Section 21 Ophthalmological Preparations

Ketorolac - Addition

Application submitted by International Council of Ophthalmology
1. Summary statement of the proposal for inclusion, change or deletion

We propose the inclusion of ketorolac ophthalmic solution, a nonsteroidal anti-inflammatory drug (NSAID) “that is FDA–approved for seasonal allergic conjunctivitis, post–cataract inflammation, and ocular discomfort after refractive surgery.”\(^1\) A recent review of NSAIDs suggests that ketorolac can be used to treat postoperative inflammation, cystoid macular edema following surgical procedures and allergic conjunctivitis and to relieve discomfort and pain after ocular surgery and trauma.

The November 2009 approval of generic ketorolac by the U.S. Food and Drug Administration has reduced the cost associated with the use of this drug and has made it a practical option for use in the developing world.

2. Name of the focal point in WHO submitting or supporting the application (where relevant)

Ivo Kocur

3. Name of the organization(s) consulted and/or supporting the application

International Council of Ophthalmology

4. International Nonproprietary Name (INN, generic name) of the medicine

Keto rolac ophthalmic solution

5. Formulation proposed for inclusion; including adult and paediatric (if appropriate)

Ketorolac tromethamine ophthalmic solution, 0.5%

6. International availability - sources, if possible manufacturers and trade names

Generic ketorolac ophthalmic solution is available in the US, the UK, Canada, Australia, Mexico, India as well as several other countries.

7. Whether listing is requested as an individual medicine or as an example of a therapeutic group

Individual medicine

8. Information supporting the public health relevance (epidemiological information on disease burden, assessment of current use, target population)

"Older population studies estimate a prevalence of 15–20% of allergic conjunctivitis, but more recent studies implicate rates as high as 40%. Ocular symptoms are common and contribute to the burden of allergic rhinitis and lower quality of life. Ocular allergies rank a very close second and at times may overcome the primary complaints of nasal congestion in rhinoconjunctivitis patients.”\(^2\) “Topical 0.5% ketorolac is the only NSAID that is FDA – approved for the treatment of seasonal allergic rhinoconjunctivitis.”\(^1\)
NSAIDs are one of the most commonly prescribed classes of medications worldwide. Aspirin and other chemically related compounds, used systemically for many decades for their analgesic, antipyretic, and anti-inflammatory properties, have more recently been prepared in topical ophthalmic formulations. As such, they have proven useful to enhance mydriasis, reduce postoperative inflammation, and prevent and treat cystoid macular edema associated with cataract surgery. In addition, they can be used to decrease pain and photophobia after refractive surgery and to alleviate itching associated with allergic conjunctivitis. A growing body of scientific evidence suggests that NSAIDs may be beneficial in diabetic retinopathy, age-related macular degeneration, and ocular tumors.1

At present, the WHO list of essential medicines lacks a topical ophthalmic NSAID, and adding one to the list would be helpful for developing countries.

9. Treatment details (dosage regimen, duration; reference to existing WHO and other clinical guidelines; need for special diagnostics, treatment or monitoring facilities and skills)

Per http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=32234:

The recommended dose of ketorolac tromethamine ophthalmic solution, 0.5%, is one drop four times a day for relief of ocular itching due to seasonal allergic conjunctivitis.

For the treatment of postoperative inflammation in patients who have undergone cataract extraction, one drop of ketorolac tromethamine ophthalmic solution, 0.5%, should be applied to the affected eye(s) four times daily beginning 24 hours after cataract surgery and continuing through the first 2 weeks of the postoperative period.

10. Summary of comparative effectiveness in a variety of clinical settings:

"Prevention of Surgically Induced Miosis"

Suprofen 1% and flurbiprofen 0.03% were the first NSAIDs approved by the FDA for intraoperative use to prevent miosis during cataract surgery. Several clinical studies have subsequently demonstrated similar mydriatic properties for both 0.1% diclofenac and 0.4% and 0.5% ketorolac. At least one study suggests that ketorolac tromethamine 0.5% may provide more stable mydriasis than diclofenac sodium 0.1%.1

Postoperative inflammation after cataract surgery

"There is good evidence that topical NSAIDs reduce postoperative inflammation after cataract surgery."1 Randomized, prospective, double-masked, placebo, and active drug–controlled clinical studies with adequate numbers of patients have shown that topically applied 0.4% and 0.5% ketorolac decrease postoperative inflammation after cataract surgery without significant toxicity when used appropriately.1 “Thus, there is good evidence that topical NSAIDs may be used in place of or in addition to topical corticosteroids after cataract surgery to avoid excessive inflammation and to improve visual recovery.”1

"An important and frequently asked question is, Which topical NSAID is most effective in preventing excessive postoperative inflammation following cataract surgery?... In a well–designed study using an adequate patient population and evaluating inflammation with both slit lamp and laser cell flare meter to compare ketorolac's to diclofenac's ability to prevent excessive
postoperative inflammation, both drugs were equally effective. Furthermore, a subsequent comparison of these same NSAID–treated populations revealed no difference in effectiveness or complications, including CME and posterior capsular opacification, between diclofenac and ketorolac 3 years after surgery. A subsequent study with fewer patients and shorter follow-up reached similar conclusions. Therefore, at present, there is no evidence to suggest one topical NSAID treatment is better than another in controlling postoperative inflammation with the exception that flurbiprofen 0.03% appears less effective than other NSAIDs. 

*Postoperative inflammation after glaucoma surgery*

"The effect of topical NSAIDs in minimizing inflammation following glaucoma procedures appears modest, and thus far the FDA has not approved any for this indication. Yet, excessive inflammation can complicate glaucoma surgery and result in serious problems. Published studies suggest that topical flurbiprofen 0.03% and diclofenac 0.1% decrease inflammation and may reduce pain following laser trabeculoplasty, and to a lesser extent after cyclocryotherapy. In addition, there is recent evidence that 0.1% indomethacin and ketorolac 0.5% may share similar therapeutic effects." 

*Postoperative inflammation after vitreoretinal surgery*

A recent prospective, randomized, double-masked, placebo-controlled trial demonstrated "reduction of anterior chamber cell and flare after vitrectomy by 0.4% ketorolac. The anti-inflammatory effect of ketorolac was substantial, with four times as many patients compared to placebo demonstrating no inflammation after vitrectomy. Furthermore only one ketorolac eye, versus six for placebo, demonstrated severe inflammation. This same study found that severity of inflammation significantly correlated with increased retinal thickness, which in turn resulted in reduced visual improvement."

*Relieving Discomfort and Pain after Ocular Surgery and Trauma*

"Pain often occurs after radial keratotomy (RK) and excimer laser photorefractive keratectomy (PRK). Both 0.4% and 0.5% ketorolac tromethamine are FDA–approved to reduce pain and photophobia after refractive surgery. Several reports have shown that ketorolac also decreases normal corneal sensitivity and reduce pain after corneal abrasions." Although diclofenac's anesthetic effect appears to be more pronounced and longer lasting than ketorolac’s, this difference does not appear to correlate with postoperative pain relief.

"Topically applied NSAIDs also appear to minimize ocular discomfort following cataract and retinal surgery. Prospective, randomized studies have demonstrated that 0.4% ketorolac has this effect. Furthermore, in vitreoretinal surgery, intravenous ketorolac significantly reduces postoperative pain and nausea and recent prospective, randomized studies have demonstrated similar benefits with prophylactic use of 0.4% ketorolac. Finally, ketorolac has some benefit following laser photocoagulation procedures."

*Allergic Conjunctivitis*

"Topical 0.5% ketorolac is the only NSAID that is FDA–approved for the treatment of seasonal allergic rhinoconjunctivitis.... Ketorolac tromethamine 0.5% ophthalmic solution is approved for the relief of ocular itching in patients with seasonal allergic rhinoconjunctivitis. Two multicenter studies verify the efficacy of this treatment. One double-masked, placebo-controlled study of 148 patients evaluated treatment given four times daily over a 7–day period and showed that
Ketorolac was significantly better than placebo in regards to ocular itching, conjunctival inflammation, conjunctival injection, swollen eyes, foreign-body sensation, and ocular discharge. A second study of 93 subjects with similar design, but lacking slit-lamp observations, reported ketorolac was significantly more beneficial than placebo in reducing conjunctival inflammation and photophobia after 7 days of treatment."¹ Ketorolac 0.5% has also been shown to effective in treating vernal keratoconjunctivitis.¹

11. Summary of comparative evidence on safety*:

"Transient burning, stinging, and conjunctival hyperemia are common ocular side effects after the topical instillation of NSAIDs, and differences exist in the discomfort produced by the various commercially available formulations. Properly controlled, prospective, double-masked clinical studies have failed to demonstrate significant differences in patient acceptance, however. As with all commercially available eye drops, allergic and hypersensitivity reactions occur with topical NSAIDs. In addition, superficial punctate keratitis, corneal infiltrates, and epithelial defects have been reported... At present, there is no evidence that one NSAID is less toxic than another."¹

"Postcataract surgery atonic mydriasis has been reported in some patients receiving topical NSAIDs prior to surgery. This potential adverse event is mentioned in the package insert of flurbiprofen and suprofen. Apparently, the NSAID-induced mydriasis that is helpful during cataract extraction and lens insertion may be resistant to reversal from parasympathomimetics such as acetylcholine and carbachol. The pharmacodynamics of this are poorly understood, but atonic mydriasis may also occur without NSAID use following uncomplicated cataract surgery.

Severe corneal toxicity has been reported with 0.5% ketorolac. Although uncommon, these events are frequently referred to as corneal melts."¹ "Inconsistent and variable dose–toxicity relationships suggest that factors other than simple NSAID toxicity, including concurrent corticosteroid use, may be contributory... The over two dozen cases of corneal perforations reported with the introduction of topical corticosteroids over 30 years ago were likely related to improper clinical use and patient follow-up... Thus, many topical medications have the potential for toxicity if unmonitored or used inappropriately. In conclusion, despite proposed theories to explain their pathogenesis, a definite link between NSAID use and corneal melt remains tenuous. Application of topical NSAIDs for reasonable lengths of time in appropriate patients with proper monitoring appears safe."¹

12. Summary of available data on comparative cost** and cost-effectiveness within the pharmacological class or therapeutic group:

Comparative cost and cost-effectiveness data on generic topical ophthalmic ketorolac tromethamine is not readily available, possibly because ophthalmic ketorolac tromethamine became generic fairly recently.

However, ketorolac eye drops are generic and can be purchased relatively inexpensively, especially in India. The generic version of the drops costs Indian Rs. 3.78/ml, so the cost of a 10 ml bottle would be less than 1 US dollar.

13. Summary of regulatory status of the medicine (in country of origin, and preferably in other countries as well)
Generic ketorolac ophthalmic solution was approved by the US Food and Drug Administration in November 2009.


Ketorolac tromethamine met United States, British and European pharmacopoeial standards.

15. Proposed (new/adapted) text for the WHO Model Formulary

Per http://dailymed.nlm.nih.gov:

DESCRIPTION

Ketorolac tromethamine ophthalmic solution, 0.5% 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) and has the following structure:

Ketorolac tromethamine ophthalmic solution, 0.5% is supplied as a sterile isotonic aqueous 0.5% solution, with a pH of 7.4. Ketorolac tromethamine ophthalmic solution, 0.5% 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. The osmolality of ketorolac tromethamine ophthalmic solution, 0.5% is 290 mOsmol/kg.

Each mL of ketorolac tromethamine ophthalmic solution, 0.5% contains: Active: ketorolac tromethamine 0.5%. Inactives: benzalkonium chloride 0.01%; edetate disodium 0.1%; octoxynol 40; purified water; sodium chloride; hydrochloric acid and/or sodium hydroxide to adjust pH.

CLINICAL PHARMACOLOGY

Ketorolac tromethamine is a 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 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 miotic response produced during ocular surgery by constricting the iris sphincter independently of cholinergic mechanisms.

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 (mean ketorolac concentration 95 ng/mL aqueous humor, range 40 to 170 ng/mL). Ocular administration of ketorolac tromethamine reduces prostaglandin E2 (PGE2) levels in aqueous humor. 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 ketorolac tromethamine 0.5% ophthalmic solution.

One drop (0.05 mL) of 0.5% ketorolac tromethamine 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. When ketorolac tromethamine 10 mg is administered systemically every 6 hours, peak plasma levels at steady state are around 960 ng/mL.

Two controlled clinical studies showed that ketorolac tromethamine ophthalmic solution, was significantly more effective than its vehicle in relieving ocular itching caused by seasonal allergic conjunctivitis.

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

Results from clinical studies indicate that ketorolac tromethamine has no significant effect upon intraocular pressure; however, changes in intraocular pressure may occur following cataract surgery.

**INDICATIONS AND USAGE**

Ketorolac tromethamine ophthalmic solution, 0.5%, is indicated for the temporary relief of ocular itching due to seasonal allergic conjunctivitis. Ketorolac tromethamine ophthalmic solution, 0.5% is also indicated for the treatment of postoperative inflammation in patients who have undergone cataract extraction.

**CONTRAINDICATIONS**

Ketorolac tromethamine ophthalmic solution, 0.5% is contraindicated in patients with previously demonstrated hypersensitivity to any of the ingredients in the formulation.

**WARNINGS**

There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other nonsteroidal anti-inflammatory agents. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.

With some nonsteroidal anti-inflammatory drugs, there exists the potential for increased bleeding time due to interference with thrombocyte aggregation. There have been reports that
ocularly applied nonsteroidal anti-inflammatory drugs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery.

PRECAUTIONS

General:

All topical nonsteroidal anti-inflammatory drugs (NSAIDs) may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.

Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation. These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs and should be closely monitored for corneal health.

Postmarketing experience with topical NSAIDs suggests that patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients.

Postmarketing experience with topical NSAIDs also suggests that use more than 24 hours prior to surgery or use beyond 14 days post surgery may increase patient risk for the occurrence and severity of corneal adverse events.

It is recommended that ketorolac tromethamine ophthalmic solution, 0.5% be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

Information for Patients:

Ketorolac tromethamine ophthalmic solution, 0.5% should not be administered while wearing contact lenses.

Carcinogenesis, Mutagenesis, and Impairment of Fertility:

Ketorolac tromethamine was not carcinogenic in rats given up to 5 mg/kg/day orally for 24 months (151 times the maximum recommended human topical ophthalmic dose, on a mg/kg basis, assuming 100% absorption in humans and animals) nor in mice given 2 mg/kg/day orally for 18 months (60 times the maximum recommended human topical ophthalmic dose, on a mg/kg basis, assuming 100% absorption in human and animals).

Ketorolac tromethamine was not mutagenic in vitro in the Ames assay or in forward mutation assays. Similarly, it did not result in an in vitro increase in unscheduled DNA synthesis or an in vivo increase in chromosome breakage in mice. However, ketorolac tromethamine did result in an increased incidence in chromosomal aberrations in Chinese hamster ovary cells.

Ketorolac tromethamine did not impair fertility when administered orally to male and female rats at doses up to 272 and 484 times the maximum recommended human topical ophthalmic dose, respectively, on a mg/kg basis, assuming 100% absorption in humans and animals.

PREGNANCY
Teratogenic Effects: Pregnancy Category C.

Ketorolac tromethamine, administered during organogenesis, was not teratogenic in rabbits or rats at oral doses up to 109 times and 303 times the maximum recommended human topical ophthalmic dose, respectively, on a mg/kg basis assuming 100% absorption in humans and animals. When administered to rats after Day 17 of gestation at oral doses up to 45 times the maximum recommended human topical ophthalmic dose, respectively, on a mg/kg basis, assuming 100% absorption in humans and animals, ketorolac tromethamine resulted in dystocia and increased pup mortality. There are no adequate and well-controlled studies in pregnant women. Ketorolac tromethamine ophthalmic solution, 0.5% should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects:

Because of the known effects of prostaglandin-inhibiting drugs on the fetal cardiovascular system (closure of the ductus arteriosus), the use of ketorolac tromethamine ophthalmic solution, 0.5% during late pregnancy should be avoided.

Nursing Mothers:

Caution should be exercised when ketorolac tromethamine ophthalmic solution, 0.5% is administered to a nursing woman.

Geriatric Use:

No overall differences in safety or effectiveness have been observed between elderly and younger patients.

ADVERSE REACTIONS

The most frequent adverse events reported with the use of ketorolac tromethamine ophthalmic solutions have been transient stinging and burning on instillation. These events were reported by up to 40% of patients participating in clinical trials.

Other adverse events occurring approximately 1 to 10% of the time during treatment with ketorolac tromethamine ophthalmic solutions included allergic reactions, corneal edema, iritis, ocular inflammation, ocular irritation, superficial keratitis, and superficial ocular infections.

Other adverse events reported rarely with the use of ketorolac tromethamine ophthalmic solutions included: corneal infiltrates, corneal ulcer, eye dryness, headaches, and visual disturbance (blurry vision).

Clinical Practice: The following events have been identified during postmarketing use of ketorolac tromethamine ophthalmic solution, 0.5% in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The events, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to topical ketorolac tromethamine ophthalmic solution, 0.5%, or a combination of these factors, include corneal erosion, corneal perforation, corneal thinning, and epithelial breakdown (see PRECAUTIONS, General).
DOSAGE AND ADMINISTRATION

The recommended dose of ketorolac tromethamine ophthalmic solution, 0.5%, is one drop (0.25 mg) four times a day for relief of ocular itching due to seasonal allergic conjunctivitis.

For the treatment of postoperative inflammation in patients who have undergone cataract extraction, one drop of ketorolac tromethamine ophthalmic solution, 0.5%, should be applied to the affected eye(s) four times daily beginning 24 hours after cataract surgery and continuing through the first 2 weeks of the postoperative period.

Ketorolac tromethamine ophthalmic solution, 0.5% has been safely administered in conjunction with other ophthalmic medications such as antibiotics, beta blockers, carbonic anhydrase inhibitors, cycloplegics, and mydriatics.

HOW SUPPLIED

Ketorolac tromethamine ophthalmic solution, 0.5% is supplied sterile in a white LDPE plastic DROP-TAINER® bottle, a natural dropper tip and a gray polypropylene cap as follows:
- 5 mL in 8 mL bottle NDC 61314-126-05
- 10 mL in 10 mL bottle NDC 61314-126-10

Storage: Store at room temperature 15°-30°C (59°-86°F) with protection from light.

FOR TOPICAL OPHTHALMIC USE ONLY

References