PRODUCT MONOGRAPH

Pr SANDOZ OLOPATADINE 0.2%

Olopatadine Hydrochloride Ophthalmic Solution
0.2% w/v olopatadine (as olopatadine hydrochloride)

Mfr. Std.

Anti-allergy Agent

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Olopatadine Hydrochloride Ophthalmic Solution

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Topical Ophthalmic	Ophthalmic Solution 0.2% w/v olopatadine (as olopatadine hydrochloride)	Preservative: benzalkonium chloride Non-medicinal ingredients: dibasic sodium phosphate, edetate disodium, hydrochloric acid and/or sodium hydroxide (to adjust pH), povidone, purified water, sodium chloride

INDICATIONS AND CLINICAL USE

Sandoz Olopatadine 0.2% (olopatadine hydrochloride ophthalmic solution) is indicated for the treatment of ocular itching associated with seasonal allergic conjunctivitis.

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

Paediatrics (<18 years): The effectiveness of Sandoz Olopatadine 0.2% has not been established in paediatric patients <18 years of age. No overall difference in safety has been observed between paediatric 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.

Sandoz Olopatadine 0.2% should not be used to treat contact lens related irritation. The preservative in Sandoz Olopatadine 0.2%, benzalkonium chloride, may cause eye irritation and is known to discolour soft contact lenses. Contact with soft contact lenses should be avoided. Patients must be instructed to remove contact lenses prior to application of Sandoz Olopatadine 0.2%, and wait at least 15 minutes before they insert their contact lenses.

If using other eye drops, patients should wait at least five minutes between putting in Sandoz Olopatadine 0.2% 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 Sandoz Olopatadine 0.2%, 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. Studies in animals with olopatadine have shown reproductive toxicity following systemic administration considered sufficiently in excess of the maximum human exposure. Olopatadine was found not to be teratogenic in rats and rabbits at oral doses >90,000 and >60,000 times the maximum recommended ocular human use level, respectively (see TOXICOLOGY). Because animal studies are not always predictive of human responses, Sandoz Olopatadine 0.2% should be used in pregnant women only if the potential benefit to the mother justifies the potential risk to the embryo or fetus.

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 Sandoz Olopatadine 0.2% is administered to a nursing mother.

Paediatrics (<18 years): Effectiveness in paediatric patients has not been established. No

overall difference in safety has been observed between paediatric 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

In clinical trials involving 1137 patients dosed with long-term ophthalmic topical therapy, olopatadine hydrochloride ophthalmic solution 0.2% was administered once-daily for 4 to 12 weeks. The most frequently reported treatment-related undesirable effects were headache (0.8%), eye irritation (0.5%), dry eye (0.4%), and eyelid margin crusting (0.4%). No serious adverse drug reactions related to olopatadine hydrochloride ophthalmic solution 0.2% were reported in the clinical trials.

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.

No treatment-related adverse drug reactions occurred at an incidence ≥ 1%.

Less Common Clinical Trial Adverse Drug Reactions

The most frequently reported adverse drug reactions (>0.1%) are presented in Table 1.

Table 1: Treatment-Related Adverse Drug Reactions >0.1% – Long-Term Exposure

MedDRA Preferred Term (Version 11.0)	Olopatadine N = 1137 (%)	Placebo N = 631 (%)
Eye Disorders		
Eye Irritation	0.5%	0.6%
Dry Eye	0.4%	0.5%
Eyelid Margin Crusting	0.4%	
Eye Pruritus	0.2%	0.3%
Gastrointestinal Disorders		
Dry Mouth	0.2%	
Nervous System Disorders		
Headache	0.8%	
Dysgeusia	0.4%	

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

Eye disorders: asthenopia, eye swelling, eyelid disorder, eyelids pruritus, ocular hyperaemia, and vision blurred;
Investigations: heart rate increased;
Respiratory, Thoracic, and Mediastinal disorders: nasal dryness

Post-Market Adverse Drug Reactions

Approximately 5.4 million units of olopatadine hydrochloride ophthalmic solution 0.2% have been sold worldwide. The reporting rate of all reaction terms reported between 22 December 2004 and 31 August 2009 was 0.005%, and no single reaction term occurred with a reporting rate greater than 0.0007%. No post-market reports of serious adverse reactions have been received to date. The most frequent events reported being eye irritation, ocular hyperaemia, eye pain and vision blurred. There were no new major findings bearing on the established overall safety profile of Sandoz Olopatadine 0.2%. Other events include dizziness, eye discharge, punctate keratitis, keratitis, erythema of eyelid, dermatitis contact, fatigue, hypersensitivity, ocular discomfort, lacrimation increased and nausea.

DRUG INTERACTIONS

No clinical interaction studies have been conducted with olopatadine hydrochloride ophthalmic solution 0.2%. *In vitro* studies have shown that olopatadine does not inhibit metabolic reactions which involve cytochrome P-450 isoenzymes 1A2, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4. Olopatadine is moderately bound to plasma proteins (approximately 55%). These results indicate that olopatadine is unlikely to result in interactions with other concomitantly administered medications. Due to the low systemic exposure following topical ocular dosing, it is unlikely that Sandoz Olopatadine 0.2% would interfere with immediate hypersensitivity skin testing.

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 Sandoz Olopatadine 0.2%.

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 data are available in humans regarding overdose by accidental or deliberate ingestion of olopatadine hydrochloride ophthalmic solution 0.2%. No reports of overdose were received during the clinical studies of olopatadine hydrochloride ophthalmic solution 0.2%.

If a topical overdose of olopatadine occurs, the eye(s) may be flushed with tap water.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Olopatadine, a structural analog of doxepin, is a non-steroidal, non-sedating, topically effective anti-allergic molecule that exerts its effects through multiple distinct mechanisms of action. Olopatadine is a mast cell stabilizer and a potent, selective histamine H_1 antagonist (10,12) that inhibits the *in vivo* type 1 immediate hypersensitivity reaction (13). Olopatadine inhibits the release of mast cell inflammatory mediators [i.e., histamine, tryptase, prostaglandin D2 and TNFα (4,10,12,13)] as demonstrated in *in vitro* studies and confirmed in patients (8). Olopatadine is also an inhibitor of pro-inflammatory cytokine secretion from human conjunctival epithelial cells (14).

Pharmacodynamics

Effects on cardiac repolarization (QTc):

In two placebo-controlled, two-way crossover cardiac repolarization studies, no signal of QT interval prolongation was observed relative to placebo following twice daily 5 mg oral doses for 2.5 days in 102 healthy volunteers, or following twice daily 20 mg oral doses for 13.5 days in 32 healthy volunteers. In addition, no evidence of QT interval prolongation was observed, relative to placebo, in 429 perennial allergic rhinitis patients given olopatadine hydrochloride nasal spray, 665 micrograms twice daily for up to 1 year.

Pharmacokinetics

Following topical ocular administration in man, olopatadine was shown to have low systemic exposure. Two studies in healthy volunteers (totalling 24 subjects) dosed bilaterally with Olopatadine 0.15% ophthalmic solution once every 12 hours for 2 weeks demonstrated plasma concentrations to be generally below the quantitation limit of the assay (<0.5 ng/mL).

In multiple oral dose studies, olopatadine plasma concentrations were shown to increase in proportion to the dose increment. The elimination half-life in plasma was 7-14 hours, and elimination was predominantly through renal excretion. Approximately 60-70% of the oral dose was recovered in the urine as parent drug. Peak plasma concentrations of the active metabolite, N-desmethyl olopatadine and inactive N-oxide metabolite were low, less than 1% and 3% of parent, respectively.

Special Populations and Conditions

Paediatrics: Effectiveness in paediatric patients has not been established. No overall difference in safety has been observed between paediatric and adult patients.

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

Gender: In multiple oral dose studies, plasma concentrations of olopatadine are higher in female subjects, however, the differences are small and not clinically meaningful.

Race: No specific pharmacokinetic study examining the effect of race has been conducted.

Hepatic Insufficiency: No specific pharmacokinetic study examining the effect of hepatic impairment was conducted. Since metabolism of olopatadine is a minor route of elimination, no adjustment of the dosing regimen of olopatadine hydrochloride ophthalmic solution 0.2% is warranted in patients with hepatic impairment.

Renal Insufficiency:

The mean plasma C_{max} values for olopatadine following single intranasal doses of olopatadine hydrochloride nasal spray 0.6% (665 µg/spray) were not markedly different between healthy subjects (18.1 ng/mL) and patients with mild, moderate and severe renal impairment (range 15.5 to 21.6 ng/mL). Plasma AUC was 2.5-fold higher in patients with severe impairment (creatinine clearance <30 mL/min/1.73m2). Predicted peak steady-state plasma concentrations of olopatadine in patients with renal impairment following administration of olopatadine hydrochloride ophthalmic solution, 0.1% are at least 10-fold lower than those observed following administration of olopatadine nasal spray 0.6%, and approximately 300-fold lower than those observed following the safe and well-tolerated administration of 20 mg oral doses for 13.5 days. These findings indicate that no adjustment of the dosing regimen of olopatadine hydrochloride ophthalmic solution 0.2% is warranted in patients with renal impairment.

STORAGE AND STABILITY

Store at 4° - 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 Sandoz Olopatadine 0.2% contains:
Medicinal ingredient: 2.22 mg olopatadine hydrochloride equivalent to 2 mg olopatadine.
Preservative: benzalkonium chloride 0.01%.
Non-medicinal ingredients: dibasic sodium phosphate, edetate disodium, povidone, sodium chloride, hydrochloric acid/sodium hydroxide (to adjust pH), and purified water.

Sandoz Olopatadine 0.2% has a pH of approximately 7 and an osmolality of approximately 300 mOsm/kg.

Sandoz Olopatadine 0.2% 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 2.5 mL in a 4 mL bottle.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: olopatadine hydrochloride

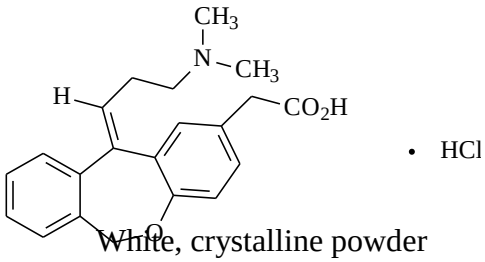
Chemical name:

(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: $C_{21}H_{23}NO_3 \bullet HCl$; 373.88

Structural formula:



• HCl

Description: White, crystalline powder

Solubility: Sparingly soluble in methanol and water. Insoluble in chloroform.

pH (1% aqueous solution): 2.5

CLINICAL TRIALS

Study demographics and trial design

A summary of the patient demographics for each of the 7 studies relevant to the evaluation of the efficacy of olopatadine hydrochloride ophthalmic solution 0.2% is provided in Table 1. Overall, these demographics are representative of the population that would be expected to receive this medicinal product.

Table 1: Summary of trial design and patient demographics for clinical trials

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
C-00-36 CAC	randomized, double-masked, placebo-controlled	Olopatadine 0.2% or placebo, 1 drop each eye at each visit, dosed contra-laterally; visits on 3 non-consecutive days	n = 45	42.3 yrs (19 – 70)	18 M 27 F
C-01-18 CAC	randomized, double-masked, placebo-controlled	Olopatadine 0.2%, placebo, or Olopatadine 0.2% and placebo dosed contra-laterally, 1 drop each eye at each visit, visits on 2 non-consecutive days	n = 36	38.1 yrs (20-58)	16 M 20 F
C-01-100 CAC	randomized, double-masked, placebo-controlled	Olopatadine 0.2% (OU), placebo (OU), Olopatadine 0.2% (OS) and placebo (OD), or Olopatadine 0.2% (OD) and placebo (OS), 1 drop each eye at each visit, visits on 2 non-consecutive days	n = 92	39.2 yrs (20-67)	38 M 54 F
C-02-67 Environmental (grass)	randomized, double-masked, placebo-controlled parallel group	Olopatadine 0.2% or placebo, 1 drop each eye once daily, 10 weeks	n = 260	36.4 yrs (11-75)	123 M 137 F
C-04-60 Environmental (grass)	randomized, double-masked, placebo-controlled parallel group	Olopatadine 0.2% or placebo, 1 drop each eye once daily, 6 weeks	n = 287	36.4 yrs (10-81)	127 M 160 F
C-01-10 Environmental (ragweed)	randomized, double-masked, placebo-controlled, parallel group	Olopatadine 0.2% or placebo, 1 drop each eye once daily, 12 weeks	n = 240	37.3 (10-66)	94 M 146 F
C-01-90 Environmental (grass)	randomized, double-masked, placebo-controlled, parallel group	Olopatadine 0.2% or placebo, 1 drop each eye once daily, 12 weeks	n = 239	37.4 (10-73)	94 M 145 F

OU= both eyes, OD=right eye, OS=left eye

Study results

Conjunctival Allergen Challenge (CAC) Studies

Three studies were conducted to assess the safety and efficacy of olopatadine hydrochloride ophthalmic solution 0.2% versus placebo in the treatment of allergen-mediated conjunctivitis

using the CAC model at 27 minutes (onset-of-action), and either 16 hours or 24 hours or both (duration-of-action), after instillation. All three studies demonstrated that olopatadine hydrochloride ophthalmic solution 0.2% dosed once daily was statistically superior to placebo in the treatment of ocular itching, has a rapid onset-of-action and a prolonged duration-of-action.

Table 2: CAC Itching Results from Contralateral Eye Analyses in Studies with olopatadine hydrochloride ophthalmic solution 0.2%

		Onset-of-Action					**24Hr Duration-of-Action**					**16Hr Duration-of-Action**				
		time post-challenge					time post-challenge					time post-challenge				
		3 min	5 min	7 min	10 min	20 min	3 min	5 min	7 min	10 min	20 min	3 min	5 min	7 min	10 min	20 min
C-00-36 Olopatadine 0.2% - Placebo	Mean Diff	**-1.31**			**-1.60**	**-1.13**	**-0.93**			**-0.99**	**-0.65**	**-0.93**			**-0.88**	**-0.39**
	pvalue	<0.001			<0.001	<0.001	<0.001			<0.001	<0.001	<0.001			<0.001	0.014
C-01-18 Olopatadine 0.2% - Placebo	Mean Diff	**-1.50**			**-1.67**	**-0.79**						**-1.25**			**-1.04**	**-0.50**
	pvalue	0.0002			0.0003	0.0180						0.0011			0.0044	0.0456
C-01-100 Olopatadine 0.2% - Placebo	Mean Diff	**-1.56**	**-1.66**	**-1.53**								**-0.98**	**-1.07**	**-1.07**		
	pvalue	<0.0001	<0.0001	<0.0001								<0.0001	<0.0001	<0.0001		

Shaded areas indicate that ocular itching was not evaluated at these time-points; bold numbers indicate statistical significance.

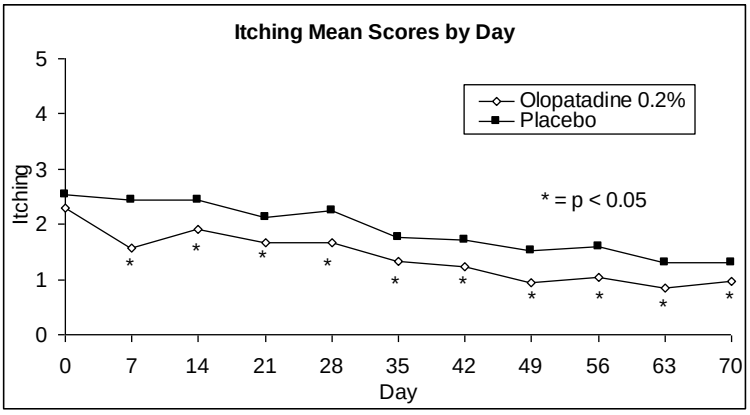
Environmental Studies

Four environmental studies were designed to assess the safety and efficacy of olopatadine hydrochloride ophthalmic solution 0.2% in comparison with placebo in the treatment of the signs and symptoms of seasonal allergic conjunctivitis. All studies were randomized, double-masked, placebo-controlled, multi-centre, parallel group studies. Three studies (C-02-67, C-04-60, and C-01-90) enrolled patients with a history of seasonal allergic conjunctivitis, a positive diagnostic skin prick test for grass antigen within the past 2 years, and a positive response to grass in the Conjunctival Allergen Challenge model of the required magnitude. One study (C-01-10) enrolled patients with a positive skin prick test for ragweed antigen. Daily pollen counts were recorded for each study site.

Clinical Study C-02-67

Two hundred and sixty (260) patients were enrolled in this 10-week environmental study. The primary efficacy analysis was based on the subject self-evaluation of the frequency of ocular itching during the three days prior to each weekly assessment visit. The results showed that olopatadine hydrochloride ophthalmic solution 0.2% statistically significantly reduced the effects of pollen on ocular itching relative to vehicle when dosed once a day (Figure 1).

Figure 1: Mean Scores for Itching Frequency by Visit Day (Intent-to-Treat) (C-02-67)



An analysis of the slopes of the lines measuring the effects of pollen on ocular itching also showed a statistically significant difference between olopatadine hydrochloride ophthalmic solution 0.2% and placebo when pollen counts were taken into consideration.

The secondary analysis showed that olopatadine hydrochloride ophthalmic solution 0.2%, dosed once a day, statistically significantly reduced the effects of pollen on daily itching severity when compared to vehicle (Table 3).

Table 3: Mean Itching Severity during 14 Consecutive Days of Peak Pollen (Intent-to-Treat) (C-02-67)

		ITCHING
Olopatadine 0.2%	Mean	1.10
	Std	0.92
	N	127
PLACEBO	Mean	1.48
	Std	1.04
	N	129
Difference from Vehicle		**-0.38**
p-value (t-test)		**0.0023**

Clinical Study C-04-60

Two hundred and eighty-seven (287) patients were enrolled in this 6-week environmental study. Severity scores for daily ocular itching, as recorded by patients three times per day in their diaries, were statistically significantly lower compared to placebo in the morning, mid-day, and evening when *averaged over* the 14 consecutive days of the peak pollen period. Additionally, the average diary itching scores are statistically significantly reduced in patients treated with olopatadine hydrochloride ophthalmic solution 0.2% compared with placebo (Table 4).

Table 4: Average Diary Itching Over the Peak Pollen Period by Time (Intent-to-Treat) (C-04-60)

		Average Diary Itching			
		Mean	**Std**	**N**	**P-value**
Morning	**Olopatadine 0.2%**	0.55	0.60	144	0.0204
	Vehicle	0.72	0.64	143	
Mid-Day	**Olopatadine 0.2%**	0.50	0.61	144	0.0130
	Vehicle	0.69	0.63	143	
Evening	**Olopatadine 0.2%**	0.54	0.65	144	0.0084
	Vehicle	0.74	0.67	143	

Clinical Study C-01-10
A total of 240 patients were enrolled in this 12-week environmental study during ragweed season. The primary efficacy endpoint was subject self-evaluation of the frequency scores of ocular itching over a 12-week study period. The primary efficacy endpoint did not show any statistically significant difference between olopatadine hydrochloride ophthalmic solution 0.2% and placebo in this study.

Clinical Study C-01-90
A total of 239 patients were enrolled in a 12-week environmental study during grass season. The primary efficacy endpoint was subject self-evaluation of the worst daily ocular itching averaged over a two-week, peak pollen period. The primary efficacy endpoint did not show any statistically significant difference between olopatadine hydrochloride ophthalmic solution 0.2% and placebo in this study. The planned secondary efficacy analysis showed that olopatadine hydrochloride ophthalmic solution 0.2% statistically significantly reduced the effects of pollen on ocular itching.

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 (11) 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 (4,10,12,13)] 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 (12). Olopatadine is also an inhibitor of pro-inflammatory cytokine secretion from human conjunctival epithelial cells (14). Decreased chemotaxis and inhibition of eosinophil activation has also been reported (6,9). Olopatadine is devoid of effects on alpha-adrenergic, dopamine, muscarinic type 1 and 2, and serotonin receptors.

Human Pharmacodynamics

Olopatadine had no observed effect on heart rate, cardiac conduction (PR and QRS interval duration), cardiac repolarization (QT duration) or wave form morphology relative to placebo in 2 double-masked, placebo controlled, 2-way crossover studies of 102 subjects given 5-mg oral doses of olopatadine every 12 hours for 2.5 days and 32 subjects given 20-mg oral doses twice-daily for 13.5 days. No clinically relevant or statistically significant changes in mean QTcF (determined to be the most appropriate heart correction formula for both study populations) at steady-state from baseline were observed in either study. A categorical analysis of QTc (< 30 ms, 30 ms-60 ms, or > 60 ms) showed no statistically significant differences between olopatadine and placebo in both studies. An analysis of the maximal change from baseline in QTcF showed the difference was higher for placebo than for olopatadine.

Human Pharmacokinetics

Systemic bioavailability data upon topical ocular administration of Sandoz Olopatadine 0.2% are not available. Following topical ocular administration in man, olopatadine was shown to have low systemic exposure. Two studies in normal volunteers (totalling 24 subjects) dosed bilaterally with Olopatadine 0.15% ophthalmic solution once every 12 hours for 2 weeks demonstrated plasma concentrations to be generally below the quantitation limit of the assay (< 0.5 ng/mL). Samples in which olopatadine was quantifiable were typically found within 2 hours of dosing and ranged from 0.5 to 1.3 ng/mL. These plasma concentrations were greater than 300 fold below those observed with a well-tolerated 20 mg oral multiple-dose regimen. In oral studies, olopatadine was found to be well absorbed. The half-life in plasma was 7-14 hours, and elimination was predominantly through renal excretion. Approximately 60-70% of the dose was recovered in the urine as parent drug. Two metabolites, the mono-desmethyl and the N-oxide, were detected at low concentrations in the urine.

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 one-month topical ocular study was conducted with 0.1% QID or 0.2% olopatadine hydrochloride QID and HID 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 hydrochloride 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 hydrochloride in rabbits and monkeys. Administration of olopatadine hydrochloride 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 hydrochloride 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 hydrochloride 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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PART III: CONSUMER INFORMATION

Pr SANDOZ OLOPATADINE 0.2%
olopatadine hydrochloride ophthalmic solution

This leaflet is part III of a three-part "Product Monograph" published when Sandoz Olopatadine 0.2% was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Sandoz Olopatadine 0.2%. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Sandoz Olopatadine 0.2% is used for the treatment of itchy eyes associated with seasonal allergic conjunctivitis.

Allergic conjunctivitis: Some materials (allergens) like pollens, house dust or animal fur may cause allergic reactions resulting in itching, redness as well as swelling of the surface of your eye.

What it does:
Sandoz Olopatadine 0.2% is a medicine for treatment and control of allergic conditions of the eye. It works in two different ways by reducing and controlling the intensity of the allergic reaction.

When it should not be used:
Sandoz Olopatadine 0.2% should not be used if you are allergic (*hypersensitive*) to olopatadine hydrochloride or any of the other ingredients (see **What the non-medicinal ingredients are**).

Tell your doctor if you have allergies.

Do not use Sandoz Olopatadine 0.2% in children under the age of 16 years.

What the medicinal ingredient is:
olopatadine hydrochloride

What the nonmedicinal ingredients are:
Preservative: benzalkonium chloride
Other ingredients include: dibasic sodium phosphate, edetate disodium, povidone, purified water and sodium chloride. Tiny amounts of hydrochloric acid or sodium hydroxide are sometimes added to maintain proper pH balance.

What dosage forms it comes in:
Ophthalmic solution (eye drops). Each mL contains 2 mg olopatadine.

WARNINGS AND PRECAUTIONS

BEFORE you use Sandoz Olopatadine 0.2% talk to your doctor or pharmacist.

Pregnancy or breast-feeding

If you are pregnant, or planning to become pregnant, talk to your doctor before you use Sandoz Olopatadine 0.2%. If you are breast-feeding, do not use Sandoz Olopatadine 0.2%; it may get into your milk.

Use of Sandoz Olopatadine 0.2% and use of contact lenses

- Do not wear contact lenses if your eyes are red.
- Sandoz Olopatadine 0.2% contains a preservative, benzalkonium chloride, which may cause eye irritation and is known to discolour soft contact lenses. Do not use the drops while wearing contact lenses.
- Remove your contacts before applying Sandoz Olopatadine 0.2% and wait at least 15 minutes before putting your contacts back in.

Use of Sandoz Olopatadine 0.2% with other eye drops or ointments

- If you use other eye drops, wait at least 5 minutes between putting in Sandoz Olopatadine 0.2% and the other drops.
- Apply eye ointments last.

Driving and using machines: You may find that your vision is blurred for a time just after you use Sandoz Olopatadine 0.2%. Do not drive or use machines until your vision is clear.

INTERACTIONS WITH THIS MEDICATION

Please tell your doctor if you are taking or have recently taken any other medicines, even products you have bought yourself without prescription or natural health products.

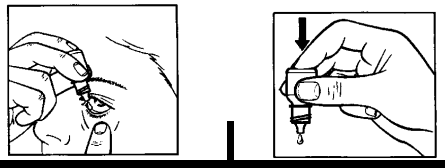
There are no known drugs that interact with Sandoz Olopatadine 0.2%.

PROPER USE OF THIS MEDICATION

Sandoz Olopatadine 0.2% is an eye drop. Only use it in your eye(s).

If you are using other eye drops, wait at least 5 minutes before putting in Sandoz Olopatadine 0.2% and the other eye drops. If you are using an eye ointment, you should apply it last.

Usual dose:
Adults: 1 drop in each affected eye once daily.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Instructions for use:
1. Get the Sandoz Olopatadine 0.2% bottle and a mirror if needed.

2. Wash your hands.
3. Twist off the cap, being careful not to touch the dropper tip.
4. Hold the bottle, pointing it down, between your thumb and middle finger.
5. Tilt your head back. Pull down your eyelid with a clean finger, until there is a 'pocket' between the eyelid and your eye. The drop will go in there (Figure 1).
6. 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.** It could contaminate the drops, cause an eye infection and damage the eyes.
7. Gently press the bottom of the bottle with your forefinger to release one drop (Figure 2). Do not squeeze the bottle: it is designed so that just a gentle press on the bottom is all that it needs.
8. If you use drops in both eyes, repeat the steps for the other eye.
9. Put the bottle cap firmly back on immediately after use.

Overdose:

If you think you have used too much Sandoz Olopatadine 0.2%, contact a 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 Sandoz Olopatadine 0.2%, use a single drop 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 missed.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

A small number of people who use Sandoz Olopatadine 0.2% may get side effects. They can be unpleasant, but most of them disappear rapidly.

You can usually continue using the drops, unless the effects are serious. If you're worried, talk to a doctor or pharmacist.

Side effects may include:
In the eye:

- eye problems such as dry, itchy, red, irritated or crusted eyes
- eye surface inflammation with or without surface damage
- eye discharge
- eye pain
- increased tear production
- eyelid redness, swelling
- sensitivity to light
- blurred vision
- staining in your eye
- burning, stinging or gritty feeling or a feeling as if something is trapped in the eye.

Other areas of your body:

- headache
- dizziness
- fatigue or tiredness
- nasal dryness
- increased heart rate
- a dry mouth
- a change in your sense of taste
- nausea
- red or itchy skin.

If you notice any side effects, other than discomfort, please inform your doctor or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Rare	**Allergic reactions:** swelling of the mouth and throat, shortness of breath, hives, severe itching and rash			✓

This is not a complete list of side effects. For any unexpected effects while taking Sandoz Olopatadine 0.2%, contact your doctor or pharmacist.

HOW TO STORE IT

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

REPORTING SIDE EFFECTS

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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.

MORE INFORMATION

This document plus the full Product Monograph, prepared for health professionals can be found by contacting the sponsor, Sandoz Canada Inc. at:

1-800-361-3062

or by written request at:
145 Jules-Léger
Boucherville QC
J4B 7K8

or by e-mail at :
medinfo@sandoz.com

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