

WYOMING PDLAC THERAPEUTIC CLASS REVIEW

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OPHTHALMIC NSAIDS

This publication is a result of the collaboration of the Goold Health Systems, Inc. Clinical Workgroup and represents the opinion of these authors based on a review of the literature available at the time it was written. It is intended for the sole purpose of providing information to committee members in order to compare medications within a specified subset of clinical parameters. It is not intended to provide specific clinical advice for any condition, or to be an exhaustive review of all potential aspects of pharmacotherapies for any given condition. Medical evidence is rapidly changing, and no representation is made regarding the use of this material beyond the stated purpose.

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SYNOPSIS

Postoperative inflammation after ophthalmic surgery presents a major cause of patient discomfort and potential delayed recovery. Studies in animal models conclude that prostaglandins mediate intraocular inflammation, and can cause disruption of the blood-aqueous humor barrier, vasodilation, increased vascular permeability, leukocytosis and increased intraocular pressure (IOP).

Topically applied NSAIDs, due to their prostaglandin-inhibitor activity, are useful in the management of ocular inflammation and cystoid macular edema (CME) following cataract surgery, as well as in the management of pain following corneal refractive surgery. Flurbiprofen (Ocufen®), specifically, can also inhibit prostaglandin-induced miosis during ocular surgery. Ophthalmic NSAIDs present an advantage over ocular corticosteroids, which can cause ocular hypertension and potential damage to the optic nerve, as well as defects in visual acuity and fields of vision.

The drugs included in this therapeutic class review include bromfenac (Xibrom®), diclofenac (Voltaren®), flurbiprofen (Ocufen®), ketorolac (Acular®, Acular LS®, Acular PF®) and nepafenac (Nevanac®)

FDA APPROVED INDICATIONS^{1-3, 17}

Drug	Postoperative cataract extraction inflammation	Postoperative pain or photophobia after corneal ^a or incisional ^b refractive surgery	Inhibition of intraoperative miosis
bromfenac (Xibrom®)	X ¹		
diclofenac (Voltaren®)	X	X ^a	
flurbiprofen (Ocufen®)			X
ketorolac (Acular®)	X ¹		
ketorolac (Acular LS®)		X ^a	
ketorolac (Acular PF®)		X ^b	
nepafenac (Nevanac®)	X		

¹ also indicated for postoperative pain

DOSAGE FORMS, DOSE, AND MANUFACTURER^{1-3, 17}

All dosage forms are to be applied to the affected eye(s).

Drug	Dosage forms	Dose	Manufacturer
bromfenac (Xibrom®)	<u>Solution:</u> 0.09%	1 drop BID, starting 24 hrs after cataract surgery for 2 weeks	ISTA Pharmaceuticals
diclofenac (Voltaren®)	<u>Solution:</u> 0.1%	<i>Cataract surgery:</i> 1 drop QID, starting 24 hrs after surgery through 2 weeks <i>Corneal refractive surgery:</i> 1-2 drops 1 hr prior to surgery, then 1-2 drops 15 min after surgery, then QID for up to 3 days	Various generic manufacturers (Novartis)
flurbiprofen (Ocufen®)	<u>Solution:</u> 0.03%	1 drop every 1/2 hr starting 2 hrs before surgery	Various generic manufacturers Allergan
ketorolac (Acular®) (Acular LS®) (Acular PF®)	<u>Acular®/PF solution:</u> 0.5% <u>LS Solution</u> 0.4%	<i>Cataract surgery:</i> 1 drop QID starting 24 hrs after cataract surgery for 2 weeks <i>Corneal refractive surgery:</i> 1 drop QID prn pain/photophobia for up to 3-4 days after surgery	Allergan
nepafenac (Nevanac®)	<u>Suspension:</u> 0.1%	1 drop TID the day prior to surgery, the day of surgery, and through the first 2 weeks	Alcon Laboratories, Inc.

PHARMACOLOGY^{1-3, 17}

Although each of the drugs in this class inhibits conversion of cyclooxygenase (COX) and lipoxygenase, causing reduced prostaglandin synthesis and thereby exerting an anti-inflammatory effect, the exact mechanism of action is unknown.

PHARMACOKINETICS^{1-3, 17}

The extent of systemic absorption of ophthalmic NSAIDs after administration is generally not noted in product or clinical information. Information for bromfenac, diclofenac and ketorolac indicate detectable but not quantifiable steady-state drug concentrations, less than 50ng/ml or up to 95ng/ml for ketorolac.

Nepafenac is a pro-drug which is metabolized to amfenac, its active metabolite. Steady-state concentrations of nepafenac and amfenac (0.310 ± 0.104 ng/ml and 0.422 ± 0.121 ng/ml respectively) have been observed in the majority of patients 2-3 hours after ophthalmic administration.

CLINICAL TRIALS

Clinical trials performed to obtain FDA approval confirmed bromfenac, diclofenac, ketorolac and nepafenac to be superior in efficacy, as well as showing safety of the drug, when compared to placebo. FDA-approved labeling for flurbiprofen, marketed either as Ocufer® or flurbiprofen sodium, while mentioning clinical trials in two sections, does not allude to trials vs. placebo. The majority of clinical trials surveyed indicate research support as non-governmental.

Donnenfeld et al conducted two randomized, double-blind, placebo-controlled trials involving 527 patients, to evaluate the safety and efficacy of bromfenac 0.09% for treatment of postoperative inflammation and reduction of pain after cataract extraction.¹³ Bromfenac or placebo was instilled BID for 14 days, and then the patient was observed another 14 days for safety evaluation. The bromfenac group exhibited a significantly higher percentage of patients with no ocular inflammation at day 15, and also had resolution of ocular pain in 2 days vs. 5 days for placebo. Eye irritation, burning or stinging, and photophobia were reported in a lower percentage of bromfenac subjects vs. placebo. In addition to fewer adverse events for the bromfenac group, no serious adverse effects were reported.

Lane et al studied 476 patients at 21 ophthalmology clinics in a randomized, double-blind, placebo-controlled study, administering nepafenac 0.1% TID per manufacturer's label directions starting 1 day before cataract surgery and continuing for 14 days postoperatively.¹⁴ Their findings showed a significant difference in elimination of postoperative pain and ocular inflammation in the nepafenac group vs. placebo.

Caldwell et al, in a double-blind study of 66 patients undergoing bilateral photorefractive keratectomy (PRK), administered nepafenac 0.1% TID per manufacturer's label directions in one eye and placebo balanced salt solution TID in the other eye.¹⁵ Patients were evaluated daily for 4 days, and no statistical difference was found between treatments in time to reepithelialization. Patients reported significantly less pain on postoperative days 1 and 2, and a greater percentage of patients reported superior pain relief in the nepafenac-treated eye during the first 3 days after surgery.

Stewart et al analyzed 527 subjects in two randomized, double-blind, placebo-controlled studies to determine incidence of treatment-related systemic adverse effects and/or hepatotoxicity in patients treated with bromfenac 0.09% post-cataract surgery vs. placebo.¹⁶ The treatments were self-administered BID for 14 days, then both treatment groups were followed for an additional 14 days for safety evaluation. Neither clinically significant systemic adverse effects nor changes in liver chemistry were observed in either group.

Comparator Trials

A Cochrane Review by Sivaprasad et al²¹ was published in 2004. This review was to establish if non-steroidal anti-inflammatory agents were useful for treating cystoid macular edema (CME) after cataract surgery. CME is considered to be the most frequent source of weak visual outcomes that may occur after cataract surgery. Seven randomized controlled trials were included in the review, with three studies evaluating the effects on acute treatment of CME following cataract surgery and four trials evaluating the effects on NSAID use on chronic CME. Five of the studies observed the effects of topical ketorolac 0.5%. Three of these trials were placebo controlled trials, and the other two trials were comparator trials. The comparator trials included one comparing ketorolac with topical diclofenac (Rho 2003 included in table below) and the other comparing ketorolac, prednisolone, and ketorolac/prednisolone combination.

Results of these trials for acute CME suggest that, while all three trials evaluating treatment effect for acute CME included ketorolac, only two of the three trials found that the use of NSAIDs was effective treatment. One of these trials (Rho 2003) found both ketorolac and topical diclofenac 0.1% to be effective treatment.

Four studies examined the treatment of chronic CME. Two of these four studies utilized ketorolac 0.5%, and these studies found a statistically significant benefit with use. The other two studies examined use of an oral NSAID and topical fenoprofen as treatment for chronic CME; however, neither was found to be effective treatment. It can be concluded from this review that a topical NSAID (ketorolac) can have a beneficial effect as treatment for chronic CME; however, due to the small size of the studies looking at acute CME, more information is needed to determine the effectiveness of topical NSAIDs as treatment for acute CME.

The following table discusses additional comparator studies regarding ophthalmic NSAID use.

Ophthalmic NSAIDS-6

Study	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Conclusions
Bucci, et al ⁸ 2007	Single-center randomized, double-blind study ketorolac 0.4% vs. nepafenac 0.1%	N=132 2 days before cataract surgery	Cataract surgery patients	-Prostaglandin E(2) levels (PGE(2)) and aqueous concentrations obtained at surgery	-Compared with nepafenac treated eyes, more ketorolac treated eyes had PGE (2) levels less than the level of detection (p<0.001). -Ketorolac treated eyes had mean lower PGE (2) levels than nepafenac treated eyes (p<0.001). -Aqueous levels for ketorolac was 1079.1 +/-881.5ng/ml, while nepafenac levels (of the inactive molecule) were 588.4 +/-394.6 ng/ml (p<0.001 vs ketorolac).	-Findings showed significantly greater prostaglandin inhibition (lower PGE(2) concentrations) and significantly higher aqueous humor drug penetration among the group receiving ketorolac 0.4% compared with those receiving nepafenac.
Bucci, et al ⁹ 2008	Single center, randomized, investigator masked study ketorolac 0.4% vs. bromfenac 0.09%	N=56 1 drop 6hrs & 12hrs preop	Cataract surgery patients	Prostaglandin E(2) (PGE(2)) levels and aqueous drug concentrations between the two treatment groups	-PEG (2) level for those treated with ketorolac was 204.2pg/ml compared with 263.7pg/ml in those treated with bromfenac (p=0.02). -The mean aqueous concentration of ketorolac was 130.5 ng/ml compared with 6.2ng/ml with bromfenac (p=0.004).	-Statistically lower PGE (2) concentrations and statistically higher aqueous humor drug penetration were observed in the ketorolac group compared with the bromfenac group. -The findings suggest to the investigators that QID ketorolac dosing may provide better inflammation control than BID bromfenac dosing.

Ophthalmic NSAIDs-7

Study	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Conclusions
Durrie, et al ¹⁰ 2007	Prospective, randomized, double-blind, controlled, single-site study bromfenac 0.09% and gatifloxacin vs. ketorolac 0.4% and gatifloxacin vs. nepafenac 0.1% and moxifloxacin	N=29 8 days	Patients undergoing photorefractive keratectomy (PRK)	-Postoperative pain control and effects on corneal reepithelialization after undergoing PRK -Self-evaluation of pain relief was recorded on postop days 1 and 3 using a visual analog scale (VAS)	-Time to reepithelialization was 5.5 days for those treated with nepafenac compared with 5.62 days for the ketorolac group and 7.25 days for the bromfenac group. A significant difference was found between the nepafenac and bromfenac group and between the ketorolac and bromfenac group ($p < 0.05$). -The nepafenac treatment group was seen to have significant reduction in pain scores on day 1 (-1.13) and day 3 (-1.32), ketorolac on day 3 (-0.88) and bromfenac on day 3 (-0.83). - No adverse reactions to any of the agents were reported.	-Complete reepithelialization occurred significantly faster in eyes treated with nepafenac or ketorolac than with bromfenac. - Pain relief was achieved significantly sooner with nepafenac than with either bromfenac or ketorolac. -Please note that nepafenac had a different antibiotic in the treatment arms.
Donnenfeld, et al ¹¹ 2007	Double-blind, randomized, contralateral eyes, multicenter study ketorolac 0.4% vs. nepafenac 0.1%	N=40 7 days	Patients undergoing sequential bilateral photorefractive keratectomy (PRK)	-Assessed on days 1, 3, 4, 5, and 7 postop for effects on corneal reepithelialization and pain.	-Average time-to-healing was 4.18 days for nepafenac and 4.00 day for ketorolac ($p = 0.3134$). -No statistical difference in reepithelialization time (approximately 4 days) was noted between the two agents. -Patients treated with nepafenac showed significantly lower mean sensation scores than the ketorolac	-Both ketorolac and nepafenac provide postop pain relief without adverse events on corneal epithelial healing. -Treatment with Nepafenac may provide a greater comfort with instillation compared with ketorolac in those who have undergone PRK.

Study	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Conclusions
					<p>group for after-drop pain (p=0.0090), irritation (p=0.0007), and burning or stinging (p=0.0003)</p> <p>-Mean overall comfort score was significantly greater with nepafenac on day 3 (7.43 vs 6.41; p<0.0001) compared with ketorolac.</p>	
Duong, et al ¹² 2007	<p>Randomized study utilizing two groups</p> <p>ketorolac 0.4% & gatifloxacin 0.3% & prednisolone acetate 1% vs. nepafenac 0.1% & moxifloxacin 0.5% & prednisolone acetate</p>	N=183	Visually significant cataracts and candidates for cataract surgery	<p>-Subjective complaints including burning, itching, foreign-body sensation, and plain level after surgery</p> <p>-Objective findings including visual function, degree of inflammation in the anterior segment, and complications</p>	<p>-There was no statistical difference between treatment groups for visual outcomes and anterior chamber inflammation (p=0.33).</p> <p>-The nepafenac group had a higher incidence of posterior capsule opacification (p=0.019)</p> <p>The ketorolac treatment group had a greater (statistically significant) patient satisfaction, patient compliance, and postoperative pain control compared with the nepafenac group (p=0.022; p=0.023; and p=0.025 respectively).</p>	-Ketorolac was statistically significantly better than nepafenac in patient satisfaction, compliance, and postoperative pain.
Flach et al ¹⁸ 2001	Randomized, double-masked, prospective trial	N=120		-To compare efficacy and toxicity by using objective and subjective	-There were no statistical differences found between the two treatment groups for their antiinflammatory effects at any of the post-op visits.	-This study showed that ketorolac and diclofenac are equally effective for treatment of postoperative inflammation after cataract surgery.

Ophthalmic NSAIDs-9

Study	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Conclusions
	Ketorolac 0.5% Vs Diclofenac 0.1%	30 days beginning 1 st day of postop, with 3 post-op office visits		measurements of inflammation and toxicity -Objective measurements were done by way of Kowa FC 1000 laser cell and flare meter. -Subjective measurement was done by way of slit-lamp biomicroscope	-Adverse events were not reported or observed. -There was no statistical difference between the two treatment arms in regards to ocular discomfort after the drops were instilled. In regards to tolerability, ocular discomfort was the only event reported.	-Both medications were well tolerated, with ocular discomfort being the only reported tolerability issue. The reports of ocular discomfort were comparable for both agents.
Wittpenn et al ¹⁹ 2008	Prospective, randomized, investigator-masked, multicenter clinical trial. Prednisolone 1% Vs Prednisolone 1% and ketorolac 0.4%	N=183	-Patients having cataract surgery without known risk factors for cystoids macular edema (CME)	-CME incidence, retinal thickness measured by optical coherence tomography (OCT), best-corrected visual acuity, and contrast sensitivity	-Both treatment groups received 4 doses of ketorolac one hour prior to surgery -Five patients in the steroid group and no patients in the ketorolac/steroid group had clinically apparent CME (p=0.032). -As noted by OCT, the ketorolac/steroid treatment group did not have any patient with definite or probable CME, compared with six patients from the steroid treatment group (p=0.018).	-This study shows that the incidence of CME and macular thickening in cataract surgery patients is significantly reduced in those treated with ketorolac/steroid combination compared with a steroid alone.

Study	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Conclusions
					<p>-Retinal thickening was less in the ketorolac/steroid treatment group vs the steroid group (p=0.003).</p> <p>-Fewer patients had retinal thickening of more than 10µm in the ketorolac/steroid group compared with the steroid group (p<0.001).</p>	
Rho 2003 ²⁰	<p>Randomized, prospective study</p> <p>Diclofenac 0.1% Vs. Ketorolac 0.5%</p>	<p>N=34</p> <p>26 weeks</p>	<p>Subjects with clinical cystoid macular edema (CME) after phaco-emulsification cataract extraction with posterior chamber intraocular lens (IOL)</p>	<p>-Observing for improvement in CME and visual acuity</p>	<p>- Both treatment groups resulted in a significant reduction in CME, as well as significant improvement in visual acuity.</p> <p>-16 patients treated with diclofenac had a reduction in CME (89%), whereas 14 patients treated with ketorolac had a reduction in CME (88%) (p=0.92) within 26 weeks.</p> <p>-Within 26 weeks, diclofenac eliminated CME in 14 patients (78%) and 12 patients in those treated with ketorolac (75%) (p=0.86).</p> <p>-Initial CME reduction was seen within 7.5 weeks with diclofenac and 8.0 weeks with ketorolac (p=0.41).</p>	<p>-Both diclofenac and ketorolac were equally efficacious in treating to reduce the severity and duration of CME after phacoemulsification with posterior chamber IOL implantation.</p>

Study	Design & Comparators	Sample Size & Duration	Patient characteristics	Assessed Outcomes	Results	Conclusions
					<p>-The mean time to CME resolution with diclofenac was 13.6 weeks compared with 12.8 weeks with ketorolac (p=0.49).</p>	
<p>Sher et al²³ 2009</p>	<p>Randomized, open label trial</p> <p>bromfenac 0.09% Vs ketorolac 0.4%</p>	<p>N=149 (212 eyes)</p>	<p>Patients who underwent photorefractive keratectomy (PRK)</p> <p>-If both eyes treated, ketorolac went into one eye and bromfenac in the other</p>	<p>Compare safety efficacy of two treatments, including pain, burning, photophobia, foreign body sensation, and epithelial healing rates</p> <p>-Postop results recorded by patient was done by visual analog scale (VAS)</p>	<p>-All patients also cold saline, prednisolone 1%, gatifloxacin 0.3%, and some received mitomycin C 0.02%.</p> <p>-Both the bromfenac and ketorolac treatment group reported similar effects in regards to postoperative pain, burning, foreign-body sensation, and photophobia. There were not any significant differences reported between the two groups.</p> <p>-Adverse events were not reported for either treatment group.</p>	<p>-Bromfenac and ketorolac were found to have comparable treatment outcomes in regards to discomfort and safety when added to other postoperative PRK treatment measure, as no significant differences were reported.</p>

CONTRAINDICATIONS ^{1-3, 17}

All medications in this therapeutic class are contraindicated in patients hypersensitive to the drug itself or any of its components. There are several drugs that carry their own contraindications unique to the class. These contraindications are listed in the table below.

Drug	Contraindication
bromfenac (Xibrom®)	ASA/NSAID-induced asthma, third trimester of pregnancy
ketorolac (Acular®) (Acular LS®) (Acular PF®)	Hypersensitivity to aspirin
nepafenac (Nevanac®)	Hypersensitivity to other NSAIDs

SPECIAL POPULATIONS ^{1-3, 17}

Most medications in this therapeutic class are not indicated for use in the pediatric population. The table below clarifies which products are available for use. No information was found on required dosage changes in those with hepatic or renal insufficiency, probably due to the limited systemic exposure with use.

Drug	Pediatrics	Pregnancy Category
bromfenac (Xibrom®)	No	C
diclofenac (Voltaren®)	No	C
flurbiprofen (Ocufen®)	No	C
ketorolac (Acular®) (Acular LS®) (Acular PF®)	≥ 3 yrs	C**
nepafenac (Nevanac®)	≥ 10yrs	C**

** Avoid use in third trimester because of possible premature closure of the ductus arteriosus.

ADVERSE DRUG REACTIONS ^{1-3, 17}

Nepafenac (Nevanac®) may cause capsular opacity, GI upset, hyperemia, hypertension, photophobia and sinusitis; however, there was no incidence provided.

Please refer to the table below for additional adverse events.

Adverse effect	bromfenac (Xibrom®)	diclofenac (Voltaren®)	flurbiprofen (Ocufer®)	ketorolac (Acular®) (Acular LS®) (Acular PF®)	nepafenac (Nevanac®)
Abnormal/blurred vision	-	<5%	-	-	-
Conjunctivitis/redness	√	<5%	-	-	-
Corneal edema	-	<5%	-	√	-
Corneal deposits/lesions/discharge	-	<5%	-	-	-
Corneal opacity	-	<5%	-	-	-
Decreased visual acuity	-	-	-	-	√
Eyelid swelling	-	<5%	-	-	-
Fibrosis	-	-	√	-	-
Foreign body sensation	-	-	-	-	√
Headache	√	-	-	-	√
Increased IOP	-	15%	-	-	√
Increased ocular bleeding	-	-	-	√	-
Iritis/ irritation/itching	√	<5%	-	-	-

Adverse effect	bromfenac (Xibrom®)	diclofenac (Voltaren®)	flurbiprofen (Ocufen®)	ketorolac (Acular®) (Acular LS®) (Acular PF®)	nepafenac (Nevanac®)
Keratitis	-	28%	-	√	-
Lacrimation	-	30%	-	-	-
Lacrimation disorder	-	<5%	-	-	-
Lid margin crusting	-	-	-	-	√
Miosis/ Mydriasis	-	-	√	-	-
Ocular allergy	-	<5%	-	√	-
Pruritus	√	-	-	-	√
Sticky sensation	-	-	-	-	√
Tearing, vitreous detachment	-	-	-	-	√
Transient burning and stinging	-	15%	√	-	-

DRUG-DRUG INTERACTIONS ^{1-3, 17}

Bromfenac (Xibrom®), ketorolac (Acular®), and nepafenac (Nevanac®) should be administered cautiously with ocular corticosteroids due to additive effects which may delay wound healing. Use of this combination is also a risk factor for development of corneal erosion.

All ophthalmic NSAIDS have a warning indicating a potential risk of increased bleeding. Use in combination with oral NSAIDs and/or warfarin with caution, due to possible reduced platelet aggregation and potential bleeding complications.

Diminished miotic effects had been reported with concomitant use of flurbiprofen (Ocufen®) and acetylcholine or carbachol, although recent clinical and animal studies suggest no interaction with either agent.

SUMMARY

Prostaglandins are the key constituents resulting in postoperative ocular inflammation. Diminishing the release of prostaglandins that occurs with ocular surgery is important to help limit the inflammatory response that may lead to postoperative discomfort and a hindered recovery. Furthermore, if inflammation is not treated, resultant effects such as cystoid macular edema may occur.²²

Topical NSAIDs are frequently used to help treat postoperative inflammation and pain, as well as to reduce the risk of complications such as cystoid macular edema. The efficacy and safety of the class as a whole has been reinforced by the current studies surveyed. Current head-to-head trials of the drugs in the class under review do show some superiority of ketorolac or nepafenac to the other drugs surveyed, but the small total number of head-to-head trials, and the overall significance of their composite results make a strong case for further examination. It should be note that one trial (Durrie 2007¹⁰) had more than one variable due to using different antibiotics as comparators, as well as different non steroidal. Based on these considerations, there is insufficient evidence to suggest one agent is clinically superior to another within a given indication.

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