PRODUCT MONOGRAPH

NU-KETOROLAC

Ketorolac Tromethamine Ophthalmic Solution

0.5%

Topical Anti-Inflammatory Agent

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PRODUCT MONOGRAPH

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PHARMACOLOGIC/THERAPEUTIC CLASSIFICATION

Topical Anti-Inflammatory Agent

ACTIONS AND CLINICAL PHARMACOLOGY

Ketorolac tromethamine is a non-steroidal, anti-inflammatory agent demonstrating analgesic and anti-inflammatory activity. At concentrations of 0.02% to 0.5%, ketorolac tromethamine solution did not irritate the eyes of rats, dogs and monkeys. Up to 4.0% concentrations were nonirritating in albino rabbits.

Ketorolac tromethamine has demonstrated anti-inflammatory activity when applied topically in several animal models of ocular inflammation. The compound significantly inhibited the inflammatory responses to silver nitrate-induced cauterization of the corneas of rat eyes at concentrations of 0.25% and 0.5%. Concentrations of ketorolac ranging from 0.02% to 0.5% blocked vascular permeability changes caused by endotoxin-induced uveitis in the eyes of rabbits. Using the same model, ketorolac also blocked endotoxin-induced elevation of aqueous humor PGE2. It 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.*

Applications of a 0.5% ketorolac solution did not delay the healing of experimental corneal wounds in rabbits. This solution did not enhance the spread of experimental ocular infections induced in rabbits with *Candida albicans, Herpes simplex* virus type one, or *Pseudomonas aeruginosa*.

Two drops (0.1 mL) of 0.5% ketorolac tromethamine 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. The mean ketorolac concentration was 95 ng/mL in the aqueous humor and the range was 40 ng/mL to 170 ng/mL. The mean concentration of PGE2 was 80 pg/mL in the aqueous humor of eyes receiving vehicle and 28 pg/mL in the eyes receiving 0.5% ketorolac tromethamine ophthalmic solution.

One drop (0.05 mL) of 0.5% ketorolac tromethamine ophthalmic solution was instilled into one eye and one drop of the vehicle into the other eye t.i.d. for 21 days in 26 healthy subjects. Only 5 of 26 subjects had detectable amounts of ketorolac in their plasma (range 10.7 and 22.5 ng/mL) when tested 15 minutes after the morning dose on day 10.

When ketorolac is given systemically to relieve pain, the average plasma level following chronic systemic treatment was approximately 850 ng/mL.

The recommended daily dose for ophthalmic use topically is from 1/20th to 1/50th of the recommended oral daily dose used to relieve pain.

Ketorolac tromethamine given systemically does not cause pupil constriction. Results from clinical studies indicate that ketorolac tromethamine ophthalmic solution has no significant effect upon intraocular pressure.

INDICATIONS AND CLINICAL USE

NU-KETOROLAC (ketorolac tromethamine) Ophthalmic Solution 0.5% is indicated for the prophylaxis and the relief of postoperative ocular inflammation in patients undergoing cataract extraction with or without implantation of an intraocular lens.

CONTRAINDICATIONS

NU-KETOROLAC (ketorolac tromethamine) Ophthalmic Solution 0.5% should not be used in patients who have previously exhibited hypersensitivity to any of the ingredients in the formulation.

The potential for cross-sensitivity to acetylsalicylic acid and other nonsteroidal anti-inflammatory drugs exists although it has not been reported. NU-KETOROLAC (ketorolac tromethamine) Ophthalmic Solution 0.5% therefore should not be used in patients who have previously exhibited sensitivities to these drugs.

WARNINGS

Pregnancy

Ketorolac tromethamine ophthalmic solution 0.5% is not recommended during pregnancy, labor or delivery.

Lactation

Ketorolac tromethamine ophthalmic solution is not recommended for treatment of nursing mothers. Secretion of ketorolac tromethamine in human milk after systemic administration is limited. The milk-to-plasma ratio of ketorolac tromethamine concentrations ranged between 0.015 and 0.037 in a study of 10 women.

PRECAUTIONS

General

It is recommended that ketorolac tromethamine ophthalmic solution be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

Children

Safety and efficacy in children have not been established.

Drug Interactions

There have been no reports in the controlled trials of interactions of ketorolac tromethamine ophthalmic solution with topical or injectable drugs used pre-, intra-, or post-operatively including antibiotics (e.g., gentamicin, tobramycin, neomycin, polymyxin), sedatives (e.g., diazepam, hydroxyzine, lorazepam, promethazine HCl), miotics, mydriatics, cycloplegics (e.g., acetylcholine, atropine, epinephrine, physostigmine, phenylephrine, timolol maleate),

hyaluronidase, local anesthetics (e.g., bupivacaine HCl, cyclopentolate HCl, lidocaine HCl, tetracaine) or corticosteroids.

Carcinogenesis, Mutagenesis and Impairment of Fertility

Long-term studies in mice and rats have shown no evidence of carcinogenicity, teratogenicity or impairment of fertility, with ketorolac tromethamine. No mutagenic potential of ketorolac was found in the Ames bacterial or the micronucleus test for mutagenicity.

Infection

In common with other anti-inflammatory drugs, ketorolac tromethamine may mask the usual signs of infection.

Ophthamology

Blurred and/or diminished vision has been reported with the use of ketorolac tromethamine and other nonsteroidal anti-inflammatory drugs. If such symptoms develop this drug should be discontinued and an ophthalmologic examination performed. Ophthalmic examination should be carried out at periodic intervals in any patient receiving this drug for an extended period of time.

ADVERSE REACTIONS

Since other nonsteroidal anti-inflammatory drugs have been known to irritate the eye upon topical application, ketorolac tromethamine was studied for its ocular irritation potential in animals and man.

In two multidose studies in healthy volunteers, one drop of 0.5% ketorolac tromethamine ophthalmic solution was applied three times daily for 21 days. Mild to moderate transient ocular burning/stinging was reported.

Most ocular complaints reported in clinical studies could not be distinguished from adverse events caused by the trauma of cataract surgery and the insertion of an intraocular lens.

The most frequent adverse reactions were conjunctivitis (redness, scratchiness, foreign body sensation, 10%) eye pain (pain, ache and burn, 6%), ptosis (5%) and keratitis (corneal edema, 3%). Iritis, corneal lesion, eye disorder, photophobia pupillary disorder, blepharitis and glaucoma were each reported with a prevalence of 2%.

Up to two drops (0.1 mL or 0.5 mg) of 0.5% ketorolac tromethamine ophthalmic solution per eye every 6 to 8 hours have been administered postsurgically.

None of the typical adverse reactions reported with the systemic nonsteroidal anti-inflammatory agents or ketorolac tromethamine have been observed at the doses used in topical ophthalmic therapy.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

The absence of experience with acute overdosage systemically or topically precludes characterization of sequelae and assessment of antidotal efficacy at this time. If ingested accidentally, drink fluids to dilute.

DOSAGE AND ADMINISTRATION

The recommended dose of NU-KETOROLAC (ketorolac tromethamine) Ophthalmic Solution 0.5% is one to two drops (0.25 to 0.5 mg) every six to eight hours beginning 24 hours before surgery and continuing for three to four weeks for prophylaxis and relief of postoperative ocular inflammation.

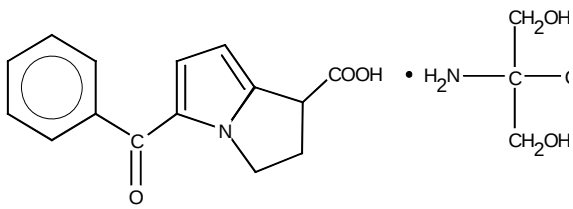
PHARMACEUTICAL INFORMATION

Drug Substance

Proper/Common Name: Ketorolac tromethamine

Chemical Name: (±)-5-Benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid, 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1)

Structural Formula:



Molecular Formula: $C_{19}H_{24}N_2O_6$
Molecular Weight: 376.41

Description: Ketorolac tromethamine (pKa = 3.46) is an off-white to white crystalline powder that melts at about 162°C with decomposition. It is freely soluble in water and methanol, slightly soluble in tetrahydrofuran, 190 proof and 200 proof ethanol and practically insoluble in acetone, dichloromethane, toluene, ethyl acetate, dioxane, hexane, butanol and acetonitrile. The pH of a 1% (w/v) solution in distilled water is 5.7 - 6.7.

COMPOSITION

Each mL of NU-KETOROLAC Ophthalmic Solution, 0.5% contains ketorolac tromethamine 5 mg, with the following non-medicinal ingredients: benzalkonium chloride 0.01% as the preservative and edetate disodium; octoxynol 40; sodium chloride; sodium hydroxide or hydrochloric acid solution to adjust pH.

STABILITY AND STORAGE RECOMMENDATIONS

Store at 15-30°C (59-86°F). Protect from light. Discard 28 days after opening.

AVAILABILITY OF DOSAGE FORMS

NU-KETOROLAC Ophthalmic Solution, 0.5%, preserved, is supplied as a sterile ophthalmic solution in white opaque plastic multidose bottles of 5 and 10 mL with a controlled dropper tip.

INFORMATION FOR THE PATIENT

HOW TO MAKE NU-KETOROLAC WORK BEST FOR YOU

Your doctor has decided that NU-KETOROLAC (ketorolac tromethamine) Ophthalmic Solution 0.5% is the best treatment for you. Remember that your chances of controlling your symptoms are greater if you cooperate fully with your doctor and try to become well informed about your condition.

This insert is not as thorough as the official Product Monograph on NU-KETOROLAC Ophthalmic Solution (which your doctor or pharmacist has available), and is meant to supplement what your doctor has told you. Your doctor knows and understands your personal condition; be sure to follow your doctor's instructions carefully and read any materials he or she gives you. If you have any questions after reading this patient package insert, be sure to ask your doctor.

WHAT IS NU-KETOROLAC?

NU-KETOROLAC is the product name for ketorolac tromethamine, a medicine used for the prevention and relief of post-operative eye inflammation. It belongs to a family of drugs known as non-steroidal anti-inflammatory drugs (NSAIDs) or anti-prostaglandin drugs.

WHAT DOES NU-KETOROLAC LOOK LIKE?

NU-KETOROLAC Ophthalmic Solution is supplied in a white opaque plastic bottle with a controlled dropper tip.

HOW DOES NU-KETOROLAC WORK?

Conditions like yours are usually associated with inflammation. Research shows that NU-KETOROLAC works by reducing the production of certain substances (called prostaglandins) that the body normally produces to help control such functions as muscle contraction, inflammation, and numerous other body processes.

Clinical studies indicate that when prostaglandin levels are reduced, the intensity of pain, and inflammation is reduced as well.

BEFORE USING THIS MEDICINE

To decide on the best treatment for your medical problem, your doctor should be told:

- If you have ever had any unusual or allergic reaction to NU-KETOROLAC.
- If you are allergic to any substance. Most medicines contain more than their active ingredient. Your doctor, nurse, or pharmacist can help you avoid products that may cause a problem.
- If you are pregnant or if you may become pregnant. NU-KETOROLAC is not recommended during pregnancy, labor or delivery.
- If you are breast-feeding. NU-KETOROLAC is not recommended for treatment of nursing mothers.
- If you have any medical problems.

- If you are taking any other prescription or nonprescription (over-the-counter (OTC)) medicine.

HOW SHOULD YOU TAKE NU-KETOROLAC TO MAKE IT WORK BEST FOR YOU?

Use this medicine only as directed. Do not use more of it and do not use it more often than your doctor ordered. To do so may increase the chance of too much medicine being absorbed into the body and the chance of side effects.

TO USE

- First, wash your hands. With the middle finger, apply pressure to the inside corner of the eye (and continue to apply pressure for one or two minutes after the medicine has been placed in the eye). Tilt the head back and with the index finger of the same hand, pull the lower eyelid away from the eye to form a pouch. Drop the medicine into the pouch and gently close the eyes. Do not blink. Keep the eyes closed for one or two minutes to allow the medicine to be absorbed.
- Immediately after applying the eye drops, wash your hands to remove any medicine that may be on them.
- To keep the medicine as germ-free as possible, do not touch the applicator tip to any surface (including the eye). Also, keep the container tightly closed.

If you miss a dose of this medicine, apply it as soon as possible. However, if it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do not double dose.

TO STORE THIS MEDICINE

- Keep out of the reach of children.
- Store containers at room temperature between 15 - 30°C (59 - 86°F). Protect from light. Discard 28 days after opening.

IMPORTANT! You doctor may give you different instructions better suited to your specific needs. If you need more information about how to take NU-KETOROLAC properly, double-check with your doctor or pharmacist.

WILL THE AMOUNT OF NU-KETOROLAC YOU TAKE EVER CHANGE?

It might change. As time goes by, your doctor may decide that it is advisable to make adjustments in the dosage of NU-KETOROLAC you are taking. He or she may suggest that you increase or decrease your medication according to how severe your symptoms are or how active you are.

Follow instructions; your doctor understands how to set the upper and lower dosage limits so that you get the greatest benefit from NU-KETOROLAC.

DOES NU-KETOROLAC HAVE SIDE EFFECTS?

Along with its needed effects, a medicine may cause some unwanted effects.

Most eye complaints reported in clinical studies could not be distinguished from side effects caused by the cataract surgery and the insertion of an intraocular lens. The most frequently reported complaints after NU-KETOROLAC therapy include transient stinging and burning, redness, itching and/or swelling and visual blurring following instillation of the eye drops.

If you are allergic to ASA or to any of the other non-steroidal anti-inflammatory drugs (e.g., diclofenac, diflunisal, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, mefenamic acid, piroxicam, sulindac, tiaprofenic acid, tolmetin) used to treat arthritis or other muscle and joint conditions, do not take NU-KETOROLAC. You may be allergic to it, too.

ARE THERE ANY SPECIAL DO'S AND DON'T'S ABOUT TAKING NU-KETOROLAC?

DO tell your doctor and pharmacist about any other medications you take, both prescription and nonprescription. This is important because some drugs can interact with each other and produce undesirable effects.

DO check with your doctor if:
- you are not getting relief
or
- you have any problems while taking NU-KETOROLAC.

DO tell your physician if you are pregnant or are planning to become pregnant.

DON'T take NU-KETOROLAC if you are breast-feeding. Some drug does pass into the milk of nursing women.

DON'T take NU-KETOROLAC if you are allergic to it, or if you have had an allergic-type reaction to ASA or to any other drug used for pain relief or arthritis. **DO** check with your doctor.

DO cooperate with your doctor if he or she wants you to take certain lab tests to monitor the effectiveness of treatment or possible side effects.

CONTAINS

Each millilitre contains ketorolac tromethamine 5 mg, with the following non-medical ingredients: benzalkonium chloride 0.01% as the preservative and edetate disodium; octoxynol 40; sodium chloride; sodium hydroxide or hydrochloric acid solution to adjust pH.

PHARMACOLOGY

Animal Pharmacology

As outlined below and on the next several pages, several studies have been conducted in animals with ketorolac acid or ketorolac tromethamine solutions demonstrating: minimal eye irritation; anti-inflammatory activity in several models of ocular inflammation; prevention of arachidonic acid induced increases in intraocular pressure with no affect on normal intraocular pressure; no impairment of corneal wound healing; no potentiation of ocular infections; and no effects on the proliferation of endothelial cells.

Model	Species	Treatment Groups (Route)	Concentration	Number of Animals
Eye Irritation	Rat	Ketorolac tromethamine (topical)	0.02% 0.1% 0.5%	4 4 4

Method:

One drop vehicle to left eye followed by one drop active into right eye.

- Number of blinks/minute was measured.
- This was repeated the next day with vehicle in right eye and active in left eye.

Activity:

Ketorolac tromethamine was more irritating to the rat eye than vehicle, however, the degree of irritation was minimal compared to that caused by known irritants. There was no dose-related increase in the number of blinks.

Model	Species	Treatment Groups (Route)	Concentration	Number of Animals
Eye Irritation	Rat	Ketorolac acid (topical)	0.02% 0.1% 0.5%	4 4 4
Eye Irritation (Cont'd)	Rhesus monkey	Ketorolac acid (topical)	0.02% 0.1% 0.5%	1 1 1
	Dog	Ketorolac acid (topical)	0.02% 0.1%	1 1

Method:

One drop vehicle to left eye followed by one drop active into left eye.

- Number of blinks/minute was measured.

Activity:

Ketorolac did not cause a statistically significant increase in blinking when applied at concentrations of 0.2%-0.5% to the eyes of rats, dogs and monkeys.

Model	Species	Treatment Groups (Route)	Concentration	Number of Animals
Eye Irritation	Rabbit	Ketorolac acid (topical)	0.5%	Not reported

Method:

One drop applied to one eye every 30 minutes for a total of 12 doses.

Activity:

Ketorolac caused minimal to moderate irritation. Conjunctival congestion and discharge was minimal in nature but had a high incidence in the test group. Overall judgement was minimal conjunctival irritation with corneal cloudiness which reversed after 24 hours.

Model	Species	Treatment Groups (Route)	Concentration	Number of Animals
Silver nitrate induced neovascularization	Rat	Vehicle Ketorolac acid (topical)	— 0.1% 0.5%	12 12 12
		Vehicle Ketorolac acid (topical)	— 0.1% 0.25% 0.5%	12 12 12 12

Method:

One drop to each eye four times daily for five days.

Activity:

Ketorolac significantly ($p<0.05$) inhibited neovascularization caused by silver nitrate applied at concentrations of 0.25% and 0.5%. Although the 0.1% concentration of Ketorolac caused a decrease in neovascularization scores this effect was not statistically significant.

Model	Species	Treatment Groups (Route)	Concentration	Number of Animals
Endotoxin-induced uveitis	Rabbit	Ketorolac acid (topical)	0.5%	6

Method:

One drop active to right eye and vehicle to left eye, 2 hours and 1 hour pre-endotoxin and 30 minutes and 60 minutes post-endotoxin.

Activity:

Topically applied Ketorolac significantly reduced the degree of vascular permeability caused by systemic endotoxin administration ($p<0.01$).

Model	Species	Treatment Groups (Route)	Concentration	Number of Animals
Endotoxin-induced uveitis	Rabbit	Vehicle Ketorolac tromethamine (topical)	— 0.001% 0.003% 0.01% 0.03% 0.1% 0.5%	8 8 7 9 9 10 13

Method:

0.05 mL active (or vehicle) to right eye and vehicle to left eye, 2 hours and 1 hour pre-endotoxin, at endotoxin challenge and one hour post-endotoxin. Vascular permeability changes monitored by fluorophotometry.

Activity:

The two lowest concentrations of ketorolac tromethamine (0.001%, 0.003%) did not significantly inhibit vascular permeability changes induced by endotoxin whereas concentrations of 0.01% to 0.5% were able to prevent these changes ($p<0.026$).

Model	Species	Treatment Groups (Route)	Concentration	Number of Animals
Endotoxin-induced elevation of aqueous humor PGE2	Rabbit	Vehicle Ketorolac tromethamine (topical)	— 0.1% 0.5%	8 8 5

Method:

0.05 mL active (or vehicle) to right eye and vehicle to left eye 20 minutes pre-endotoxin. At 90 minutes post-endotoxins, aqueous humor samples were assayed. An additional group (n=6) was given vehicle and no endotoxin.

Activity:

The 0.5% ketorolac tromethamine concentration was significantly (p=0.03) more active than the 0.1% concentration in preventing PGE2 increases. There were no significant differences in PGE2 levels (p=0.08) between the 0.5% ketorolac tromethamine group and the group given vehicle and no endotoxin.

Model	Species	Treatment Groups (Route)	Concentration	Number of Animals
Substance P-induced uveitis	Rabbit	Ketorolac acid (topical)	0.5%	8

Method:

One drop to the eye 60 minutes and 30 minutes prior to substance P (30 nM or 1 nM) and immediately following substance P injection.

Activity:

The miosis caused by intraocular injection of substance P was not significantly altered by ketorolac. The data suggests, however, that supra optimal concentrations of substance P were used.

Model	Species	Treatment Groups (Route)	Concentration	Number of Animals
Ocular inflammation induced by BW 48/80 (a stimulator or mast cell degranulation	Rabbit	Ketorolac acid (topical)	0.5%	2

Method:

One drop active to the right eye and one drop vehicle to left eye 60, 30, 15 minutes and just prior to BW 48/80. Eyes were scored for inflammatory response 10, 20 and 30 minutes post-BW 48/80 treatment.

Activity:

At 30 minutes post-challenge ketorolac-treated eyes were nearly normal, whereas vehicle-treated eyes still showed slight inflammation. Due to limited data no statistics were done.

Model	Species	Treatment Groups (Route)	Concentration	Number of Animals
Arachidonic acid-induced leakage of protein	Rabbit	Vehicle Ketorolac acid (topical)	— 0.00001% 0.0001% 0.001% 0.01% 0.1% 1.0%	4 6 12 12 6 12 4

Method:

Each rabbit eye pretreated with 50 µL of Ketorolac or vehicle prior to topical application of sodium arachidonate.

Activity:

Ketorolac inhibited arachidonic acid induced leakage of protein. The ED_{50} was estimated to be $4x10^{-5}$ g/100 mL. Corneal irritation was present but minimal with corneal cloudiness reversing after 24 hours.

Model	Species	Treatment Groups (Route)	Concentration	Number of Animals
Leukocyte migration	Rabbit	Ketorolac acid (topical)	0.5%	Not reported

Method:

Not reported.

Activity:

Ketorolac at 0.5% was found to decrease migration of the PMNs by 39%, which is equivalent to agents such as indomethacin.

Model	Species	Treatment Groups (Route)	Concentration	Number of Animals
Effect on intraocular pressure	Rabbit	Ketorolac acid (topical)	0.5%	10

Method:

One drop active to left eye and one drop vehicle to right eye, IOP determined pre-dose and 2 hours post-dose.

Activity:
Ketorolac did not significantly affect normal intraocular pressure in rabbits.

Model	Species	Treatment Groups (Route)	Concentration	Number of Animals
Effect on intraocular pressure	Rabbit	Ketorolac acid (topical)	0.5%	10

Method:
One drop active to left eye and one drop vehicle to right eye, 30 minutes and 15 minutes prior to arachidonic acid administration. IOPs determined prior to ketorolac and vehicle 15 minutes post-arachidonic acid.

Activity:
In comparison to vehicle ketorolac 0.5% diminished the effect on intraocular pressure caused by topical application of arachidonic acid to a statistically significant degree ($p<0.01$).

Model	Species	Treatment Groups (Route)	Concentration	Number of Animals
Lens aldose reductase	Rabbit	Ketorolac acid (*in vitro*)	1×10^{-6}M 1×10^{-5}M	Not applicable

Method:
Aldose reductase prepared from rabbit lenses.

Activity:
Ketorolac 1×10^{-5}M was found to inhibit lens aldose reductase *in vitro* by 30% which is not considered a meaningful level of inhibition.

Model	Species	Treatment Groups (Route)	Concentration	Number of Animals
Corneal wound healing	Rabbit	Vehicle Ketorolac acid (topical)	— 0.5%	10 11

Method:

Active (or vehicle) in right eye and vehicle in left eye t.i.d. for 7 days following ocular surgery. Tensile strength measured 21 days post surgery.

Activity:

Ketorolac did not influence wound healing as measured by the mean tensile strength.

Model	Species	Treatment Groups (Route)	Concentration	Number of Animals
Corneal wound healing	Rabbit	Saline Vehicle Ketorolac tromethamine (topical)	— — 0.5%	9 9 9

Method:

One drop of test material every 4 hours for 40 hours in surgically-treated eye. Wound areas measured by staining with fluorescein and photographing.

Activity:

Ketorolac tromethamine did not impair healing of a corneal epithelial abrasion.

Model	Species	Treatment Groups (Route)	Concentration	Number of Animals
Effect on *Canadida albicans* ocular infection	Rabbit	Vehicle Ketorolac tromethamine (topical)	— 0.5%	10 10

Method:

Staring 1 day post-infection 2 drops 4 times daily for 7 days.

Activity:

Ketorolac tromethamine did not potentiate a *C. albicans* ocular infection in rabbits.

Model	Species	Treatment Groups (Route)	Concentration	Number of Animals
Herpes simplex virus type one keratitis	Rabbit	Vehicle Ketorolac tromethamine (topical)	— 0.5%	10 10

Method:

Staring 1 day post-infection 2 drops 4 times daily for 7 days.

Activity:

Ketorolac tromethamine did not potentiate an HSV-1 ocular infection in rabbits.

Model	Species	Treatment Groups (Route)	Concentration	Number of Animals
Effect on *Pseudomonas aeruginosa* ocular infection	Rabbit	Vehicle Ketorolac tromethamine (topical)	— 0.5%	12 12

Method:

Staring 1 day post-infection 2 drops 4 times daily for 7 days.

Activity:

Ketorolac tromethamine did not potentiate a *Pseudomonas aeruginosa* ocular infection in rabbits.

Model	Species	Treatment Groups (Route)	Concentration	Number of Animals
Antiproliferative effects on capillary endothelial cells	Rabbit	Ketorolac acid (*in vitro*)	0.0001 µM-0.01 µM	Not applicable

Method:

Murine lung capillary endothelial cells were cultured and used for testing antiproliferative activity in both cells and exponentially-growing cells and quiescent cells.

Activity:

Ketorolac had no effect on the proliferation of exponentially growing capillary endothelial cell and slight inhibitory activity on the proliferation of quiescent cells stimulated with endothelial cell growth factor.

Model	Species	Treatment Groups (Route)	Concentration	Number of Animals

Antiproliferative effects on vascular endothelial cells	Rabbit	Ketorolac tromethamine (*in vitro*)	0.001 µM-0.01 µM	Not applicable

Method:

Fetal bovine heart endothelial cells were cultured and used for testing antiproliferative activity.

Activity:

Ketorolac tromethamine did not slow the proliferation of the cultured vascular endothelial cells.

Animal Pharmacokinetics

A series of studies were conducted with ophthalmic formulations of ketorolac acid and ketorolac tromethamine in rabbits and cynomolgus monkeys. Two different preservatives were used throughout these studies, namely a thimerosal (THIM) or a benzalkonium chloride (BAC) system. The benzalkonium chloride system was the final form selected for development due to its greater preservative efficacy and acceptability.

Single dose studies were performed using topical application, intracameral injection or intravenous administration in rabbits and/or cynomolgus monkeys. In the rabbit studies topical doses of 0.5% ketorolac tromethamine were delivered via microliter syringe drop-wise onto the eye (50 µL (0.25 mg) per eye). Intracameral injections consisted of 20 µL (0.25 mg) of the dose solution injected directly into the anterior chamber. Intravenous doses were delivered via the marginal ear vein.

In those studies involving monkeys the target dose for intravenous administration was 0.25 mg/kg. The topical ocular dose consisted of 100 µL per eye of 0.5% ketorolac tromethamine.

Ocular Absorption and Kinetics

Ocular absorption studies were conducted in female New Zealand white rabits. Each topical formulation (50 µL, 0.25 mg), containing either BAC or THIM preservative systems, was applied to both eyes of six rabbits. An equivalent dose (0.25 mg per eye) was injected intracamerally to both eyes of six additional rabbits. The rabbits were kept anesthetized throughout the study.

Peak concentrations of ^{14}C-ketorolac were 100-fold greater after intracameral injection compared with topical administration (Table 1). The ocular absorption of the BAC formulation was 93% relative with the thimerosal formulation. The ocular bioavailability of the topical formulations averaged 4%.

After topical ocular doses, the half-life of total radioactivity in aqueous humor using the BAC formulation (3.8 - 6.4 hours) was longer than after intracameral injection (2.1 hours). This suggests that topical dosing may lead to a "reservoir" effect in the corneal epithelium and continued flux of drug from the reservoir into the aqueous humor. In the anterior chamber, clearance of ^{14}C-ketorolac averaged 11 µL/min while apparent volume of distribution averaged 1.93 mL. (Table 1).

Table 1: Bioavailability Parameters of ^{14}C-Ketorolac in Anterior Chamber After Topical Application of 50 mcL of 0.5% Ketorolac Tromethamine or Intracameral Injection of 0.25 mg ^{14}C-Ketorolac Tromethamine to Rabbits

		Topical		
Parameter		**THIM**	**BAC**	**Intracameral**
No. of Animals		**6**	**8**	**6**
Aqueous humor Concentration (mcg-equiv/mL)	0.5 hr	0.860 (75)	0.856 (49)	188.0 (52)
	1 hr	0.875 (42)	1.019 (61)	106.1 (52)
	2 hr	1.431 (51)	1.607 (69)	58.2 (52)
	4 hr	1.249 (50)	1.501 (36)	27.6 (46)
	6 hr	0.776 (45)	1.049 (36)	10.7 (50)
	8 hr	0.644 (50)	0.684 (45)	7.6 (75)
Tmax, (hr)		1.92 (45)	3.38 (50)	0.5 (0)
Cmax, (mcg-equiv/mL)		1.575 (49)	1.905 (49)	188.0 (52)
AUC (0-8 hr), (mcg-equiv.hr/mL)		7.93 (44)	9.39 (59)	335.3 (55)
Total AUC, (mcg-equiv.hr/mL)		14.61 (55)	13.53 (42)	—
Half-life, (hr)		6.43 (76)	3.77 (43)	2.11 (46)
Faq[1], (%)		4.2	3.7	—
CLaq[2], (mcL/min)		—	—	11 (64)
VDaq[3], (mL)		—	—	1.93 (80)

[1] $Faq = \frac{AUCaq\ (topical)}{AUCaq\ (intracameral)} \times \frac{Dose\ (intracameral)}{Dose\ (topical)} \times 100\%$

[2] $CLaq = \frac{Dose\ (intracameral)}{AUCaq\ (intracameral)}$

[3] $VDaq = \frac{Claq}{\beta\ (aq)}$

Systemic Absorption

The extent of systemic absorption of the ocular dose in the rabbit was estimated using both plasma AUC and urinary excretion data. Plasma concentrations of total radioactivity and intact ketorolac were measured in the rabbit after topical (n=6), intracameral (n=6), and intravenous (n=3) administration of ^{14}C-ketorolac tromethamine.

After a single ophthalmic dose (50 µL) in the rabbit, intact ketorolac was absorbed rapidly into the systemic circulation (Tmax, 15 minutes) (Table 2). The plasma half-life after ophthalmic

doses (6.9 hours) was longer than after i.v. administration (1.1 hour), suggesting that removal of drug from the eye into the venous circulation may be rate-limiting. By comparison of drug levels in aqueous humor after intracameral injection vs. plasma levels after i.v. administration, ketorolac was shown to clear more rapidly in plasma (6 mL/min) than in the anterior chamber (11 µL/min).

Table 2: Mean Computed Bioavailability and Pharmacokinetic Parameters of Intact Ketorolac in Plasma of Rabbits and Cynomolqus Monkey

	Rabbit			Monkey	
Parameter	**Topical**	**Intracameral Injection**	**I.V.**	**Topical**	**I.V.**
No. of Animals	**6**	**6**	**3**	**3**	**3**
Dose	0.505 mg	0.509 mg	1.0 mg	0.078 (65) mg/kg	0.253 (14) mg/kg
Tmax, min	15 (0)	36 (37)*	5 (0)	65 (67)	0.08 (0)
Cmax, (mcg-equiv/mL)	0.185 (14)	0.116 (34)*	2.689 (19)	0.421 (68)	3.40 (17)
Total AUC, (mcg or mcg.eq) hr/mL	1.074 (40)	1.342 (44)*	2.009 (36)	1.33 (67)	6.01 (69)
AUC ratio (Ket/TR)	0.91	0.78	0.80	0.96 (9)	0.96 (4)
$^{T}1/2,\ ^{hr}$	6.89 (31)	7.40 (46)*	1.06 (33)	1.82 (25)	1.55 (16)
^{F}plasma, %	106	131	—	76.4 (19)	—

Values represent mean (% coefficient of variation)
* Due to insufficient sample, values computed from 5 rabbits.

$$^{F}\text{plasma} = \frac{\text{AUC (ophthalmic)}}{\text{AUC (i.v.)}} \times \frac{\text{Dose (i.v.)}}{\text{Dose (ophthalmic)}} \times 100\%$$

In a study involving 3 cynomolgus monkeys, ^{14}C-ketorolac tromethamine solution was administered intravenously and in a topical ocular solution. Peak plasma levels of ketorolac occurred at 1.1 hour after the ophthalmic dose. The plasma half-life of ketorolac was similar after ophthalmic (1.8 hours) and i.v. doses (1.6 hours) (Table 3).

The majority of the ophthalmic dose was excreted in urine (66% in rabbit (n=24) and 75% in monkey (n=3)) and a small amount in feces (11% in rabbit (n=24) and 2% in monkey (n=3)). The extent of systemic absorption based upon urinary data after ophthalmic dosing averaged 73% (n=3) and 74% (n=24) in rabbit and 76% (n=3) in the cynomolgus monkey. The systemic absorption estimated from the AUC data were 40% (n=3) and 64% (n=24) in rabbit and 73% in the cynomolgus monkey.

Concentrations of ketorolac tromethamine in aqueous humor and plasma were determined in a six-month ocular toxicity study in the cynomolgus monkey. Two drops (100 µL) per eye of the ophthalmic solution were applied 3, 6 and 9 times daily over 8 hours to groups of 12 cynomolgus monkeys. Plasma concentrations of ketorolac tromethamine were determined on day 1 and at the end of 3 and 6 months. Aqueous humor was also assayed at 3 and 6 months.

Concentrations of ketorolac in the aqueous humor confirmed drug absorption in the eye of monkeys and were directly proportional to the administered dose. Relative to the 3X/day dose, concentrations of ketorolac in the aqueous humor after the 6X and 9X daily dose averaged 2.1 and 3.1 times higher respectively at the end of 3 months, and 1.8 and 2.7 fold higher levels respectively at the end of 6 months. A dose-proportional increase in plasma trough levels was demonstrated at the end of 6 months. Mean plasma levels of ketorolac were 2.2-fold and 3.3-fold higher after the 6X and 9X daily dose, respectively, compared with the 3X daily dose. The results indicted that there was no accumulation of drug levels in aqueous humor and in plasma with repeated ophthalmic dosing.

In a similar study two drops (100 µL) per eye of the ophthalmic solution were applied 3 or 9 times daily over 8 hours for one month to groups of 4 cynomolgus monkeys. Plasma concentrations were determined on day 1 and at the end of the study, and aqueous humor concentrations of ketorolac were measured at 1 month. Relative to the 3X/day dose, concentrations of ketorolac in the aqueous humor after the 9X/dose averaged 5.3-fold higher at the end of 1 month. Plasma levels at 1 month were 5-fold higher in the 9X/day dose relative to the 3X/day dose. The results of the one-month study also showed a low degree of systemic exposure and relatively higher levels in the aqueous humor compared to plasma levels of ketorolac.

Ocular Distribution

The intraocular distribution of ^{14}C-ketorolac tromethamine was determined in the rabbit (n=24) after topical application of 50 µL of 0.5% ^{14}C-ketorolac tromethamine optical solution containing benzalkonium chloride as the preservative. Peak concentrations of radioactivity were achieved within 1 hour in the ocular tissues and were highest in the cornea (6.06 µg-eg/mL) (Table 3). At 1 hour, the majority of the radioactivity (0.9% of administered dose) was recovered in the sclera (0.58%) and cornea (0.26%), vitreous humor (0.023%), retina-choroid (0.018%), iris-ciliary body (0.007%) and lens (0.002%).

Table 3: Pharmacokinetic Parameters of Total Radioactivity in Eye Tissues and Plasma After Topical Application of 50 µL of 0.5% ^{14}C-Ketorolac Tromethamine in Rabbits Eyes (n=24)

Tissue Fluid	Tmax (hr)	Cmax (µg eq/mL)	Total AUC (µg eq hr/mL)	AUC[b] Ratio	Half-Life[a] (hr)

Cornea	1.0	6.058	72.809	103.9	8.2
Sclera	1.0	1.728	18.775	26.8	22.3
Iris-ciliary body	4.0	0.306	4.049	5.8	10.4
Lens	0.5	0.013	0.417	0.6	35.4
Retina-choroid	1.0	0.418	3.902	5.6	10.6
Aqueous humor	1.0	0.217	2.330	3.3	7.1
Vitreous humor	0.5	0.036	0.373	0.5	14.9
Plasma	0.5	0.139	0.701	1.0	4.5

[a] Half life determined by linear regression of the log tissue or plasma concentration at 6, 8 and 24 hours.
[b] AUC (tissue/fluid)/AUC (plasma)

Relative to plasma AUC values, the AUCs were higher for cornea (104-fold), sclera (27-fold), iris-ciliary body (5.8-fold), retina-choroid (5.6-fold), aqueous humor (3.3-fold) and approximately one-half in the vitreous humor and lens (Table 4). When compared with an intravenous dose equivalent to twice the ophthalmic dose of ^{14}C-ketorolac tromethamine administered via the marginal ear vein (n=3), concentrations of drug-related radioactivity were higher in the ocular tissues and lower in plasma after ophthalmic administrations (Table 4).

Table 4: Influence of Route of Administration of ^{14}C-Ketorolac Tromethamine on the Concentrations of Total Radioactivity (μg Eq. per mL of G) in Ocular Tissues and Plasma of Rabbits

		Route Administered		
Ocular Tissue/Fluid	**Time (Hr)**	**Ophthalmic**	**I.V.**	**Oph/I.V.**
Cornea	0.5	5.417	0.0084	645
	1	6.058	0.0303	200
	5	4.004[b]	0.0118	339
Iris-ciliary body	0.5	0.301	0.1443	2.6
	1	0.301	0.0377	8.0
	5	0.253[b]	0.0202	12.5
Lens	0.5	0.0133	BDL[c]	—
	1	0.0124	BDL	—
	5	0.0085[b]	BDL	—
Retina-choroid	0.5	0.359	0.0641	5.6
	1	0.418	0.0647	6.5
	5	0.169[b]	0.0177	9.5
Aqueous humor	0.5	0.111	0.0014	79
	1	0.217	0.0013	167
	5	0.158[b]	0.0006	263
Vitreous humor	0.5	0.036	0.0022	16
	1	0.027	0.0025	11
	5	0.011[b]	0.0007	16
Plasma	0.5	0.139	0.971[d]	0.14
	1	0.085	0.742[d]	0.11
	5	0.045[b]	0.066[d]	0.68

[a] The total ophthalmic dose (0.493 mg) instilled on both eyes of each rabbit was approximately one-half of the intravenous dose (1 mg).
[b] Interpolated from 4 and 6 hours values.
[C] BDL = below detectable limit.
[d] Values averaged from three rabbits after a single intravenous dose of 1 mg of ^{14}C-ketorolac tromethamine.

Animal Metabolism

The metabolite profile in aqueous humor was determined in the rabbit, while plasma and urinary metabolite profiles were determined in both the rabbit and cynomolgus monkey after ophthalmic and i.v. dosing.

After ophthalmic administration in rabbits, ketorolac represented the major component (>90%) of radioactivity in aqueous humor and plasma and the p-hydroxy metabolite accounted for 5 % of radioactivity in plasma. Ketorolac was also the major component (96%) of plasma radioactivity after ophthalmic dosing in monkeys (n=3) (Table 5).

After ophthalmic dosing in the rabbit, 72%, 17% and 6% of the total radioactivity in urine was comprised of intact ketorolac, p-hydroxy ketorolac and other polar metabolites. After i.v. dosing, the relative proportions of total radioactivity averaged 6% as intact ketorolac, 68% as p-hydroxy ketorolac and ~22% as polar metabolites (Table 5).

In the monkey, intact ketorolac and its polar metabolite (possibly the glucuronide conjugate of ketorolac) accounted for 32% and 65% of the total radioactivity in urine, respectively after ophthalmic dosing, and 50% and 49% of the radioactivity in urine, respectively after i.v. dosing (Table 5). Thus, the metabolism of ketorolac was qualitatively very similar after ophthalmic and i.v. administration in the monkey.

Table 5: Metabolic Profiles in Plasma and Urine Following Ophthalmic and I.V. Administration

				% of Total Radioactivity						
				Plasma AUC[3]				Urine[4]		
Species	Route of Administration Dosage Form	Dose[1]	N[2]	p-OH Ketorolac	Ketorolac	Conjugate 1	Conjugate 2	p-OH Ketorolac	Ketorolac	Ref
Rabbit	I.V. Solution	1.0 mg	3	11.3 (46)	81.9 (7)	9.7	11.8	68.2	6.4	7
Rabbit	Ophthalmic BAC	0.505 mg	6	5.1 (21)	92.2 (4)	NA	NA	NA	NA	7
Rabbit	Ophthalmic BAC	0.510 mg	3	NA[5]	NA	1.4	4.4	17.1	71.7	7
Monkey	I.V. Solution	0.253 mg/kg	3	ND[6]	96.1	ND	48.5	ND	49.8	17
Monkey	Ophthalmic BAC	0.078 mg/kg	3	ND	95.9	ND	64.8	ND	32.3	17

Values represent mean (% coefficient of variation)

[1] Dose of ketorolac tromethamine administered per rabbit or monkey; 50 mcL of the ophthalmic dose solution was applied to each rabbit eye and 100 mcL applied to each monkey eye.
[2] N = number of animals.
[3] Total AUC (rabbits) or 0-10 hour AUC (monkeys).
[4] Metabolic profile of 0-24 hours pooled urine (85-RB-33 OPH 4, 86-CMK-20) or urine pooled for 3 rabbits at each time point (Study 84-RB-36).
[5] NA = Not available.
[6] ND = Not detected.

Human Studies

The penetration of ketorolac ophthalmic solution into the anterior chamber of the eye was studied in patients undergoing unilateral cataract extraction with intra-ocular lens implantation. The average concentration of ketorolac in the aqueous humor was 95 ng/mL following the instillation of two drops of the 0.5% solution approximately 12 hours and 1 hour before surgery. The concentration of ketorolac in the aqueous humor was below the detection limit of the assay (40 ng/mL) when two drops of 0.1% solution were instilled into the eyes of another group of patients undergoing the same surgical procedure.

Concentrations of PGE2 in the aqueous humor were depressed following the instillation of both the 0.1% and 0.5% ketorolac solutions. However, compared to the vehicle-treated group, the depression of PGE was not statistically significant.

In a 21-day multiple (t.i.d.) dose study in healthy volunteers, five of the 26 subjects had detectable (>10 ng/mL) plasma levels of ketorolac (11 ng/mL to 22 ng/mL) following 10 days of instillation of one 0.5% ketorolac ophthalmic solution. One subject had detectable levels before the first morning dose on Day 10 and the other 4 subjects had detectable levels when tested 15 minutes after the morning dose on Day 10. None of the volunteers had detectable levels on Day 24, three days after the end of dosing.

To put these plasma levels into perspective, when 10 mg of ketorolac was given a single intramuscular or oral dose or as multiple doses, the plasma level of ketorolac was approximately 850 mg/mL 30 minutes after dosing.

TOXICOLOGY

Acute Toxicity Studies

Species **Strain** **Regimen** **Group Size** **Preservative**	**Route** **Concentration*** **(mg/mL)**	**Mortality**	**Clinical** **Ophthalmology**

Rabbit New Zealand One dose in right eye followed by a 72-hour observation 3 females 0.01% BAC	Ocular 2.5 5.0 10.0 20.0 40.0	 0/3 0/3 0/3 0/3 0/3	 NDE NDE NDE NDE NDE
Rabbit New Zealand One dose every one-half hour for a total of 12 doses to both eyes. Eyes were examined after the last dose and on days 1, 2, 3 and 6 following dosing 6 males 0.01% BAC	Ocular Saline control Vehicle control 5.0	 0/6 0/6 0/6	 NDE

NDE = No drug effect (no indications of irritation or toxicity)
BAC = Benzalkonium Chloride
*Volume = 0.1 mL/eye

Subchronic/Chronic Toxicity Studies

Species	Rabbit
Strain	New Zealand
Regimen	Twice daily for 10 days
Group Size	3 females
Preservative	0.01% BAC
Route	Ocular
Concentration* (mg/mL) Saline 2.5 5.0 10.0 20.0 40.0	**Mortality** 0/3 0/3 0/3 0/3 0/3 0/3
Clinical Ophthalmology	No drug effect
Pathology	No drug effect

BAC = Benzalkonium Chloride
*Volume = 0.1 mL/eye

Subchronic/Chronic Toxicity Studies

Species	Rabbit
Strain	Dutch Belted
Regimen	Three times daily for 28 days
Group Size	6 females
Preservative	0.01% BAC
Route	Ocular

Concentration* (mg/mL) Saline Vehicle 2.5 10.0 40.0	**Mortality** 0/6 0/6 0/6 0/6 0/6
Clinical Ophthalmology	Corneal epithelial straining in ophthalmology vehicle and drug treated groups, the severity decreasing with increasing drug concentration.
Pathology	Corneal epithelial thinning in vehicle and drug-treated groups. The severity decreased with increasing drug concentration. These ocular changes have been demonstrated with other ophthalmic formulations containing benzalkonium chloride.

BAC = Benzalkonium Chloride
*Volume = 0.1 mL/eye

Subchronic/Chronic Toxicity Studies (Cont'd)

Species **Strain** **Regimen** **Group Size** **Preservative** **Route**	Rabbit 6 New Zealand/Group 6 Dutch Belted/Group Three times daily for 28 days followed by a 28-day recovery period 12 animals (8-9 males, 3-4 females) 0.01% BAC Ocular
Concentration* (mg/mL) Saline Vehicle 2.5 10.0 40.0 **Clinical Ophthalmology** **Pathology**	**Mortality** 0/12 1/12 0/12 0/12 0/12 BAC-related corneal staining and lesions, primarily in low-dose group. No drug effect.

BAC = Benzalkonium Chloride
*Volume = 0.1 mL/eye

Species **Strain** **Regimen** **Group Size** **Preservative** **Route**	Rabbit Dutch Belted Three times daily for 36 days 6 females 0.01% BAC Ocular
Concentration* (mg/mL) Vehicle 2.5 10.0 40.0 **Clinical Ophthalmology** **Pathology**	**Mortality** 0/6 0/6 0/6 0/6 All groups had evidence of corneal epithelial staining. Effects were not concentration-related. Corneal epithelial thinning was noted in all groups. Effects were not concentration-related. These ocular changes have been demonstrated with other ophthalmic formulations containing benzalkonium chloride.

BAC = Benzalkonium Chloride
*Volume = 0.1 mL/eye

Subchronic/Chronic Toxicity Studies (Cont'd)

Species	Rabbit
Strain	New Zealand
Regimen	Three times daily for 42 days
Group Size	6 females
Preservative	0.0025% Thimerosal
Route	Ocular
Concentration* (mg/mL)	**Mortality**
Saline	0/6
Vehicle	0/6
2.5	0/6
10.0	0/6
40.0	0/6
Clinical Ophthalmology	No drug effect
Pathology	No drug effect

*Volume = 0.1 mL/eye

Species	Monkey
Strain	Cynomolgus
Regimen	29 days (3 X or 9 X/day)
Group Size	2 males and 2 females
Preservative	0.01% BAC
Route	Ocular
Concentration* (mg/mL)	**Mortality**
Saline	0/4
Vehicle	0/4
5.0 (3 X/day)	0/4
5.0 (9 X/day)	0/4
Clinical Ophthalmology	Punctate corneal staining in vehicle and drug-treated groups.
Pathology	No drug effect

BAC = Benzalkonium Chloride
*Volume = 0.1 mL/eye

Subchronic/Chronic Toxicity Studies (Cont'd)

Species	Monkey
Strain	Cynomolgus
Regimen	Three times daily for 28 days
Group Size	2 females
Preservative	0.0025% Thimerosal
Route	Ocular
Concentration* (mg/mL)	**Mortality**
Saline	0/2
Vehicle	0/2
2.5	0/2
10.0	0/2
40.0	0/2
Clinical Ophthalmology	No drug effect
Pathology	No drug effect

*Volume = 0.1 mL/eye

Species	Monkey
Strain	Cynomolgus
Regimen	6 months (3 month interim sacrifice)
Group Size	6 males and 6 females
Preservative	0.0025% Thimerosal
Route	Ocular
Concentration* (mg/mL)	**Mortality**
Saline	0/12
5.0 (3 X/day)	0/12
5.0 (6 X/day)	0/12
5.0 (9 X/day)	0/12
Clinical Ophthalmology	No drug effect
Pathology	No drug effect

*Volume = 0.1 mL/eye

The results of the preclinical toxicology studies indicate no adverse drug-related effects to ketorolac tromethamine. No adverse effects were observed in monkeys following 6 months of treatment with the thimerosal formulation. However, in studies with the BAC (benzalkonium chloride) formulation, corneal fluorescein staining, accompanied by thinning of the epithelium, was seen in vehicle-treated and drug-treated animals. The Dutch Belted rabbit was most sensitive to these effects, with the New Zealand rabbit and the monkey showing decreasing sensitivities. Since the effects were seen primarily in vehicle and low-dose groups and since similar effects have been reported for BAC, the corneal changes were attributed to the preservative. The difference in sensitivity shown by the rabbit compared to the primate may be explained physiologically because of the greater blinking rate and lacrimal response to irritation in primates, including humans. In fact, formulations containing 0.01% BAC are well tolerated by humans and are approved as over-the-counter ophthalmic medications.

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