

AUSTRALIAN PRODUCT INFORMATION

PALADOPT

olopatadine eye drops



1 NAME OF THE MEDICINE

Olopatadine

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mL of eye drops contains 1.11 mg of olopatadine hydrochloride (equivalent to 1 mg olopatadine) as the active ingredient.

For the full list of excipients, see section 6.1 List of Excipients.

3 PHARMACEUTICAL FORM

The solution is clear and colourless..

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

PALADOPT is indicated for the treatment of the signs and symptoms of seasonal allergic conjunctivitis. Treatment may be maintained for up to 14 weeks, if considered necessary.

4.2 DOSE AND METHOD OF ADMINISTRATION

The recommended therapy is one to two drops of PALADOPT in the affected eye(s) twice daily for up to 14 weeks.

PALADOPT is for individual patient use only.

4.3 CONTRAINDICATIONS

Olopatadine eye drops are contraindicated in patients hypersensitive to olopatadine hydrochloride or any other component of the preparation (see section 6.1 List of Excipients).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Not for injection or oral ingestion

Use in the Elderly

No data available.

Paediatric Use

Safety and effectiveness have not been established in children below 3 years of age.

Effects on Laboratory Tests

No data available.

Instruction to Patients

PALADOPT contains the preservative benzalkonium chloride, which may cause eye irritation and be deposited in or discolour soft (hydrophilic) contact lenses. Avoid contact with soft contact lenses. Patients who wear soft contact lenses should remove their lenses prior to instilling PALADOPT and should not reinsert their lenses until at least 15 minutes after instillation of the eye drops.

To prevent contaminating the dropper tip and solution, care should be taken not to touch the eyelids or surrounding areas with the dropper tip of the bottle. The bottle should be tightly closed when not in use.

Each bottle of PALADOPT should be discarded after 28 days of opening.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Interactions with other medications have not been investigated *in vivo*. Drug interaction studies on human liver microsomal preparation have shown that olopatadine is not an inhibitor of cytochrome P-450 isozymes 1A2, 2C8/9, 2C19, 2D6, 2E1 or 3A1. Olopatadine eye drops have low drug interaction potential as systemic levels of olopatadine achieved after ocular dosing are negligible and 60 – 70 % of the drug is excreted unchanged in the urine.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

There are no human data addressing the effects of topical ocular administration of olopatadine on human fertility. In animal reproductive/fertility studies, olopatadine had no effect on the fertility of male and female rats at oral doses up to 50 mg/kg/day (7,800 times the maximum recommended ocular human use level). However, decreases in the fertility index, number of corpora lutea and implantation rate were seen at an oral dose of 400 mg/kg/day.

Use in Pregnancy

Pregnancy Category: B1

Studies in animals with olopatadine have shown reproductive toxicity following systemic administration. Olopatadine was not teratogenic in rats and rabbits at oral doses of 600 mg/kg and 400 mg/kg, respectively (> 90,000 and > 60,000 times the maximum recommended ocular human use level, respectively). Given that animal studies are not always predictive of human responses, and that no adequate and well controlled studies in pregnant women have been performed, it should be carefully considered whether the potential benefit to the mother justifies the potential risk to the embryo or fetus.

Use in Lactation

Olopatadine has been identified in the milk of nursing rats following oral administration. Rat pups of mothers administered olopatadine orally at greater than 4 mg/kg/day showed (625 times - but not at 312 times - the maximum recommended ocular human use level demonstrated) reduced body weight gain during the nursing period. It is not known whether topical ocular administration could result in sufficient systemic absorption to produce detectable quantities of olopatadine/metabolites in human breast milk. Olopatadine eye drops should be used with caution in breastfeeding woman.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Instillation of eye drops may cause transient blurring of vision or other visual disturbances which may affect the ability to drive or use machines. The patient must wait until vision clears before driving or operating machinery if blurred vision is experienced.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Headaches have been reported at an incidence of 7 %. The following adverse experiences have been reported in less than 5 % of patients: asthenia, blurred vision, burning or stinging, cold syndrome, dry eye, foreign body sensation, hyperaemia, hypersensitivity, keratitis, lid oedema, nausea, pharyngitis, pruritus, rhinitis, sinusitis and taste perversion. Some of these events are similar to the underlying disease being studied.

Post Marketing Experience

The following adverse reactions have been reported during clinical studies with olopatadine eye drops and are classified according to the subsequent convention: very common ($\geq 1/10$), common ($\geq 1/100$ to $<1/10$),

uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$) and very rare ($< 1/10,000$). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Eye Disorders

Uncommon ($\geq 0.1\%$ to $< 1\%$): punctate keratitis, keratitis, eye pain, dry eye, eyelid oedema, eye pruritus, eye discharge, ocular hyperaemia, eyelid margin crusting, ocular discomfort

Rare ($\geq 0.01\%$ to $< 0.1\%$): photophobia, vision blurred, erythema of eyelid

Nervous System Disorders

Uncommon ($\geq 0.1\%$ to $< 1\%$): headache, dysgeusia

Rare ($\geq 0.01\%$ to $< 0.1\%$): dizziness

Respiratory, Thoracic and Mediastinal Disorders

Uncommon ($\geq 0.1\%$ to $< 1\%$): nasal dryness

Gastrointestinal Disorders:

Rare ($\geq 0.01\%$ to $< 0.1\%$): dry mouth

Skin and Subcutaneous Tissue Disorders:

Rare ($\geq 0.01\%$ to $< 0.1\%$): dermatitis contact

General Disorders and Administration Site Conditions:

Uncommon ($\geq 0.1\%$ to $< 1\%$): fatigue

Additional adverse reactions identified from post-marketing surveillance include the following. Frequencies cannot be estimated from the available data.

Eye Disorders

Lacrimation increased

Immune System Disorders

Hypersensitivity

Gastrointestinal Disorders

Nausea

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

No specific ocular side effects are known for a topical overdosage of olopatadine eye drops. Results from studies indicated that topical ocular administration resulted in very low systemic concentrations. Multiple oral doses that resulted in plasma concentrations at least 2 to 3 orders of magnitude greater than those from topical ocular dosing were well tolerated.

A topical overdose of olopatadine eye drops may be flushed from the eye(s) with warm tap water.

If olopatadine eye drops are accidentally ingested the following information may be useful. One bottle contains 5 mg of olopatadine. In single dose oral studies, olopatadine was well tolerated up to a dose of 360 mg, with rapid absorption and rapid excretion of the parent drug in the urine. Approximately 84 % of the dose was recovered in the urine as parent drug within the first 24 hours. The most often observed side effect was tiredness usually of a mild to moderate nature, although severe tiredness has been reported.

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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Olopatadine is an anti-allergic compound which has been demonstrated to stabilize human conjunctival tissue mast cells, preventing the release of histamine and other inflammatory mediators. Olopatadine is a selective histamine H₁-antagonist (K_i values for Histamine H₁, H₂ and H₃ receptors were 32 nM, 100 μM and 79 μM, respectively) that inhibits Type I immediate hypersensitivity reactions. It has been shown to inhibit the release of pro-inflammatory mediators from human conjunctival mast and epithelial cells. Olopatadine has no significant effects on alpha-adrenergic, dopamine and muscarinic Type 1 and 2 receptors.

Clinical Trials

The safety of olopatadine eye drops was evaluated in 15 clinical studies in which 1,208 patients were evaluated for safety. These studies included three clinical pharmacology plasma level and tear studies, three comfort studies, five conjunctival antigen challenge studies, an environmental study, an adjunct study to loratadine and two additional safety studies. These 15 studies show no clinically significant change observed in visual acuity, pupil diameter, pupillary response, intraocular pressure, dilated fundus parameters, blood chemistry, haematology, urinalysis, pulse or mean arterial pressure in patients receiving olopatadine eye drops.

Three studies assessed the comfort of olopatadine eye drops relative to other agents. Each included 30 subjects. They were single dose crossover studies in which all subjects received all test agents, and single-blinded because the subjects themselves reported the comfort of the agents tested. In one study olopatadine 0.1% was compared to ketorolac 0.5%. In the two other studies, olopatadine 0.1% was compared to ketorolac 0.5% and levocabastine 0.05%. The studies showed that olopatadine eye drops 0.1 % was significantly more comfortable than ketorolac 0.5 % and levocabastine 0.05 %.

Results from three pivotal conjunctival antigen challenge studies involving 278 patients demonstrated that, when subjects were challenged with antigen both initially and up to 8 hours after dosing, olopatadine eye drops were significantly more effective than the placebo in preventing chemosis, ocular itching and redness.

Results are also available from a randomised, placebo-controlled environmental study conducted during the ragweed pollen season, involving 159 patients with symptomatic allergic conjunctivitis, known to be sensitive to ragweed. The trial showed that olopatadine eye drops reduces consistently more signs and symptoms than placebo, although these results did not attain statistical significance. Post-hoc analyses showed a correlation of increased pollen counts with increased ocular signs and symptoms of SAC. In the olopatadine eye drops group, the slopes of the lines predicting ocular itching, redness and tearing were lower than the slopes for placebo, indicating that olopatadine eye drops significantly reduces the effects of pollen levels on ocular redness (p=0.0413), itching (p=0.0075) and tearing (p=0.0059).

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Following topical ocular administration in humans, olopatadine was shown to have low systemic exposure. Two studies in normal volunteers (totalling 24 subjects) dosed bilaterally with olopatadine 0.15% ophthalmic solution once every 12 hours for two 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.

Metabolism

Two metabolites, the mono-desmethyl and the N-oxide, were detected at low concentrations in the urine.

Excretion

The half-life in plasma was approximately 8 - 12 hours and elimination was predominantly through renal excretion. Approximately 60 – 70% of the dose was recovered in the urine as parent drug.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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.

Carcinogenicity

Long term studies in mice and rats did not provide any evidence of carcinogenicity at oral olopatadine doses up to 500 mg/kg/day and 200 mg/kg/day, respectively (78,000 and 31,000 times the maximum recommended ocular human use level, respectively).

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The inactive ingredients in PALADOPT are: benzalkonium chloride, dibasic sodium phosphate, hydrochloric acid, sodium chloride, sodium hydroxide, water for injections.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Discard 4 weeks after opening.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type: Bottle (LDPE).

Pack sizes: 5 mL

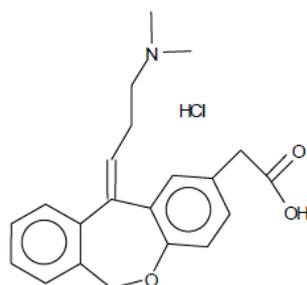
Some strengths, pack sizes and/or pack types may not be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure



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

Molecular formula: C₂₁H₂₃NO₃ •HCl

Molecular weight: 373.88

Olopatadine hydrochloride, a dibenzoxepine derivative, is a white, crystalline, water-soluble powder (Figure 1). It has a melting point of 248°C (decomposition).

PALADOPT is a sterile, isotonic, preserved solution for topical application to the eye. The solution is buffered to a pH of approximately 7 so that it is within the physiological range of the ocular surface fluid.

CAS Number

140462-76-6

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

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9 DATE OF FIRST APPROVAL

23/10/2015

10 DATE OF REVISION

16/09/2020

Summary Table of Changes

Section Changed	Summary of New Information
All	Reformat to align to TGA's Form for Providing Product Information
1; 2; 3; 4.1; 4.4; 4.6; 4.8; 6.1; 6.4; 6.5; 7; 9; 10	Minor editorial changes
8	Sponsor change following transfer of sponsorship.

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