopatadine hydrochloride (0.1%)

Preservative: benzalkonium chloride

Excipients: dibasic sodium phosphate, sodium chloride, hydrochloric acid and / or sodium hydroxide (to adjust pH), purified water.

3. PHARMACEUTICAL FORM

Sterile ophthalmic solution

Colorless to pale yellow solution

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of signs and symptoms of allergic conjunctivitis.

4.2 Posology and Method of Administration

Adults

One drop of PATANOL* in the conjunctival sac of the affected eye(s) twice daily (every 6 - 8 hours). Treatment may be maintained for up to 4 months, if considered necessary.

Elderly

No dosage adjustment in elderly patients is necessary.

Pediatric population

The safety and effectiveness has been established in pediatric patients 3 years of age and above.

Special populations

PATANOL* 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.
- PATANOL*, Solution 0.2% should not be used to treat contact lens related irritation.

4.3 Contraindications

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

4.4 Special Warnings and Precautions for Use

PATANOL*, Solution contains benzalkonium chloride which may cause eye irritation and is known to discolour soft contact lenses. Avoid contact with soft contact lenses. Patients must be instructed to remove contact lenses prior to application of PATANOL*, Solution and wait at least 15 minutes before reinsertion.

4.5 Interaction with other Medicinal Products and Other Forms of Interaction

No clinically relevant interactions have been described.

4.6 Pregnancy and lactation

Fertility

No effects on human fertility are anticipated since systemic exposure to Olopatadine is negligible by the topical ocular route (AUC₀₋₆ 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

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 (AUC₀₋₆ 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 5.3). 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 AUC₀₋₂₄ in lactating rat plasma) following a 1 mg/kg oral administration of ¹⁴C-Olopatadine.

Based upon the low level of Olopatadine present in human plasma following topical ocular administration (AUC₀₋₆ 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.

4.7 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.

4.8 Undesirable Effects

4.8.1 Olopatadine hydrochloride ophthalmic solution, 0.1%

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 ($\geq 1/10$), common ($\geq 1/100$ to $<1/10$), uncommon ($\geq 1/1,000$ to $<1/100$), rare ($\geq 1/10,000$ 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	<i>Uncommon:</i> headache, dysgeusia <i>Rare:</i> dizziness
Eye disorders	<i>Uncommon:</i> punctate keratitis, keratitis, eye pain, dry eye, eyelid oedema, eye pruritus, eye discharge, ocular hyperaemia, eyelid margin crusting, ocular discomfort <i>Rare:</i> photophobia, vision blurred, erythema of eyelid
Respiratory, thoracic and mediastinal disorders	<i>Uncommon:</i> nasal dryness
Gastrointestinal disorders	<i>Rare:</i> dry mouth
Skin and subcutaneous tissue disorders	<i>Rare:</i> dermatitis contact
General disorders and administration site conditions	<i>Uncommon:</i> fatigue

Post-Marketing Surveillance

Additional adverse reactions identified from post-marketing surveillance include the following. Frequencies cannot be estimated from the available data. Within each System Organ Class adverse reactions are presented in order of decreasing seriousness.

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

4.9 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

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. 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 PATANOL*, 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.

5.2 Pharmacokinetic Properties

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, fourtimes-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 Table 5.2.-1. 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 AUC₀₋₁₂ (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	Cmax (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: AUC0-6 *2: Not calculated because of insufficiency of samples *3: AUC0-12 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 ¹⁴C 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.

5.3 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Benzalkonium Chloride, as solution
Sodium Chloride
Dibasic Sodium Phosphate (Anhydrous) or Disodium Phosphate (Dodecahydrate)
Sodium Hydroxide and/or Hydrochloric Acid
Purified Water

6.2 Incompatibilities

None known.

6.3 Special Precautions for Storage

Store at temperatures below 30 ° C.

6.4 Nature and Contents of Container

Low-density polyethylene (LDPE) DROP-TAINER ® bottle with LDPE dispensing plug and polypropylene closure.

Available fill sizes include:

5 mL bottle containing 2.5 mL solution
5 mL bottle containing 5 mL solution
10 mL bottle containing 10 mL solution
15 mL bottle containing 15 mL solution
Carton contains 1 bottle.

6.5 Instructions for Use and Handling <and Disposal>

No special requirements.

Made by:
Alcon Laboratories, Inc.
Fort Worth, Texas 76134 Usa

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