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# PHYSICIANS' DESK REFERENCE®

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# **NAPHCON® A** Eye Drops Relieves Itching & Redness EYE ALLERGY RELIEF

OTC

Temporary relief of the minor eye symptoms of itching and redness caused by ragweed, pollen, grass, animal hair, and dander.

## **DESCRIPTION**

**Active:** Pheniramine Maleate 0.3%, Naphazoline Hydrochloride 0.025%. **Preservative:** Benzalkonium Chloride 0.01%. **Inactive:** Sodium Chloride, Boric Acid, Sodium Borate, Edetate Disodium 0.01%, Sodium Hydroxide and/or Hydrochloric Acid (to adjust pH), Purified Water. The sterile ophthalmic solution has a pH of about 6 and a tonicity of about 270 mOsm/Kg.

## **DIRECTIONS**

Instill 1 or 2 drops in the affected eye(s) up to 4 times daily.

## **WARNINGS**

To avoid contamination, do not touch tip of container to any surface. Replace cap after using.  
If solution changes color or becomes cloudy, do not use.  
If you experience eye pain, changes in vision, continued redness or irritation of the eye, or if the condition worsens, or persists for more than 72 hours, discontinue use and consult a physician. Overuse of this product may produce increased redness of the eye.  
If you are sensitive to any ingredient in this product, do not use. Do not use this product if you have heart disease, high blood pressure, difficulty in urination due to enlargement of the prostate gland or narrow angle glaucoma unless directed by a physician.  
Accidental oral ingestion in infants and children may lead to coma and marked reduction in body temperature. Before using in children under 6 years of age, consult your physician.  
Keep this and all drugs out of reach of children. In case of accidental ingestion, seek professional assistance or contact a Poison Control Center immediately.  
Remove contact lenses before using.  
Store at 36°–80°F (2°–27°C).  
Protect from light.  
Use before the expiration date marked on the carton or bottle.  
Keep this and all drugs out of reach of children.

# **PATANOL®** (olopatadine hydrochloride ophthalmic solution) 0.1%

Rx

## **DESCRIPTION**

PATANOL® (olopatadine hydrochloride ophthalmic solution) 0.1% is a sterile ophthalmic solution containing olopatadine, a relatively selective H<sub>1</sub>-receptor antagonist and inhibitor of histamine release from the mast cell for topical administration to the eyes. Olopatadine hydrochloride is a white, crystalline, water-soluble powder with a molecular weight of 373.88.

**Chemical Name:** 11-[(Z)-3-(Dimethylamino)propylidene]-6,11-dihydrodibenz[b,e] oxepin-2-acetic acid hydrochloride. Each mL of PATANOL contains: **Active:** 1.11 mg olopatadine hydrochloride equivalent to 1 mg olopatadine. **Preservative:** benzalkonium chloride 0.01%. **Inactives:** dibasic sodium phosphate; sodium chloride; hydrochloric acid/sodium hydroxide (adjust pH); and purified water.  
It has a pH of approximately 7 and an osmolality of approximately 300 mOsm/kg.

## **CLINICAL PHARMACOLOGY**

Olopatadine is an inhibitor of the release of histamine from the mast cell and a relatively selective histamine H<sub>1</sub>-antagonist that inhibits the *in vivo* and *in vitro* type 1 immediate hypersensitivity reaction. Olopatadine is devoid of effects on alpha-adrenergic, dopamine, muscarinic type 1 and 2, and serotonin receptors. Following topical ocular administration in man, olopatadine was shown to have low systemic exposure. Two studies in normal volunteers (totaling 24 subjects) dosed bilaterally with olopatadine 0.15% ophthalmic solution once every 12 hours for 2 weeks demonstrated plasma concentrations to be generally below the quantitation limit of the assay (<0.5 ng/mL). Samples in which olopatadine was quantifiable were typically found within 2 hours of dosing and ranged from 0.5 to 1.3 ng/mL. The half-life in plasma was approximately 3 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. 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.

## **INDICATIONS AND USAGE**

PATANOL (olopatadine hydrochloride ophthalmic solution) 0.1% is indicated for the temporary prevention of itching of the eye due to allergic conjunctivitis.

## **CONTRAINDICATIONS**

PATANOL is contraindicated in persons with a known hypersensitivity to olopatadine hydrochloride or any components of PATANOL.

## **WARNINGS**

PATANOL® is for topical use only and not for injection or oral use.

## **PRECAUTIONS**

**Information for Patients:** 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. Keep bottle tightly closed when not in use.  
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. The preservative in PATANOL, benzalkonium chloride, may be absorbed by soft contact lenses. Patients who wear soft contact lenses and whose eyes are not red, should be instructed to wait at least ten minutes after instilling PATANOL before they insert their contact lenses.

**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, these doses were 78,125 and 31,250 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 62,500 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 7,800 times the maximum recommended ocular human use level.

**Pregnancy: Pregnancy Category C.** Olopatadine was found not to be teratogenic in rats and rabbits. However, rats treated at 600 mg/kg/day, or 93,750 times the MROHD and rabbits treated at 400 mg/kg/day, or 62,500 times the MROHD, during organogenesis showed a decrease in live fetuses. 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 PATANOL® is administered to a nursing mother.

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

## **ADVERSE REACTIONS**

Headaches were reported at an incidence of 7%. The following adverse experiences were reported in less than 5% of patients: Asthenia, burning or stinging, cold syndrome, dry eye, foreign body sensation, hyperemia, keratitis, lid edema, pharyngitis, pruritus, rhinitis, sinusitis, and taste perversion. Some of these events were similar to the underlying disease being studied.

## **DOSE AND ADMINISTRATION**

The recommended dose is one to two drops in each affected eye two times per day at an interval of 6 to 8 hours.

## **HOW SUPPLIED**

PATANOL® (olopatadine hydrochloride ophthalmic solution) 0.1% is supplied as follows: 5 mL in plastic DROP-TAINER® dispenser.

5 mL: NDC 0065-0271-05

**Storage:** Store at 39°F to 86°F (4°C to 30°C).

U.S. Patents Nos. 4,871,865; 4,923,892; 5,116,863; 5,641,805.

**Rx Only.**

# **TEARS NATURALE® II** Lubricant Eye Drops **TEARS NATURALE FREE®** Lubricant Eye Drops

OTC

## **DESCRIPTION**

**TEARS NATURALE® II** is the only lubricant eye drop preserved with safe, nonsensitizing POLYQUAD 0.001%. *In vitro* studies have shown that POLYQUAD substantially avoids the damaging effects of epithelial cell toxicity possible with other tear substitute preservatives and allows epithelial cell growth. POLYQUAD has been shown to be 99% reaction-free in normal subjects and 97% reaction-free in subjects known to be preservative sensitive. **TEARS NATURALE FREE** is a preservative-free version of **TEARS NATURALE II**.

With their unique mucin like polymeric formulation, and with their natural pH, low viscosity, and isotonicity, **TEARS NATURALE II** and **TEARS NATURALE FREE** provide dry eye patients with comfort and prompt relief of dry eye symptoms.

Sterile-For Topical Eye Use Only

## **INGREDIENTS**

**TEARS NATURALE II:** Each mL contains: **Active:** DUASORB®, a water soluble polymeric system containing Dextran 70 0.1% and Hydroxypropyl Methylcellulose 2910 0.3%.

**Preservative:** POLYQUAD® (Polyquaternium-1) 0.001%. **Inactive:** Sodium Borate, Potassium Chloride, Sodium Chloride, Purified Water. May contain Hydrochloric Acid and/or Sodium Hydroxide to adjust pH.

**TEARS NATURALE FREE:** Each mL contains:

**Active:** DUASORB®, a water soluble polymeric system containing Dextran 70 0.1% and Hydroxypropyl Methylcellulose 2910 0.3%.

**Inactives:** Sodium Borate, Potassium Chloride, Sodium Chloride, Purified Water. May contain Hydrochloric Acid and/or Sodium Hydroxide to adjust pH.

## **INDICATIONS**

For the temporary relief of burning and irritation due to dryness of the eye and for use as a protectant against further irritation. For the temporary relief of discomfort due to minor irritations of the eye or to exposure to wind or sun.

## **WARNINGS**

If you experience eye pain, changes in vision, continued redness or irritation of the eye, or if the condition worsens or persists for more than 72 hours, discontinue use and consult a doctor.

If solution changes color or becomes cloudy, do not use.

To avoid contamination, do not touch tip of container to any surface. Replace cap after using. Keep this and all drugs out of the reach of children. In case of accidental ingestion, seek professional assistance or contact a Poison Control Center immediately.

## **DIRECTIONS**

**TEARS NATURALE® II:** Instill 1 or 2 drops in the affected eye(s) as needed. **TEARS NATURALE FREE:** Make sure container is intact before use. To open, completely TWIST off tab. DO NOT pull off. Instill 1 or 2 drops in the affected eye(s) as needed. To close, align cap at right angle (90°) to vial and firmly press down. Improved vial design reduces chance of leakage. **DISCARD CONTAINER 12 HOURS AFTER OPENING.**

## **HOW SUPPLIED**

**TEARS NATURALE II** Lubricant Eye Drops are supplied in 15 mL and 30 mL plastic DROP-TAINER® bottles.

15 mL NDC 0065-0418-15

30 mL NDC 0065-0418-30

**TEARS NATURALE FREE** Lubricant Eye Drops are supplied in boxes of 35 0.03 fl. oz. re-closable vials.

NDC 0065-0416-32

**STORAGE:** Store at room temperature.

# **TOBRADEX®** (tobramycin and dexamethasone ophthalmic suspension and ointment) Sterile

Rx

## **DESCRIPTION**

**TOBRADEX®** (tobramycin and dexamethasone ophthalmic suspension and ointment) are sterile, multiple dose antibiotic and steroid combinations for topical ophthalmic use.

**Tobramycin**

**Chemical name:**

O-3-Amino-3-deoxy-α-D-glucopyranosyl-(1→4)-O-[2,6-di-amino-2,3,6-trideoxy-α-D-ribo-hexopyranosyl-(1→6)]-2-deoxy-L streptamine

**Dexamethasone**

**Chemical Name:**

9-Fluoro-11β,17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione

Each mL of **TOBRADEX®** Suspension contains: **Active:** Tobramycin 0.3% (3 mg) and Dexamethasone 0.1% (1 mg). **Preservative:** Benzalkonium Chloride 0.01%. **Inactives:** Tyloxapol, Edetate Disodium, Sodium Chloride, Hydroxyethyl Cellulose, Sodium Sulfate, Sulfuric Acid and/or Sodium Hydroxide (to adjust pH) and Purified Water.

Each gram of **TOBRADEX®** Ointment contains: **Actives:** Tobramycin 0.3% (3 mg) and Dexamethasone 0.1% (1 mg). **Preservative:** Chlorobutanol 0.5%. **Inactives:** Mineral Oil and White Petrolatum.

## **CLINICAL PHARMACOLOGY**

Corticoids suppress the inflammatory response to a variety of agents and they probably delay or slow healing. Since corticoids may inhibit the body's defense mechanism against infection, a concomitant antimicrobial drug may be used when this inhibition is considered to be clinically significant. Dexamethasone is a potent corticoid.

The antibiotic component in the combination (tobramycin) is included to provide action against susceptible organisms. *In vitro* studies have demonstrated that tobramycin is active against susceptible strains of the following microorganisms:

Staphylococci, including *S. aureus* and *S. epidermidis* (coagulase-positive and coagulase-negative), including penicillin-resistant strains.  
Streptococci, including some of the Group A-beta-hemolytic species, some nonhemolytic species, and some *Streptococcus pneumoniae*.

*Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter aerogenes*, *Proteus mirabilis*, *Moraxella*, *Haemophilus influenzae* and *H. aegyptius*, *Moraxella lacunata*, *Acinetobacter calcoaceticus* and some *Neisseria* species.



Bacterial susceptibility studies demonstrate that in some cases microorganisms resistant to gentamicin remain susceptible to tobramycin. No data are available on the extent of systemic absorption of TOBRADEX® Ophthalmic Suspension or Ointment; however, it is known that some systemic absorption can occur with ocularly applied drugs. If the maximum dose of TOBRADEX® Ophthalmic Suspension is given for the first 48 hours (two drops in each eye every 2 hours) and complete systemic absorption occurs, which is highly unlikely, the daily dose of dexamethasone would be 2.4 mg. The usual daily dose of dexamethasone is 0.75 mg daily. If TOBRADEX® Ophthalmic Suspension is given after the first 48 hours as two drops in each eye every 4 hours, the administered dose of dexamethasone would be 1.2 mg daily. The administered dose of TOBRADEX Ophthalmic Ointment in both eyes four times daily would be 0.4 mg of dexamethasone daily.

## INDICATIONS AND USAGE

TOBRADEX® Ophthalmic Suspension and Ointment are indicated for steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists.

Ocular steroids are indicated in inflammatory conditions of the palpebral and bulbar conjunctiva, cornea and anterior segment of the globe where the inherent risk of steroid use in certain infective conjunctivitis is accepted to obtain a diminution in edema and inflammation. They are also indicated in chronic anterior uveitis and corneal injury from chemical, radiation or thermal burns, or penetration of foreign bodies.

The use of a combination drug with an anti-infective component is indicated where the risk of superficial ocular infection is high or where there is an expectation that potentially dangerous numbers of bacteria will be present in the eye.

The particular anti-infective drug in this product is active against the following common bacterial eye pathogens: *Staphylococci*, including *S. aureus* and *S. epidermidis* (coagulase-positive and coagulase-negative), including penicillin-resistant strains.

*Streptococci*, including some of the Group A-beta-hemolytic species, some nonhemolytic species, and some *Streptococcus pneumoniae*.

*Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter aerogenes*, *Proteus mirabilis*, *Morganella morganii*, most *Proteus vulgaris* strains, *Haemophilus influenzae* and *H. aegyptius*, *Moraxella lacunata*, *Acinetobacter calcoaceticus* and some *Neisseria* species.

## CONTRAINDICATIONS

Epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, and many other viral diseases of the cornea and conjunctiva. Mycobacterial infection of the eye. Fungal diseases of ocular structures. Hypersensitivity to a component of the medication.

## WARNINGS

NOT FOR INJECTION INTO THE EYE. Sensitivity to topically applied aminoglycosides may occur in some patients. If a sensitivity reaction does occur, discontinue use.

Prolonged use of steroids may result in glaucoma, with damage to the optic nerve, defects in visual acuity and fields of vision, and posterior subcapsular cataract formation. Intraocular pressure should be routinely monitored even though it may be difficult in children and uncooperative patients. Prolonged use may suppress the host response and thus increase the hazard of secondary ocular infections. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. In acute purulent conditions of the eye, steroids may mask infection or enhance existing infection.

## PRECAUTIONS

**General.** The possibility of fungal infections of the cornea should be considered after long-term steroid dosing. As with other antibiotic preparations, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, appropriate therapy should be initiated. When multiple prescriptions are required, or whenever clinical judgement dictates, the patient should be examined with the aid of magnification, such as slit lamp biomicroscopy and, where appropriate, fluorescein staining. Cross-sensitivity to other aminoglycoside antibiotics may occur; if hypersensitivity develops with this product, discontinue use and institute appropriate therapy.

**Information for Patients:** Do not touch dropper or tube tip to any surface, as this may contaminate the contents.

**Carcinogenesis, Mutagenesis, Impairment of Fertility.** No studies have been conducted to evaluate the carcinogenic or mutagenic potential. No impairment of fertility was noted in studies of subcutaneous tobramycin in rats at doses of 50 and 100 mg/kg/day.

**Pregnancy Category C.** Corticosteroids have been found to be teratogenic in animal studies. Ocular administration of 0.1% dexamethasone resulted in 15.6% and 32.3% incidence of growth retardation in two groups of pregnant rabbits. Fetal growth retardation and increased mortality rates have been observed in rats with chronic dexamethasone therapy. Retardation studies have been performed in rats and rabbits with tobramycin at doses up to 100 mg/kg/day parenterally and have revealed no evidence of impaired fertility or harm to the fetus. There are no adequate and well-controlled studies in pregnant women. TOBRADEX® Ophthalmic Sus-

pension and Ointment should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nursing Mothers.** Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Because many drugs are excreted in human milk, caution should be exercised when TOBRADEX® Ophthalmic Suspension or ointment is administered to a nursing woman.

**Pediatric Use.** Safety and effectiveness in pediatric patients have not been established.

## ADVERSE REACTIONS

Adverse reactions have occurred with steroid/anti-infective combination drugs which can be attributed to the steroid component, the anti-infective component, or the combination. Exact incidence figures are not available. The most frequent adverse reactions to topical ocular tobramycin (TOBREX®) are hypersensitivity and localized ocular toxicity, including lid itching and swelling, and conjunctival erythema. These reactions occur in less than 4% of patients. Similar reactions may occur with the topical use of other aminoglycoside antibiotics. Other adverse reactions have not been reported; however, if topical ocular tobramycin is administered concomitantly with systemic aminoglycoside antibiotics, care should be taken to monitor the total serum concentration. The reactions due to the steroid component are: elevation of intraocular pressure (IOP) with possible development of glaucoma, and infrequent optic nerve damage; posterior subcapsular cataract formation; and delayed wound healing.

**Secondary Infection.** The development of secondary infection has occurred after use of combinations containing steroids and antimicrobials. Fungal infections of the cornea are particularly prone to develop coincidentally with long-term applications of steroids. The possibility of fungal invasion must be considered in any persistent corneal ulceration where steroid treatment has been used. Secondary bacterial ocular infection following suppression of host responses also occurs.

## OVERDOSAGE

Clinically apparent signs and symptoms of an overdose of TOBRADEX Ophthalmic Suspension or Ointment (punctate keratitis, erythema, increased lacrimation, edema and lid itching) may be similar to adverse reaction effects seen in some patients.

## DOSAGE AND ADMINISTRATION

**Suspension:** One or two drops instilled into the conjunctival sac(s) every four to six hours. During the initial 24 to 48 hours, the dosage may be increased to one or two drops every two (2) hours. Frequency should be decreased gradually as warranted by improvement in clinical signs. Care should be taken not to discontinue therapy prematurely. **Ointment:** Apply a small amount (approximately 1/2 inch ribbon) into the conjunctival sac(s) up to three or four times daily. Not more than 20 mL or 8 g should be prescribed initially and the prescription should not be refilled without further evaluation as outlined in PRECAUTIONS above.

## HOW SUPPLIED

Sterile ophthalmic suspension in 2.5 mL (NDC 0065-0647-25), 5 mL (NDC 0065-0647-05) and 10 mL (NDC 0065-0647-10) DROP-TAINER® dispensers. Sterile ophthalmic ointment in 3.5 g ophthalmic tube (NDC 0065-0648-35).

## STORAGE

Store at 8° to 27°C (46° to 80°F).

Store suspension upright and shake well before using.

Rx Only.

U.S. Patent No. 5,149,694

## Allergan, Inc.

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## OPHTHALMIC PRODUCTS

For information on Allergan, Inc., prescription, OTC, and ophthalmic products, consult the Physicians' Desk Reference for Ophthalmology. For literature, service items, or sample material, contact Allergan directly. See a complete listing of products in the Manufacturers' Index section of this book.

**ACULAR®**  
(ketorolac tromethamine ophthalmic solution) 0.5%  
Sterile

## PRODUCT OVERVIEW

ACULAR® (ketorolac tromethamine ophthalmic solution) 0.5% is the only topical NSAID indicated for the temporary

relief of ocular itching due to seasonal allergic conjunctivitis. ACULAR® is also indicated for the treatment of postoperative inflammation in patients who have undergone cataract extraction.

ACULAR® relieves the ocular itch associated with seasonal allergic conjunctivitis and inflammation following cataract surgery due in part to its ability to inhibit prostaglandin biosynthesis.

In two double-masked, paired studies (N=241), ACULAR® Solution was found to be superior to placebo in relieving the ocular itch of seasonal allergic conjunctivitis.<sup>1</sup>

Two controlled clinical studies showed that patients treated for two weeks with ACULAR® ophthalmic solution were less likely to have measurable signs of inflammation (cell and flare) than patients treated with its vehicle.

ACULAR® Solution is also proven safe in clinical trials, and avoids steroid-like side effects (e.g., no significant effect upon IOP).<sup>1</sup> There is no significant ocular toxicity reported in clinical studies to date with ACULAR®.

The most frequently reported adverse events have been transient stinging and burning on instillation (approximately 40%). Caution should be used in patients with sensitivities to other NSAIDs.

ACULAR® Solution is available in 3 mL, 5 mL and 10 mL plastic bottles with a controlled-dropper tip.

Please see full prescribing information included.

1. Data on file, Syntex (U.S.A.) Inc.

ACULAR®, a registered trademark of Syntex (U.S.A.) Inc., is manufactured and distributed by Allergan, Inc. under license from its developer, Syntex (U.S.A.) Inc., Palo Alto, CA.

ACULAR® is marketed by Allergan, Inc.

## PRESCRIBING INFORMATION

**ACULAR®**  
(ketorolac tromethamine ophthalmic solution) 0.5%  
Sterile

## DESCRIPTION

ACULAR® (ketorolac tromethamine ophthalmic solution) is a member of the pyrrolo-pyrrole group of nonsteroidal anti-inflammatory drugs (NSAIDs) for ophthalmic use. Its chemical name is (+)-5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1).

ACULAR® is supplied as a sterile isotonic aqueous 0.5% solution, with a pH of 7.4. ACULAR® is a racemic mixture of R-(+)- and S-(-)- ketorolac tromethamine. Ketorolac tromethamine may exist in three crystal forms. All forms are equally soluble in water. The pKa of ketorolac is 3.5. This white to off-white crystalline substance discolors on prolonged exposure to light. The molecular weight of ketorolac tromethamine is 376.41. Each mL of ACULAR® ophthalmic solution contains: Active: ketorolac tromethamine 0.5%. Preservative: benzalkonium chloride 0.01%. Inactives: edetate disodium 0.1%; octoxynol 40; sodium chloride; hydrochloric acid and/or sodium hydroxide to adjust the pH; and purified water. The osmolality of ACULAR® is 290 mOsmol/kg.

## ANIMAL PHARMACOLOGY

Ketorolac tromethamine prevented the development of increased intraocular pressure induced in rabbits with topically applied arachidonic acid. Ketorolac did not inhibit rabbit lens aldose reductase *in vitro*.

Ketorolac tromethamine ophthalmic solution did not enhance the spread of ocular infections induced in rabbits with *Candida albicans*, *Herpes simplex virus* type one, or *Pseudomonas aeruginosa*.

## CLINICAL PHARMACOLOGY

Ketorolac tromethamine is nonsteroidal anti-inflammatory drug which, when administered systemically, has demonstrated analgesic, anti-inflammatory, and anti-pyretic activity. The mechanism of its action is thought to be due, in part, to its ability to inhibit prostaglandin biosynthesis. Ketorolac tromethamine given systemically does not cause pupil constriction.

Prostaglandins have been shown in many animal models to be mediators of certain kinds of intraocular inflammation. In studies performed in animal eyes, prostaglandins have been shown to produce disruption of the blood-aqueous humor barrier, vasodilation, increased vascular permeability, leukocytosis, and increased intraocular pressure. Prostaglandins also appear to play a role in the miosis response produced during ocular surgery by constricting the iris sphincter independently of cholinergic mechanisms.

Two drops (0.1 mL) of 0.5% ACULAR® ophthalmic solution instilled into the eyes of patients 12 hours and 1 hour prior to cataract extraction achieved measurable levels in 8 of 9 patients' eyes (mean ketorolac concentration 95 ng/mL aqueous humor, range 40 to 170 ng/mL). Ocular administration of ketorolac tromethamine reduces prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) levels in aqueous humor. The mean concentration of PGE<sub>2</sub> was 80 pg/mL in the aqueous humor of eyes receiving vehicle and 28 pg/mL in the eyes receiving ACULAR® 0.5% ophthalmic solution.

One drop (0.05 mL) of 0.5% ACULAR® ophthalmic solution was instilled into one eye and one drop of vehicle into the other eye TID in 26 normal subjects. Only 5 of 26 subjects had a detectable amount of ketorolac in their plasma (range 10.7 to 22.5 ng/mL) at Day 10 during topical ocular treatment.

Innopharma EX1039, Page 3

Continued on next page