PRODUCT MONOGRAPH

[Pr]**PAZEO**[*]

Olopatadine Hydrochloride Ophthalmic Solution:

0.7% w/v olopatadine (as olopatadine hydrochloride)

Mfr. Std.

Anti-allergy Agent

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[*]a trademark of Novartis

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Pr PAZEO*

Olopatadine Ophthalmic Solution

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Topical Ophthalmic	Ophthalmic Solution 0.77% (w/v) olopatadine (as olopatadine hydrochloride)	Preservative: benzalkonium chloride Inactive Ingredients: boric acid, hydroxypropyl-gamma-cyclodextrin, hydroxypropyl methylcellulose, mannitol, polyethylene glycol 400, povidone,purified water and hydrochloric acid and/or sodium hydroxide (to adjust pH)

INDICATIONS AND CLINICAL USE

PAZEO* (olopatadine ophthalmic solution) is indicated for the treatment of ocular itching associated with allergic conjunctivitis.

Geriatrics: No overall differences in safety and effectiveness have been observed between elderly and other adult patients.

Pediatrics (≥2 years): The safety and effectiveness of PAZEO* in pediatric patients below the age of 2 years has not been established. Use of PAZEO* in these pediatric patients is supported by evidence from adequate and well-controlled studies of PAZEO* in adults and an adequate and well controlled study evaluating the safety of PAZEO* in pediatric and adult patients.

CONTRAINDICATIONS

Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see Dosage Forms, Composition and Packaging section of the Product Monograph.

WARNINGS AND PRECAUTIONS

General

For topical ocular use only. Not for injection or oral use.

As with any eye drop, to prevent contamination of the dropper tip and solution, care should be taken not to touch the eyelids or surrounding areas with the dropper tip of the bottle. Keep bottle tightly closed when not in use.

Patients should be advised not to wear contact lenses if their eye(s) are red.

PAZEO* should not be used to treat contact lens related irritation. The preservative in PAZEO*, benzalkonium chloride, may cause eye irritation and is known to discolour soft contact lenses. Contact with soft contact lenses should be avoided. Patients who wear soft contact lenses and whose eyes are not red, should be instructed to wait at least 15 minutes after instilling PAZEO* before they insert their contact lenses.

If using other eye drops, patients should wait at least five minutes between putting in PAZEO* and the other drops. Eye ointments should be applied last.

Driving and Using Machinery: Olopatadine is a non-sedating anti-histamine. Temporary blurred vision or other visual disturbances, after the use of PAZEO*, may affect the ability to drive or use machines. If blurred vision occurs after instillation, patients must wait until vision clears before driving or using machinery.

Sexual Function/Reproduction

Studies have not been performed to evaluate the effect of topical ocular administration of olopatadine on human fertility.

Special Populations

Pregnant Women: There are no adequate and well-controlled studies in pregnant women. Olopatadine was found not to be teratogenic in rats and rabbits. However, rats treated at 150,000 times the maximum recommended ocular human dose (MROHD) and rabbits treated at approximately 100,000 times the MROHD, during organogenesis showed a decrease in live fetuses (see TOXICOLOGY). Because animal studies are not always predictive of human responses, this drug should be used in pregnant women only if the potential benefit to the mother justifies the potential risk to the embryo or fetus (See ACTION AND CLINICAL PHARMACOLOGY).

Nursing Women:

Olopatadine has been identified in the milk of nursing rats following oral administration. It

is not known whether topical ocular administration could result in sufficient systemic absorption to produce detectable quantities in human breast milk. Nevertheless, caution should be exercised when PAZEO* is administered to a nursing mother (See ACTION AND CLINICAL PHARMACOLOGY).

Pediatrics (≥2 years): The safety and effectiveness of PAZEO* in pediatric patients below the age of 2 years has not been established. No overall difference in safety has been observed between pediatric and adult patients.

Geriatrics: No overall differences in safety and effectiveness have been observed between elderly and other adult patients.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Overall, a total of 1125 subjects were included in the safety population, which included 561 subjects exposed to PAZEO* administered in both eyes once-daily for up to 6 weeks. The safety profile of PAZEO* is primarily derived from a 6 week clinical safety study. The most commonly reported adverse reactions occurred in 2-5% of patients treated with either PAZEO* or vehicle included blurred vision, dry eye, abnormal sensation in eye, corneal staining, and dysgeusia (See Table 1). No treatment-emergent serious adverse events were reported in any of the clinical studies involving PAZEO*.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions, the adverse drug reaction rates observed in the clinical trials may not reflect the rates observed in practice and should also not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

In a randomized, double-masked, vehicle-controlled trial, patients at risk for developing allergic conjunctivitis received one drop of either PAZEO* (N=330) or vehicle (N=169) in both eyes for 6 weeks. The mean age of the population was 32 years (range 2 to 74 years). This study included 75 subjects between the ages of 2-17 years of age. Thirty-five percent were male. Fifty-three percent had brown iris color and 23% had blue iris color.
A total of 53 subjects (16.1%) reported adverse drug reactions in the PAZEO*(olopatadine HCl solution, 0.77%) group, and 31 subjects (18.3%) reported adverse drug reactions in the Vehicle group.

The most frequent adverse drug reactions (ie, adverse drug reactions occurring in ≥ 1% of the subjects in any treatment group) are presented in Table 1.

Table 1: Treatment-Related Adverse Drug Reactions ≥ 1% for Safety Study (C-12-028)

MedDRA Preferred Term (Version 15.0)	PAZEO* N=330		Vehicle N=169	
	N	%	N	%
Eye disorders				
Vision blurred	15	4.5	7	4.1
Abnormal sensation in eye	7	2.1	7	4.1
Dry eye	8	2.4	5	3.0
Eye irritation	1	0.3	5	3.0
Investigations				
Corneal staining	8	2.4	7	4.1
Conjunctival staining	6	1.8	1	0.6
Nervous system disorders				
Dysgeusia	8	2.4	-	-
PAZEO = Olopatadine hydrochloride ophthalmic solution, 0.77% Vehicle = Olopatadine hydrochloride ophthalmic solution, 0.77% Vehicle				

Less Common Clinical Trial Adverse Drug Reactions

Additional treatment-related adverse drug reactions that occurred at an incidence of ≥0.1% to <1% included the following:

Eye disorders: eye pain, eye irritation, eye pruritus, ocular hyperaemia, eyelid margin crusting, and superficial punctate keratitis;
Nervous system disorders: headache;
Respiratory, Thoracic, and Mediastinal disorders: dry throat.

Post-Market Adverse Drug Reactions

PAZEO* is recently marketed in the United States. Currently, Alcon has registered olopatadine-containing products for ocular use (ophthalmic olopatadine at concentrations of 0.1% and 0.2%) in over 100 countries world-wide.
Approximately 29 million units of PATADAY* (olopatadine HCl solution, 0.2%) and 203 million units of PATANOL*(olopatadine HCl solution, 0.1%) have been sold worldwide. There were no new major findings bearing on the established overall safety profile of both PATADAY* and PATANOL*. Additional adverse reactions identified from post-marketing

surveillance include hypersensitivity, lacrimation increased and nausea. Frequencies cannot be estimated from the available data.

DRUG INTERACTIONS

No drug interactions were reported in any of the clinical studies involving PAZEO*. No drug interaction studies have been performed with PAZEO*. In vitro studies have shown that olopatadine did not inhibit metabolic reactions which involve cytochrome P-450 isozymes 1A2, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4. These results indicate that olopatadine is unlikely to result in metabolic interactions with other concomitantly administered active substances.

Interactions with other drugs, food, herbal products or laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosage Considerations

No special dosage considerations are necessary for PAZEO*.

Recommended Dose and Dosage Adjustment

The recommended dose is one drop in each affected eye once a day.
No dosage adjustment is required in hepatic or renal impairment.

Missed Dose

If a dose is missed, a single drop should be taken as soon as possible before reverting to regular routine. Do not use a double dose to make up for the one missed.

OVERDOSAGE

For management of suspected drug overdose, consult your regional poison control centre.

No information is available on overdosage in humans.

If topical overdose of PAZEO* occurs, the eye(s) may be flushed with tap water. Treatment of an overdose would include supportive and symptomatic therapy. No reports of overdose were received during the clinical studies with PAZEO*.

Accidental ingestion of a 4 ml bottle (2.5 ml fill volume) of PAZEO may occur; this will deliver a maximum systemic exposure of 19.3 mg olopatadine. In the case of overdose, appropriate monitoring and management of the patient should be implemented.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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.

Pharmacodynamics

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

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 Table 2. Compared with the oral administration exposure on Day 12, the mean exposure estimates show Olopatadine C_{max} (1.64 ng/mL) and AUC $_{0\text{-}12}$ (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 $_{0\text{-}12}$ (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.

Table 2 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

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 humans, urinary excretion of unchanged drug is the major route of elimination. 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.

Special Populations and Conditions:

The pharmacokinetic properties of PAZEO® have not been assessed in special populations (e.g. pediatrics, geriatrics, gender, race).

Hepatic/Renal Insufficiency: No specific pharmacokinetic study examining the effect of renal or hepatic impairment was conducted. Since metabolism of olopatadine is a minor route of elimination, no adjustment of the dosing regimen of PAZEO* is warranted in patients with hepatic impairment.

STORAGE AND STABILITY

Store at 2° - 25°C. Discard the container at the end of treatment. Keep out of the reach and sight of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Each mL of PAZEO* contains:
Active: 7.76 mg olopatadine hydrochloride equivalent to 7 mg olopatadine.
Preservative: benzalkonium chloride 0.015%.
Inactives: Boric acid; hydroxypropyl-gamma-cyclodextrin; hydroxypropyl methylcellulose; mannitol; polyethylene glycol 400; povidone; hydrochloric acid/sodium hydroxide (to adjust pH); and purified water.

PAZEO* has a pH of approximately 7 and an osmolality of approximately 300 mOsm/kg.

PAZEO* is supplied in a white, round, low density polyethylene DROP-TAINER* dispenser bottle with a natural low density polyethylene dispensing plug and a white polypropylene cap. Tamper evidence is provided with a shrink band around the closure and neck area of the package.

Net contents are the following: 2.5 mL in a 4 mL bottle

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: olopatadine hydrochloride

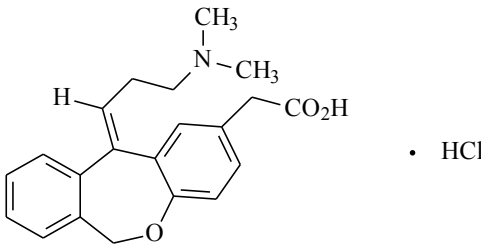
Chemical name:

(1) Dibenz[*b,e*]oxepin-2-acetic acid, 11-[3-(dimethylamino)propylidene]-6,11-dihydro-, hydrochloride, (*Z*)-

(2) 11-[(*Z*)-3-(Dimethylamino)propylidene]-6,11-dihydrodibenz[*b,e*]oxepin-2-acetic acid, hydrochloride

Molecular formula and molecular mass: $C_{21}H_{23}NO_3 \bullet HCl$; 373.87

Structural formula:



Description:	White, crystalline powder
Solubility:	Sparingly soluble in methanol and water. Insoluble in chloroform.
pH (1% solution):	between 2.0 and 4.0

CLINICAL TRIALS

Study demographics and trial design

The efficacy of PAZEO* was established in two randomized, double-masked, vehicle and active controlled, conjunctival allergen challenge (CAC) clinical studies in patients with a history of allergic conjunctivitis (C-10-126 and C-12-053). In C-10-126, patients were randomized to receive one of the following study treatments: PAZEO*, PATADAY*, or vehicle ophthalmic solutions. In C-12-053, patients were randomized to receive one of the following study treatments: PAZEO*, PATADAY*, PATANOL*, or vehicle ophthalmic solutions.

Both studies were conducted in patients at least 18 years of age with a history of seasonal and/or perennial allergic conjunctivitis for at least 1 year prior to study entry and a positive allergic skin test within 24 months prior to study entry. Both studies evaluated the same efficacy endpoints (itching and redness) for the onset of action and the 24 hours duration of action. The primary efficacy variable for both studies was patient-evaluated ocular itching severity scores ranging from 0 (no itching) to 4 (incapacitating itch). In Study C-10-126, the primary efficacy endpoints were patient-evaluated ocular itching at 3, 5, and 7 minutes post-CAC for 16-hour duration-of-action and onset-of-action. In Study C-12-053, the primary efficacy endpoints were patient-evaluated ocular itching at 3, 5, and 7 minutes post-CAC for 24-hour duration-of-action and onset-of-action.

A total of 547 patients were enrolled in the pivotal studies. The mean age of the study population was 40 years, about 60% were female, and about 17% were African Americans.

Study results

Table 3 displays the mean ocular itching severity scores averaged over all post-CAC time points after ocular administration of a specific antigen using the CAC model in C-10-126 and C-12-053, respectively. A one unit difference compared to vehicle is considered a clinically meaningful change in the ocular itching severity score.

In Study C-10-126, the mean differences from vehicle averaged over the 3 post-CAC time points were -1.52($p<0.0001$), -1.45($p<0.0001$) and -1.52($p<0.0001$) at onset, 16 hours duration and 24 hours duration of action CACs, while the mean difference from PATADAY* averaged over the 3 post-CAC time points was -0.44 ($p=0.0022$) at 24 hours duration of action CAC, see Table 3. The observed differences in mean ocular itching compared to Vehicle was greater than 1 unit at all post-CAC time points for onset of action, 16 and 24 hours duration-of-action. These results demonstrate that PAZEO* is superior to Vehicle for the treatment of ocular itching associated with allergic conjunctivitis. PAZEO* demonstrated

statistically significant improved relief of ocular itching when compared to PATADAY at 24 hours after study treatment.

In Study C-12-053, the mean differences from vehicle averaged over the 3 post-CAC time points were -1.39 ($p<0.0001$) and -1.11 ($p<0.0001$) at onset and 24 hours duration of action CACs. The mean differences from PATANOL* and PATADAY* averaged over the 3 post-CAC time points were -0.46 ($p<0.0001$) and -0.24 ($p=0.0456$) respectively at 24 hours duration of action CAC. These results demonstrate that PAZEO* is superior to Vehicle for the treatment of ocular itching associated with allergic conjunctivitis. PAZEO* demonstrated statistically significant improved relief of ocular itching when compared to PATANOL and PATADAY at 24 hours after study treatment.

Table 3: Mean Ocular Itching Scores by Treatment Group and Treatment Difference in Mean Itching

	Time Point	PAZEO* Olopatadine, 0.77%	PATADAY* (Olopatadine, 0.2%)		PATANOL* (Olopatadine, 0.1%)		Vehicle	
C-10-126		(N = 66)	(N = 68)				(N = 68)	
		Mean	Mean	Difference (95% CI)†	Mean	Difference (95% CI)†	Mean	Difference (95% CI)†
	Onset	0.46	0.54	-0.08 (-0.37, 0.21)			1.98	-1.52 (-1.81, -1.23)
	16 h	0.75	0.96	-0.21 (-0.49, 0.07)			2.20	-1.45 (-1.73, -1.17)
	24 h	1.04	1.48	-0.44 (-0.72, -0.16)			2.55	-1.51 (-1.79, -1.24)
C-12-053		(N = 98)	(N = 99)		(N = 99)		(N = 49)	
	Onset	0.52	0.56	-0.05 (-0.24, 0.14)	0.74	-0.22 (-0.41, -0.03)	1.91	-1.39 (-1.62, -1.16)
	24 h	1.16	1.40	-0.24 (-0.48, -0.00)	1.62	-0.46 (-0.70, -0.23)	2.27	-1.11 (-1.40, -0.82)

†Treatment difference is PAZEO minus control (active or Vehicle). CI=95% Confidence Interval;*
The ocular itching score range is 0-4, where 0 is none and 4 is incapacitating itch.

Evaluation of conjunctival redness was a secondary endpoint in studies C-10-126 and C-12-053. Patients were evaluated for their conjunctival redness severity scores ranging from 0 (none) to 4 (extremely severe) at several time points after CAC administration.

In study C-10-126, the mean differences from vehicle averaged over the 3 post-CAC time points for the treatment of conjunctival redness are -1.19 ($p<0.0001$), -0.48($p=0.0001$) and -0.53($p<0.0001$) at onset, 16 hours and 24 hours duration of action CACs. The mean

differences from PATADAY* averaged over the 3 post-CAC time points are -0.67($p<0.0001$), -0.34($p=0.0053$) and -0.38 ($p=0.0041$) at onset, 16 hours and 24 hours duration of action CACs. These results demonstrate that PAZEO* was superior to Vehicle for the treatment of conjunctival redness associated with allergic conjunctivitis.
PAZEO* demonstrated statistically significant improved relief of ocular redness when compared to PATADAY.

In study C-12-053, the mean difference from vehicle averaged over the 3 post-CAC time points was -0.52 ($p<0.0001$) at onset of action CAC. The mean differences from PATADAY* and PATANOL* averaged over the 3 post-CAC time points were -0.30($p=0.0061$) and -0.31($p=0.0042$) respectively at onset of action CACs. PAZEO* demonstrated statistically significant improved relief of ocular redness when compared to Vehicle, PATANOL, and PATADAY.

DETAILED PHARMACOLOGY

Olopatadine is an anti-allergic agent that exerts its effects through multiple distinct mechanisms of action. Olopatadine is a mast cell stabilizer and a potent, selective histamine H_1 antagonist that inhibits the *in vivo* type 1 immediate hypersensitivity reaction. *In vitro* studies have demonstrated the ability of olopatadine to stabilize rodent basophils and human conjunctival mast cells and inhibit immunologically-stimulated release of histamine. In addition, olopatadine inhibits the release of other mast cell inflammatory mediators [i.e., histamine, tryptase, prostaglandin D2 and TNFα as demonstrated in *in vitro* studies.

Olopatadine is a selective histamine H_1 receptor antagonist *in vitro* and *in vivo* as demonstrated by its ability to inhibit histamine binding and histamine-stimulated vascular permeability in the conjunctiva following topical ocular administration. Olopatadine is also an inhibitor of pro-inflammatory cytokine secretion from human conjunctival epithelial cells. Decreased chemotaxis and inhibition of eosinophil activation has also been reported. Olopatadine is devoid of effects on alpha-adrenergic, dopamine, muscarinic type 1 and 2, and serotonin receptors.

The topical ocular efficacy of two clinical formulations (0.2% and 0.7%) of olopatadine was investigated in a preclinical model of histamine-induced vascular permeability using Guinea Pigs. Olopatadine exhibited dose-dependent inhibition of histamine-induced vascular permeability of conjunctiva in Guinea Pigs 30 minutes and 24 hours following a single application of 0.2% and 0.7% olopatadine. This study demonstrated that the efficacy of the 0.7% olopatadine solution was significantly greater than that achieved with the 0.2% solution.

No significant interaction was noted between olopatadine (10 μM) and α-adrenergic, muscarinic cholinergic, dopamine, and numerous other receptors. Extensive neuropharmacological studies indicate that olopatadine at oral doses as high as 300 mg/kg, did not inhibit motor coordination, phenylbenzoquinone induced writhing, reserpine induced blepharoptosis or physostigmine induced lethality, nor did it exhibit any anticonvulsant activity.

The effects of olopatadine (3-100 mg/kg) on the circulatory system (ie, electrocardiogram (ECG), heart rate and blood pressure) were investigated following oral administration in conscious dogs. Over the dose range 3-30 mg/kg, oral administration of olopatadine did not affect ΔQTc. No significant effects on blood pressure were observed at olopatadine oral doses as high as 100 mg/kg. Importantly, no significant change in heart rate or prolongation of the QT interval was observed when olopatadine administered by oral route (30 mg/kg) was used in combination with the CYP3A4 inhibiting drug itraconazole administered orally (100 mg/kg).

Pharmacokinetics

An ocular tissue distribution study was conducted to characterize the ocular distribution and systemic pharmacokinetics of olopatadine following single bilateral topical ocular instillation of 0.2% and 0.7% olopatadine solutions to male NZW rabbits. Olopatadine was absorbed into the eye and reached maximal levels within 30 minutes to 2 hours for most ocular tissues and plasma except lens (T_{max}: 4.0 to 8.0 hours). Tissues associated with the site of dosing, i.e., conjunctiva and cornea, had the highest concentrations of olopatadine at the 0.2% (609 ng/g and 720 ng/g, respectively) and 0.7% (3000 ng/g and 2230 ng/g, respectively) concentrations. The mean C_{max} estimates in aqueous humor, choroid, iris-ciliary body (ICB), and lens increased with increasing concentrations of olopatadine. A similar trend was observed with respect to AUC across all ocular tissues.

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 that 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.

TOXICOLOGY

The acute toxicity of olopatadine hydrochloride has been investigated in mice, rats and dogs. Mice and rats demonstrated that olopatadine hydrochloride was not an acute toxicity hazard with oral LD_{50} values greater than 1150 mg/kg and 3870 mg/kg for mice and rats,

respectively.
Subchronic and chronic oral toxicity studies in rats and dogs demonstrated that the liver and kidney were target organs for olopatadine hydrochloride toxicity. In rats, ophthalmology and hematology parameters were unaffected following chronic administration of olopatadine hydrochloride. In chronic dog studies, ophthalmology, hematology, blood chemistry and organ weight parameters were unaffected by olopatadine hydrochloride administration.

A three-month repeated-dose topical ocular study in pigmented rabbits was conducted with the clinical formulation of 0.7% olopatadine solution containing hydroxypropyl-γ-cyclodextrin (QID, 1 drop/eye). No ocular or systemic toxicity was observed and therefore, the 0.7% olopatadine ophthalmic solution was considered the No observed adverse effect level (NOAEL). In a 3 kg rabbit, the maximum dose of olopatadine was 750µg/kg/day, which is 76-times higher than the maximum clinical dose (9.8 µg/kg/day) of olopatadine in a 50 kg man.
Chronic 6-month studies were performed using NZW rabbits (0.1-1.0%, 2 drops to OD, 4 times per day) and nonhuman primates (up to 0.5%, 2 drops to OD, 4 times per day). No treatment-related deaths were reported in either of the studies and no significant treatment-related clinical findings were noted.

In the six-month rabbit study, animals were treated with up to a 1.0 % olopatadine ophthalmic solution 2 drops OD four times a day. Ocular examinations included slit-lamp biomicroscopy, indirect ophthalmoscopy and pachymetry. All clinical observations were unremarkable and no treatment-related histopathological changes were observed in the eyes, ocular adnexa or in any organs.

In the six-month nonhuman primate study, cynomolgus monkeys were treated with olopatadine solutions ranging from 0.1 to 0.5% administered in two drops four times a day to the right eye only. Ocular examinations included slit-lamp biomicroscopy, indirect ophthalmoscopy, specular microscopy and pachymetry. No deaths were reported, no adverse clinical signs were noted, and no microscopic changes were found related to treatment with olopatadine.

Additionally, previous studies performed for both the 0.1% and 0.2% olopatadine solutions provided ample evidence to support the topical ocular and systemic safety of the 0.7% olopatadine solution.

A one-month topical ocular study was conducted with 0.1% QID or 0.2% olopatadine hydrochloride QID (4 times a day) and HID (6 times a day) ophthalmic solution in New Zealand White (NZW) rabbits. No signs of pharmacotoxicity were observed. Slit-lamp and indirect ocular evaluations and pachymetry revealed no treatment-related findings. Clinical pathology data and histopathology were unremarkable.

Two one-day topical ocular studies were conducted in NZW rabbits with 0.2% olopatadine formulations containing povidone. Each animal received two drops of the test article to one eye every 30 minutes for a total of ten doses. Slit lamp biomicroscopic examinations were conducted at 1, 2, 3 days following treatment. No significant ocular irritation was observed. Chronic topical ocular studies were conducted with olopatadine in rabbits and monkeys. Administration of olopatadine at concentrations of 0.1, 0.5 and 1.0% QID to NZW rabbits elicited no signs of pharmacotoxicity. No treatment-related findings were observed during slit-lamp and indirect ocular evaluations and pachymetry measurements. Clinical pathology data and histopathology were unremarkable. Similar findings were observed following six months of topical ocular administration of olopatadine hydrochloride at concentrations of 0.1, 0.2 and 0.5% QID to cynomolgus monkeys and following three months of topical ocular administration of formulations containing 0.2 and 0.4% of olopatadine with povidone TID to rabbits.

Olopatadine was found not to be teratogenic in rats and rabbits. However, rats treated at 600 mg/kg/day, or 150,000 times the MROHD and rabbits treated at 400 mg/kg/day, or approximately 100,000 times the MROHD, during organogenesis showed a decrease in live fetuses. In addition, rats treated with 600 mg/kg/day of olopatadine during organogenesis showed a decrease in fetal weight. Further, rats treated with 600 mg/kg/day of olopatadine during late gestation through the lactation period showed a decrease in neonatal survival and body weight.

Antigenicity: Olopatadine was demonstrated to have a low potential for antigenicity when tested in mice and guinea pigs or in an *in vitro* passive hemagglutination test.
Olopatadine was tested in a series of *in vitro* and *in vivo* mutagenesis studies. The results of these studies demonstrated that treatment with olopatadine did not induce genetic mutations or chromosomal aberrations. Long-term carcinogenicity studies in rats and mice also demonstrated that treatment with olopatadine did not increase the potential for cancer up to 500 mg/kg/day or over 200,000 fold greater than the maximum recommended daily dose.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

Pr PAZEO*

Olopatadine Hydrochloride Ophthalmic Solution: 0.7% w/v olopatadine (as olopatadine hydrochloride)

Read this carefully before you start taking **PAZEO*** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **PAZEO***.

What is PAZEO* used for?

PAZEO* is used to treat itchy eyes associated with allergic conjunctivitis.

Allergic conjunctivitis is caused when you have an allergic reaction to substances like pollen, house dust or animal fur that result in:

- your eye(s) feeling itchy
- redness in your eye(s)
- swelling on the surface of your eye(s)

How does PAZEO* work?

PAZEO* works by treating the symptoms of your eyes that are caused by allergies.

What are the ingredients in PAZEO*?

Medicinal ingredients: olopatadine (as olopatadine hydrochloride)
Preservative: benzalkonium chloride
Non-medicinal ingredients: boric acid, hydrochloric acid and/or sodium hydroxide (to adjust pH), hydroxypropyl-gamma-cyclodextrin, hydroxypropyl methylcellulose, mannitol, polyethylene glycol 400, povidone and purified water.

PAZEO*comes in the following dosage forms:

Ophthalmic solution: 0.7% w/v

Do not use PAZEO* if:

- you are allergic to:

- olopatadine hydrochloride
- any of the other ingredients in PAZEO* or
- the components of the container (polyethylene or polypropylene)

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take PAZEO*. Talk about any health conditions or problems you may have, including if you are:

- pregnant or planning to become pregnant
- breast-feeding. Do not use PAZEO*. It may get into your breast milk.

Other warnings you should know about:

General: PAZEO* contains benzalkonium chloride (a preservative) which may cause eye irritation and is known to change the colour of soft contact lenses. Do not use the drops while wearing contact lenses. Remove your lenses before applying PAZEO* and wait at least 15 minutes before putting your lenses back in.

Do not wear contact lenses if your eyes are red.

Using other eye drops: if you are using other eye drops, you should wait at least 5 minutes between putting in PAZEO* and the other drops. If you are using an eye ointment, you should apply it last.

Driving and using machines: You may find that your vision is blurred for a time just after you use PAZEO*. Do not drive or use machines until your vision is clear.

Children less than 2 years old: PAZEO* has not been studied in children under the age of 2 years.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

There are no known drugs that interact with PAZEO*.

How to use PAZEO*:

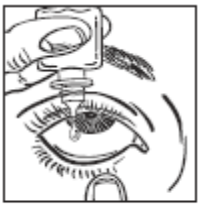
PAZEO* is an eye drop. Only use it in your eye(s).

To prevent contamination of the dropper tip and solution, you should be careful not to touch your eye, eyelids or any surface with the dropper tip. Keep bottle tightly closed when you are not using it.

Remember: If you are using other eye drops, wait at least 5 minutes between putting in PAZEO* and the other drops. If you are using an eye ointment, you should apply it last.

Usual Dose:
Adults and Children (2 years and older): 1 drop in each affected eye once a day

Instructions for Use:



1

2

- Get the PAZEO* bottle and a mirror.
- Wash your hands.
- Twist off the cap. Hold the bottle, pointing down, between your thumb and fingers.
- Tilt your head back. Pull down your eyelid with a clean finger, until there is a 'pocket' between your eyelid and your eye. The drop will go in here (picture 1).
- Bring the bottle tip close to the eye. Use the mirror if it helps.
- **Do not touch your eye or eyelid, or any surface with the dropper.**
- Gently squeeze the bottle to release one drop of PAZEO* (picture 2).
- If you need to use the drops in both of your eyes, repeat the steps for the other eye. Put the bottle cap firmly back on immediately after you are done using it.

Overdose:

If you think you have used too much PAZEO*, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

If you get too much in your eyes, rinse it all out with warm water. Don't put in any more drops until it's time for your next regular dose.

Missed Dose:

If you forget to use PAZEO*, use it as soon as you remember, and then go back to your regular routine. **Do not** use a double dose to make up for the one you missed.

What are possible side effects from using PAZEO*?

These are not all the possible side effects you may feel when taking PAZEO*. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- headache
- a dry throat
- a change in your sense of taste
- eye problems such as:
    - dry, itchy, red, irritated or crusted eyes
    - eye pain
    - blurred vision
    - staining in your eye
    - burning, or gritty feeling or a feeling as if something is trapped in the eye

You can usually continue using the eye drops even if you experience the side effects listed above, unless the side effects become serious. If you're worried, you should talk to a doctor or pharmacist.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
RARE **Allergic reactions:** swelling of the mouth and throat, shortness of breath, hives, severe itching and rash			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect;
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 1908C
    Ottawa, ON
    K1A 0K9

  Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store at room temperature or between 2-25°C
- Throw away the bottle at the end of 4 weeks
- Keep out of reach and sight of children

If you want more information about PAZEO*:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; the manufacturer's website www.novartis.ca, or by calling 1-800-363-8883.

This leaflet was prepared by Novartis Pharmaceuticals Canada Inc.

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