SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

OPATANOL®
(olopatadine hydrochloride)

0.1% eye drops, solution

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

Opatanol®

Ophthalmologicals; decongestant and antiallergics; other antiallergics

DESCRIPTION AND COMPOSITION

Pharmaceutical form(s)

Eye drops, solution

Colorless to pale yellow solution

Active substance(s)

1.11 mg of olopatadine hydrochloride in one mL solution (0.1%).

Excipients

Benzalkonium chloride (solution), sodium chloride, dibasic sodium phosphate (anhydrous) or disodium phosphate (dodecahydrate), sodium hydroxide and/or hydrochloric acid, purified water.

Pharmaceutical formulations may vary between countries.

INDICATIONS

Treatment of signs and symptoms of allergic conjunctivitis.

DOSAGE REGIMEN AND ADMINISTRATION

Dosage regimen

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

Special populations

Renal impairment

No studies have been performed in patients with renal impairment. No dosage regimen adjustment is required for patients with renal impairment.

Hepatic impairment

No studies have been performed in patients with hepatic impairment. No dosage regimen adjustment is required for patients with hepatic impairment.

Pediatric patients (below 18 years)

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

Geriatric patients (65 years of age or above)

No dosage regimen adjustment is required in patients 65 years of age or above.

Method of administration

- For topical ocular use only. Not for injection or oral use.
- After the bottle cap is removed, if the tamper evident snap collar is loose, snap collar should be removed before using the product.
- To avoid contamination, the dropper tip should not touch any surface. The dropper tip should also not come into contact with the eye as this may cause injury to the eye.
- When using nasolacrimal occlusion or closing the eyelids for 2 minutes, the systemic absorption is reduced. This may result in a decrease in systemic side effects and an increase in local activity.
- The bottle should be kept tightly closed when not in use.
- If more than one topical ophthalmic medicinal product is being used, the medicinal products must be administered at least 5 minutes apart. Eye ointments should be administered last.
- Patients should be advised not to wear a contact lens if their eye is red.
- Opatanol should not be used to treat contact lens related irritation.

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Special excipients

Opatanol contains benzalkonium chloride which may cause eye irritation and may possibly discolor soft contact lenses. Contact lenses must be removed before administration of Opatanol and reinserted at least 15 minutes later.

ADVERSE DRUG REACTIONS

Tabulated summary of adverse drug reactions from clinical trials

Adverse drug reactions from clinical trials (Table 1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency

category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 1 Adverse drug reactions in clinical trials

System Organ Classification	Frequency	Adverse drug reactions
Nervous system disorders	**Uncommon**	headache
		dysgeusia
	Rare	dizziness
Eye disorders	**Common**	ocular discomfort
	Uncommon	punctate keratitis
		keratitis
		eye pain
		dry eye
		blurred vision
		eyelid oedema
		eye pruritus
		eye discharge
		ocular hyperaemia
	Rare	photophobia
		erythema of eyelid
Respiratory, thoracic and mediastinal disorders	**Uncommon**	nasal dryness
Skin and subcutaneous tissue disorders	**Rare**	contact dermatitis
General disorders and administration site conditions	**Uncommon**	fatigue

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse drug reactions have been derived from post-marketing experience with Opatanol via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Table 2 Adverse drug reactions from spontaneous reports and literature (frequency not known)

System Organ Classification	Adverse drug reactions
Immune system disorders	hypersensitivity
Eye disorders	lacrimation increased
Gastrointestinal disorders	nausea

INTERACTIONS

No clinically relevant interactions have been described.

PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Pregnancy

Risk summary

There is a limited amount of data from the use of olopatadine in pregnant women. Studies in rats and rabbits in which olopatadine was orally administered did not show any embryo fetal toxicity up to 2480-times the maximum recommended ocular human dose (MROHD) (one drop of 0.7 % olopatadine ophthalmic solution in each eye, based on body surface area (BSA)). Reduction in the fetal weight was not observed in rats up to 25 times the MROHD, based on BSA.

No effects during pregnancy are anticipated since systemic exposure to olopatadine is negligible by the topical ocular route. However, the possibility of harm to the fetus cannot be ruled out.

Data

Animal data

In an embryo-fetal development (EFD) study in rats, olopatadine (60, 200 and 600 mg/kg/day) was administered orally throughout the period of organogenesis. Mydriasis, hyperaemia and congestion of the ocular fundus, abnormal respiratory sounds were observed in treated dams at high dose levels and the maternal no-effect dose level was 60 mg/kg/day (corresponding to 746-times the MROHD, based on BSA). In offspring, decrease in body weight of live fetuses and decrease in number of ossification were observed at 600 mg/kg/day (corresponding to 7460-times the MROHD, based on BSA). At 60 mg/kg/day, cleft palate was observed in 2 fetuses but not at higher doses. No dose related abnormalities were observed in external, skeletal and visceral examination and hence the no effect dose for offspring was 200 mg/kg/day (corresponding to 2480-times the MROHD, based on BSA).

In a rabbit EFD study, olopatadine (25, 100 and 400 mg/kg/day) was administered orally during the period of organogenesis. Abnormal respiration and lacrimation was seen at the 400 mg/kg/day dose and the maternal no effect dose level was 100 mg/kg/day (corresponding to 2480-times the MROHD, based on BSA). No effects on the fetuses were observed and hence the no effect dose for offspring was 400 mg/kg/day (corresponding to 9950-times the MROHD, based on BSA).

In a peri-/postnatal toxicity study, rats received oral doses of olopatadine up to 600 mg/kg/day during late gestation and throughout lactation. Maternal toxicity was observed at 600 mg/kg/day. Olopatadine produced decreased neonatal survival at 60 mg/kg/day and reduced body weight gain in offspring at 4 mg/kg/day (50-times the MROHD, based on BSA) which is attributed to milk as demonstrated in a cross-fostered study (see Animal Data under Lactation).

Lactation

Risk summary

It is not known if olopatadine is transferred into human milk after administration of Opatanol. There are no data on the effects of olopatadine on the breastfed child or on milk production. Based upon the low level of olopatadine present in human plasma following topical ocular administration, the concentration of olopatadine potentially present in breast milk is expected to be negligible. However, as there is no data available on the concentration of olopatadine/metabolites in human milk following topical ocular administration, a risk to the breast-feeding child cannot be excluded.

Olopatadine is transferred into the milk of lactating rats after oral administration and was associated with fetal toxicity (see Animal Data).

Patients should be informed that antihistamines may affect the milk production of a nursing mother. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Opatanol and any potential adverse effects on the breast-fed child from Opatanol.

Data

Animal Data

In a cross-fostered study in which pups of untreated dams were nursed by olopatadine (60 mg/kg/day) treated dams, the body weight gain of pups was suppressed confirming that the effect of olopatadine was through milk.

Oral administration of 1 mg/kg radiolabelled olopatadine in rats demonstrated that olopatadine and/or its metabolites were significantly transferred into milk with milk:plasma ratio ($AUC_{0-\infty}$) of 1.5. Maximal levels of radioactivity in the milk was determined at around 1 hour post-dose, with an elimination half-life of 28.3 hours.

Females and males of reproductive potential

Studies have not been performed to evaluate the effect of administration of olopatadine on human fertility. Effects in non-clinical fertility studies in male and female animals were observed only at dosages considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

No effects on human fertility are anticipated since systemic exposure to olopatadine is negligible by the topical ocular route.

Olopatadine can be used by women of childbearing potential.

OVERDOSAGE

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

CLINICAL PHARMACOLOGY

Pharmacodynamics (PD)

Olopatadine is a potent selective antiallergic/antihistaminic agent that exerts its effects through multiple distinct mechanisms of actions. It antagonizes histamine (the primary mediator of allergic response in humans) and prevents histamine induced inflammatory cytokine production by human conjunctival epithelial cells. Data from *in vitro* studies suggest that it may act on human conjunctival mast cells to inhibit the release of pro-inflammatory mediators. In patients with patent nasolacrimal ducts, topical ocular administration of olopatadine eye drops, solution was suggested to reduce the nasal signs and symptoms that frequently accompany seasonal allergic conjunctivitis. It does not produce a clinically significant change in pupil diameter.

Pharmacokinetics (PK)

Absorption

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

In the humans, plasma levels following topical ocular administration and oral administration are shown in Table 3. Compared with the oral administration exposure on Day 12, the mean exposure estimates show olopatadine C_{max} (1.64 ng/mL) and AUC_{0-12} (9.68 ng*h/mL) after multiple 0.77% topical ocular doses was 184-fold and 102-fold lower than the C_{max} (302

ng/mL) and AUC_{0-12} (987 ng*h/mL) after multiple 20 mg oral doses of olopatadine. These data indicate that topical ocular doses of 0.77% olopatadine hydrochloride ophthalmic solution resulted in a systemic exposure that is much lower than that after oral doses of 20 mg olopatadine hydrochloride.

Table 3 Comparison of olopatadine plasma concentration after topical ocular dosing and oral dosing

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

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

Distribution

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

Biotransformation/metabolism

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

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

Elimination

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

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

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

Linearity/non-linearity

In a single dose study, olopatadine showed a dose proportional increase in exposure (C_{max} and AUC) in ocular tissues after topical ocular instillation.

CLINICAL STUDIES

Opatanol is a well-established product.

NON-CLINICAL SAFETY DATA

Non-clinical data reveal no special hazard for humans treated with olopatadine hydrochloride eye drops, solution at concentrations up to and including 0.7% based on conventional studies of single dose toxicity, repeated dose toxicity, genotoxicity, carcinogenic potential and in ocular irritation studies.

For information on embryo-fetal, peri- and post-natal toxicity, see section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL.

INCOMPATIBILITIES

None known.

STORAGE

See folding box.

Opatanol should not be used after the date marked “EXP” on the pack.

Opatanol must be kept out of the reach and sight of children.

INSTRUCTIONS FOR USE AND HANDLING

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Manufacturer:

See folding box.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

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® = registered trademark

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