1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

1. **NAME OF THE MEDICINAL PRODUCT**
   OPTALYN (Olopatadine Hydrochloride Ophthalmic Solution USP 0.2%)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Qualitative Declaration:

Olopatadine Hydrochloride Ophthalmic Solution USP 0.2%

- **Olopatadine Hydrochloride**

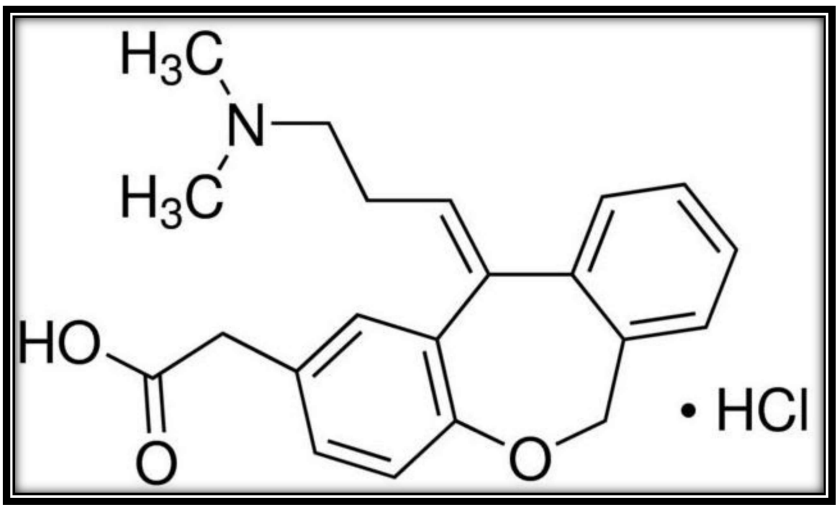
Chemical Name:

{(11*Z*)-11-[3-(dimethylamino) propylidene]-6, 11-dihydrodibenzo [*b,e*]oxepin-2-yl}acetic acid

Molecular Weight: - 373.877 g/mol

Molecular Formula: - $C_{21}H_{24}ClNO_3$

Structural Formula:-



Pharmaceutical Form Visual description of the appearance of product:

Clear Colourless to slightly yellow colour solution, free from any type of visible particles.

Quantitative Declaration:

Composition:

Olopatadine Hydrochloride	USP	
Eq. to Olopatadine		0.2% w/v
Benzalkonium Chloride Solution (As Preservative)	NF	0.01% w/v
Sterile aqueous base		Q.S

3. PHARMACEUTICAL FORM

Eye Drops

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

INDICATIONS AND USAGE

Olopatadine hydrochloride ophthalmic solution 0.2% is indicated for the treatment of the signs and symptoms of allergic conjunctivitis.

4.2 Posology and method of administration

DOSAGE AND ADMINISTRATION

The recommended dose is one drop in each affected eye two times per day at an interval of 6 to 8 hours. Treatment may be maintained for up to four months, if considered necessary.

4.3 Contraindications

Contraindications

Olopatadine hydrochloride ophthalmic solution 0.2% is contraindicated in persons with a known hypersensitivity to Olopatadine hydrochloride or any components of the drug.

4.4 Special warnings and precautions for use

Warnings and Precautions
Olopatadine hydrochloride ophthalmic solution 0.2% is for topical use only and not for injection or oral use.

Olopatadine hydrochloride ophthalmic solution 0.2% is an antiallergic/antihistaminic agent and, although administered topically, is absorbed systemically. If signs of serious reactions or hypersensitivity occur, discontinue the use of this treatment.

Benzalkonium chloride, which is commonly used as a preservative in ophthalmic products, has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy. Since Olopatadine hydrochloride ophthalmic solution 0.2% contains Benzalkonium chloride, close monitoring is required with frequent or prolonged use in dry eye patients, or in conditions where the cornea is compromised.

As with any eye drop, temporary blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs at instillation, the patient must wait until the vision clears before driving or using machinery.

Use in Hepatic and Renal impairment
Olopatadine hydrochloride ophthalmic solution 0.2% 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.

Pregnancy
Pregnancy Category C
There are no adequate and well-controlled studies in pregnant women. 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.

Lactation
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 the human breast milk. Olopatadine hydrochloride ophthalmic solution 0.2% is not recommended for breast-feeding mothers.

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

Geriatric Use
No overall differences in safety or effectiveness have been observed between elderly and younger patients.

4.5 Interaction with other medicinal products and other forms of interaction

Drug Interactions

Adverse Reactions
Symptoms similar to cold syndrome and pharyngitis were reported at an incidence of approximately 10%.

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

Ocular: blurred vision, burning or stinging, conjunctivitis, dry eye, foreign body sensation, hyperemia, hypersensitivity, keratitis, lid edema, pain and ocular pruritus.

Non-ocular: asthenia, back pain, flu syndrome, headache, increased cough, infection, nausea, rhinitis, sinusitis and taste perversion.

Some of these events were similar to the underlying disease being studied.

4.6 Fertility, pregnancy and lactation

USE IN SPECIFIC POPULATIONS

Pregnancy
Teratogenic effects: Pregnancy Category C
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. There are, however, no adequate and well- controlled studies in pregnant women. 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.

Nursing Mothers
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 the human breast milk. Nevertheless, caution should be exercised when Olopatadine hydrochloride ophthalmic solution 0.2% is administered to a nursing mother.

Pediatric Use
Safety and effectiveness in pediatric patients below the age of 2 years have not been established.

Geriatric Use
No overall differences in safety and effectiveness have been observed between elderly and younger patients.

4.7 Effects on ability to drive and use machines

Effect on ability to drive and use machines as with any eye drops, temporary blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs at instillation, the patient should wait until their vision clears before driving or using machinery.

4.8 Undesirable effects

In clinical studies involving 1680 patients, Olopatadine hydrochloride ophthalmic solution 0.2% was administered one to four times daily in both eyes for up to four months as monotherapy or adjunctive therapy to loratadine 10 mg. Approximately 4.5% of patients can be expected to experience undesirable effects associated with the use of Olopatadine hydrochloride ophthalmic solution 0.2%; however, only 1.6% of patients discontinued from the clinical studies due to these undesirable effects. No serious ophthalmic or systemic undesirable effects related to Olopatadine hydrochloride ophthalmic solution 0.2% were reported in clinical studies. The most frequent treatment-related undesirable effect was eye pain, reported at an overall incidence of 0.7%.

The following undesirable effects were assessed to be treatment-related and are classified according to the following convention: very common (≥1/10), common (>1/100 to 1/1,000 to ≤1/100), rare (>1/10,000 to ≤1/1000), or very rare (≤1/10,000). Within each frequency grouping, undesirable effects are presented in decreasing order of seriousness.

Infections and Infestations
Uncommon: rhinitis

Nervous System Disorders
Common: headache, dysgeusia
Uncommon: dizziness, hypoesthesia

Eye Disorders
Common: eye pain, eye irritation, dry eye, abnormal sensation in eyes.
Uncommon: corneal erosion, corneal epithelium defect, corneal epithelium disorder, punctate keratitis, keratitis, corneal staining, eye discharge, photophobia, vision blurred, visual acuity reduced, blepharospasm, ocular discomfort, eye pruritus, conjunctival follicles, conjunctival disorder, foreign body sensation in eyes, lacrimation increased, eyelids pruritus, erythema of eyelid, eyelid oedema, eyelid disorder, conjunctival hyperaemia, ocular hyperaemia , burning or stinging

Respiratory, Thoracic, and Mediastinal Disorders
Common: nasal dryness

Skin and Subcutaneous Tissue Disorders
Uncommon: dermatitis contact, skin burning sensation, dry skin

General Disorders and Administration Site Conditions
Common: fatigue

Not known (Cannot be Estimated from the Available Data):
Adverse reactions identified from post-marketing experience that have not been reported previously in clinical trials with Olopatadine hydrochloride ophthalmic solution 0.2% include those detailed below. Unlike data from clinical trials, due to the nature of post-marketing surveillance, the frequency at which these events occur is not known and cannot be estimated based upon the available data.

Ocular: corneal oedema, conjunctivitis, eye oedema, eye swelling, mydriasis, visual disturbance, eyelid margin crusting
Systemic: hypersensitivity, dyspnea, somnolence, swelling face, dermatitis, erythema, nausea, vomiting, pharyngitis, taste perversion, sinusitis, asthenia, malaise, cold syndrome.

4.9 Overdose

OVERDOSAGE

No data are available in humans regarding overdose by accidental or deliberate ingestion.
Olopatadine has a low order of acute toxicity in animals. Accidental ingestion of the entire contents of a bottle of Olopatadine hydrochloride ophthalmic solution 0.2% would deliver a maximum systemic exposure of 5 mg Olopatadine. This exposure would result in a final dose of 0.5 mg/kg in a 10 kg infant, assuming 100% absorption.

Prolongation of the QTc interval in dogs was observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use. A 5 mg oral dose was administered twice-daily for 2.5 days to 102 young and elderly male and female healthy volunteers with no significant prolongation of QTc interval compared to placebo. The range of peak steady-state Olopatadine plasma concentrations (35 to 127 ng/ml) seen in this study represents at least a 70-fold safety margin for topical Olopatadine with respect to effects on cardiac repolarisation.

In the case of overdose, appropriate monitoring and management of the patient should be implemented.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacodynamics properties:

Pharmacotherapeutic group: Anticholinergic
ATC code: S01GX09

Pharmacodynamics properties:

Used to treat allergic conjunctivitis (itching eyes), Olopatadine inhibits the release of histamine from mast cells. It is a relatively selective histamine H1 antagonist that inhibits the in vivo and in vitro type 1 immediate hypersensitivity reaction including inhibition of histamine induced effects on human conjunctival epithelial cells.

Olopatadine is a potent selective antiallergic/antihistaminic agent that exerts its effects through multiple distinct mechanisms of action. It antagonises 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 also invivo data suggest that it inhibits type 1 hypersensitivity reaction. In patients with patent nasolacrimal ducts, topical ocular administration of Olopatadine hydrochloride ophthalmic solution 0.2% 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. Olopatadine is devoid of effects on alphaadrenergic, dopamine, and muscarinic type 1 and 2 receptors.

Mechanism of action:

Olopatadine is a selective histamine H1 antagonist that binds to the histamine H1 receptor. This blocks the action of endogenous histamine, which subsequently leads to temporary relief of the negative symptoms brought on by histamine. Olopatadine is devoid of effects on alpha-adrenergic, dopamine and muscarinic type 1 and 2 receptors.

Olopatadine is a mast cell stabilizer and a histamine H1 antagonist. Decreased chemotaxis and inhibition of eosinophil activation has also been demonstrated.

Application:

Olopatadine is an antihistamine that reduces the natural chemical histamine in the body. Histamine can produce symptoms of itching or watery eyes. Olopatadine ophthalmic is used to treat ocular (eye) symptoms of allergic conditions, such as inflammation, itching, watering, and burning.

Preclinical Pharmacology/Toxicology

Alcon Research, Ltd. (Alcon) developed Olopatadine hydrochloride ophthalmic solution, 0.2% for the treatment of allergic conjunctivitis (NDA 20-688). Olopatadine Ophthalmic Solution, 0.2% was subsequently developed to provide a once daily treatment regimen for itching associated with allergic conjunctivitis (NDA 21-545). Olopatadine 0.6% was developed for the treatment of nasal allergy symptoms (NDA 21-861). The currently proposed product (Olopatadine hydrochloride ophthalmic solution, 0.7%) was intended to increase the duration of efficacy over the existing marketed products

No significant interaction was noted between Olopatadine (10 μM) and α-adrenergic, muscarinic cholinergic, dopamine. 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 (i.e., 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. 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).

To support the development of Olopatadine HCl Solution, 0.7%, a nonclinical 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% PATADAY or Olopatadine HCl Solution, 0.7% (Clinical Formulation) to male New Zealand White (NZW) rabbits a). Plasma and ocular tissues (aqueous humor, choroid, cornea, bulbar conjunctiva, iris-ciliary body (ICB), whole lens and retina) were collected in a sparse fashion up to 24 hours post-dose to measure AL-4943 using a validated LC tandem mass spectrometry (LC/MS/MS) method. Olopatadine was absorbed into the eye and reached maximal levels within 30 minutes to 2 hours for most ocular tissues and plasma except lens (Tmax: 4.0 hours to 8.0 hours). Tissues associated with the site of dosing, i.e., conjunctiva and cornea had the highest concentrations of Olopatadine in both PATADAY (609 ng/g and 720 ng/g) and Olopatadine HCl Solution, 0.7% (3000 ng/g and 2230 ng/g) treatment group, respectively. The mean Cmax estimates in aqueous humor, choroid, ICB and lens increased with increasing concentrations of Olopatadine.

A two-week topical ocular study of two prototype 0.7% Olopatadine ophthalmic formulations was conducted in pigmented rabbits (NZW x New Zealand Red (NZR): F1-Cross rabbits). Additionally, a 3-month repeated topical ocular dose study using pigmented rabbits was conducted with the 0.7% Olopatadine ophthalmic solution formulation proposed for marketing in order to qualify the use of the excipients by the ocular route of administration. These studies were conducted in accordance to GLP regulation. Five non-GLP local tolerance studies using either NZW or pigmented rabbits were conducted with various prototype formulations of 0.7% Olopatadine ophthalmic solutions to evaluate the topical irritation potential as well as the ocular toxicity potential of the higher concentration formulation.

Species Study design	Daily dose (mg/day or mg/kg) (Sex)	N	Systemic exposure		
			Analyte	Cmax [ng/mL]	AUC(0-4hr) [ng·h/mL]
Rabbit 2 week topical ocular	0.7% HD Olopatadine with SBCD (2.95 mg/day)a (M/F)	4	AL-24956	0.215	0.629
			AL-38189	0.108	0.0876
			AL-4943	12.7	34.0
	0.7% HD Olopatadine with HPBCD (2.75 mg/day)b (M/F)	4	AL-24956	0.241	0.681
			AL-38189	0.0999	0.0730
			AL-4943	15.2	39.2
Rabbit 3 month topical ocular	High Dose Olopatadine Ophthalmic Solution, 0.7%	4	AL-24956	0.200	0.546
			AL-38189	0.135	0.0598
			AL-4943	15.1	37.4

AL-4943 (Olopatadine) and its Metabolites, AL-24956 (M1) and AL-38189 (M3)
[a] Based on an average drop size of 52.6 µL [b] Based on an average drop size of 49.1 µL

Olopatadine Nonclinical Studies Submitted to Previous Olopatadine Applications

Type of Study	Duration of Dosing	Route of Admin	Species
Single Dose	Single dose	Oral, IV, Topical Ocular	Mouse, Rat, Rabbit, Dog
Repeat Dose	4-, 13-, 52-week	Oral	Rat, Dog
	4-week, 1-, 3-, 6-mon	Topical Ocular	Rabbit, Monkey
Genotoxicity	Ames, Chrom. Ab.	*In vitro*	*In vitro*
	Micronucleus	Oral	Mouse
Carcinogenicity	78-, 104-week	Oral/Diet	Mouse, Rat
Reproductive and Developmental	Seg I	Oral	Rat
	Seg II	Oral	Rat, Rabbit
	Seg III	Oral	Rat
Local Tolerance	1 day	Topical Ocular	Rabbit
Sensitization	Intradermal injection / topical challenges		Guinea Pig
Antigenicity	Oral/IP, Oral/IM		Mouse, Guinea Pig
Impurities	1 day	Topical Ocular	Rabbit
Degradation Products	Ames, Mouse Lymphoma, SHE cell, Micronucleus, 28-day SC, 26-week SC, 1-month Topical Ocular, 1-day Oral		*In vitro*, Mouse, Rabbit

Reviewer's Comments:
Oral doses of 1 mg/kg/day of Olopatadine in rats have resulted in plasma CMAX levels ranging from 208-339 ng/mL and plasma AUC of 431-1437 ng.hr/mL. The CMAX and AUC levels have been shown to be dose proportional for oral doses between 1mg/kg and 25 mg/kg. Plasma levels for doses above 25 mg/kg have not been reported in the application and do not appear to have been measured.

The CMAX levels noted above, following oral dosing of 1 mg/kg/day in rats, are 145-230 times the CMAX level seen in humans following a topical ophthalmic dose to humans. A 1 mg/kg oral Olopatadine dose in rats resulted in an AUC level that was 50-160 times the level seen following a human ophthalmic dose. Subjects in the human study averaged 70.6 kg and had an average body service 1.8 meter squared. If

calculated on a mg/kg basis, with a drop size of 0.04 mL, the ratio is approximately 125 (1 mg/kg/day divided by 0.008mg/kg/day). If calculated on a mg/m^2 basis, the ratio is approximately 19.5 (6 mg/m^2 divided by 0.308 mg/m^2).

Review Strategy
All submitted studies were adequate and well controlled studies. The cross-over study provided information on the "acceptability" of the product but was not designed to demonstrate efficacy. The two conjunctival antigen challenge (CAC) studies provided data to support the initial efficacy of the drug product and the duration of its action. The six week safety study provided safety information in subjects who may use the product in the future.

Discussion of Individual Studies/Clinical Trials
The efficacy studies, C-10-126 and C-12-053, were multicentre, randomized, double-masked, vehicle controlled, parallel-group studies and used the CAC model. The CAC design has been used to support the majority of drug products approved for the treatment of ocular itching. The study design is shown on the table below and includes a study visit in which patients with an allergic history are conjunctively challenged in both eyes with progressively higher doses of antigen until they demonstrate a ≥2+ itching and redness reaction. These patients return for a second visit in which the dose which elicited a ≥2+ reaction is administered and only patients who demonstrate a reproducible ≥2+ reaction continue in the study. Patients return for a third visit, during which the test drug product is administered to both eyes and after 24 hours, the antigen which reproducibly elicited a ≥2+ reaction is again administered. The patient's itching reactions are recorded at 3, 5 and 7 minutes after antigen administration, the patient's redness reactions are recorded 7, 15 and 20 minutes after antigen administration. The patient's fourth visit is a repeat of the third visit except that the time after test product administration is reduced to 16 hours. The patient's fifth visit is a repeat of the third visit, except that the time after test product administration is reduced to27 minutes.

The study designs were similar for both studies with the exception that C-12-053 did not include the 16 hour duration efficacy evaluation visit and had an additional active comparator, PATANOL. Both studies evaluated the same efficacy endpoints (itching and redness) for the onset of action and the 24 hours duration of action. Study C-10-126 included PATADAY (Olopatadine hydrochloride ophthalmic solution) 0.2% and Vehicle as comparators; Study C-12-053 included PATADAY, PATANOL (Olopatadine hydrochloride ophthalmic solution) 0.2% and Vehicle as comparators. The randomization ratio in C-10-126 was 1:1:1 and in C-12-053, it was 2:2:2:1 (Olopatadine HCl Solution, 0.7%: PATADAY: PATANOL: Vehicle).

In past CAC Studies, differences of 0.9-1 unit between test product and vehicle observed in the majority of time points (two out of three in the case of these studies) has been considered clinically significant.

The safety information for this application is primarily derived from Study C-12-028, a 6 week, multicenter, randomized, double-masked, vehicle-controlled, parallel-group study. Subjects at risk for developing allergic conjunctivitis, at least 2 years of age or older with asymptomatic eyes at the time of study entry were randomized in a 2:1 ratio to, Olopatadine HCl Solution, 0.7% or vehicle respectively. Subjects younger than 6 years of age were randomized from 1 randomization schedule; subjects 6 years of age or older were randomized from another randomization schedule. Safety variables and assessments included best-corrected visual acuity, slit-lamp, intraocular pressure (IOP), dilated fundus evaluations, pulse, blood pressure, and adverse events.

Review of Safety

Methods

Studies/Clinical Trials Used to Evaluate Safety Study 12-028 was a 6 week, multicenter, randomized, double-masked, vehicle-controlled, parallel-group study evaluating the safety of Olopatadine HCl Solution, 0.7% compared to Vehicle when administered once daily in both eyes for 6 weeks. Subjects were randomized 2:1, Olopatadine HCl Solution, 0.7%: Vehicle. Subjects younger than 6 years of age were randomized from one randomization schedule; subjects 6 years of age or older were randomized from another randomization schedule. All randomized subjects received 1 drop of either Olopatadine HCl Solution, 0.7% or Vehicle in both eyes for 6 weeks. Subjects were contacted by telephone 1 week after the last dose of study medication to assess changes in concomitant medications and report adverse events. Safety variables and assessments included best-corrected visual acuity, slit-lamp, intraocular pressure (IOP), dilated fundus evaluations, pulse, blood pressure, and adverse events. At the Baseline Visit (Day 0) and at each subsequent office visit (Week 1, Week 3, Week 6), best-corrected visual acuity was measured and slit-lamp evaluations were performed for the eyelids, conjunctiva, cornea, iris/anterior chamber, and lens. At the Baseline Visit (Day 0) and at the last office visit (Week 6), IOP was measured, a dilated fundus examination (DFE) of the vitreous, retina/macula/choroid, and optic nerve was performed, and vital signs (pulse and blood pressure) were taken. At each office visit and during telephone contacts at Weeks 2, 4, and 5, adverse events and dosing compliance were recorded and concomitant medications updated. The Exit Visit occurred via telephone contact at Week 7. Adverse events were recorded and concomitant medications updated.

Schedule of Safety-Related Parameter Measurements

Study Activity	Visit 1 Baseline	Visit 2 Week 1	TC Week 2	Visit 3 Week 3	TC Week 4	TC Week 5	Visit 4 Week 6	TC/Exit Visit Week 7
Day Number	Day 0	Day 7 ±3 Days	Day 14 ±3 Days	Day 21 ±3 Days	Day 28 ±3 Days	Day 35 ±3 Days	Day 42 ±3 Days	Day 49 ±3 Days
Visual acuity	X	X		X			X	
Ocular signs	X	X		X			X	
Intraocular pressure	X						X	
Fundus examination	X						X	
Vital signs	X						X	

TC = telephone contact

7.1.2 Categorization of Adverse Events

Study 12-028	Olopatadine 0.7%		Vehicle	
Adverse Events	N=330		N=169	
Deaths	0		0	
Discontinue due to Adverse Event	0		2	1.2%
Vision blurred	16	4.8%	7	4.1%
Dry eye	11	3.3%	5	3%
Corneal Staining	8	2.4%	7	4.1%
Dysgeusia	8	2.4%	0	
Abnormal sensation in eye	7	2.1%	7	4.1%
Nasopharyngitis	6	1.8%	3	1.8%
Upper respiratory tract infection	6	1.8%	3	1.8%
Conjunctival staining	6	1.8%	1	0.6%
Eye puritus	5	1.5%	2	1.2%
Headache	5	1.5%	3	1.8%
Eye irritation	1	0.3%	5	3%
Ligament sprain	1	0.3%	2	1.2%
Cough	1	0.3%	2	1.2%
Conjunctival hemorrhage	0		2	1.2%
Diarrhea	0		2	1.2%
Gastroenteritis viral	0		2	1.2%

Adequacy of Safety Assessments

Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations
The safety study includes a six week duration of use which is typical of an allergy season. The subjects were individuals at risk for developing allergic conjunctivitis. The population was an appropriate population to monitor for the potential to develop an adverse reaction.

5.2 Pharmacokinetics Properties

Pharmacokinetics

Systemic bioavailability data upon topical ocular administration of solution are not available. Following topical ocular administration of Olopatadine 0.2% ophthalmic solution in man, Olopatadine was shown to have a low systemic exposure. Two studies in normal volunteers (totalling 24 subjects) dosed bilaterally with Olopatadine 0.2% 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. The elimination half-life in plasma following oral dosing was 8 to 12 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.

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 0.2% 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. The half-life in plasma was approximately 3 hours (8-12), 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.

Results from an environmental study demonstrated that Olopatadine hydrochloride ophthalmic solution 0.2% was effective in the treatment of the signs and symptoms of allergic conjunctivitis when dosed twice daily for up to 6 weeks. Results from conjunctival antigen challenge studies demonstrated that Olopatadine hydrochloride ophthalmic solution 0.2%, when subjects were challenged with antigen both initially and up to 8 hours after dosing, was significantly more effective than its vehicle in preventing ocular itching associated with allergic conjunctivitis.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Olopatadine administered orally was not carcinogenic in mice and rats in doses up to 500 mg/kg/day and 200 mg/kg/day, respectively. Based on a 40 μL drop size and a 50 kg person, these doses were approximately 150,000 and 50,000 times higher than the maximum recommended ocular human dose (MROHD). No mutagenic potential was observed when Olopatadine was tested in an in vitro bacterial reverse mutation (Ames) test, an in vitro mammalian chromosome aberration assay or an in vivo mouse micronucleus test. Olopatadine administered to male and female rats at oral doses of approximately 100,000 times MROHD level resulted in a slight decrease in the fertility index and reduced implantation rate; no effects on reproductive function were observed at doses of approximately 15,000 times the MROHD level.

5.3 Preclinical safety data

CLINICAL PHARMACOLOGY

Clinical Studies
Results from clinical studies of up to 12 weeks duration demonstrate that Olopatadine HCL solution when dosed once a day is effective in the treatment of ocular itching associated with allergic conjunctivitis.

Olopatadine hydrochloride ophthalmic solution 0.2% is supplied in a white, oval, low density polyethylene DROP-TAINER dispenser 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.

Concomitant Use of Contact Lenses Patients should be advised not to wear a contact lens if their eyes are red. Patients should be advised that OLOPATADINE HCL solution should not be used to treat contact lens-related irritation. Patients should also be advised to remove contact lenses prior to instillation of OLOPATADINE HCL solution. The preservative in OLOPATADINE HCL solution Benzalkonium chloride may be absorbed by soft contact lenses. Lenses may be reinserted following administration of OLOPATADINE HCL solution.

Pharmacokinetics and safety of Olopatadine hydrochloride 0.2% in healthy subjects with asymptomatic eyes: data from 2 independent clinical studies

Abstract

Introduction

Ocular allergy includes a spectrum of disorders, such as seasonal allergic conjunctivitis, perennial allergic conjunctivitis, vernal keratoconjunctivitis, and atopic keratoconjunctivitis.1 Seasonal and perennial allergic conjunctivitis, collectively known as allergic conjunctivitis, are the most common forms of ocular allergy, caused by immunoglobulin E-mediated reaction to allergens. The overall prevalence of ocular allergy is reported to be ~15%–25% in the USA. Although not life threatening, symptoms of allergic conjunctivitis, such as ocular itching, redness, eyelid swelling, chemosis, and tearing, significantly impact quality of life, particularly in the pediatric population. Therefore, multiple pathways need to be targeted to effectively alleviate these symptoms.

Unlike other topical ocular medications available for the management of allergic conjunctivitis, Olopatadine hydrochloride (HCl) ophthalmic solution acts through multiple pathways. Olopatadine is a selective antagonist of histamine H1 receptors as well as a mast cell stabilizer and prevents histamine-induced inflammatory cytokine production by conjunctival epithelial cells. In several clinical studies, Olopatadine has consistently been shown to be well tolerated and an effective medication for the treatment of allergic conjunctivitis. Olopatadine 0.2% and 0.2% are approved for the management of ocular itching associated with allergic conjunctivitis in >100 countries, including the USA and Canada, as twice-daily and once-daily treatments, respectively.

Because of limited aqueous solubility of Olopatadine HCl at neutral pH, a new ophthalmic formulation containing Olopatadine HCl at an increased concentration of 0.77% (7.76 mg/mL, which is equivalent to 0.7% [7 mg/mL] Olopatadine as free base) was developed to allow Olopatadine HCl to remain dissolved in a stable solution. In a preclinical study, Olopatadine was observed at higher concentrations with

prolonged presence in the target tissue (rabbit conjunctiva) following dosing with Olopatadine 0.77% compared to that with Olopatadine 0.2%. The new Olopatadine 0.77% formulation has demonstrated a longer, 24-hour duration of action and superior efficacy compared to Olopatadine 0.2% formulation in Phase III clinical studies. This new formulation of Olopatadine 0.77% (marketed as PAZEO® by Alcon Research Ltd.) was approved by the US Food and Drug Administration (FDA) in 2015 as once-daily product for the treatment of ocular itching associated with allergic conjunctivitis. The ocular safety profile of different Olopatadine formulations is well documented, including the 0.77% formulation; however, long-term ocular safety data of Olopatadine 0.77% in human subjects and more importantly in the pediatric subjects, who are more prone to allergic conjunctivitis, are lacking.

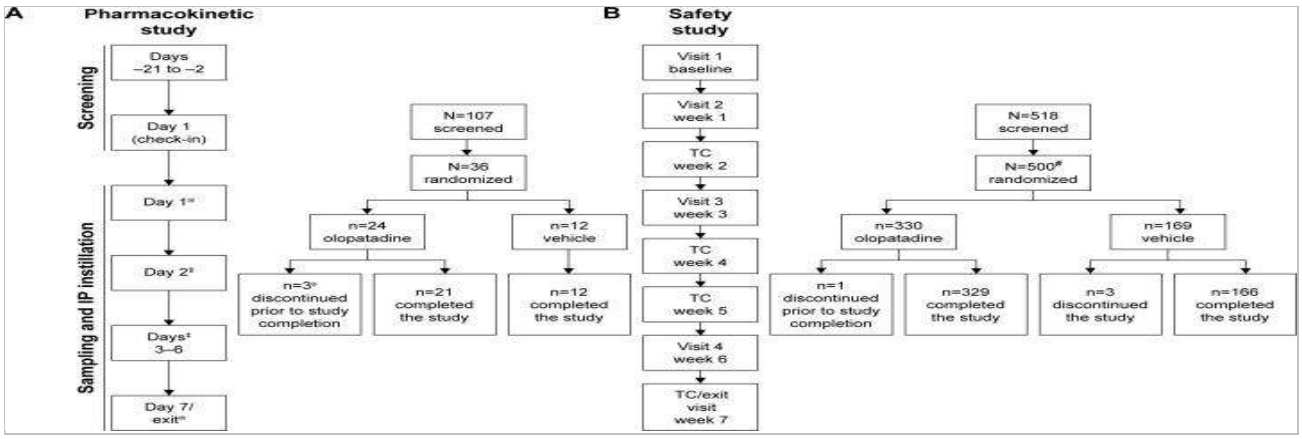
Here, we describe the results from both a Phase I pharmacokinetic study and a Phase III safety study, which included subjects as young as 2 years of age.

Materials and methods

Study design

The pharmacokinetic study was a Phase I, single-center, randomized, double-masked, vehicle-controlled, parallel-group, multiple-dose study (Figure 1). The study was conducted at West Coast Clinical Trials (Cypress, CA, USA) and was approved by the Integ Review Ethical Review Board, Austin, TX, USA. Subjects received 1 drop of Olopatadine 0.77% or vehicle once daily in the morning for 7 days. Pre-dose blood samples were collected 30 minutes before dosing. A ±5-minute margin from the dosing time established on Day 1 was allowed for dose administration. Post-dose blood samples were collected at pre-specified time points and analysed for the pre-defined pharmacokinetic parameters (Figure 1).

Figure 1



The safety study (NCT01698814) was a Phase III, 6-week, multicenter (15 investigational sites in the USA that included eye care clinics and research centers), randomized, double-masked, vehicle-controlled, parallel-group study conducted in subjects 2 years of age and older with asymptomatic eyes (Figure 1). The study was approved by the Chesapeake Institutional Review Board, Columbia, MD, USA. Subjects received 1 drop of Olopatadine 0.77% or vehicle in each eye once daily in the morning throughout the study.

In both studies, the subjects were randomized 2:1 to receive Olopatadine 0.77% or vehicle. Both studies were conducted in the USA and complied with the Declaration of Helsinki 2013 and Good Clinical Practice E6 (R1) guidelines. All subjects or their parents/legal guardians (for subjects <18 years of age) provided written informed consent before entering the study.

Subjects

The Phase I pharmacokinetic study included adult subjects, at least 50% of whom were to be of Japanese ethnicity (participants of Japanese ethnicity within the third generation as proven by passport, birth certificate, or family tree) who were aged 18–65 years at the time of screening, were in good health, and agreed to comply with the study visits and dosing requirement as per study protocol. Subjects with any medical condition that may have precluded safe participation or may have affected results of the study were not enrolled. Other key exclusion criteria were history of allergy or hypersensitivity to any component of the test articles; use of any prescription or non-prescription systemic or topical medications; use of vitamins or dietary supplements within 14 days before the Day 1 visit or any prescribed drugs for psychiatric disorders within 4 months of the Day 1 visit; Fridericia-corrected QT interval >430 and >450 ms for male and female subjects, respectively, or any other significant electrocardiogram abnormality at screening visit; history of HIV, hepatitis B, or hepatitis C infection or active hepatitis A infection; values of vital signs outside of protocol-defined ranges; clinical laboratory and liver function test results at screening outside of protocol-defined ranges; systemic immunotherapy within 90 days before the Day 1 visit; body mass index <18.5 or ≥30 kg/m^2; best-corrected visual acuity (BCVA) score <55 early treatment diabetic retinopathy study (ETDRS) letters; current or history of glaucoma, ocular hypertension, or intraocular pressure (IOP) <8 or >21 mmHg at Day 1 visit; current or history of chronic or recurrent severe inflammatory eye disease; current or history of severe dry eye condition in either eye; history or evidence of punctal or nasolacrimal duct stenosis or occlusion; punctal plugs in either eye; ongoing or history of clinically relevant or progressive retinal disease (eg, retinal degeneration, diabetic retinopathy, or retinal detachment) in either eye; history of ocular trauma; intraocular or laser surgery in either eye within 6 months prior to the Day 1 visit as determined by subject history and/or examination; and female subjects who were pregnant, who had a positive pregnancy test, or who were planning pregnancy during the trial period.

The Phase III safety study included subjects with asymptomatic eyes, aged ≥2 years, with BCVA ≥55 ETDRS letters at baseline (for subjects <10 years of age, a best attempt at visual acuity was made using an age appropriate measurement method in accordance with the American Academy of Pediatrics Vision Screening Guidelines), who could avoid the use of contact lens during each study visit, with no evidence of either contact lens care solution-related ocular surface damage or giant papillary conjunctivitis, and who were able and willing to comply with study protocol and follow protocol instructions. Females of child-bearing potential, who were not pregnant (negative urine pregnancy test), and were willing to adopt adequate birth control methods for the duration of the study were also eligible. Subjects with any medical condition that may have precluded safe participation or may have affected the results of the study were not enrolled. Other key exclusion criteria were any ocular infection in either eye or history of ocular infection within 30 days prior to Visit 1; use of systemic medications within 30 days prior to Visit 1; current or with history of glaucoma, ocular hypertension, or IOP <5 or >21 mmHg at Visit 1; history of retinal detachment, diabetic retinopathy, or progressive retinal disease; presence of blepharitis, active rosacea affecting the ocular adnexa, meibomian gland dysfunction, follicular conjunctivitis, IOP, or any other ophthalmic abnormality that may affect the study outcomes; corneal conditions affecting the corneal structure; history or evidence of any ocular surgical procedure within 1 year prior to Visit 1; prior (within 5 days prior to Visit 1), current, or anticipated use of ophthalmic agents other than investigational product during study participation; and known contraindications, hypersensitivities to any of the study medications, or their components.

Objectives

Primary objective of the pharmacokinetic study was to assess the pharmacokinetics and safety of single and multiple doses of Olopatadine 0.77% compared with vehicle, when administered once daily in both eyes for 7 days.

Primary objective of the safety study was to evaluate the ocular safety of Olopatadine 0.77% compared with vehicle, when administered once daily in both eyes for up to 6 weeks.

Assessments

In the pharmacokinetic study, plasma concentrations of Olopatadine and its metabolites, *N*-desmethyl Olopatadine and *N*-oxide Olopatadine , were assessed on Day 1 (following the first [single] dose) and Day 7 (after multiple doses) at 0 hour before dosing and at 0.25, 0.5, 1, 2, 4, 8, and 12 hours post-dose; on Day 2 at 0 hour (24 hours after the first drop-trough sample and prior to dosing); and trough sample on Day 3 through Day 6 at 0 hour. Plasma concentrations of Olopatadine and its metabolites were determined using validated high-performance liquid chromatography coupled with tandem mass spectrometry methods at Tandem Labs, Salt Lake City, UT, USA. Analytical methods were fully validated with respect to accuracy, precision, and sample stability consistent with the sample collection and storage procedures.

The single- and multiple-dose pharmacokinetic parameters estimated included peak plasma concentration (C_{max}), time to reach maximum plasma concentration (T_{max}), area under the plasma concentration–time curve (AUC) from 0 to 12 hours ($AUC_{0–12}$), AUC from 0 to the last quantifiable concentration at time t ($AUC_{0–t}$), and elimination half-life ($t_{1/2}$) and the elimination rate constant (Kel). In addition, trough (24-hour pre-dose) samples were also obtained from Day 2 to Day 6. In the absence of pharmacokinetic plasma sampling beyond 12 hours after last dosing, $AUC_{0–12}$ was used for assessing any accumulation following repeated daily dosing instead of $AUC_{0–24}$. AUC time curve and half-life ($t_{1/2}$) were estimated using non-compartmental analysis (NCA) methods.

In the safety study, the following safety variables were assessed: adverse events (AEs) and serious adverse events (SAEs) at baseline and Weeks 1–7 or at the Early Exit visit, BCVA and ocular signs (eyelids, conjunctiva, cornea, iris, anterior chamber, and lens) at baseline and Weeks 1, 3, and 6 or at the Early Exit visit, and IOP, fundus examination (optic nerve, peripheral retina, vitreous, choroid, and macula), and vital signs (blood pressure and pulse) at baseline and Week 6 or at the Early Exit visit. The safety analysis also included an evaluation of both AEs and other safety-related parameters according to age. For all AEs, an assessment of the causality (related or not related to study treatment) was determined by the investigator.

Statistical analyses

In the pharmacokinetic study, all subjects who received the test article, satisfied protocol criteria, and had ≥1 post-dose blood draw were considered evaluable for the pharmacokinetic analysis. Subjects with inadequate pharmacokinetic data, any collection, or analytical deviations that would have affected integrity of the data were excluded from pharmacokinetic analysis. Descriptive statistics were used to summarize the pharmacokinetics of Olopatadine 0.77% after single and multiple doses. Non-compartmental descriptive pharmacokinetic methods and compartmental modeling methods were used for the pharmacokinetic analyses. AUC and $t_{1/2}$ were estimated using NCA methods.

In the safety study, safety analysis set included all subjects who received the study treatment. Safety results were summarized descriptively. No formal statistical hypothesis testing was planned or conducted.

Results

Baseline characteristics and subject demographics

In the pharmacokinetic study, a total of 36 healthy subjects were randomized to receive either Olopatadine 0.77% (n=24) or vehicle (n=12). All 24 subjects (12 Japanese and 12 non-Japanese) who received Olopatadine 0.77% were included in the pharmacokinetic data, and all 36 subjects who received either Olopatadine 0.77% or vehicle were included in the safety data. The rationale for recruiting at least 50% Japanese subjects to this study was that the same population has been previously evaluated for the pharmacokinetics parameters following oral administration of Olopatadine. Overall, 21 (87.5%) subjects in the Olopatadine 0.77% group and 12 (100%) subjects in the vehicle group completed the study. Three

(8.3%) subjects discontinued study in the Olopatadine 0.77% group due to consent withdrawal (Figure 1). Overall, the baseline demographic characteristics were comparable between the treatment groups (Table 1). Majority of the subjects in both treatment groups were of Asian ethnicity (≥50%).

Table 1
Baseline characteristics and subject demographics

Characteristics	**Pharmacokinetic study* (N=36)**		**Safety study** (N=499)**	
	Olopatadine 0.77% (n=24)	**Vehicle (n=12)**	**Olopatadine 0.77% (n=330)**	**Vehicle (n=169)**
Age (years)				
Mean (SD)	42.0 (11.7)	42.8 (12.9)	32.4 (17.1)	31.5 (15.7)
2–17, n (%)	0	0	51 (15.5)	24 (14.2)
≥18, n (%)	24 (100.0)	12 (100.0)	279 (84.5)	145 (85.8)
Sex, n (%)				
Female	10 (41.7)	7 (58.3)	214 (64.8)	111 (65.7)
Male	14 (58.3)	5 (41.7)	116 (35.2)	58 (34.3)
Race, n (%)				
Asian	14 (58.3)	6 (50.0)	12 (3.6)	4 (2.4)
Black or African American	2 (8.3)	1 (8.3)	20 (6.1)	17 (10.1)
White	7 (29.2)	5 (41.7)	289 (87.6)	140 (82.8)
Multi-racial	1 (4.2)	0	4 (1.2)	3 (1.8)
Others#	0	0	5 (1.5)	5 (3.0)
Iris color, n (%)				
Blue	1 (4.2)	0	86 (26.1)	29 (17.2)
Brown	21 (87.5)	11 (91.7)	169 (51.2)	93 (55.0)
Green	1 (4.2)	0	26 (7.9)	18 (10.7)
Hazel	1 (4.2)	1 (8.3)	45 (13.6)	29 (17.2)
Gray	0	0	4 (1.2)	0
Contact lens use, n	NA	NA	51 (15.5)	24 (14.2)

Characteristics	Pharmacokinetic study* (N=36)		Safety study** (N=499)	
	Olopatadine 0.77% (n=24)	Vehicle (n=12)	Olopatadine 0.77% (n=330)	Vehicle (n=169)

(%)

In the safety study, of the 500 subjects randomized, 499 (Olopatadine 0.77%, n=330; vehicle, n=169) were included in the safety data. One subject in the Olopatadine 0.77% group was erroneously randomized and hence not included in the safety data set. Overall, 329 (99.7%) subjects in the Olopatadine 0.77% group and 166 (98.2%) in the vehicle group completed the study (Figure 1). Two (1.8%) subjects discontinued the study due to non-SAEs not related to the treatment in the vehicle group, with no discontinuations in the Olopatadine 0.77% group.

Overall, the demographic characteristics were comparable between treatment groups (Table 1). In the Olopatadine 0.77% and vehicle groups, 51 (15.5%) and 24 (14.2%) subjects, respectively, were aged between 2 and 17 years. The proportions of subjects using contact lenses were 15.5% and 14.2% in the Olopatadine 0.77% and vehicle groups, respectively.

Single- and multiple-dose systemic pharmacokinetics of Olopatadine

Olopatadine was absorbed slowly and reached a C_{max} in 2 hours following bilateral topical administration of Olopatadine 0.77% (Table 2). The Day 1 (single-dose) and Day 7 (multiple-dose) mean Olopatadine plasma concentration vs time profile is shown in Figure 2A. After reaching peak plasma concentrations, the single- and multiple-dose Olopatadine showed mono-exponential decay with similar mean $t_{1/2}$ (Figure 2A; Table 2). The single- and multiple-dose individual and mean $AUC_{0–12}$ are given in Figure 2B and Table 2.

Figure 2

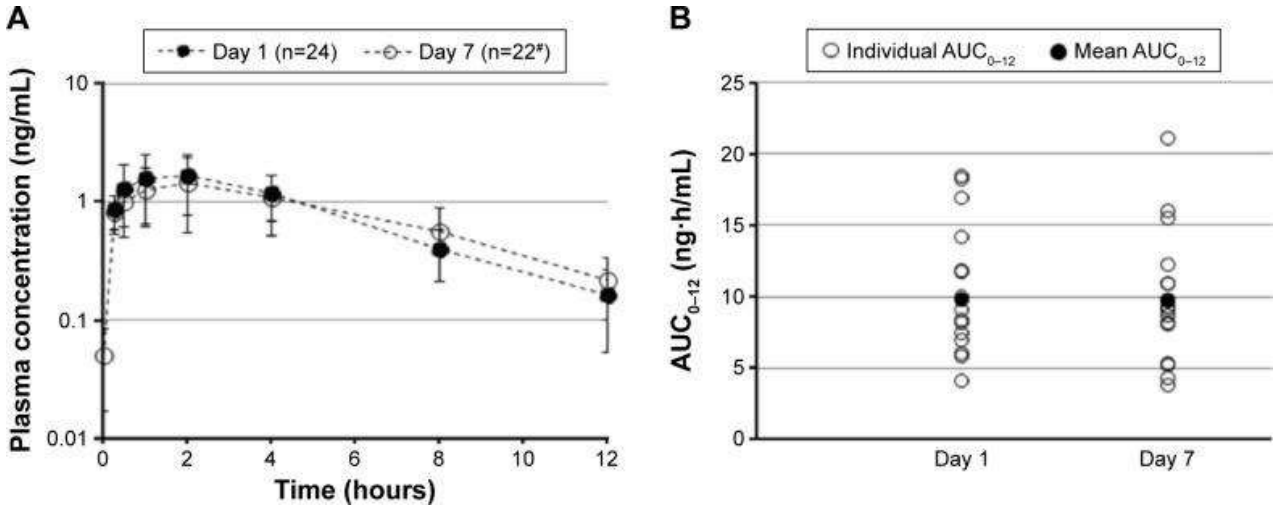


Table 2

Pharmacokinetic parameters following single- and multiple-dose exposures of Olopatadine 0.77% (pharmacokinetics population)

Pharmacokinetic parameters	Single dose (Day 1) (n=24)	Multiple dose (Day 7) (n=22)
C_{max}, ng/mL* (range)	1.65 (0.62–4.12)	1.45 (0.61–4.50)
T_{max}, h** (range)	2.00 (0.25–4.02)	2.00 (0.25–8.00)
$AUC_{0–12}$, ng·h/mL* (range)	9.04 (4.05–18.40)	8.78 (3.72–21.20)
$t_{1/2}$, h# (range)	2.90 (2.05–5.78)	3.40 (2.13–7.77)

Notes:

*C_{max} and $AUC_{0–12}$ expressed as geometric means,
**T_{max} expressed as median,
#$t_{1/2}$ expressed as arithmetic mean. $AUC_{0–12}$, area under the plasma concentration–time curve from 0 to 12 hours; C_{max}, peak plasma concentration; T_{max}, time to reach maximum plasma concentration; $t_{1/2}$, elimination half-life.

No accumulation in Olopatadine exposure (C_{max} and $AUC_{0–12}$) was evident at Day 7 compared to Day 1 (Table 2). In addition, the maximum trough plasma concentration of Olopatadine observed over the duration of treatment ranged from 0.108 to 0.247 ng/mL (individual data points not given).

The Day 1 and Day 7 pharmacokinetic parameters were comparable between the Japanese and non-Japanese subjects (Table S1). However, the Day 1 systemic Olopatadine 0.77% exposure was marginally higher in the non-Japanese (C_{max}, 2.07 ng/mL; $AUC_{0–12}$, 10.55 ng·h/mL) than that in the Japanese subjects (C_{max}, 1.75 ng/mL; $AUC_{0–12}$, 9.25 ng·h/mL).

Single- and multiple-dose pharmacokinetics of Olopatadine metabolites
N-desmethyl Olopatadine, the minor active metabolite of Olopatadine, was non-quantifiable (≤0.050 ng/mL) in the plasma samples collected from all the subjects. *N*-oxide Olopatadine metabolite was observable up to 4 hours in 6 of 24 subjects who received Olopatadine 0.77% on Day 1 and in 1 subject on Day 7. C_{max} of *N*-oxide Olopatadine observed on Day 1 and Day 7 was 0.121 and 0.174 ng/mL, respectively.
Safety data from the Phase I pharmacokinetic study
No descriptive safety data from this study have been presented here due to small sample size. In brief, no deaths or SAEs were reported during the study, and no subject discontinued the study due to an AE. No subject in the Olopatadine 0.77% group reported a treatment-related AE, whereas only 1 subject in the vehicle group reported treatment-related AE (eye irritation).

Phase III safety study
Treatment-emergent adverse events (TEAEs)
Overall incidence of TEAEs was comparable between the treatment groups (Table 3). In total, 88 (26.7%) subjects from the Olopatadine 0.77% group and 53 (31.4%) subjects from the vehicle group reported ≥1% TEAE (Table 3). Among the ocular TEAEs reported in the safety population, blurred vision was the most frequent (n=16; 4.8%) followed by dry eye (n=11; 3.3%) in the Olopatadine 0.77% group, whereas blurred vision, corneal staining, and abnormal sensation in eye were the most frequent ocular TEAEs (n=7; 4.1% each) reported in the vehicle group. Among the non-ocular TEAEs, dysgeusia was only reported in the Olopatadine 0.77% group (n=8) and had the highest incidence rate (2.4%), whereas

headache, upper respiratory tract infection, and nasopharyngitis had the highest incidence rates (1.8% each) in the vehicle group.

Table 3

Summary of TEAEs regardless of study drug relationship by treatment (safety population)

AEs (MedDRA PT), n (%)	**Olopatadine 0.77% (n=330)**	**Vehicle (n=169)**
At least 1 TEAE, total	88 (26.7)	53 (31.4)
Most frequent TEAEs, ≥1%		
Ocular AEs		
Vision blurred	16 (4.8)	7 (4.1)
Dry eye	11 (3.3)	5 (3.0)
Abnormal sensation in the eye	7 (2.1)	7 (4.1)
Corneal staining*	8 (2.4)	7 (4.1)
Conjunctival staining*	6 (1.8)	1 (0.6)
Eye pruritus	5 (1.5)	2 (1.2)
Eye irritation	1 (0.3)	5 (3.0)
Conjunctival hemorrhage	0	2 (1.2)
Non-ocular AEs		
Diarrhea	0	2 (1.2)
Headache	5 (1.5)	3 (1.8)
Dysgeusia	8 (2.4)	0
Upper respiratory tract infection	6 (1.8)	3 (1.8)
Nasopharyngitis	6 (1.8)	3 (1.8)
Gastroenteritis viral	0	2 (1.2)
Ligament sprain	1 (0.3)	2 (1.2)
Cough	1 (0.3)	2 (1.2)

TEAEs with an incidence of ≥1% in the age groups are summarized in Table 4. Overall, the incidences of ocular TEAEs were lower in the 2–17 age group compared to the ≥18 age group in both treatment groups (Table 4). The most frequent ocular TEAEs reported in the 2–17 age group were abnormal sensation in

eye and conjunctival staining (3.9% each) in the Olopatadine 0.77% group and conjunctival staining, chalazion, and eye irritation (4.2% each) in the vehicle group. Among the non-ocular TEAEs reported in the 2–17 age group, upper respiratory tract infection (5.8%) and pyrexia (3.9%) were most common with Olopatadine 0.77% and with vehicle, pyrexia and sinus congestion (4.2% each). In the ≥18 age group, blurred vision was the most frequent ocular TEAE (5.7%) with Olopatadine 0.77%, whereas blurred vision, abnormal sensation in eye, and corneal staining were equally frequent in the vehicle group (4.8% each). No subject exposed to Olopatadine 0.77% discontinued the study due to an AE, whereas 2 (1.2%) subjects in the vehicle group discontinued due to AEs not related to treatment. No deaths or other SAEs were reported during the study.

Table 4

Summary of TEAEs in the selected age subgroups occurring at an incidence of ≥1% by treatment

AEs (MedDRA PT), n (%)	**Olopatadine 0.77% (n=330)**		**Vehicle (n=169)**	
	2–17 years (n=51)	**≥18 years (n=279)**	**2–17 years (n=24)**	**≥18 years (n=145)**
Ocular AEs				
Vision blurred	0	16 (5.7)	0	7 (4.8)
Dry eye	0	11 (3.9)	0	5 (3.4)
Abnormal sensation in the eye	2 (3.9)	5 (1.8)	0	7 (4.8)
Corneal staining*	1 (2.0)	7 (2.6)	0	7 (4.8)
Conjunctival staining*	2 (3.9)	4 (1.5)	1 (4.2)	0
Eye pruritus	1 (2.0)	4 (1.4)	0	2 (1.4)
Eye pain	0	3 (1.1)	0	0
Eye irritation	0	1 (0.3)	1 (4.2)	4 (2.7)
Chalazion	0	0	1 (4.2)	0
Ocular hyperemia	0	3 (1.1)	0	1 (0.7)
Conjunctival hemorrhage	0	0	0	2 (1.4)
Non-ocular AEs				
Headache	1 (2.0)	4 (1.4)	0	3 (2.1)
Diarrhea	0	0	0	2 (1.4)
Nausea	1 (2.0)	0	0	1 (0.7)

AEs (MedDRA PT), n (%)	Olopatadine 0.77% (n=330)		Vehicle (n=169)	
	2–17 years (n=51)	≥18 years (n=279)	2–17 years (n=24)	≥18 years (n=145)
Tongue discoloration	1 (2.0)	0	0	0
Vomiting	1 (2.0)	0	0	0
Dysgeusia	0	8 (2.9)	0	0
Upper respiratory tract infection	3 (5.8)	3 (1.1)	0	3 (2.1)
Nasopharyngitis	0	6 (2.2)	0	3 (2.1)
Urinary tract infection	1 (2.0)	2 (0.7)	0	1 (0.7)
Pharyngitis streptococcal	1 (2.0)	0	0	0
Gastroenteritis viral	0	0	0	2 (1.4)
Influenza	1 (2.0)	2 (0.7)	0	1 (0.7)
Pyrexia	2 (3.9)	0	1 (4.2)	0
Sinus congestion	0	2 (0.7)	1 (4.2)	0
Skin discoloration	1 (2.0)	0	0	0
Ligament sprain	0	1 (0.3)	0	2 (1.4)
Ligament injury	0	0	1 (4.2)	0

Treatment-related AEs

Overall incidence of treatment-related AEs was similar between the treatment groups: 16.1% and 18.3% with Olopatadine 0.77% and vehicle, respectively (Table S2). Among the most frequent treatment-related AEs (≥1%), dysgeusia was uniquely reported with Olopatadine 0.77% (n=8; 2.4%). Observed incidence of the most frequent treatment-related AEs in different age subgroups is given in Table S3. In the 2–17 age group, the most frequent ocular treatment-related AEs with Olopatadine 0.77% was conjunctival staining (n=2; 3.9%), whereas with vehicle, conjunctival staining, and eye irritation were observed in 1 subject each (4.2%), as shown in Table S3.

BCVA

During the study, no discernible trend toward BCVA loss was observed in either treatment group (Table 5). Mean change in BCVA from baseline to Day 42 or at the Early Exit visit was −0.5 (±3.5) and 0.3 (±4.2) letters with Olopatadine 0.77% and vehicle, respectively. No concerns were identified with respect to visual acuity change in the individual age subgroups during this study (Table 5). In the 2–17 age group, the mean BCVA change from baseline to Week 6 or at the Early Exit visit was 0.3 (±3.2) and 0.4 (±2.6) letters with Olopatadine 0.77% and vehicle, respectively (Table 5).

Table 5
Summary of safety parameters in the overall safety population and selected age subgroups at Week 6 or at the Early Exit visit by treatment

	Olopatadine 0.77%			**Vehicle**		
	Overall (n=330)	**2–17 years (n=51)**	**≥18 years (n=279)**	**Overall (n=169)**	**2–17 years (n=24)**	**≥18 years (n=145)**
Mean change in BCVA (SD)	−0.5 (3.5)	0.3 (3.2)	−0.7 (3.5)	0.3 (4.2)	0.4 (2.6)	0.3 (4.4)
Slit-lamp findings, abnormal, n (%)						
Eyelids						
Baseline	3 (0.9)	0	3 (1.1)	1 (0.6)	0	1 (0.7)
Week 6	2 (0.6)	0	2 (0.7)	1 (0.6)	0	1 (0.7)
Conjunctiva						
Baseline	4 (1.2)	0	4 (1.4)	0	0	0
Week 6	3 (0.9)	0	3 (1.1)	0	0	0
Cornea						
Baseline	3 (0.9)	0	3 (1.1)	1 (0.6)	0	1 (0.7)
Week 6	1 (0.3)	0	1 (0.4)	1 (0.6)	0	1 (0.7)
Lens						
Baseline	32 (9.7)	0	32 (11.5)	13 (7.7)	0	13 (9.0)
Week 6	32 (9.7)	0	32 (11.5)	13 (7.7)	0	13 (9.0)
Mean change in IOP (SD), mmHg	0.5 (2.3)	−0.1 (2.4)	0.5 (2.3)	−0.2 (2.1)	0.6 (1.2)	−0.2 (2.1)
Dilated fundus parameters, abnormal, n (%)						
Vitreous						
Baseline	0	0	8 (2.9)	3 (1.8)	0	3 (2.1)
Week 6	7 (2.1)	0	7 (2.5)	3 (1.8)	0	3 (2.1)
Peripheral retina						

	Olopatadine 0.77%			Vehicle		
	Overall (n=330)	**2–17 years (n=51)**	**≥18 years (n=279)**	**Overall (n=169)**	**2–17 years (n=24)**	**≥18 years (n=145)**
Baseline	2 (0.6)	0	2 (0.7)	2 (1.2)	0	2 (1.4)
Week 6	2 (0.6)	0	2 (0.7)	1 (0.6)	0	1 (0.7)
Macula						
Baseline	1 (0.3)	0	1 (0.4)	1 (0.6)	0	1 (0.7)
Week 6	1 (0.3)	0	1 (0.4)	0	0	0
Choroid						
Baseline	1 (0.3)	0	1 (0.4)	0	0	0
Week 6	1 (0.3)	0	1 (0.4)	0	0	0
Mean change in vital signs (SD)						
Pulse, bpm	0.7 (9.0)	1.9 (14.2)	0.5 (7.9)	0.4 (8.8)	−3.3 (7.7)	1.0 (8.8)
Systolic BP, mmHg	−0.3 (8.5)	0.6 (6.6)	−0.4 (8.8)	−0.7 (9.4)	0.6 (6.0)	−0.9 (9.8)
Diastolic BP, mmHg	−0.6 (6.7)	1.8 (4.9)	−1.0 (6.8)	−1.2 (7.9)	−1.5 (6.2)	−1.1 (8.2)

Ocular sign

No discernible trend indicating a safety concern in any ocular sign parameter was observed in the overall safety population as well as in the individual age subgroups. In the overall safety population, the number of subjects with abnormal eyelids, conjunctiva, and cornea remained largely similar from baseline to Week 6 or at the Early Exit visit in the Olopatadine 0.77% group as compared to vehicle (eyelids, 0.9% vs 0.6%; conjunctiva, 1.2% vs 0.9%; cornea, 0.9% vs 0.3%; Table 5). No subject in the 2–17 age group experienced abnormal ocular sign parameters in either treatment group (Table 5).

Intraocular pressure

No clinically relevant differences were noted between Olopatadine 0.77% and vehicle for changes in IOP in the overall population as well as in the individual age subgroups. Overall, mean IOP remained similar from baseline to Week 6 or at the Early Exit visit in both treatment groups, with mean changes of 0.5 (±2.3) and −0.2 (±2.1) mmHg in the Olopatadine 0.77% and vehicle groups, respectively (Table 5). In the 2–17 age group, mean change in IOP from baseline to Week 6 or at the Early Exit visit was similar between the Olopatadine 0.77% (−0.1 [±2.4] mmHg) and vehicle (0.6 [±1.2] mmHg) groups (Table 5).

Fundus examination

No subjects experienced a change from normal to abnormal in any dilated fundus parameters from baseline to Week 6 or at the Early Exit visit (Table 5).

Vital signs

Mean change in pulse rate and systolic and diastolic pressures by visit are summarized in Table 5. Mean change from baseline in the vital signs was minimal in both the overall population group and the age subgroups (Table 5).

Discussion

Over the past few decades, ocular allergy, particularly seasonal and perennial allergic conjunctivitis, has shown a trend toward increased prevalence, more importantly in the pediatric population.17–22 the new ophthalmic formulation of Olopatadine at an increased concentration of 0.77% was developed with the aim to increase the aqueous solubility of Olopatadine at neutral pH and to provide better efficacy in the management of ocular allergy compared with the previously approved Olopatadine ophthalmic formulations (0.1% and 0.2%). Superior efficacy of Olopatadine 0.77% over 0.1% and 0.2% formulations was recently shown in Phase III clinical trials.14,15 In a pre-clinical study, Olopatadine 0.77% formulation showed improved solubility and a 4-fold increase in the concentration of Olopatadine in the aqueous humor when compared to Olopatadine 0.2%, with no sign of capacity-limit kinetics.16 Likewise, in the conjunctiva, a slightly greater dose proportional increase in Olopatadine was observed after an ocular dose of Olopatadine 0.77% compared with Olopatadine 0.2%, suggesting potentially longer anti-allergic activity.

In the pharmacokinetic study, following topical ocular administration of Olopatadine 0.77% once daily for 7 days, measurable Olopatadine concentrations were observed at all-time points after single- and multiple-dose exposures in healthy subjects. Olopatadine 0.77% was slowly absorbed in all the subjects analyzed, followed by rapid elimination from the body (single-dose geometric mean $t_{1/2}$, 2.78 hours; multiple-dose geometric mean $t_{1/2}$, 3.26 hours). When compared with the single- and multiple-dose oral exposure of 10 mg Olopatadine , the pharmacokinetic parameters of topical ocular exposure of Olopatadine 0.77% were substantially lower23 (Table S4). The mean single-dose topical ocular C_{max} (1.88 ng/mL) and mean $AUC_{0–12}$ (9.79 ng·h/mL) of Olopatadine 0.77% were ~70- and 43.5-fold lower, respectively (mean C_{max}, 131.10 ng/mL and mean $AUC_{0–12}$, 426.00 ng·h/mL). Similarly, following multiple ocular doses of Olopatadine 0.77%, the mean C_{max} (1.64 ng/mL) and mean $AUC_{0–12}$ (9.68 ng·h/mL) were ~89.5- and 49.5-fold lower than the multiple oral doses of 10 mg Olopatadine, respectively (mean C_{max}, 146.82 ng/mL and mean $AUC_{0–12}$, 479.00 ng·h/mL).23 These data indicate that topical ocular doses of Olopatadine 0.77% have a wide margin of safety since it resulted in low systemic exposure than that of oral doses of 10 mg Olopatadine HCl. No statistically significant difference was observed in the pharmacokinetic parameters between Japanese and non-Japanese subjects. Plasma concentration of the metabolite *N*-desmethyl Olopatadine was non-quantifiable and that of *N*-oxide Olopatadine was low and sparse after topical bilateral dosing of once-daily Olopatadine 0.77%.

Although the new Olopatadine 0.77% ophthalmic formulation was recently shown to be well tolerated in the adult population,14,15 the safety profile of Olopatadine 0.77% with long-term use in adults and safety information in the pediatric population were lacking. This safety study is the first clinical trial to describe the safety of Olopatadine 0.77% with 6 weeks dosing in both the pediatric (2–17 age group) and adult (≥18 age group) populations. The overall types of AEs and their characteristics with Olopatadine 0.77% were comparable with its vehicle in the overall safety population as well as in the age subgroups. Olopatadine, although administered topically, is absorbed systemically as are other topically administered medicinal products, and thus, some systemic/non-ocular side-effects are possible. The commonly reported non-ocular AEs associated with Olopatadine include headache, dysgeusia, nasal dryness, and fatigue that are a known class-effect of antihistamines.24 The incidence of treatment-related non-ocular AEs with Olopatadine 0.77% was low during the 6-week study period. In adults, dysgeusia, which is not an

uncommon association with the instillation of eye drops and does not represent a safety concern, was the only most frequent treatment-related AE (≥1%) uniquely reported in the Olopatadine 0.77% group. The similar incidence of dysgeusia (reported in 2 subjects) and other AEs reported previously following the topical ocular administration of Olopatadine 0.77%14 supports the findings of this study. Other treatment-related non-ocular AEs (≥1.5%–2%) reported in this study, both with Olopatadine and vehicle, were headache, nasopharyngitis, and upper respiratory tract infection. The overall incidence of AEs was comparable with the 0.1% and 0.2% ophthalmic formulations of Olopatadine, albeit at different frequencies.14,15 This further supports that this new Olopatadine ophthalmic formulation with almost 4-fold increased concentration than 0.2% does not raise any new safety concerns. In the 2–17 age group, the only treatment-related AEs reported were corneal staining, conjunctival staining, abnormal sensation in the eyes, and eye pruritus with no incidence of dysgeusia. Except for corneal staining and conjunctival staining, the rates of all other AEs were lower in the 2–17 age group as compared to the ≥18 age group. The AEs of corneal staining and conjunctival staining were reported without baseline measurements since fluorescein staining was not a protocol required procedure and therefore was not conducted at baseline (screening visits) for any subjects. Thus, it is unknown if this finding represents an untoward change relative to a pre-treatment baseline. Overall, these data show that Olopatadine 0.77% was well tolerated in the 2–17 age group with no new safety issues identified, which is consistent with the safety profile of Olopatadine 0.2% ophthalmic formulation in ≥3-year-old subjects.25,26 No discernible trends from baseline or clinically relevant differences were observed during the 6-week study period between the Olopatadine 0.77% and the vehicle groups based on a review of safety parameters that included BCVA ocular sign parameters, IOP, dilated fundus parameters, and vital signs.

Conclusion

Olopatadine 0.77% after topical ocular administration of single and multiple doses has a low systemic exposure with quick clearance. Olopatadine 0.77% was well tolerated with no new safety issues after once-daily topical ocular dosing for 6 weeks in adults and in pediatric subjects as young as 2 years of age. The overall safety profile of Olopatadine 0.77% is consistent with that of Olopatadine 0.1%.

Reference

1. Tsunoo M, Momomura S, Masuo M, Iizuka H. Phase 1 clinical study on KW-4679, an antiallergic drug: safety and pharmacokinetics in the single and repeated administration study in healthy subjects. Kiso to Rinsho. 1995; 29:18.

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Footnotes

Disclosure

Dr Abhijit Narvekar is an employee in Alcon Research Ltd (Fort Worth, TX, USA). The other authors report no conflicts of interest in this work.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

BENZALKONIUM CHLORIDE SOLUTION	NF
EDETATE DISODIUM	NF
SODIUM CHLORIDE	BP/USP/NF
SODIUM DIHYDROGEN PHOSPHATE	BP
ANHYDROUS DISODIUM HYDROGEN PHOSPHATE	BP
SODIUM HYDROXIDE PELLETS	NF
PURIFIED WATER	BP

6.2 Shelf life

24 months

6.3 Special precautions for storage

Store below 30 degrees C.
Do not freeze.
Protect from light.
Keep out of the reach of children.

6.4 Nature and contents of container

The liquid is filled in a multi dose container, and contain Benzalkonium Chloride Solution, Edetate Disodium, Sodium Chloride, Sodium Dihydrogen Phosphate, Anhydrous Disodium Hydrogen Phosphate, and Sodium Hydroxide Pellets for pH adjustment.

6.5 Special precaution for disposal of a used medicinal product or waste materials derived such medicinal product and other handling of the product

No special requirements

7.0 Name and complete address (es) of the Applicant & manufacturer(s) of the FPP

Applicant:

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