Drug Class Review:
Ophthalmic Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)
VHA Pharmacy Benefits Management Services and the Medical Advisory Panel

OBJECTIVES

The purposes of this document are two-fold: 1) to review the efficacy and safety of the five commercially available ophthalmic/topical NSAIDs used in a variety of ophthalmic conditions [including the prevention and treatment of postoperative inflammation following cataract surgery, prevention and treatment of cystoid macular edema (CME) following cataract surgery, ocular discomfort and pain following refractive surgery and intraoperative miosis during cataract surgery]; and 2) to determine if there are substantive differences between the available agents in terms of efficacy and safety. This review will serve as a tool to determine whether contracting for one agent is possible.

Since there are a number of alternative agents for treating seasonal allergic conjunctivitis, this review will not include an assessment of topical ophthalmic NSAIDs for that indication.

Table 1: Ophthalmic NSAIDs Available in the U.S.[1-8]

Generic Name (Chemical Class)	Trade Name®	Formulation/ Preservative (Package size)	Manufacturer	FDA Approval Date	Patent Expiration Date
Diclofenac Sodium (Phenylacetic acid)	Voltaren Ophthalmic	0.1% Sterile Solution Boric acid (2.5, 5 ml)	Novartis/Generics	3-28-91	N/A
Flubiprofen Sodium (Phenylalkanoic acid)	Ocufen	0.03% Sterile Thimerosal 0.005% Solution (2.5 ml)	Allergan/Generics	12-31-86	N/A
Ketorolac Tromethamine (Pyrrolo-pyrrole group)	Acular	0.5% Sterile Solution BAK 0.01% (3, 5, 10 ml)	Allergan	12-9-92	11-5-09
Ketorolac Tromethamine (Pyrrolo-pyrrole group)	Acular **LS**	0.4% Sterile Solution BAK 0.006% (5 ml)	Allergan	5-30-03	11-5-09
Ketorolac Tromethamine (Pyrrolo-pyrrole group)	Acular **PF**	0.5% Sterile Solution Preservative Free (12 x 0.4 ml vials)	Allergan	11-3-97	Unable to determine
Bromfenac (Phenylacetic acid)	Xibrom	0.09% Sterile BAK 0.05 mg/mL Solution (5 ml)	ISTA	3-24-05	1-24-09 Exclusive(1-27-09)
Nepafenac (Arylacetic acid)	Nevanac	0.1% Sterile BAK 0.005% Suspension	Alcon	8-19-05	6-6-14 Exclusive(8-19-10)

BAK=benzalkonium chloride, LS=low strength, N/A=not applicable; patent expired, PF=preservative free

FDA-APPROVED INDICATIONS[1-7] and OFF-LABEL USES

Table 2: FDA Approved Indications

Product	FDA Approved Indication
Diclofenac	• Treatment of postoperative inflammation in patients after cataract extraction • Temporary relief of pain and photophobia in patients undergoing corneal refractive surgery
Flurbiprofen	• Inhibition of intraoperative miosis

Ketorolac	• Temporary relief of ocular itching due to seasonal allergic conjunctivitis • Treatment of postoperative inflammation after cataract extraction
Ketorolac LS	• Reduction of ocular pain and burning/stinging following corneal refractive surgery
Ketorolac PF	• Reduction of ocular pain and photophobia following incisional refractive surgery
Bromfenac	• Treatment of postoperative inflammation and reduction in ocular pain after cataract surgery
Nepafenac	• Treatment of pain and inflammation associated with cataract surgery

Off-Label Uses

Since not all ophthalmic NSAIDs are approved for the same indications (e.g. intraoperative miosis, postoperative inflammation after cataract surgery, etc.), the term "off-label" is dependent upon the individual product (Table 2). None of the available products are FDA approved for the prevention or treatment of cystoid macular edema (CME).

DOSAGE/ADMINISTRATION/STORAGE[1-7]

Table 3: Dosage, Administration and Storage (Product Label)

Indication-Dose	Diclofenac	Flurbiprofen	Ketorolac	Bromfenac	Nepafenac
Intraoperative Miosis	--	1 d q 30 min beginning 2 h prior to surgery (total=4 drops)	--	--	--
Cataract Surgery	1 d 4 x daily, start 24 h after surgery and through 2 wks post-op	--	1 d 4 x daily, start 24 h after surgery and through 2 wks post-op (Acular)	1 d 2 x daily, start 24 h after surgery and through 2 wks post-op	1 d 3 x daily, start 1 day prior to surgery, continue on day of surgery, through 2 wks post-op
Prevention CME	--	--	--	--	--
Treatment CME	--	--	--	--	--
Corneal Refractive Surgery	1-2 d within the h prior to surgery, 15 min after surgery, and 4 x daily for up to 3 days	--	1 d 4 x daily for up to 4 days prn for pain (Acular LS) or for up to 3 days (Acular PF)	--	--
Seasonal Allergic Conjunctivitis	--	--	1 d 4 x daily	--	--
Storage Requirements	15-25ºC/59-77ºF	15-25ºC/59-79ºF	Acular/Acular LS: 15-25ºC/59-77ºF Acular PF: 15-30ºC/59-86ºF (protect from light)	15-25ºC/59-77ºF	2-25ºC/36-77ºF

d=drop, h=hour, prn-as needed, q=every, x=times *Off-label indication (Dosing used in clinical trials). Although flurbiprofen is the only ophthalmic NSAID in the U.S. FDA approved for intraoperative miosis, the other products are also commonly used for this purpose.

METHODS

1. All of the available topical ophthalmic NSAIDs approved by the U.S. FDA were included in this review. The products include: diclofenac, flurbiprofen, ketorolac, bromfenac and nepafenac.
2. A literature search was performed of MEDLINE (1966 through March 2009) using all of the generic names of the available products as well as the following terms: cataract surgery, cystoid macular edema, refractive surgery, ocular NSAIDs and ophthalmic NSAIDs.

3. Reference lists from review articles were examined for additional clinical trials and other pertinent information. Academy of Managed Care Pharmacy (AMCP) dossiers were requested from manufacturers for the branded products only (Acular, Nevanac and Xibrom).
4. Placebo-controlled trials will be referenced within the document but will not be summarized in the detailed tables; only those studies comparing two or more ophthalmic NSAIDs will be included in tables.

CURRENT VA NATIONAL FORMULARY AGENTS

- Diclofenac ophthalmic solution (available as a generic)
- Flurbiprofen ophthalmic solution (available as a generic)
- Ketorolac ophthalmic solution (Acular and Acular LS patents expire 11-2009)

PHARMACOLOGY AND PHARMACOKINETICS

Pharmacology[9-11]

Prostaglandins released in the eye may cause 1) increased intraocular pressure (IOP) leading to local vasodilation and altered permeability of the blood-aqueous humor barrier; 2) surgery induced miosis creating access difficulties for cataract removal and an increased risk for postoperative inflammation, vitreous loss and potentially rupture of the posterior capsule; and 3) increased vascular permeability and conjunctival hyperemia.

Nonsteroidal anti-inflammatory drugs (NSAIDs) act by inhibiting cyclooxygenase enzymes (COX-1 and COX-2) thereby limiting prostaglandin production and providing both analgesic and anti-inflammatory activity. In the eye, topical ophthalmic NSAIDS are preferred over systemic NSAIDs because they produce higher ocular drug concentrations while avoiding some of the systemic adverse events. Ophthalmic NSAIDs are used to limit pain, discomfort, inflammation and edema associated with ocular conditions (e.g. noninfectious ocular inflammation or allergic conjunctivitis) or following ophthalmic surgeries (e.g. cataract and corneal refractive surgeries) or trauma.

Pharmacokinetics

Table 4: Pharmacokinetics of Ophthalmic NSAIDs[1-7]

Ophthalmic NSAID	Pharmacokinetic Properties
Diclofenac	• After instillation of 2 drops in each eye, plasma levels of diclofenac were below the detectable limit (10 ng/mL) during a 4-hr period.
Flurbiprofen	• Information on systemic absorption was not provided.
Ketorolac	• Instillation of 1 drop in each eye 3 x daily in 26 patients resulted in 5/26 (19.2%) with detectable plasma levels of ketorolac (10.7-22.5 ng/mL) after 10 days. Systemically administered ketorolac 10 mg every 6 hrs results in a steady state plasma conc. of approximately 960 ng/mL.
Bromfenac	• Plasma conc. of topically administered bromfenac is not known. Based upon pharmacokinetic estimates, plasma conc. after topical administration is expected to be below the detectable limit (50 ng/mL).
Nepafenac	• Nepafenac is a prodrug. After instillation, nepafenac penetrates the cornea and is converted by ocular tissue hydrolases to its active form, amfenac. • Low but detectable plasma conc. were observed for both nepafenac and amfenac in most patients 2-3 hrs after installation of nepafenac in both eyes.

EFFICACY

Efficacy Measures

1. Intraoperative Miosis: Intraocular manipulation/surgery can lead to release of prostaglandins within the eye causing miosis. During eye cataract surgery, maintenance of mydriasis is necessary in order to optimize surgical outcomes (proper incision of the anterior capsule, safe removal of the cataract and intraocular lens implantation). Other mydriatic agents are used as well (e.g. tropicamide, phenylephrine).
    a. Measurement of horizontal and/or vertical pupil diameter, miosis rates.

2. Cataract Surgery (Inflammation): Despite advances in surgical techniques used to perform extracapsular cataract extraction (ECCE) as well as improvements in intraocular lens (IOL) materials and placement; inflammation can still occur in association with cataract surgery. Inflammatory complications after cataract surgery may include posterior synechias, chronic uveitis, secondary glaucoma, cystoid macular edema (CME) and pain. Risk factors for inflammatory complications may include those patients with anterior segment pathology, uveitis-related damage to the blood aqueous barrier, diabetes, glaucoma or those eyes previously exposed to surgery.[32] In clinical trials assessing the efficacy of topically applied NSAIDs on inflammation, there are a number of methods used to compare the degree of inflammation or the response to treatment with ophthalmic NSAIDs.
    a. Evaluation of the blood aqueous barrier (BAB) after cataract surgery (prostaglandins released in response to cataract surgery may alter the permeability of the BAB):[32] During cataract surgery, there are several variables that may affect the BAB. These variables include trauma from cataract removal, characteristics and placement of the IOL and anti-inflammatory medications used during surgery. Postoperative inflammation can be measured using slit lamp bio microscopy, anterior segment fluorophotometry and laser cell and flare meter (LCFM). The more reliable and reproducible methods of measurement used in clinical trials include the fluorophotometry and LCFM. Both methods help determine the permeability of the BAB and correlate with ocular inflammation. With mild increases in BAB permeability, some evidence supports a higher sensitivity of the fluorophotometry vs. LCFM method.[32]
    b. Best corrected visual acuity (BCVA): Best visual acuity score that can be achieved with glasses.
    c. Descemet folds: The Descemet membrane is a specialized membrane of epithelial cells located between the stroma and the epithelial cell layer. Conditions causing inflammation of the cornea or anterior chamber can lead to Descemet folds. Symptoms may include pain, foreign body sensation, blurred vision, excessive tearing, etc.

   Cataract Surgery (Pain): In clinical trials assessing the effect of ophthalmic NSAIDs on postoperative pain, questionnaires have been used. It is unclear if the questionnaires used have been validated or are similar between trials.
3. Cystoid Macular Edema (CME): CME is a painless condition affecting the central retina or macula. When present, it appears as multiple cyst-like areas of accumulated fluid in the macula causing retinal swelling or edema. CME can present as blurred or impaired central vision. It is the most common cause of reduced vision after cataract surgery. Although the pathophysiology of CME is not well understood, inflammation associated with the surgical trauma as well as alteration in the blood aqueous barrier (BAB) may be partially responsible for this post-operative complication.[9-10] The incidence of "angiographically" diagnosed CME is higher than "clinically significant or symptomatic" CME. In one study of 252 patients undergoing uncomplicated cataract surgery, 0% developed clinical CME vs. 9.1% angiographic CME.[35] One editorialist commenting on findings from a study of the incidence of CME post cataract extraction recommended that the primary endpoint of studies evaluating CME should be visual function since eyesight is the most clinically important parameter to both patients and physicians after cataract surgery.[36]

   The peak incidence of CME is estimated to occur 4-6 weeks post cataract surgery. There are a number of pre-operative factors that may place patients at a higher risk for developing post-operative CME and include pre-existing ocular inflammation, diabetes, ocular vascular or cardiovascular disease, retinitis pigmentosa, diabetic retinopathy, epiretinal or vitreoretinal interface membrane issues and previous ocular surgery. Intra-operative risk factors include complicated cataract extraction, capsular rupture, etc.[9-10] Acute CME is defined as retinal edema of less than 4 months duration and often resolves spontaneously. Chronic CME persists for four months or greater.
    a. Angiographic CME: Fluorescein angiography (FA)-diagnostic gold standard but does not necessarily correspond to visual function. Optical coherence tomography (OCT) may also be used to assess.
    b. Clinical CME: Poor visual outcome accompanied by angiographic findings. BCVA, visual contrast sensitivity (sine-wave gratings of a given spatial frequency demonstrates

the ability to discern low contrast targets over a range of target sizes and orientations) and/or Snellen visual acuity (eye chart) or ETDRS eye charts. ETDRS eye charts are accepted in studies sponsored by the National Eye Institute. They are designed for use in clinical trials and low vision evaluations where repeatable and accurate measurements are required.

4. Refractive Surgery
    a. Pain, photophobia: assessed using visual analogue scales, four-point graded scales and/or questionnaires.

Summary of Efficacy Results

In this section, the evidence for topical ophthalmic NSAIDs used for intraoperative miosis; for reducing pain and inflammation following cataract surgery; for the prevention and treatment of CME as a complication of cataract surgery; and in the management of pain associated with refractive surgery will be presented.

Intraoperative Miosis-There are several studies demonstrating the effect of various ophthalmic NSAIDs (diclofenac, ketorolac 0.5%) in preventing miosis during cataract surgery when compared to placebo.[12-13] A number of active comparator trials have demonstrated similar effectiveness between ophthalmic NSAIDs in preventing surgically-induced miosis with some minor differences observed (see table below).

Table 5: Clinical Trials Comparing Two or More Ophthalmic NSAIDs on Intraoperative Miosis

Clinical Trial	Ophthalmic NSAIDs	Time of Outcome Measurement (pupil dilation/constriction)	Results/Authors Conclusion
Psilas, et al.[14] N=164	Indomethacin 1%[a] (n=46) Diclofenac 0.1% (n=40) Flurbiprofen 0.03% (n=44) Control (n=36)	Baseline, after capsulotomy, after expression of lens, after irrigation and aspiration of cortical remnants	Less pupillary constriction at baseline and after expression of the lens in indomethacin and flurbiprofen groups vs. control (p=0.01); less constriction at baseline and after irrigation or cortical remnants in indomethacin and flurbiprofen groups vs. control and diclofenac group (p=0.001). **Indomethacin and flurbiprofen are more effective at maintaining mydriasis during cataract surgery than control or diclofenac.**
Roberts[15] N=51	Diclofenac 0.1% Flurbiprofen 0.03%	Baseline and every 5 minutes during surgery. Measurements occurred at the beginning of caspularhexis and PE; end of PE, end of cortical clean-up and prior to and after lens implantation.	No differences between treatments except at the beginning of PE, eyes more dilated in the flurbiprofen vs. diclofenac group. **Diclofenac and flurbiprofen were equally effective at maintaining mydriasis during cataract surgery.**
Gimbel, et al.[16] N=236	Flurbiprofen 0.03% Indomethacin 1%	Baseline, after PE, after irrigation and aspiration.	No differences in pupil diameters during the periods tested. **Both Flurbiprofen and Indomethacin are equally effective at maintaining mydriasis during cataract surgery.**
Soloman, et al.[17] N=118	Ketorolac 0.5% Flurbiprofen 0.03% (used as control)	Baseline, prior to PE, before and after lens implantation.	Baseline-similar pupil diameter. No differences were observed in pupil diameter between groups at any time. **Ketorolac and**

			flurbiprofen are equally effective in inhibiting miosis during cataract surgery.
Srinivasan, et al.[18] N=51	Ketorolac 0.5% Diclofenac 0.1%	Baseline, after capsulotomy, after IOL implantation and end of surgery.	Baseline-similar pupil diameter. No differences were observed in pupil diameter at any predetermined time point. **Ketorolac=diclofenac** Authors felt ketorolac had more stable mydriatic effect since there were statistical differences in miosis in favor of ketorolac after nucleus delivery and after irrigation/aspiration.
O'hara , et al.[19] N=32, n=26 historical control (diclofenac)	Bromfenac 0.1% Diclofenac 0.1% (historical control)	Baseline, irrigation and aspiration of corneal remnants, and end of surgery.	No differences were observed in pupil diameter and miosis rate between groups. **Bromfenac and diclofenac have the same antimiotic effect in cataract surgery.**

[a] Not available in the U.S. IOL=intraocular lens, PE=phacoemulsification

Cataract Surgery-Although surgical techniques and materials used in performing cataract surgery and IOL placement have evolved (resulting in a reduced incidence and degree of inflammation), there is sufficient evidence supporting the use of ophthalmic NSAIDs to further reduce pain and inflammation associated with cataract surgery. Currently, diclofenac, ketorolac 0.5%[20-22], bromfenac[23], and nepafenac are FDA approved for the treatment of postoperative pain and/or inflammation associated with cataract surgery. Nepafenac is the only ophthalmic NSAID approved by the FDA to be administered both pre- and postoperatively for cataract surgery. However, it is common practice for all of the available agents to also be administered preoperatively.[9] There is one prospective study examining the effect of preoperative diclofenac 0.1% in 60 patients undergoing phacoemulsification (PE) and lens implantation.[24] In this study, patients were randomly assigned to receive diclofenac 1 drop four times daily beginning three days before surgery then 1 drop every 15 minutes one hour before surgery, no pretreatment with diclofenac but 1 drop every 15 minutes one hour before surgery or no diclofenac before surgery. All patients were administered diclofenac ophthalmic four times daily beginning on the first postoperative day. Postoperative inflammation was measured on the first and 7th postoperative day using a laser cell and flare meter. On the first postoperative day, the flare scores were significantly different for eyes that received pretreatment with "diclofenac for three days prior to surgery" vs. "no diclofenac before surgery" (25.59 photons/ms vs. 33.07 photon/ms, respectively). The flare scores for the "pretreatment within one hour before surgery group" did not differ significantly from either the "three day pretreatment group" or the no diclofenac prior to surgery group". At one week, no differences in flare scores were observed between groups. No differences between groups were noted in the laser cell measures at postoperative day 1 or 7. The authors conclude that pretreatment with diclofenac may reduce early postoperative inflammation.

There are eight studies in which two or more ophthalmic NSAIDs were compared to determine their effectiveness in reducing pain and inflammation associated with cataract surgery.[25-31] Six trials were randomized, double-blind and prospective[25-28, 31] , one was open-label[30] and the blinding was unclear in one other study.[29] Most studies were conducted at a single institution and cataract removal done by the same surgeon. Preoperative ophthalmic NSAIDs were used in all but one investigation[28] (ranging from 60 minutes prior to surgery to up to 3 days prior to surgery). For assessment of anterior chamber inflammation, use of the LCFM provides a more reliable, reproducible result vs. the more subjective method of slit lamp bio microscopy for measuring inflammation. Overall, the ophthalmic NSAIDs demonstrated similar effectiveness in reducing pain and inflammation associated with cataract surgery, with minimal differences observed. (See table 6)

Table 6: Clinical Trials Comparing Two or More Ophthalmic NSAIDs in Cataract Surgery (Detailed summary, see Appendix 1)

Clinical Trial /Sponsor/Comparators	N=Eyes/N=Patients	Main Outcome Measurement (Pain and/or Inflammation only)	Conclusion
Diestelhorst 1996[25] Unknown Diclofenac 0.1% vs. Flurbiprofen vs. Indomethacin 1%*	117 patients	Anterior chamber inflammation (LFM-objective, no cells counted using this test, slitlamp exam-subjective), BCVA, conjunctival hyperemia, corneal edema, ocular discomfort	Diclofenac 0.1%= or slightly > Flurbiprofen 0.03% in change from baseline in laser flare at post-op day 4-5 only. No other differences in other endpoints. Diclofenac 0.1%=Indomethacin 1% Diclofenac 0.1%>Flurbiprofen 0.03% or Indomethacin 1% in ocular burning/stinging
Kocak 1998[26] Unknown Diclofenac 0.1% vs. Flurbiprofen 0.03%	43 patients	Conjunctival hyperemia, corneal thickness or surface changes, anterior chamber inflammation (slit lamp exam-subjective)	Diclofenac 0.1%=Flurbiprofen
Flach 1998[27] VA study Diclofenac 0.1% vs. Ketorolac 0.5%	120 patients	Anterior chamber inflammation (slit lamp-subjective and LCFM-objective)	Diclofenac 0.1%=Ketorolac 0.5%
Scuderi 2003[28] Unknown Diclofenac 0.1% vs. Piroxicam 0.5%*	40 patients	BCVA, anterior chamber inflammation (slit lamp-subjective), corneal edema	Diclofenac 0.1%=Piroxicam 0.5%
Kawaguchi 2003[29] Unknown Diclofenac 0.1% vs. Bromfenac 0.09%	49 eyes/38 patients	Anterior chamber inflammation (LCFM-objective), corneal epithelial damage (fluorophotometer)	Diclofenac 0.1%<Bromfenac 0.09% flare in 1st 2 weeks, = at 4 weeks Diclofenac 0.1%=Bromfenac 0.09% corneal epithelial damage
O'Hara 2004[30] Unknown Diclofenac 0.1% vs. Bromfenac 0.09%	127 eyes/111 patients	Anterior chamber inflammation (slit lamp bio microscopy-subjective), Corneal epithelial damage	Diclofenac 0.1 %< Bromfenac 0.09% flare on day 3 post-op. Diclofenac 0.1%=Bromfenac 0.09% flare and corneal epithelial damage1,2,4 weeks post-op
Duong 2007[31] Industry supplied medications Ketorolac 0.4% vs. Nepafenac 0.1%	193 eyes/183 patients	Anterior chamber inflammation (unclear method used, likely subjective from report), BCVA	Ketorolac 0.4%=Nepafenac 0.1% for BCVA, inflammation, pre-op pain/discomfort, subjective eye complaints. Ketorolac>Nepafenac for post-op pain control, patient satisfaction, compliance and PCO development.
Sandoval 2006 Allergan Ketorolac 0.4% vs. Ketorolac 0.5%	40 eyes/40 patients	BCVA (Snellen), LCFM, ocular symptoms	Ketorolac 0.4%=Ketorolac 0.5% BCVA, LCFM Ketorolac 0.4%>Ketorolac 0.5% for foreign body sensation and burning/stinging on first post-op day only.

*Topical piroxicam is not available within the US. BCVA=best corrected visual acuity, LCFM=laser cell and flare meter, LFM=laser flare meter, PCO=posterior capsule opacification

Cystoid Macular Edema (CME)-As previously noted, CME is the most common cause of poor visual outcomes following cataract surgery and can be classified as angiographic and/or clinical. The incidence of angiographic CME is higher than clinically determined CME since angiographic CME is not always

associated with visual decline. The reported incidence of CME can vary widely due to differences in surgical techniques, diagnostic methods used and yet to be identified risk factors. Acute CME is defined as lasting less than four months and often resolves spontaneously; while chronic CME lasts four months or longer.

Presently, none of the topical ophthalmic NSAIDs have been approved by the FDA for either prevention or treatment of CME. However, there are a number of placebo-controlled and non topical NSAID comparator studies examining the use of ophthalmic NSAIDs in CME. In these investigations, a significant effect on CME prevention was observed for diclofenac 0.1%[44-48], ketorolac 0.5%[49], ketorolac 0.4%[50] and nepafenac 0.1% (retrospective chart review)[51]. A significant treatment effect on angiographic and/or clinical CME was noted for diclofenac[41-43], ketorolac 0.5%[42-43,52-54], bromfenac (published meeting abstract only)[43] and nepafenac (both case series).[55-56] The Cochrane Collaboration has a developed a protocol for a systematic review that will seek to determine if prophylactic NSAIDs will prevent CME after cataract surgery.[37] Additionally, a Cochrane Systematic Review for the treatment of CME after cataract extraction has been published. In that review, seven trials of NSAIDs in CME were identified; 4 in chronic CME and 3 in acute CME. Most of the included trials had sample sizes of less than 40 for a total of 266 participants. The authors of the systematic review found two trials that demonstrated the topical NSAID ketorolac 0.5% to have a positive effect on chronic CME. However, an effect on acute CME could not be concluded and requires further study.[38]

There are five published trials comparing two or more topical NSAIDs in the prevention (n=1) or treatment (n=4) of CME. One of the five trials is a more detailed analysis of the effect of topical NSAIDs on functional vision and contract sensitivity[40] and two are only available as abstracts.[42-43] Based upon the evidence, there does not appear to be substantive differences between the available products in the prevention or treatment of CME (see Table below).

Table 7: Clinical Trials Comparing Two or More Ophthalmic NSAIDs for the Prevention or Treatment of CME (Detailed summary, see Appendix 1)

Clinical Trial /Sponsor/Comparators	N=Patients	Main Outcome Measurement (Angiographic and/or Clinical CME)	Conclusion
Solomon 1995[39], Ginsburg 1995[40] Allergan Flurbiprofen vs. Indomethacin* vs. vehicle (CME prevention)	681	Angiographic (FA) and clinical CME (VA-Snellen, contrast sensitivity) at visits 5 (day 21-60 post-op) and 7 (day 120-240 post-op)	Flurbiprofen and indomethacin: significantly less angiographic and clinical CME at visit 5 vs. vehicle. No difference at visit 7. **Flurbiprofen=Indomethacin**
Rho 2003[41] ?Sponsor Ketorolac 0.5% vs. Diclofenac (CME treatment)	34	Angiographic (FA) and clinical CME (Snellen eye chart)	**Ketorolac=Diclofenac**
Rho 2004 (abstract)[42] ?Sponsor Ketorolac 0.5% vs. Diclofenac (CME treatment)	106	Clinical CME: Time to visual improvement; mean final VA improvement	Time to visual improvement: Diclofenac 3.2 months vs. Ketorolac 4.3 months ($p<0.05$) Mean final visual improvement: Diclofenac 2.8 lines vs. Ketorolac 2.6 lines ($p<0.05$)
Rho 2006 (abstract)[43] ?Sponsor Ketorolac 0.5% vs. Diclofenac vs. Bromfenac (CME treatment)	64	Clinical CME: Improvement in VA using ETDRS eye chart (see page 4 for information)	**Ketorolac=Diclofenac=Bromfenac**

*Ophthalmic indomethacin not available in US. CME=cystoid macular edema, FA-fluorescein angiography, VA=visual acuity

Refractive Surgery-Following corneal refractive surgery, pain, photophobia and discomfort are commonly encountered in the early postoperative period. Ophthalmic NSAIDs are often used to manage these symptoms with topical diclofenac and ketorolac being FDA approved for this indication.

There are six clinical trials comparing two or more ophthalmic NSAIDs for pain, photophobia and discomfort following refractive/laser vision corrective surgeries. Visual analogue scales were used most commonly for assessment of pain and discomfort. Overall, the ophthalmic NSAIDs were equally effective in reducing pain and discomfort following laser vision corrective surgery with minimal differences observed (see table 8).

Table 8: Clinical Trials Comparing Two or More Ophthalmic NSAIDs in Refractive/Laser Vision Corrective Surgeries (Detailed summary, see Appendix 1)

Clinical Trial /Sponsor/Comparators	N=Eyes/N=Patients	Main Outcome Measurement (Pain, photophobia/burning-stinging)	Conclusion
Weinstock, et al. 1996[57] R, DB, single center, single surgeon (PRK) No industry support stated Ketorolac 0.5% vs. Diclofenac 0.1%	N=102 patients (102 eyes)	Average/peak discomfort	**Diclofenac > Ketorolac in overall discomfort but did not differ significantly for peak discomfort or need for systemic acetaminophen or codeine.**
McDonald, et al. 1999[58] R, DB, PC, 3 surgeons (RK) Allergan Ketorolac 0.5% vs. Diclofenac 0.1%	N=97	Ocular comfort	**Ketorolac=Diclofenac>moist drops for improving discomfort following RK. Some slight advantages for K in first 4 hrs post-op in foreign body sensation, functionality and compliance scores.**
Narvaez, et al. 2004[59] R, DB, single center, single surgeon, (RK) No industry support stated Ketorolac 0.5% vs. Diclofenac 0.1% (paired eye comparison)	N=30	Eye pain, post-op pain, light sensitivity, foreign body sensation, stinging	**Ketorolac=Diclofenac**
Colin, et al. 2006[60] R, DB, 2-site study (Phase II study) (excimer PRK) Alcon Diclofenac 0.1% vs. Nepafenac 0.03% vs. Nepafenac 0.1%	N=60	Pain, sensitivity and photophobia	**Nepafenac 0.1%= Diclofenac, except on post-op day 2 mean pain score at bedtime favoring nepafenac**
Trattler, et al. 2007[61] R, DB, single center study Allergan (epi-LASIK) Ketorolac 0.4% vs. Nepafenac 0.1% (paired eye comparison)	N=30 (60 eyes)	Pain, photophobia, stinging and foreign body sensation	**Trial not fully enrolled, so not adequate power to draw conclusions** N eyes exhibited significantly greater mean hazing scores at week 2 (p=0.024) and 1 month (p=0.039) vs. K (STUDY WAS HALTED DUE TO THIS FINDING)
Donnenfeld, et al. 2007[62] R, DB, MC Alcon (PRK) Ketorolac 0.4% vs. Nepafenac 0.1% (paired eye comparison)	N=40 (80 eyes)	Corneal epithelial healing, post-op pain before drops and pain, irritation, burning/stinging after drops	**Nepafanac=Ketorolac for all measurements except Nepafenac >Ketorolac for overall after-drop comfort on post-op day 3.**

DB=double-blind, DS=diclofenac sodium, K=ketorolac, LASEK=laser subepithelial keratomileusis, LASIK=laser in situ keratomileusis, MC=multicenter, N=nepafenac, PC=placebo-controlled, PRK=photoreactive keratectomy, R=randomized, RK=radial keratotomy

SAFETY/TOLERABILITY[1-7,]

Safety/Tolerability Measures

Systemic toxicity from topical NSAIDs is rare since the products are minimally absorbed. However, there have been several reported cases of asthma exacerbation associated with the use of ophthalmic NSAIDs.[63] As a result, their use should be avoided in patients with a known allergy to product ingredients on in those allergic to NSAIDs.[1-7]

Local toxicity is more frequently encountered with burning/stinging, irritation and conjunctival hyperemia being reported most commonly. Topical NSAIDs may cause keratitis. Continued treatment with ophthalmic NSAIDs may result in epithelial breakdown, corneal thinning, corneal infiltrates, corneal erosion, corneal ulceration and corneal perforation in certain susceptible patients (see warnings/precautions for at risk patients). If evidence of corneal epithelial breakdown is identified, NSAIDs should be discontinued immediately and the patient closely monitored. In one study comparing a number of ophthalmic NSAIDs (diclofenac 0.1%, indomethacin 0.1%, flurbiprofen 0.03%, and ketorolac 0.5%), placebo and oxybuprocaine 0.4% on corneal epithelium and corneal sensitivity in healthy subjects, none of the NSAIDs caused epithelial damage. All ophthalmic drugs caused a higher mean burning sensation vs. placebo and the diclofenac group demonstrated a significantly reduced corneal sensitivity vs. the other NSAIDs.[74]

Corneal complications, including corneal melts have been reported to occur with all of the available NSAIDs,[32,63] including diclofenac (brand and generic)[64-67], ketorolac[64-65,68-70], bromfenac[71-72], and nepafenac[73,76]. Just over a decade ago, the first generic ophthalmic diclofenac product became available in the U.S. Prior to 1999, there had not been any reported adverse drug reactions entered into a database established in 1997 to document adverse events associated with ocular NSAIDs. In March 1999, the first corneal erosion related to the generic diclofenac product was reported. By July 1999, there were 10 more reports of corneal erosions or melts. In September 1999, the generic diclofenac product manufactured by Falcon Laboratories was withdrawn from the market. Subsequently, an additional 17 cases of corneal melts associated with the generic product were reported.[63] One author reviewed the medical records of 11 cases of corneal melts occurring in patients receiving the generic diclofenac product (n=7) or the branded diclofenac product (n=4) in order to help identify factors that may prove useful in minimizing the occurrence of corneal toxicity.[67] The author notes that there are many known potential causes of corneal melts which did not appear to be excluded/considered prior to attributing the corneal event to diclofenac in these cases. A clinical diagnosis or indication for ophthalmic NSAID use was not documented in 8 of 11 cases. After careful review of the eleven cases, the author concluded that there is not compelling evidence of an isolated drug toxicity and that many of the cases of corneal melts are unrelated to medical treatment and may be caused by an individual's coexistent conditions/factors.

Summary of Safety Results

From the clinical trials included in the class review, small numbers of patients reported treatment related adverse events and drop out rates were minimal. In those studies comparing two or more NSAIDs, adverse events did not differ significantly between groups with the exception of the trial by Trattler, et al[61] in which mean hazing scores were significantly higher and a trend towards delayed healing was observed in the nepafenac vs. the ketorolac treated eyes. That trial was not fully enroll as a result.

In those studies comparing two or more NSAIDs, minor differences in tolerance/comfort of drop instillation (burning/stinging or irritation) were reported but the "better tolerated" product was not consistent across trials. Since not all ophthalmic NSAIDs have been directly compared, it is difficult to conclude "greatest tolerability of drop instillation" of one product over another based upon reported rates of burning/stinging from manufacturers product information or from placebo-controlled trials.

Corneal complications have been reported to occur with all of the available ophthalmic NSAIDs. The available evidence does not support a greater risk with one ophthalmic NSAID versus another; with the possible exception of the Falcon generic diclofenac product which was withdrawn from the market in 1999. Careful consideration of individual patient conditions or known risk factors for corneal complications as well as close monitoring and follow up after surgery will help to minimize these serious adverse events.[75]

Warnings/Precautions

All topical ophthalmic NSAIDs contain similar class warnings which include the potential for prolonged bleeding times, slow or delayed wound healing, and for cross-sensitivity with acetylsalicylic acid, phenylacetic acid derivatives and other NSAIDs. Use of ophthalmic NSAIDs in combination with ophthalmic steroids may increase the possibility of impaired healing.

Topical NSAIDs may cause keratitis. Continued treatment with ophthalmic NSAIDs may result in epithelial breakdown, corneal thinning, corneal infiltrates, corneal erosion, corneal ulceration and corneal perforation in certain susceptible patients. If evidence of corneal epithelial breakdown is identified, NSAIDs should be discontinued immediately and the patient closely monitored.

Based upon post-marketing evidence, corneal adverse outcomes may be increased in patients having complicated eye surgery, corneal denervation, corneal epithelial defects, diabetes, dry eye syndrome, rheumatoid arthritis or multiple eye surgeries potentially leading to loss of sight. Additionally, in patients using ophthalmic NSAIDs more than 24 hours prior to ocular surgery or for more than 14 days after surgery, the risk for occurrence and severity of corneal adverse events may increase.

Table 9: Additional Warnings/Precautions

Ophthalmic NSAID	Warnings/Precautions
Diclofenac	• Refractive stability in patients having corneal refractive surgery and treated with diclofenac is not known. Thus, patients should be monitored for 1 year. • Do not use while wearing soft contact lenses
Flurbiprofen	• No additional warnings/precautions
Ketorolac	• Do not use while wearing contact lenses
Bromfenac	• Contains sodium sulfite which could cause allergic-type reactions in susceptible patients. Sulfite sensitivity occurs more frequently in patients with asthma. • Do not use while wearing contact lenses
Nepafenac	• Do not use while wearing contact lenses

Contraindications

Table 10: Contraindications

Ophthalmic NSAID	Contraindications
Diclofenac	• Known hypersensitivity to any of the components
Flurbiprofen	• Know hypersensitivity to any of the components
Ketorolac	• Demonstrated previous hypersensitivity to any of the ingredients in the formulation
Bromfenac	• Known hypersensitivity to any ingredient in the formulation
Nepafenac	• Demonstrated previous hypersensitivity to any of the ingredients in the formulation or to other NSAIDs

DRUG INTERACTIONS

Table 11: Drug Interactions

Ophthalmic NSAID	Drug-Drug Interactions
Diclofenac	• None noted
Flurbiprofen	• None noted
Ketorolac	• Has been safely given in conjunction with other ophthalmic drugs including antibiotics, beta-blockers, carbonic anhydrase inhibitors, cycloplegics and mydriatics.
Bromfenac	• None noted
Nepafenac	• May be administered in conjuction with ophthalmic beta-blockers, carbonic anhydrase inhibitors, alpha-antagonists, cycloplegics and mydriatics.

ACQUISITION COSTS/VA PURCHASES
Refer to accompanying document for details

CONCLUSIONS
There are seven ophthalmic NSAIDs available in the United States. Three of the seven products are variations of ketorolac including the original 0.5% product, the lower strength 0.04% product and the preservative free product. Diclofenac and ketorolac are both administered four times daily, nepafenac three times daily and bromfenac twice daily. Although the FDA approved indications vary by product, there is some evidence to support the use of most of the products for maintaining intraoperative mydriasis, reducing pain and inflammation associated with cataract surgery, preventing or treating cystoid macular edema and for reducing pain, photophobia and discomfort associated with refractive/laser vision corrective surgeries. In clinical trials comparing two or more NSAIDs for the purposes mentioned, there does not appear to be substantive advantages or disadvantages of one product over another. Currently, diclofenac, flurbiprofen and ketorolac are listed on the VA National Formulary. The need for an additional ophthalmic NSAID on the VANF will be determined.

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Appendix 1 Clinical Trials of Ophthalmic NSAIDs in Cataract Surgery, Cystoid Macular Edema and Refractive Surgery (Only randomized, prospective clinical trials comparing two or more ophthalmic NSAIDs will be summarized in detail in the tables below. Those studies comparing ophthalmic NSAIDs to alternative treatments, such as corticosteroids, were not included)

Cataract Surgery (Outcome Measures: Pain and Inflammation)

Clinical Trial	Inclusion/Exclusion Criteria	Intervention/Outcome Measure(s)	Results	Adverse Events/Comments
Diestelhorst, et al[25] 1996 R, DB, MC (2-centers, 6 surgeons) N=117 **Diclofenac vs. Flurbiprofen vs. Indomethacin***	Inclusion: ECCE (PE) +IOL on one eye Exclusion: Topical or systemic NSAIDs or steroids, systemic or ocular inflammation, pre-operative complications or ocular disease aside from cataracts, IOP >26 mmHg, IDDM, uncontrolled DM, pregnancy or substance abuse, etc.	Intervention: diclofenac 0.1%, flurbiprofen 0.03% or indomethacin 1%: 1 d 4-5 X daily beginning post-op day 1. Duration not stated but followed for 14 days. Outcome Measures: (Pre-op (up to 14 days before), baseline (day 1 post-op), 4-5 days post-op and 12, 13 or 14 day post-op) BCVA, slit lamp exam, applanation tonometry, LFM (laser flare meter). Subjective local tolerance assessing burning/stinging and blurred vision on days 4-5 and 12-14 using VAS or categorical ranking scale (validated?). Bonferroni approach were used to avoid issues of multiple comparisons (p value<0.025 for significant difference)	Data analyzed for assessments on days 4-5 and 12-14 did not include all patients since a fair number of subjects did not follow up for those visits. 117 patients randomized, 107 analyzed on day 1 post-op, 99 analyzed on days 4-5 post-op and 76 analyzed on days 12-14 (35% end of study drop-out rate). Appears that similar numbers of patients dropped out for each treatment group. • LFM values=no significant differences between groups. • Change from baseline in LFM values: Diclofenac significantly reduced flare values from baseline compared to flurbiprofen (p=0.022) but no differences were seen between indomethacin and the other 2 groups. (There were 3 patients with high flare values on day 4-5, when these were removed from analysis, the differences were still present but were no longer significant) • No differences were observed between groups in clinical measures of anti-inflammatory effect (BCVA, ocular discomfort, conjunctival hyperemia, corneal	• Not intent to treat, end of study drop-out rate 35% • Has categorical ranking scale used to compare burning and stinging and blurred vision been validated (ranging from absent to intolerable) • No difference in clinical measures of anti-inflammatory effects between groups. • 3 patients in the flurbiprofen group had very high flare values on day 4-5, when those were removed from the analysis, the difference from diclofenac was no longer significant. • Day 4-5, no patients in the diclofenac group reported burnging/stinging to be severe or intolerable but 1-4 did in the other groups. Most mild-moderate • Day 12-14 no subjects

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<td>edema or sum of grades of anterior chamber cell and flare).
• Local tolerance-no differences except burning/stinging in favor of diclofenac vs. flurbiprofen or indomethacin at days 4-5 and 12-14.</td>
<td>in the diclofenac or flurbiprofen group reported severe or intolerable burning/ stinging.
Diclofenac= or slightly > Flurbiprofen LFM at day 4-5
Diclofenac-Indomethacin all efficacy measures.
Diclofenac>Flurbiprofen or Indomethacin for burning/ stinging.</td>
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<tr>
<td>Kocak, et al[26] 1998
R, DB, single center
N=21 F, 22-DS
Diclofenac vs. Flurbiprofen</td>
<td><u>Inclusion:</u> ECCE+IOL on one eye
<u>Exclusion:</u> Topical or systemic NSAIDs or steroids, systemic or ocular inflammation, pre-operative complications or ocular disease aside from cataracts</td>
<td><u>Intervention:</u> F or DS-1 d q 6 hrs begin at 6 pm night before surgery (3 doses); day of surgery-1 d 90, 60, 30, 15 min before surgery; 1 d 4 times daily for 3-6 wks after cataract surg.
<u>Outcome Measure:</u> (1, 3, 6 wks) conjunctival hyperemia, corneal thickness (pachymetry), corneal surface changes, IOP, anterior chamber inflammation (slit lamp exam for cells: 0=none, 1=5-10, 2=11-20, 3=21-50, 4=>50.</td>
<td>
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<tr><th></th><th>1 wk</th><th>3 wk</th><th>6 wk</th></tr>
<tr><td>Conjunctival hyperemia</td><td>NS*</td><td>NS</td><td>NS**</td></tr>
<tr><td>Corneal thickness</td><td>NS</td><td>NS</td><td>NS</td></tr>
<tr><td>Surface changes</td><td>NS</td><td>NS</td><td>NS</td></tr>
<tr><td>IOP</td><td>NS</td><td>NS</td><td>NS</td></tr>
<tr><td>Inflammation</td><td>NS</td><td>NS</td><td>NS</td></tr>
</table>
*13.6% F severe hyperemia **One patient in DS severe hyperemia, related to preservative. Anterior chamber cell count significantly reduced in both group by 6th week.</td>
<td>• No significant differences observed between DS and F.
• Both drugs significantly reduced inflammation as determined by anterior chamber cell count by the 6th week.
• More patients with severe conjunctival hyperemia in 1st week but not at other points tested.
• No differences in ADEs reported.
Diclofenac=Flurbiprofen</td>
</tr>
<tr>
<td>Flach, et al.[27] 1998
R, DB, single center
N=120
Diclofenac vs. Ketorolac 0.5%
(VA study)</td>
<td><u>Inclusion:</u> ECCE (PE)+IOL on one eye
<u>Exclusion:</u> Use of topical or systemic NSAIDs or steroids, serious organ impairment, other ocular diseases, etc.</td>
<td><u>Intervention:</u> 1 d F every 15 min begin 1 hr before surgery for 3 doses. On post-op day 1, DS or K were administered 4 times daily for 30 days.
<u>Outcome Measure:</u> Anterior chamber inflammation (change from baseline): (cells</td>
<td><u>Slit Lamp</u>: No significant differences between groups in cell or flare observations.
<u>LCFM:</u> No significant differences
All patients included in analysis

Findings with slit-lamp and LCFM measurements were consistent.</td>
<td>• No reported ADEs, no differences in ocular discomfort after instillation of the topical NSAIDs.
• No post-op complications.</td>
</tr>
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		and flare) (2 methods). 1) slit lamp exam by blinded investigator (subjective). Cells: 0=none, 1=1-15, 2=16-30, 3=>30. Flare: 0=none, 1=trace, 2=mild, 3=moderate, 4=strong 2) LCFM (objective). Change from baseline. Determinations made at 3-5 days, 9-12 days and 25-30 days post-op.		• Flurbiprofen given pre-op to all participants. If it had an effect on inflammation, both groups did receive it. **Diclofenac=Ketorolac 0.5%**
Scuderi B, et al.[28] 2003 R, DB, single center N=40 **Diclofenac 0.1% vs. Piroxicam 0.5%***	Inclusion: Cataract extraction with PE and IOL placement in one eye Exclusion: Topical or systemic NSAIDs or steroids, DM, ocular disease aside from cataracts	Intervention: DS or P 1 d 4 times daily for 2 wks, then 1 d 3 times daily for 2 wks. Outcome Measures: BCVA, IOP, corneal edema, Descement membrane folds, flare and cell assessment in anterior chamber assessed on days 1, 4 and 30 post-op and questionnaire for instillation of drops.	BCVA: NS IOP: NS Corneal edema: NS Flare and Cell: NS Descemet folds: NS More frequent reports of burning or stinging sensation upon instillation of drops for diclofenac vs. piroxicam (7 vs. 1, respectively), but scores were very low overall. 1=absent, 2=mild, 3=moderate but transient, 4=severe, 5=intolerable. Mean scores: 1.3 DS vs. 0.05 P ($p<0.05$)	• No post-op complication. • No significant difference in any of the outcome measurements between diclofenac and piroxicam. • There was a significant different in favor of piroxicam in reports of burning or stinging upon instillation. However, mean severity score for diclofenac was 1.3 which is between absent and mild symptoms. • *Topical piroxicam is not available in the US. **Diclofenac=Piroxicam***
Kawaguchi, et al.[29] 2003 R, blinded assessments?, single center N=27 eyes/19 patients BF N=22 eyes/19 patients DS	Inclusion: Cataract extraction with PE and IOL placement. Exclusion: Uveitis, glaucoma, DM, barrier function of corneal epithelium, cases	Intervention: DS or BF instilled in surgical eye prior to surgery. DS 3, 2, 1 and ½ hrs before, BF 3, 2 before surgery. Post-op DS 1 d 4	Authors noted significant difference in aqueous flare level in favor of BF in the first 2 post-op wks. No difference thereafter. Fluoroscein uptake concentration did	• No baseline aqueous flare noted between groups. • Unsure if assessments were blinded.

Diclofenac 0.1% vs. Bromfenac 0.09%	with 5 mm or less by modified Schirmer I Test.	times daily or BF 1 d 2 times daily for 4 wks. Outcome Measures: Aqueous flare using LCFM before surgery, days 1 and 3 and wks 1, 2, 4 and 12 after surgery to measure anterior chamber inflammation. Corneal epithelial damage: barrier function of corneal epithelium measured using an anterior fluorophotometer at wks 1, 2, 4 and 12.	not differ at any time point between groups.	• Difference only up to 2 wks after surgery. • No mention of factors such as BCVA. • Has method to test for corneal epithelial damage been validated using fluorescein and associated fluorescence uptake? **Diclofenac<Bromfenac in first 2 wks post-op in aqueous flare, no difference in corneal epithelial damage.**
O'Hara, et al.[30] 2004 OL (unsure if randomized) N=127 eyes/111 patients **Diclofenac 0.1% vs. Bromfenac 0.09%**	Inclusion: Cataract surgery with PE and IOL implantation. Exclusion: Glaucoma, uveitis, central or branch retinal vein occlusion or history of having such complications.	Intervention: 1 d DS or BF 60 and 30 minutes prior to surgery. Post-op: DS 1 d 3 times daily or BF 1 d twice daily for 4 wks. Outcome Measures: Inflammation (flare/cell) measured via slit lamp biomicroscope at day 3, 7, 14 and 28 post-op for protein and cells. Day 1 post-op was considered as the baseline value. Changes in score on day 3 and 7 were rated on a 4-grade scale correlating with improvement. Cases rated as having no cells or flare on day 1 were excluded. Corneal epithelial damage	Inflammation: • Anterior chamber protein (flare)=improvement favored BF at day 3, NS day 7 (n eyes=39-40) • Anterior chamber cells=favored BF at day 3, NS day 7 (n eyes=60-65) • Flare assessed by flare meter: NS • Corneal epithelial disorder/damage: NS	• Unclear if subjects were randomly assigned. • Open-label study • Baseline measurements were taken on the first post-operative day. Inflammation process could have begun. • Patients with no cell or flare on post-op day 1 (before intervention) were excluded from analysis • Has 4-grade scale used for determining improvement in cell/flare between groups been validated? Not all patients were included in this analysis.

				Diclofenac=Bromfenac flare and corneal epithelial disorder, bromfenac statistically less protein/cells in anterior chamber on post-op day 3 only.
Duong HVQ, et al.[31] 2007 R, DB, single center, single surgeon N=100 eyes/94 patients NP N=93 eyes/89 patients K **Ketorolac 0.4% vs. Nepafenac 0.1%**	Inclusion: Cataract surgery and IOL implantation. Exclusion: Allergy to topical NSAIDs, corneal thinning, erosion, ulcer or perforation, serious or advanced ocular diseases.	Intervention: • Pre-op=1 d 4 times daily K vs. 1 d 3 times daily NP for 3 days prior to surgery. • Post-op=K 1 d 4 times daily for 7 days, gatifloxacin 0.3%, prednisone acetate 1%(Pred Forte); NP 1 d 3 times daily for 7 days, moxifloxacin 0.5%, prednisone acetate (Econopred) Outcome Measures: Anterior chamber inflammation, IOP, BCVA at 1 day, 1 wk, 1 month post-op. Questionnaire on day 1 post-op to assess preoperative pain/discomfort, post-op pain, subjective eye symptoms, compliance, satisfaction.	Anterior chamber inflammation: NS at any time point. BCVA: NS at any time point. Posterior Capsule Opacification (PCO): 5 cases in K vs. 13 cases NP (p=0.019) Questionnaire: Subjective eye complaints, pre-op pain/discomfort were similar between groups. Post-op pain control (p=0.025) and compliance (p=0.023) was significantly better in K vs. NP. Patient satisfaction favored K vs. NP (p=0.022).	• Why were the antibiotics and topical corticosteroids used different between groups? • No difference between K and NP in anterior chamber inflammation, BCVA. • Post-op pain control, patient satisfaction and compliance favored K vs. NP. However, subjective eye complaints and pre-op complaints did not differ. • Was patient satisfaction lower due to higher cases of PCO in NP vs. K? • Cases of PCO were higher than expected in the NP group, reasons unclear. **Ketorolac=Nepafenac for BCVA, inflammation, pre-op pain/discomfort, subjective eye complaints. Ketorolac>Nepafenac for**

				post-op pain control, patient satisfaction, compliance and PCO development.
Sandoval, et al. 2006[56] R, DB, single-center, 4 weeks N=40 eyes/40 patients (Allergan) Ketorolac 0.4% vs. Ketorolac 0.5%	Inclusion: PE + IOL implant Exclusion: ocular pathology, other ocular surgery within 1-3 months, required other topical medications, use of systemic or topical steroids or NSAIDs or ASA.	Intervention: 1 d 15 minutes pre-op, applied every 5 minutes, continued post-op 4 x daily for 1 week then 2 x daily for 3 weeks. Outcome Measures: (Assessed 1, 7, 30 days) BCVA (Snellen), slit-lamp, IOP measurement, LCFM. Review of ophthalmic symptoms (deep eye pain, photophobia, itching, foreign body sensation, stinging/burning graded 0-3, 0=absent, 3=severe)	No differences in BCVA, IOP measurements, LCFM between groups. Ocular symptoms Day 1: 0.5%=70% vs. 0.4%=40 (p=0.03) Foreign body sensation and burning/stinging were significantly different in favor of 0.4%. No differences at 1 week or 1 month	• Advantage for 0.4% at day 1 for ocular symptoms (foreign body sensation and burning/stinging) over 0.5%. • No difference in ocular symptoms at 1 week and 1 month. • No other differences noted. • No ADEs reported. **Ketorolac 0.4% > Ketorolac 0.5% on day one post-op only for ocular symptoms**

*Topical piroxicam not available in US. ADEs=adverse drug effects, BCVA=best corrected visual acuity, BF=bromfenac, D=drop, DS=diclofenac sodium, DB=double-blind, DM=diabetes mellitus, ECCE+IOL=extra capsular cataract extraction with intraocular lens implantation, F-flurbiprofen, IDDM=insulin-dependent diabetes mellitus, IOP=intraocular pressure, K=ketorolac, LCFM=laser cell flare meter, NP=nepafenac, OL=open-label, P=piroxicam, PE=phacoemulsification, q=every, R=randomized

Prevention and Treatment of Cystoid Macular Edema Post-Cataract Surgery

Clinical Trial	Inclusion/Exclusion Criteria	Intervention/Outcome Measure(s)	Results	Adverse Events/Comments
Solomon, et al. 1995[39] R, DB, MC, 3 months N=681, (Allergan) Flurbiprofen vs. Indomethacin* vs. vehicle (Prevention)	Inclusion: Patients scheduled for ECCE + Posterior IOL implant Exclusion: on ASA, topical epinephrine, systemic or topical NSAIDs or oral steroids, allergy to NSAIDs, chronic ocular inflammation, etc.	Intervention: Flurbiprofen vs. indomethacin* vs. vehicle 1 d. 4 x daily begin 2 days prior to surgery and continued for 3 months. Option to continue for an added 3 months if needed. On the day of surgery, 1 d. every 30 minutes 2 hrs	~10% in each group opted for added 3 months. FA performed at visit 5 (21-60 days) and 7 (120-240 days) Visit 5: Angio CME: 16.8% flurbi vs. 12.4% Indo, vs. 32.2% vehicle (statistical difference from vehicle). Clinical CME: 10.7% flurbi,	• Rates of angiographic and clinical CME were significantly lower in both treatment groups vs. vehicle at 21-60 days post-op. No differences were seen at visit 7 (120-240 days).

		before surgery. Outcome Measures: Angio CME (FA), clinical CME (FA+BCVA, visual contrast sensitivity and visual acuity on Snellen test)	9.6% indo, 21.9% vehicle (SD) Visit 7: Angio CME 4-8% in each group, no differences, Clinical CME: <2% in all groups, (NS) **Flurbiprofen=Indomethacin* in angio and clinical CME >vehicle**	• There were no differences in angio or clinical CME between treatment groups. • Visual acuity and contrast sensitivity was worse in those with CME vs those without. • No differences in ADEs **Flurbiprofen=Indomethacin* in angio and clinical CME >vehicle**
Ginsburg, et al. 1995[40] (Extended report from reference 39) (Prevention)	See reference 39 (above)	4 Questions: 1) Is angio CME associated with visual dysfunction? 2) If so, how is contrast sensitivity altered? 3) What are the consequences of these alterations to visual function? **4) What are the prophylactic effects of flurbiprofen and indomethacin on visual function in those with CME?**	Question 4: Analysis Flurbi and indo had higher contrast sensitivity scores than vehicle treated patients (day 4-20 and day 61-120) and overall better visual acuity (? Significant differences?)	• Reported above
Rho 2003[41] R, DB, single-center, 26 weeks N=34, (Sponsor?) Ketorolac 0.5% vs. Diclofenac 0.1% (Treatment)	Inclusion: Clinical CME after PE + posterior IOL implant Exclusion: Prior ocular surgery, vitreous loss during cataract surgery, uveitis or vitreoretinal pathology, DM or pre-existing macular condition.	Intervention: Ketorolac 0.5% or DS 0.1%, 1 d 4 x daily. (Washout 14 days since many people receive topical steroids or NSAIDs with cataract surgery) Outcome Measures: Clinical CME: Snellen BCVA 20/40 or worse and Angio CME via FA.	No differences between groups in Mean final VA (CME reduced or eliminated), time to CME reduction or elimination, patients with reduced or eliminated CME.	• No ADEs reported • No differences in any measure of CME between groups. **Ketorolac 0.5%=DS 0.1% in reducing or eliminating CME**
Rho, et al. 2004[42 (abstract)] Meeting abstract, no details	Inclusion: Patients with pseudophakic CME	Intervention: DS 0.1% 1 d 4 x daily +prednisolone acetate	Time to final VA improvement: DS=3.2 months	**Diclofenac 0.1% >Ketorolac 0.5% in improving time to**

on study design. N=106, (Sponsor?) Diclofenac 0.1% vs. Ketorolac 0.5% (Treatment)	Exclusion: complicated surgery or pre-existing macular pathology	1% OR Ketorolac 0.5% 1 d 4 x daily+prednisolone acetate Outcome Measures: Time to final VA improvement and Mean final VA improvemnt	Ketorolac=4.3 months ($p<0.05$) Mean final VA improvement: DS=2.8 lines Ketorolac=2.6 lines ($p<0.05$)	**final VA improvement and mean final VA improvement. Clinical significance of final VA improvement unclear (2.8 vs. 2.6 lines) (Meeting abstract)**
Rho, et al. 2006[43 (abstract)] Meeting abstract, no details on study design. N=64, (Sponsor?) Bromfenac 0.09% vs. Diclofenac 0.1% vs. Ketorolac 0.5% (Treatment)	Inclusion: Patients with acute CME within one year after uncomplicated cataract surgery. Exclusion: Not listed	Intervention: Bromfenac 1 d 2 x daily, DS or Ketorolac 0.5% 1 d 4 x daily for 3 months. Outcome Measures: Improvement in VA using ETDRS eye charts.	Mean letters gained on the ETDRS eye charts was similar between active treatments groups.	**Bromfenac 0.09%=Diclofenac 0.1%=Ketorolac 0.5% in improving VA using ETDRS eye charts in patients with CME. (Meeting abstract)**

*Topical piroxicam not available in US. ADEs=adverse drug effects, BCVA=best corrected visual acuity, d=drop, DS=diclofenac sodium, ECCE=extracapsular cataract extraction, FA=fluorescien angiography, NS=no significant difference, SD=significant difference, VA=visual acuity

Refractive/Laser Vision Corrective Surgery (Outcome Measures: Pain and Photophobia)/Miscellaneous

<table>
<tr><th>Clinical Trial</th><th>Inclusion/Exclusion Criteria</th><th>Intervention/Outcome Measure(s)</th><th>Results</th><th>Adverse Events/Comments</th></tr>
<tr>
<td>Weinstock, et al. 1996[57]
R, DB, single center, single surgeon
N=102 patients (102 eyes)
No industry support stated
Ketorolac 0.5% vs.
Diclofenac 0.1%</td>
<td>Inclusion: Patients having PRK
Exclusion: Not stated</td>
<td>Intervention: K or DS: 2 d, 1 hr and again at 1 min. prior to surgery.
K or DS 2 d every 4 hrs (Patients were given 12 analgesic tabs containing: 325 mg acetaminophen, 15 mg caffeine and 8 mg codeine)
Outcome Measures: (18-21 hrs after procedure)
Single masked examiner administered questionnaire (2</td>
<td>
<table>
<tr><th></th><th>DS</th><th>K</th><th>p</th></tr>
<tr><td>Overall discomfort</td><td>1.5</td><td>1.9</td><td>0.004</td></tr>
<tr><td>Peak discomfort</td><td>2</td><td>2.3</td><td>NS</td></tr>
<tr><td>Acetaminophen (mg)</td><td>2000</td><td>2150</td><td>NS</td></tr>
<tr><td>Codeine (mg)</td><td>92</td><td>98</td><td>NS</td></tr>
</table>
Scale used:
0-virturally no discomfort
1-mild
2-moderate
3-severe discomfort
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Diclofenac > Ketorolac in overall discomfort but did not differ significantly for peak discomfort or need for systemic acetaminophen or codeine.

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		questions: How would you rate your average and peak ocular discomfort using 4 point scale; 0=no discomfort, 3=severe). Number of analgesic tablets ingested was recorded.		
McDonald, et al. 1999[58] R, DB, PC, 3 surgeons N=97 Allergan Ketorolac 0.5% vs. Diclofenac 0.1%	Inclusion: Patients having radial keratotomy (RK surgery chosen since it is felt to be a well known model for corneal pain and many patients experience significant pain post-op) Exclusion: not used diazepam, lorazepam, piroxicam or alcohol near the time of surgery, pregnant, ocular inflammation, corneal disorder	Intervention: K, DS or moist drops (placebo) 1 hr prior to surgery and 5 min after surgery ended. Then, 1 d 4 x daily for 24 hrs, then up to 4 x daily for pain. Outcome Measures: Modified 15-20 min questionnaire involving questions pertaining to ocular comfort and visual function on the operated and non operated eye. (Answered before RK and 30 min, 1, 2, 3, 4, 5, 6, 24 and 48 hrs after surgery)	Operative eye results: • Patients receiving moist drops (placebo) reported more symptoms than both treatment groups. • The only difference between treatment groups was foreign body sensation 1 hr after surgery with the moist drops group reporting the highest followed by DS and then K.	• 210 statistical values calculated to compare symptoms in the operative and non operative eye at 9 time points. • Questionnaire validated? • **Ketorolac=Diclofenac>moist drops for improving discomfort following RK. Some slight advantages for K in first 4 hrs post-op in foreign body sensation, functionality and compliance scores.**
Narvaez, et al. 2004[59] R, DB, single center, single surgeon, N=30 No industry support stated Ketorolac 0.5% vs. Diclofenac 0.1% (paired eye comparison)	Inclusion: Elective, bilateral simultaneous RK Exclusion: Allergy to study meds, prior RK, systemic or topical NSAIDs, recent eye disease or markedly abnormal corneal sensitivity.	Intervention: K in one eye, DS in the other: 1 d every 4 hrs while awake for 24 hrs after surgery. Outcome Measures: Eye pain recorded before and 15 min after instillation of drops. Post-op pain estimated on VAS 0-no pain, 10-worst pain ever.	• No difference in clinical parameters between groups (IOP, punctuate epithelial erosions, stromal edema, etc.) • No differences were noted in pain, light sensitivity, foreign body sensation or stinging between groups at any time point. • Preference stated based upon level of comfort: • K=48.3%	**Ketorolac=Diclofenac**

		Light sensitivity, foreign body sensation, and stinging measures on 1-4 scale; 1=none, 2=mild, 3=moderate, 4-severe	• DS=51.7% (unknown if significant) • No difference reported in stinging upon instillation.	
Colin, et al. 2006[60] R, DB, 2-site study (Phase II study) N=60, 7day Alcon Diclofenac 0.1% vs. Nepafenac 0.03% vs. Nepafenac 0.1%	Inclusion: Myopic excimer PRK in adults Exclusion: Topical or systemic analgesics (within 2 weeks), or NSAID (within 30 days)	Intervention: N 0.1%, N 0.03% or DS 0.1%: 2 d, 1 hr before surgery, 2 d, 1 hr after surgery, 1 d, 4 hrs after surgery, 1 d, 8 hrs after surgery. Post-op day 1, 1 d 4 x daily, then discontinued. Patients could take acetaminophen for pain as needed. Outcome Measures: Pain and sensitivity scores were recorded for 3 days. Pain VAS (0-none, 9-extreme). Photophobia 0=none, 3-severe	• Post-op pain: No differences between N 0.1% were observed from DS on the day of surgery or the first day after surgery. On the day of surgery, N 0.03% was statistically inferior to N 0.1%. • The only statistical difference between N 0.1% and DS were the pain scores at bedtime on day post-op day 2 in favor of N 0.1%. • Percentage of patients using acetaminophen on post-op day 1: N 0.03%=60% N 0.1%=55% DS 0.1%=45% (NS)	• **Nepafenac 0.1%= Diclofenac, except on post-op day 2 mean pain score at bedtime favoring nepafenac** • Two ocular events related to therapy was reported in the nepafenac groups (one-0.03%=corneal infiltrate, one-0.1%=ocular discomfort
Trattler, et al. 2007[61] R, DB, single center study N=30 (60 eyes) Allergan Ketorolac 0.4% vs. Nepafenac 0.1% (paired eye comparison)	Inclusion: Bilateral sheetless epi-LASIK in adult patients Exclusion: invasive ocular or intraocular procedures, chronic ocular diseases, etc.	Intervention: Immediately post-op, K was administered in one eye, N the other. Then 3 x daily for 5 days. Celecoxib was allowed as a rescue medication. Outcome Measures: Follow-up visits post-op days 1 and 5. Pain, photophobia, stinging and foreign body sensation were rated on the phone 5 hrs post-op, days 2, 3 and 4. Ratings were 0=none,	• Patients reported statistically less pain in K vs. N eyes on day 3 • No differences in photophobia, foreign body sensation or burning were seen. • Study stopped early with only 14 eyes and 7 patients due to an unacceptable amount of haze reported in the N group at weeks 2 and 1 month post-op. The difference was not significant at 2 months.	• **Trial not fully enrolled, so not adequate power to draw conclusions** • N eyes exhibited significantly greater mean hazing scores at week 2 (p=0.024) and 1 month (p=0.039) vs. K (STUDY WAS HALTED DUE TO THIS FINDING)

		10-worst. Rate of healing (day the bandage contact lens removed) and degree of haze.		
Donnenfeld, et al. 2007[62] R, DB, MC N=40 (80 eyes) Alcon Ketorolac 0.4% vs. Nepafenac 0.1% (paired eye comparison)	Inclusion: Adult patients having bilateral PRK surgery Exclusion: condition causing delayed wound healing, use of systemic NSAIDs, need for other eye drops, prior treatment with Restasis, etc.	Intervention: K or N 1 d 3 x daily for 3 days after PRK Outcome Measures: Corneal epithelial healing (3rd day), post-op pain control beginning on day 1 using VAS (1-10) before drops and secondarily, pain, irritation, burning/stinging and comfort upon instillation of drops (after drops). Patients observed on days 1,3,4,5 and 7 or when epithelial defects closed in both eyes.	Mean time to epithelial healing: K 4 days vs. N 4.18 days (p=.3134) Cumulative healing by post-op day (3, 4, 5 and 7) did not differ. General mean post-op pain: (before study intervention): no difference (p>0.05) No difference in rescue meds (hydrocodone/APAP) Pain, irritation, burning/stinging, overall comfort (after study intervention): No differences on day 1. On post-op day 3, comfort scores statistically favored N vs. K.	• 2 ADEs unrelated to treatment were reported: 1-keratitis 2 days post-op (K); 1-epithelial defect (N). • No difference between treatments with regard to epithelial healing or post-op pain. Difference in favor of N in after-drop comfort on post-op day 3. • **Nepafenac=Ketorolac for all measures except overall after-drop comfort on post-op day 3 N>K**

APAP=acetaminophen, D=drop, DS=diclofenac sodium, IOP=intraocular pressure, K=ketorolac, LASEK=laser subepithelial keratomileusis, LASIK=laser in situ keratomileusis, MC=multicenter, N=nepafenac, PC=placebo-controlled, PRK=photoreactive keratectomy, RK=radial keratotomy