NOVARTIS

1. NAME OF THE MEDICINALPRODUCT

PATANOL® 0.1% eye drops, solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution contains 1 mg olopatadine (equivalent to 1.11 mg olopatadine hydrochloride).

3. PHARMACEUTICAL FORM

Eye drops, solution.
Clear, colourless to pale yellow sterile solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PATANOL eye drops is indicated for the treatment of the signs and symptoms of allergic conjunctivitis.

4.2 Posology and method of administration

Posology

The recommended dose is 1 drop in each affected eye 2 times per day.

Use in children

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

Use in patients with renal impairment

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

Use in patients with hepatic impairment

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

Use in 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 ocular use.
After cap is removed, if tamper evident snap collar is loose, snap collar should be removed before using 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. The bottle should be kept tightly closed when

not in use.

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 effect and increase in local activity.

If more than one topical ophthalmic product is being used, the 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.

Patanol should not be used to treat contact lens related irritation.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

- For topical use only. Not for injection.
- Do not use if tamper evident seal is damaged or broken at time of purchase.
- PATANOL eye drops contains benzalkonium chloride which may cause eye irritation andmay discolor soft contact lenses. Contact lenses must be removed before administration of Patanol and reinserted at least 15 minutes later.

4.5 Interaction with other medicinal products and other forms of interaction

No clinically relevant interactions have been described.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is a limited amount of data from the use of ophthalmic 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 [1].

No effects during pregnancy are anticipated since systemic exposure to olopatadine is negliglible 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 section 4.6 Breast-feeding - Animal Data).

Breast-feeding

It is not known if olopatadine is transferred into human milk after administration of Patanol / Pataday / Pazeo. 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 suckling 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 Patanol and any potential adverse effects on the breast-fed child from Patanol.

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 (AUC0-∞) 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.

Fertility

Studies have not been performed to evaluate the effect of topical ocular 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.

4.7 Effects on ability to drive and use machines

PATANOL eye drops has no or negligible influence on the ability to drive and use machines.

Olopatadine is a non-sedating anti-histamine. Temporary blurred vision after drop use, or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs after instillation, the patient must wait until the vision clears before driving or using machinery.

4.8 Undesirable effects

Tabulated summary of adverse drug reactions from clinical trials

Adverse drug reactions from clinical trials (Table 4-1) 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 4.7-1 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 reactiong have been derived from post-marketing experience with Patanol and

Pataday 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 4.7-2 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

4.9 Overdose

An ocular overdose of PATANOL eye drops may be flushed from the eye(s) with lukewarm water. Due to the characteristics of this preparation, no toxic effects are to be expected with an ocular overdose of this product, nor in the event of accidental ingestion of the contents of one bottle.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Decongestants and antiallergics; other antiallergics.
ATC code: S01GX09

Olopatadine is a multiple-action molecule: an inhibitor of the release of histamine from the mast cell and a relatively selective histamine H_1-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 and an inhibitor of cytokine secretion. Olopatadine is devoid of effects on alpha-adrenergic, dopamine, muscarinic Type 1 and 2 receptors.

Results from conjunctival antigen challenge studies demonstrated that PATANOL® 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. Results from an environmental study demonstrated that PATANOL was effective in the treatment of the signs and symptoms of allergic conjunctivitis when dosed twice daily for up to 6 weeks.

5.2 Pharmacokinetic properties

Ocular pharmacokinetics

Following topical ocular administration of radiolabeled olopatadine in rabbits, absorption occurred with the highest amount of radioactivity in cornea, followed by the conjunctiva, iris-ciliary body and aqueous humour. Low systemic exposure was observed after topical ocular administration in rabbits. The degree of melanin binding in pigmented ocular tissues occurred but was minimal.

In man, following topical ocular administration, olopatadine was also shown to have low systemic exposure. Two studies in normal volunteers (totalling 24 subjects) dosed bilaterally with olopatadine 0.15 % eye drops 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.

Systemic pharmacokinetics

After oral administration, the half- life in plasma was approximately 7 hours in fasting subjects, which increased to approximately 10 hours with the ingestion of food. This was accompanied by a small delay in the Tmax as well as a small and minimal decrease in systemic exposure. Elimination after oral administration of olopatadine in humans 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. In rat studies after oral administration of radiolabeled olopatadine, radioactivity was principally distributed to the site of absorption and eliminating organs. There was no evidence of drug retention in most of the tissues with half-lives that typically followed the plasma half-life. Longer half-lives were observed for kidney, liver and fat tissues; however, no radioactivity was observed at 48 hours.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans treated with PATANOL eye drops based on conventional studies of single dose toxicity, repeated dose toxicity, genotoxicity, carcinogenic potential and in ocular irritation study. For information on embryo-fetal, peri- and post-natal toxicity, see section4.6 pregnancy, lactation and fertility.

6. PHARMACEUTICAL PARTICULARS

6.1 List ofexcipients

Benzalkonium chloride, sodium chloride, disodium phosphate dodecahydrate, sodium hydroxide and / or concentrated hydrochloric acid (to adjust pH), purified water.

6.2 Incompatibilities

Not applicable.

6.3 Special precautions for storage

Do not store above 30°C.

Do not use this medicine after the expiry date which is stated on the packaging.
Discard 4 weeks after first opening.
Keep this medicine out of the sight and reach of children.

6.4 Nature and contents ofcontainer

Plastic bottle dispenser containing 5 ml.

6.5 Special precautions for disposal and other handling

No special requirements.

Novartis Pharma AG, Basel, Switzerland