



Department of Vermont Health Access

Therapeutic Class Review Ophthalmic Nonsteroidal Anti-Inflammatory Drugs

Overview/Summary

There are currently seven ophthalmic nonsteroidal anti-inflammatory drugs (NSAIDs) available in the United States and these include bromfenac sodium (Bromday[®]), diclofenac sodium (Voltaren[®]), flurbiprofen sodium (Ocufen[®]), ketorolac tromethamine (Acular[®], Acular LS[®], Acuvail[®]) and nepafenac (Nevanac[®]).¹⁻¹² Ophthalmic NSAIDs are used in various non-infectious ocular conditions including management of pain and inflammation following cataract and corneal refractive surgeries, inhibition of intraoperative miosis and relief of ocular itching due to seasonal allergic conjunctivitis.¹² Although not Food and Drug Administration (FDA)-approved, ophthalmic NSAIDs have been used in the prevention and treatment of cystoid macular edema.¹³ Ophthalmic NSAIDs exert their anti-inflammatory activity primarily by nonselective inhibition of cyclooxygenase-1 and cyclooxygenase-2 enzymes.¹⁻¹³

Each of the ophthalmic NSAIDs and their respective FDA-approved indications are listed in Table 2. Bromfenac sodium (Bromday[®]) was recently approved by the FDA and has the same active ingredient, strength and indication as Xibrom[®] but is approved for once-daily dosing, compared to twice-daily dosing with Xibrom[®]. The manufacturer of Xibrom[®] discontinued the branded product in February 2011, but a generic formulation was approved in May 2011.¹³⁻¹⁵ Ophthalmic formulations of diclofenac sodium, flurbiprofen sodium, ketorolac tromethamine 0.5% and 0.4% are also available generically. The 0.45% strength of ketorolac tromethamine is dosed twice daily. Ophthalmic nepafenac is dosed three times daily and all others agents are dosed four times daily. Diclofenac sodium and ketorolac tromethamine 0.45% are the only ophthalmic NSAIDs that are preservative-free.³⁻¹²

Ophthalmic NSAIDs currently play four principal roles in ophthalmic surgery, including the prevention of intraoperative miosis during cataract surgery, management of postoperative inflammation, the reduction of pain and discomfort after cataract and refractive surgery, and the prevention and treatment of cystoid macular edema (CME) after cataract surgery.¹⁶ Ocular inflammation is a manifestation of cellular and vascular response of the host tissue to injury and involves a complex cascade of events.^{17,18} Tissue injury activates phospholipase A₂ which breaks down cell membrane phospholipids to arachidonic acid.¹⁹ The arachidonic acid then enters the cyclooxygenase pathway resulting in the formation of prostaglandins and thromboxanes, or enters the lipoxygenase pathway resulting in the formation of eicosanoids.^{17,19} Prostaglandins are implicated in the pathogenesis of ocular inflammation. Prostaglandins cause vasodilation and increase vascular permeability resulting in increased aqueous humor protein concentration. They also act on intraocular pressure (IOP) and iris smooth muscle causing miosis.

The pharmacological management of ocular inflammation involves administration of anti-inflammatory medications.¹⁷ Topical administration of anti-inflammatory agents for ocular conditions is preferred over systemic administration as it results in higher ocular drug concentrations with minimal systemic adverse effects.¹⁷⁻¹⁹ Ophthalmic corticosteroids and NSAIDs are two medication classes that are available for control and treatment of ocular inflammation. Traditionally, ophthalmic corticosteroids have been used for the management of ocular inflammation. However, due to the adverse events associated with the drug class including elevation of IOP, inhibition of wound healing and facilitation of infections, the introduction of ophthalmic NSAIDs represented a significant development in ocular pharmacotherapy. Studies that have compared ophthalmic NSAIDs to ophthalmic corticosteroids have generally demonstrated that there

are no significant differences in outcomes between these treatments.²⁰⁻²⁸ Currently the American Academy of Ophthalmology and the American Optometric Association both recommend using ophthalmic NSAIDs for preventing and treating cystoid macular edema due to cataract surgery. Neither organization recommends one ophthalmic NSAID over another.^{29,30}

The common local adverse events associated with the use of ophthalmic NSAIDs include conjunctival hyperemia, burning and stinging.¹⁸ Corneal ulceration and full-thickness corneal melts associated with the use of these agents is a serious complication. Ophthalmic NSAIDs were first reported to cause corneal melting in 1999. Several investigations determined that the majority of cases were related to the generic ophthalmic diclofenac sodium solution manufactured by Falcon Laboratories, and ultimately this product was removed from the market. There have, however, been reports of corneal melts and keratitis associated with the use of other ophthalmic NSAIDs. Various theories of potential pharmacodynamic mechanisms of NSAID injury have been purported; however, the available evidence does not alter the favorable benefit-risk ratio of the appropriate use of ophthalmic NSAIDs.¹⁸

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Bromfenac sodium ophthalmic (Bromday [®])	Nonsteroidal anti-inflammatory drugs	✓*
Diclofenac sodium ophthalmic (Voltaren [®])	Nonsteroidal anti-inflammatory drugs	✓
Flurbiprofen sodium ophthalmic (Ocufer [®])	Nonsteroidal anti-inflammatory drugs	✓
Ketorolac tromethamine ophthalmic (Acular [®] , Acular LS [®] , Acuvail ^{®†})	Nonsteroidal anti-inflammatory drugs	✓‡
Nepafenac ophthalmic (Nevanac [®])	Nonsteroidal anti-inflammatory drugs	-

*Generic bromfenac sodium 0.09% is approved for twice daily dosing, and is the generic for Xibrom[®], not Bromday[®]

†Ketorolac tromethamine ophthalmic solution 0.5% (Acular PF[®]) has been discontinued as of July 2009.

‡Ketorolac tromethamine ophthalmic solutions, 0.5% and 0.4%, are available generically.

The following ophthalmic products contain the preservative benzalkonium chloride: bromfenac sodium, ketorolac tromethamine 0.5% and 0.4% and nepafenac. Ophthalmic flurbiprofen sodium contains the preservative thimerosal.

Indications

Table 2. Food and Drug Administration Approved Indications¹⁻¹³

Indication	Bromfenac Sodium	Diclofenac Sodium	Flurbiprofen Sodium	Ketorolac Tromethamine	Nepafenac
Treatment of pain and inflammation associated with cataract surgery				✓ (0.45%)	✓
Reduction of ocular pain and burning/stinging following corneal refractive surgery				✓ (0.4%)	
Temporary relief of ocular itching due to seasonal allergic conjunctivitis				✓ (0.5%)	

Treatment of postoperative patients who have undergone cataract extraction	✓	✓		✓ (0.5%)	
Temporary relief of pain and photophobia in patients undergoing corneal refractive surgery		✓			
Inhibition of intraoperative miosis			✓		

In addition to their Food and Drug Administration approved indications, potential off-label uses of ophthalmic diclofenac sodium and ophthalmic ketorolac tromethamine include prevention or treatment of cystoid macular edema following cataract surgery.^{11,12}

Pharmacokinetics

Due to the topical nature of ophthalmic nonsteroidal anti-inflammatory drugs (NSAIDs), limited, if any, systemic absorption occurs. After topical instillation, systemic plasma concentration levels of bromfenac sodium and diclofenac sodium remain below the level of quantification. Systemic absorption of ketorolac tromethamine ophthalmic solution 0.4% and 0.45% has not been assessed in humans; however, ketorolac tromethamine ophthalmic solution 0.5% has been shown to achieve limited systemic plasma concentration. 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 majority of patients, two and three hours after ocular administration.¹⁻¹³

Clinical Trials

Cataract Surgery

The Food and Drug Administration (FDA) approval of once-daily ophthalmic bromfenac sodium was based on two, randomized, double-blind, placebo-controlled studies in patients requiring cataract surgery. Patients were assigned to receive bromfenac sodium or vehicle (placebo) dosed as one drop per eye starting the day before surgery and continuing for 14 days. The primary endpoint was clearing of ocular inflammation by day 15. The secondary endpoint was the number of patients who were pain free on day one after cataract surgery. In both studies, once-daily bromfenac sodium ophthalmic solution was significantly more effective than its vehicle for clearing inflammation by day 15 (46.1 vs 26.2% and 51.1 vs 27.4% in trials 1 and 2, respectively; $P < 0.0001$ for both comparisons). There was also a higher percentage of pain free patients at day one post-cataract surgery with daily bromfenac sodium use compared to the vehicle (87.0 vs 64.7% and 84 vs 67% in trials 1 and 2, respectively; $P < 0.0001$ for both comparisons).^{31,32}

The safety and clinical efficacy of bromfenac sodium administered twice daily for the treatment of postoperative inflammation and the reduction of ocular pain in patients undergoing cataract surgery has been established previously. Ophthalmic bromfenac sodium compared to vehicle was found to have a greater reduction in ocular inflammation ($P < 0.0001$) at day 15 after cataract surgery and faster resolution of ocular pain ($P < 0.0001$). Most commonly reported adverse effects included eye irritation including burning, stinging and photophobia. These adverse events were reported more frequently in the vehicle group compared to ophthalmic bromfenac sodium 0.09% group. In an additional study no clinically significant systemic adverse events or changes in liver enzymes were reported with ophthalmic bromfenac sodium 0.09% when compared to vehicle in post-cataract surgery patients.^{33,34}

The FDA approval of ophthalmic nepafenac was based on two published, randomized, double-blind, placebo-controlled studies.^{35,36} Lane et al (N=476) showed that a greater number of patients in the ophthalmic nepafenac 0.1% group had an elimination of ocular inflammation as compared to the vehicle group ($P < 0.0001$).³⁵ There were no treatment-related ocular adverse events that occurred in either of the

treatment groups. In another study by Maxwell et al (N=212), ophthalmic nepafenac 0.1% dosed once daily, twice daily and three times daily for 14 days following cataract surgery significantly reduced the percent of treatment failures, demonstrating effectiveness in resolving ocular inflammation, compared to vehicle ($P \leq 0.0029$).³⁶ Additionally, fewer patients in the ophthalmic nepafenac 0.1% group experienced adverse events than the vehicle group. Ophthalmic nepafenac 0.1% was compared with ophthalmic ketorolac tromethamine 0.4% in combination with different antibiotics (gatifloxacin vs moxifloxacin) and different dosage strengths of prednisolone acetate (1% vs 0.125%) in both treatment groups in post-cataract surgery patients. No differences between the two treatment groups in terms of visual acuity, anterior chamber inflammation and subjective eye complaints were found. Ophthalmic ketorolac tromethamine 0.4% had significant patient satisfaction, patient compliance and postoperative pain control compared to ophthalmic nepafenac 0.1% ($P=0.022$, $P=0.023$ and $P=0.025$, respectively). Ophthalmic nepafenac 0.1% had a higher incidence of posterior capsule opacification than ophthalmic ketorolac tromethamine 0.4% ($P=0.019$).³⁷

Ophthalmic formulations of diclofenac sodium 0.1% and ketorolac tromethamine 0.5% instilled four times daily, beginning first postoperative day after cataract extraction for 30 days, were equally tolerated and had similar anti-inflammatory effects at three postoperative visits.³⁸ Kocak et al compared ophthalmic diclofenac sodium 0.1% and ophthalmic flurbiprofen sodium 0.03% in 43 patients, and found no statistically significant differences between the treatment groups for conjunctival hyperemia, corneal surface changes, intraocular pressure (IOP) or anterior chamber inflammation.³⁹

Two ophthalmic formulations of ketorolac tromethamine, 0.4% and 0.5%, were compared for effectiveness and patient tolerance in 40 patients undergoing phacoemulsification and intraocular lens implantation.⁴⁰ There were no significant differences between the two groups for best-corrected visual acuity, IOP, slit-lamp assessment of cells or cell/flare measured using the laser cell/flare meter. More patients in the ophthalmic ketorolac tromethamine 0.5% group than the 0.4% group reported ophthalmic symptoms (foreign body sensation, burning, stinging) at day-one postoperatively ($P=0.03$), however, there were no differences in reporting of ophthalmic symptoms at one week or one month postoperatively (P values not reported). There were no adverse drug events reported in either of the two treatment groups.

Ophthalmic NSAIDs have been compared with ophthalmic corticosteroids for the treatment of inflammation associated with cataract surgery. In three separate randomized controlled trials, ophthalmic diclofenac sodium 0.1% was compared with ophthalmic prednisolone acetate 1% and ophthalmic dexamethasone 0.1%.²⁰⁻²² No significant differences were found between the treatment groups at any observation time in terms of postoperative inflammatory reaction. There was a statistically significant mean decrease from baseline in IOP at week-one and month-one in the ophthalmic diclofenac sodium 0.1% group compared to the ophthalmic prednisolone 1% group ($P=0.007$).²⁰ At one month, the IOP was higher in the ophthalmic dexamethasone 0.1% group than in the ophthalmic diclofenac sodium 0.1% group ($P < 0.05$).²² Ophthalmic ketorolac tromethamine 0.5% has been compared with ophthalmic formulations of loteprednol 0.5%, rimexolone 1%, prednisolone acetate 1% and fluorometholone in several clinical trials.^{23-27, 41, 42} Overall, no differences were found between the treatment groups in measurements of postoperative inflammation or IOP. In a study by Hirneiss et al, there was a difference seen with overall aqueous flare in the anterior chamber between the treatment groups, lowest being in the ophthalmic ketorolac tromethamine 0.5% group, followed by the ophthalmic prednisolone 1% group and then the ophthalmic rimexolone 1% group ($P=0.008$).²⁸ Ophthalmic ketorolac tromethamine 0.5% had statistically significant higher IOP values followed by ophthalmic rimexolone 1%. Ophthalmic prednisolone acetate 1% had the lowest IOP values of the three treatment groups ($P=0.030$ for overall group difference). Patients more frequently complained about stinging and itching associated with the application of drops in the ophthalmic ketorolac tromethamine 0.5% group than the ophthalmic rimexolone 1% group. Patient comfort was highest with the prednisolone acetate 1% group ($P=0.041$ for overall group difference).²⁸

Corneal Refractive Surgery

Ophthalmic ketorolac tromethamine 0.5% has been compared with ophthalmic diclofenac sodium 0.1% for efficacy in relieving corneal pain following refractive surgery.^{43,44} Narvaez et al showed that both treatment groups were similarly effective in relieving ocular pain and there were no significant differences in pain relief or stinging on instillation between the two treatment groups ($P=0.29$).⁴³ Another study showed that ophthalmic diclofenac sodium 0.1% was more effective than ophthalmic ketorolac tromethamine 0.5% in corneal sensitivity assessment after controlling for the effects of time ($P<0.01$).⁴⁴ However, there was no difference in burning sensation between the groups ($P=0.12$).

Cystoid Macular Edema

None of the available ophthalmic NSAIDs have been FDA-approved for either the prevention or treatment of cystoid macular edema. However, there are a number of placebo-controlled and ophthalmic corticosteroid comparator studies evaluating the use of ophthalmic NSAIDs in cystoid macular edema.⁴⁵⁻⁵⁰ Based upon available evidence, there are no substantive differences when comparing the ophthalmic NSAIDs to each other or to ophthalmic steroids in the prevention or treatment of cystoid macular edema.

Intraoperative Miosis

Several trials have demonstrated efficacy of ophthalmic NSAIDs including flurbiprofen sodium 0.03%, ketorolac tromethamine 0.5% and diclofenac sodium 0.1% in preventing intraoperative miosis during cataract surgery.⁵¹⁻⁵³ A number of active comparator studies have demonstrated similar efficacy between the agents in preventing intraoperative miosis.

Seasonal Allergic Conjunctivitis

Ophthalmic ketorolac tromethamine 0.5% was compared to ophthalmic diclofenac sodium 0.1% in 60 patients for 14 days, with no significant differences found between the two treatment groups for the individual parameters of itching and bulbar conjunctival injection.⁵⁴ Ophthalmic ketorolac tromethamine 0.5% was also compared against ophthalmic olopatadine 0.1% in a randomized controlled trial (N=40) and ocular itching and hyperemia were found to improve in both the treatment groups ($P<0.05$).⁵⁵ However, itching scores were significantly lower in the ophthalmic olopatadine 0.1% group on days two, seven and 15 ($P=0.018$, $P=0.007$ and $P=0.036$, respectively).

Table 3. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Cataract Surgery				
<p>Silverstein et al³¹</p> <p>Bromfenac 0.09% 1 drop in the affected eye once daily</p> <p>vs</p> <p>vehicle 1 drop in the affected eye once daily</p> <p>Dosing began one day before surgery (day one), continued on the day of cataract surgery (day zero), and continued for 14 days after cataract surgery (days 1 to 14), for a maximum of 16 doses.</p>	<p>DB, MC, PC, PG, RCT (Pooled analysis of 2 trials)</p> <p>Patients ≥18 years of age who were only scheduled for unilateral cataract surgery with posterior chamber IOL implantation and best-corrected visual acuity of ≥20/200 in the non-study eye</p>	<p>N=455</p> <p>15 days</p>	<p>Primary: Proportion of patients with cleared ocular inflammation, the absence of anterior chamber cell or flare (SOIS grade=0) by day 15</p> <p>Secondary: Proportion of patients who had no ocular pain by the subject-reported Ocular Comfort Grading Assessment (OCGA score=0) at day 1 and adverse events</p>	<p>Primary: The percentage of patients with cleared ocular inflammation by day 15, was significantly higher for patients treated with bromfenac compared to the placebo (46.1 vs 26.2%; $P<0.0001$). Significant differences in ocular inflammation between treatment groups occurred as early as day eight of treatment, but not at day one ($P=0.81$), or day three ($P=0.60$).</p> <p>Secondary: The proportion of subjects free of ocular pain after day one of treatment was significantly higher in the bromfenac group compared to patients randomized to receive placebo (87.0 vs 64.7%, $P<0.0001$). For patients who reported ocular pain at day one, the median time to pain resolution was twice as fast in the bromfenac group compared to the placebo group (two vs four days; P value not reported).</p> <p>In trial 1, the incidence of adverse events was 27.4% in the bromfenac group and 42.5% in the placebo group. In trial 2, adverse events occurred in 46.9% of patients in bromfenac arm and 59.7% in the placebo arm. In trial 1, the most commonly reported eye-related adverse events in the bromfenac-treated group were eye inflammation (5.5%), eye pain (2.7%) and foreign body sensation (1.4%). The incidences in the placebo group were 13.7%, 6.8%, and 1.4%, respectively. In trial 2, the most commonly reported eye-related adverse events in the bromfenac-treated group were foreign body sensation (12.2%), eye inflammation (10.2%), vision blurred (10.2%) and eye pain (8.8%). The respective incidences in the placebo group were 13.9%, 14.6%, 7.6%, and 23.6%. In the study, premature discontinuation due to the occurrence of an adverse event was significantly lower in the bromfenac treatment group at 5.7% compared to the placebo group (16%; $P=0.0004$).</p>
<p>Henderson et al³²</p> <p>Bromfenac 0.09% 1 drop in the affected eye</p>	<p>AC, DB, MC, PC, RCT (Pooled analysis of 4 trials)</p>	<p>N=1149</p> <p>15 days</p>	<p>Primary: Proportion of patients with cleared ocular inflammation, the</p>	<p>Primary: The percentage of patients who had cleared ocular inflammation by day 15 was significantly higher in the bromfenac group compared with the placebo group (51.1 vs 27.4%; $P<0.0001$). In addition, patients treated</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>once daily</p> <p>vs</p> <p>bromfenac 0.18% 1 drop in the affected eye once daily (data not reported for this dose)</p> <p>vs</p> <p>vehicle 1 drop in the affected eye once daily</p> <p>Dosing began one day before surgery (day one), continued on the day of cataract surgery (day zero), and continued for 14 days after cataract surgery (days 1 to 14), for a maximum of 16 doses.</p>	<p>Patients ≥18 years of age who were only scheduled for unilateral cataract surgery with posterior chamber IOL implantation and best-corrected visual acuity of ≥20/200 in the non-study eye</p>		<p>absence of anterior chamber cell or flare (SOIS grade=0) by day 15</p> <p>Secondary: Proportion of patients who had no ocular pain by the subject-reported Ocular Comfort Grading Assessment (OCGA score=0) at day 1 and adverse events</p>	<p>with bromfenac had a lower mean SOIS score at days three, eight, 15, and 22 compared to placebo ($P<0.0001$).</p> <p>Secondary: After the first day of treatment (day one) the proportion of patients who reported to be pain-free was significantly higher in the bromfenac group compared with the placebo group (84 vs 67%; $P<0.0001$). More patients treated with bromfenac continued to be pain-free at days three, eight and 15 compared to placebo (91 to 96% vs 67 to 71%, respectively; P value not reported).</p> <p>Patients treated with bromfenac experienced significantly fewer adverse events compared to patients receiving placebo (35.1 vs 55.0%; $P<0.0001$). In the bromfenac group, the most commonly reported study adverse events associated with the eye were eye inflammation (11.8%), conjunctival hyperemia (8.5%), eye pain (8.2%) and foreign body sensation (8.2%), whereas in the placebo group, these events occurred at a frequency of 13.9%, 3.7%, 14.5%, and 8.0%, respectively.</p> <p>The proportion of subjects discontinuing treatment because of adverse events was significantly higher in the placebo group compared to the bromfenac treatment group (16.2 vs 5.2%; $P<0.0001$). By day 15, the discontinuation rates because of lack of efficacy were 32.7% in the placebo group and 2.9% in the bromfenac ($P<0.0001$).</p>
<p>Donnenfeld et al³³</p> <p>Bromfenac 0.09% 1 drop in the affected eye(s) BID for 14 days administered 16 to 32 hours after surgery</p> <p>vs</p> <p>vehicle 1 drop in the</p>	<p>2 DB, MC, PC, PG, Phase III, RCT</p> <p>Patients ≥18 years of age (mean age of 69 years) with uncomplicated unilateral cataract surgery (phaco-emulsification or extracapsular</p>	<p>N=527</p> <p>29 days</p>	<p>Primary: Proportion of patients with cleared ocular inflammation determined by anterior chamber cells (0=no cells, trace cells=1 to 5 cells) and a flare grade; summed ocular inflammation score of zero in the study eye on study day 15, 24 to 48</p>	<p>Primary: A greater proportion of bromfenac (64.0%) than vehicle patients (43.3%) achieved complete clearance (summed ocular inflammation score=0) of ocular inflammation at day 15 ($P<0.0001$).</p> <p>Secondary: There was a statistically significant difference in the outcome of cleared ocular inflammation when the patients were on bromfenac alone compared with vehicle alone ($P<0.0001$).</p> <p>There was a statistically significant difference in the outcome of cleared</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>affected eye(s) BID for 14 days administered 16 to 32 hours after surgery</p>	<p>cataract extraction) with posterior chamber intraocular lens implantation with summed ocular inflammation score of ≥ 3, 16 to 32 hours after cataract extraction</p>		<p>hours after administration of dose</p> <p>Secondary: Proportion of patients with summed ocular inflammation score of zero while on bromfenac or placebo alone, proportion of protocol-compliant patients with summed ocular inflammation score of zero, evaluation of primary efficacy outcome at each study visit, marked improvement (summed ocular inflammation score ≤ 1) in ocular inflammation at each study visit, mean cells and flare at each visit, time to resolution of ocular pain and proportion pain free, and photophobia while on bromfenac or placebo alone before administration of rescue medication; safety outcomes including ocular adverse events and tolerability assessed by subjective ocular discomfort scores</p>	<p>ocular inflammation within the protocol-compliant patients treated with bromfenac compared with vehicle (89.4 vs 80.3%; $P=0.038$).</p> <p>There was a statistically significant difference in the proportion of patients with a marked improvement in ocular inflammation (summed ocular inflammation score ≤ 1) in the bromfenac group compared with the vehicle group (85.1 vs 52.6%; $P<0.0001$).</p> <p>The median time to resolution of ocular pain after cataract surgery was two days for bromfenac vs five days for vehicle ($P<0.0001$).</p> <p>Numbers of most ocular adverse events were lower for the bromfenac group than for the vehicle group. Eye irritation including burning and stinging was reported in a lower percentage of patients for bromfenac compared to vehicle (2.5 vs 4.7%), as was photophobia (2.0 vs 11.1%). There were no serious adverse events reported in either of the two treatment groups.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Lane et al³⁵</p> <p>Nepafenac 0.1% 1 drop in the affected eye(s) TID 1 day before surgery, continuing on day of surgery (day 0) for 14 days</p> <p>vs</p> <p>vehicle 1 drop in the affected eye(s) TID 1 day before surgery, continuing on day of surgery (day 0) for 14 days</p> <p>Each patient also received one drop of their respective study medication 30 to 120 minutes prior to surgery and moxifloxacin TID for one to two days preoperatively and one week postoperatively.</p>	<p>DB, MC, PC, RCT</p> <p>Patients ≥18 years of age (mean age of 70 years) scheduled to undergo cataract extraction surgery with posterior chamber intraocular lens implantation</p>	<p>N=476</p> <p>16 days</p>	<p>Primary: Percentage of patients cured of ocular inflammation at day 14 (cure defined as aqueous cells score and aqueous flare score=0)</p> <p>Secondary: Comparison of cure rates by visit, percentage of patients pain free at all visits and aqueous cells, flare, and cells and flare scores</p>	<p>Primary: 62.6% patients in the nepafenac group and 17.2% patients in the vehicle group were cured at day 14 ($P<0.0001$).</p> <p>81.9% of patients in the nepafenac group and 25.3% in the vehicle group were clinically cured by day 14 ($P<0.0001$).</p> <p>Secondary: Nepafenac resulted in a higher percentage of cures at all visits as compared to vehicle ($P\leq0.005$).</p> <p>A higher percentage of patients in the nepafenac group was pain free at all visits ($P<0.0001$, all visits).</p> <p>Nepafenac had lower mean aqueous cells scores, mean aqueous flare scores, and mean aqueous cells and flare scores at all visits ($P<0.0001$).</p> <p>No clinically relevant treatment-related changes from baseline in visual acuity, ocular signs (corneal edema, bulbar conjunctival injection, and chemosis), IOP, or dilated fundus parameters (retina, macula, choroid, and optic nerve) were observed in either group.</p> <p>Slightly higher incidences of ocular hyperemia and photophobia were observed in the vehicle group (P values not reported).</p>
<p>Maxwell et al³⁶</p> <p>Nepafenac 0.1% 1 drop in the affected eye(s) once daily, BID, or TID beginning 1 day before surgery, continuing on the day of surgery and for 14 days thereafter</p>	<p>DB, MC, PC, PRO, RCT</p> <p>Patients ≥18 years of age scheduled to undergo cataract extraction by phacoemulsification followed by posterior chamber</p>	<p>N=212</p> <p>16 days</p>	<p>Primary: Percent of treatment failures (≥16 aqueous cells, aqueous flare=severe, or ocular pain score=moderately severe or severe) through postoperative day 14, adverse events, best-corrected visual acuity,</p>	<p>Primary: Nepafenac once daily, BID and TID groups had a lower percentage of patients with treatment failures through day 14 compared to vehicle ($P<0.0020$). Treatment failure rates for nepafenac once daily, BID, TID and vehicle groups were 25.0%, 30.0%, 19.6% and 60.3%, respectively. The results were statistically significant after correction for multiplicity ($P=0.0007$, $P=0.0020$, and $P<0.0001$ for nepafenac once daily, BID and TID groups, respectively).</p> <p>Nepafenac once daily, BID and TID groups all had significantly lower</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>vs</p> <p>vehicle 1 drop in the affected eye(s) once daily, BID, or TID beginning 1 day before surgery, continuing on the day of surgery and for 14 days thereafter</p> <p>Each patient also received one drop of their respective study medication 30 to 120 minutes prior to surgery and topical antibiotic therapy for one week after surgery per investigator's standard of care.</p>	<p>intraocular lens implantation</p>		<p>ocular signs, IOP, surgically related expected conditions, abnormalities during dilated fundus examinations of retina, macula, choroid and optic nerve</p> <p>Secondary: Cumulative percent of treatment failures at each postoperative visit, exploratory analyses of the percentage of patients with no ocular pain and inflammation by visit (clinical success defined as patient with aqueous cells \leq grade 1 and aqueous flare=grade 0 at the current and all subsequent visits)</p>	<p>incidences of treatment failure, compared to vehicle on days seven and 14 ($P \leq 0.0029$ and $P \leq 0.0009$, respectively). Nepafenac TID group showed a significantly lower incidence of treatment failures by day three compared to vehicle ($P \leq 0.0080$).</p> <p>Vehicle-treated patients (40.7%) had the greatest frequency of adverse events, compared to patients receiving nepafenac (once daily, 32.0%; BID, 24.5%; and TID, 25.9%). Events reported as related to therapy consisted of eye discomfort (nepafenac once daily, 2%), eye disorder (nepafenac BID, 2%), eye pain (nepafenac BID, 1.9% and vehicle, 1.7%), capsular opacity (vehicle, 1.7%), hyphema (vehicle, 1.7%), and macular edema (vehicle, 1.7%). No serious ocular adverse events occurred during the study.</p> <p>Secondary: Nepafenac treatment significantly increased proportion of patients with resolved ocular inflammation beginning on day one for TID dosing ($P \leq 0.0208$) and day 3 for once daily dosing ($P \leq 0.0483$) compared to vehicle.</p> <p>All nepafenac groups had treatment of ocular pain at postoperative days three through 14 compared to vehicle ($P \leq 0.0220$).</p>
<p>Flach et al³⁸</p> <p>Ketorolac 0.5% 1 drop in the affected eye(s) QID beginning the first postoperative day after surgery</p> <p>vs</p> <p>diclofenac 0.1% 1 drop in the affected eye(s) QID</p>	<p>DB, PRO, RCT, SC</p> <p>Patients ≥ 21 years of age (median age of 71 years) admitted for elective, unilateral, cataract surgery and implantation of an intraocular lens</p>	<p>N=120</p> <p>30 days</p>	<p>Primary: Subjective measurement of anterior chamber inflammation determined by anterior chamber cells (0=none to 3=greater than 30 cells) and anterior chamber flare (0=none to 4=strong intensity) through slit-lamp biomicroscope measurements, objective</p>	<p>Primary: The two treatment groups were not statistically different at any of the three postoperative visits (visits one, two and three = three to five days, nine to 12 days and 25 to 30 days, respectively) in terms of flare or cells as measured with the laser cell and flare meter. P values for flare and cells as measured by laser cell and flare meter at visit three were $P=0.10$ and $P=0.55$, respectively. P values for flare and cells as measured by slit-lamp examinations at visit three were $P=0.95$ and $P=0.08$, respectively.</p> <p>The slit-lamp measurements of cells and flare correlated with the laser cell and flare meter.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>beginning the first postoperative day after surgery</p> <p>Each patient also received tropicamide 0.5% solution one drop TID for two weeks and ofloxacin 0.3% solution one drop QID for seven days after surgery.</p>			<p>measurement of anterior chamber inflammation determined by laser cell and flare meter</p> <p>Secondary: Toxicity during three separate postoperative visits</p>	<p>Secondary: There were no adverse reactions reported or observed during the study. There was no statistical difference between the reports and descriptions of ocular discomfort upon instillation between the two treatment groups ($P=0.30$).</p>
<p>Kocak et al³⁹</p> <p>Diclofenac 0.1% 1 drop in the affected eye(s) every 6 hours in 3 doses beginning at 6 PM on evening prior to surgery; at 90, 60, 30, and 15 minutes before surgery; and QID for 3 to 6 weeks after surgery</p> <p>vs</p> <p>flurbiprofen 0.03% 1 drop in the affected eye(s) every 6 hours in 3 doses beginning at 6 PM on evening prior to surgery; at 90, 60, 30, and 15 minutes before surgery; and QID for 3 to 6 weeks after surgery</p> <p>Each patient also received tobramycin 0.3% one drop</p>	<p>DB, PRO, RCT</p> <p>Patients (mean age of 64 years) undergoing extracapsular cataract extraction with lens implantation with no preoperative complications</p>	<p>N=43</p> <p>6 weeks</p>	<p>Primary: Conjunctival hyperemia (0=no sign of intolerance to 3=severe), corneal thickness and corneal surface changes, IOP, inflammation of anterior chamber</p> <p>Secondary: Not reported</p>	<p>Primary: Both groups showed a consistent decrease in the severity of the hyperemia at weeks three and six following surgery. One patient in the diclofenac group had severe conjunctival hyperemia at the final visit and the authors thought of this to be an allergic reaction to preservatives. The difference between the two treatment groups was not statistically significant at any time ($P>0.05$).</p> <p>At weeks one, three, and six following surgery, the differences between the two treatment groups in terms of corneal thickness were not statistically significant ($P>0.05$).</p> <p>The mean IOP values of both groups were within normal limits throughout the study and were slightly lower in flurbiprofen group than in diclofenac group at all visits, but the difference was not statistically significant ($P>0.05$).</p> <p>Both treatment groups showed corneal punctation at first visit and it was less severe in the diclofenac group, but the difference was not statistically significant ($P>0.05$). One patient in the diclofenac group had marked corneal punctation and this was the same patient who also had severe conjunctival hyperemia.</p> <p>There was no statistically significant difference between the two treatment groups at week one, three or six ($P>0.05$).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
in the affected eye(s) QID for one week.				Secondary: Not reported
<p>Duong et al³⁷</p> <p>Ketorolac 0.4% 1 drop in the affected eye(s) QID for 7 days and gatifloxacin 0.3% 1 drop in the affected eye(s) QID for 7 days and prednisolone acetate 1% 1 drop in the affected eye(s) QID for 7 days and tapered thereafter (ketorolac group)</p> <p>vs</p> <p>nepafenac 0.1% 1 drop in the affected eye(s) TID for 7 days and moxifloxacin 0.5% 1 drop in the affected eye(s) QID for 7 days and prednisolone acetate 0.125%* 1 drop in the affected eye(s) QID for 7 days and tapered thereafter (nepafenac group)</p>	<p>DB, PRO, RCT, SC</p> <p>Patients (mean age of 69 years) with visually significant cataract and candidate for cataract surgery</p>	<p>N=183</p> <p>1 month</p>	<p>Primary: Objective findings (visual function, degree of inflammation in the anterior segment and complications) and subjective complaints (burning, itching, foreign body sensation and pain level after surgery)</p> <p>Secondary: Not reported</p>	<p>Primary: Visual recovery was slightly better in the ketorolac group than in the nepafenac group one day postoperatively; however, this difference was not statistically significant (0.54 vs 0.63; <i>P</i> value not reported).</p> <p>Visual acuities were comparable between the two treatment groups at one week and one month postoperatively (<i>P</i>=0.66 and <i>P</i>=0.16 respectively).</p> <p>There was no difference between the two treatment groups in anterior chamber inflammation (mean <i>P</i>>0.05).</p> <p>Nepafenac had a higher incidence of posterior capsule opacification than ketorolac (13 cases vs 5 cases; <i>P</i>=0.019).</p> <p>Ketorolac had significant patient satisfaction, patient compliance, and postoperative pain control compared to nepafenac (<i>P</i>=0.022, <i>P</i>=0.023 and <i>P</i>=0.025, respectively).</p> <p>Secondary: Not reported</p>
<p>Sandoval et al⁴⁰</p> <p>Ketorolac 0.5% 1 drop in the affected eye(s) every 5 minutes, starting 15</p>	<p>DB, PRO, RCT, SC</p> <p>Patients ≥40 years of age (mean age of 71 years)</p>	<p>N=40</p> <p>4 weeks</p>	<p>Primary: Best-corrected visual acuity, slit-lamp examination, IOP, laser cell and flare</p>	<p>Primary: There were no significant differences between the two treatment groups found at any time (day one, seven, and 30 postoperatively) for mean, median and range of best-corrected visual acuity, IOP, slit-lamp cell count, laser flare-cell meter cells and flare over time (<i>P</i> values not</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>minutes before surgery, then 1 drop in the affected eye(s) QID for 1 week, then BID for 3 weeks</p> <p>vs</p> <p>ketorolac 0.4% 1 drop in the affected eye(s) every 5 minutes, starting 15 minutes before surgery, then 1 drop in the affected eye(s) QID for 1 week, then BID for 3 weeks</p> <p>Each patient received ofloxacin 0.3% one drop in the affected eye(s) QID for one week starting right after surgery.</p>	<p>scheduled to undergo routine phacoemulsification and intraocular lens implantation</p>		<p>measurements, subjective patient tolerance evaluated postoperatively at days 1, 7, and 30</p> <p>Secondary: Adverse events</p>	<p>reported).</p> <p>There was a significant improvement in best-corrected visual acuity in both the treatment groups compared to preoperative at one week and one month ($P<0.001$).</p> <p>There were no significant differences found in IOP in either of the treatment groups over time (P values not reported).</p> <p>A significant higher percentage of patients in the ketorolac 0.5% reported ophthalmic symptoms (deep eye pain, light sensitivity, itching, foreign body sensation, stinging and burning) compared to patients in the ketorolac 0.4% group (70 vs 40%; $P=0.03$) at day one postoperatively.</p> <p>There were no significant differences in the reporting of ophthalmic symptoms between the two treatment groups at one week or one month (P values not reported).</p> <p>Secondary: No adverse drug events were reported in either of the two treatment groups (P values not reported).</p>
<p>Maca et al⁵⁶</p> <p>diclofenac 0.1% (preservative-free) 1 drop in the affected eye 4 times daily, starting on the first postoperative day after surgery</p> <p>vs</p> <p>diclofenac 0.1% 1 drop in the affected eye 4 times daily, starting on the first</p>	<p>SB, OL, PG, PRO, RCT</p> <p>Patients ≥ 40 years of age who scheduled for phacoemulsification surgery of cataract with posterior chamber intraocular lens implantation, who had no history of intraocular</p>	<p>N=102</p> <p>4 weeks</p>	<p>Primary: Anti-inflammatory effect (via anterior chamber flare), retinal thickness (mean foveal thickness), tolerability (with use of a visual analog scale), Subjective ocular discomfort (with use of a 0 to 4 scale), conjunctival hyperemia (use of observer-based grading scale of 0 to 4), visual acuity and intraocular</p>	<p>Primary: During the treatment period, there was no significant difference between the treatment groups in regard to changes in anterior chamber flare. The values of all groups showed a significant increase after surgery ($P<0.001$ for all groups compared to baseline) and thereafter a decrease at each postoperative (day one, week one and one month $P<0.001$).</p> <p>There was no significant change in retinal thickness observed for subsequent measurements on day 1 ($150.8 \pm 22.4 \mu\text{m}$), after one week ($155.9 \pm 20.4 \mu\text{m}$), or one month ($152.7 \pm 20.0 \mu\text{m}$). No patients had visible cystoid macular edema on scans within 1 month after surgery. In the one treatment groups, there was no correlation between mean foveal thickness and anterior chamber flare.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>postoperative day after surgery</p> <p>vs</p> <p>ketorolac tromethamine 0.5% 1 drop in the affected eye 4 times daily, starting on the first postoperative day after surgery</p>	<p>inflammation or uveitis, pseudoexfoliation syndrome, significant posterior segment disease involving the macular region, and previous ocular surgery, recent topical glaucoma treatment, or both</p>		<p>pressure</p> <p>Secondary: Not reported</p>	<p>Conjunctival hyperemia was significantly increased on day one in all three treatment groups compared with baseline values ($P<0.01$ for all groups), with no differences between treatment groups. The incidence of conjunctival injection in all groups decreased from day one to one week ($P=0.03$ for all groups). Patients receiving treatment with the preservative-free diclofenac eye drops experienced less conjunctival injection compared to the groups receiving preserved diclofenac, or ketorolac ($P=0.029$). After the first week of treatment, no significant differences in conjunctival injection were reported.</p> <p>In patients receiving preservative-free diclofenac, the VAS scores for tolerability remained stable, whereas patients randomized to receive preserved diclofenac and preserved ketorolac eye drops experienced a rise in scores (less comfortable) from one day to one week and one week to one month ($P=0.005$ and $P<0.001$, repeated-measures analysis of variance), which also were higher than those of the preservative-free diclofenac group (one week, $P=0.001$, and one month, $P=0.033$, respectively).</p> <p>Patients treated with preservative-free diclofenac eye drops experienced less local discomfort compared to preserved diclofenac and preserved ketorolac eye drops ($P=0.02$ and $P=0.012$, respectively). One week post-surgery, only patients receiving preservative-free diclofenac eye drops reported less local discomfort than at day one ($P=0.008$). At one month, there was no difference in ocular discomfort scores between treatment groups (P values not reported).</p> <p>There was no difference between treatment groups in regard to visual acuity at all time points post-surgery. In addition, all three treatments significantly reduced IOP by one month after surgery ($P=0.001$), and there were no significant differences between treatment arms.</p> <p>Secondary: Not reported</p>

<p>Roberts et al²⁰</p> <p>Diclofenac 0.1% 1 drop in the affected eye(s) QID for 1 week then 1 drop in the affected eye(s) BID for next 3 weeks</p> <p>vs</p> <p>prednisolone acetate 1% 1 drop in the affected eye(s) QID for 1 week then 1 drop in the affected eye(s) BID for next 3 weeks</p> <p>Each patient also received gentamicin sulfate eye drops.</p>	<p>DB, RCT</p> <p>Patients who underwent phacoemulsification with posterior chamber intraocular lens implantation</p>	<p>N=52</p> <p>1 month</p>	<p>Primary: Subjective postoperative inflammation evaluation by slit-lamp assessment of cell and flare and objective evaluation by measurement of cell and flare with a laser of cell and flare meter on 1 day, 1 week and 1 month after surgery</p> <p>Secondary: IOP</p>	<p>Primary: Inflammation scores for the diclofenac group were lower than the prednisolone acetate group at one week and one month after surgery. However, the results were not statistically significant (flare; $P=0.138$ and $P=0.196$, cell; $P=0.588$ and $P=0.218$, slit-lamp score; $P=0.139$ and $P=0.521$ for between group differences).</p> <p>Secondary: Both treatment groups had a mean decrease from baseline in IOP at one week and one month. The mean decrease in the prednisolone acetate group was 0.9 mmHg, and the mean decrease in the diclofenac group was 4.7 mmHg. This mean decrease within the diclofenac group was statistically significant ($P=0.007$). The difference between the two groups, after adjusting for the baseline difference in the analysis, was not statistically significant ($P=0.074$).</p>
<p>Reddy et al²¹</p> <p>Diclofenac 0.1% 1 drop in the affected eye(s) six times a day</p> <p>vs</p> <p>dexamethasone 0.1% 1 drop in the affected eye(s) six times a day</p> <p>Each patient also received tropicamide 1% for preoperative dilatation and it was also included in the postoperative regimen.</p>	<p>DB, PRO, RCT</p> <p>Patients >25 years of age (mean age of 57 years) who underwent uncomplicated extracapsular cataract extraction with posterior chamber intraocular lens implantation</p>	<p>N=60</p> <p>21 days</p>	<p>Primary: Aqueous flare and cells in anterior chamber, conjunctival congestion, and corneal edema on days 1, 3, 7, 14, and 21 after surgery; severity of inflammation graded on a 4-point scale ranging from 0-3, with a score of 3 reflecting greatest severity of inflammation</p> <p>Secondary: Not reported</p>	<p>Primary: There was no significant difference in anti-inflammatory activity between the two treatment groups on days three, seven, 14, and 21 after surgery for signs of flare and cell in the anterior chamber, conjunctival congestion, and corneal edema (P values not reported).</p> <p>The time to achieve anti-inflammatory activity was significant ($P<0.0001$). The drug x time interaction was not significant, indicating that the rate of improvement in the two drugs did not differ statistically (P values not reported).</p> <p>In terms of response of cells in the anterior chamber, the trend for improvement seemed to be faster and greater in magnitude with dexamethasone compared to diclofenac (P values not reported).</p> <p>Best corrected visual acuity was assessed at endpoint only and the results between the two groups did not differ statistically (P values not reported).</p>

<p>Laurell et al²²</p> <p>Diclofenac 0.1% 1 drop in the affected eye(s) QID for 1 week after surgery, then 1 drop in the affected eye(s) BID for 3 weeks</p> <p>vs</p> <p>dexamethasone 0.1% 1 drop in the affected eye(s) QID for 1 week after surgery, then 1 drop in the affected eye(s) BID for 3 weeks</p> <p>vs</p> <p>placebo 1 drop in the affected eye(s) QID for 1 week after surgery, then 1 drop in the affected eye(s) BID for 3 weeks</p>	<p>DB, PRO, RCT, SC</p> <p>Patients 64 to 85 years of age (mean age of 75 years) scheduled to undergo cataract surgery by phacoemulsification and intraocular lens implantation</p>	<p>N=180</p> <p>4 years</p>	<p>Primary: Inflammatory reaction in the anterior chamber measured with laser flare photometry preoperatively and 1, 3, and 8 days, 2 and 4 weeks, 2 and 6 months, and 1, 2 and 4 years postoperatively, inflammatory symptoms</p> <p>Secondary: Visual acuity, rate of striate keratopathy, IOP, capsulotomy rate</p>	<p>Secondary: Not reported</p> <p>Primary: There were no significant differences between the three treatment groups on first postoperative day ($P=0.830$).</p> <p>The flare values at three and eight days, two weeks, and one month after surgery were significantly lower in diclofenac and dexamethasone groups compared to placebo ($P<0.0001$, $P<0.0001$, $P<0.0001$ and $P=0.0013$, respectively).</p> <p>There were no significant differences between the treatment groups. Additionally, there were no significant differences between diclofenac and dexamethasone at any observation time (P values not reported).</p> <p>Inflammatory symptoms were found in 11 of 60 patients (18.3%) at day three and in 18 of 59 patients (30.5%) at day 8 in placebo group.</p> <p>The rate of patients with inflammatory symptoms was greater in the placebo group at day three ($P<0.001$) and day eight ($P<0.001$) but not at two weeks and subsequently.</p> <p>There were no significant differences found between diclofenac and dexamethasone at any observation time.</p> <p>Secondary: With regards to visual acuity, the only significant difference between the treatment groups was found at day eight when visual acuity was better in the dexamethasone group than the placebo group (81.7 vs 62.7%; $P<0.05$).</p> <p>At day eight, striate keratopathy was more frequent in the placebo group than in the other two treatment groups ($P=0.01$). There were no subsequent corneal reactions. There were no epithelial complications found in any of the three treatment groups.</p> <p>Median IOP was significantly higher in the dexamethasone group than in the placebo group after eight days (16 vs 13 mmHg; $P<0.05$), and at one</p>
--	---	-----------------------------	--	---

				<p>month it was slightly higher in dexamethasone group than in diclofenac group (15 vs 14 mmHg; $P<0.05$). No significant IOP differences were found at other observation times.</p> <p>The rate of Nd:YAG laser posterior capsulotomies were equal in the three treatment groups after two years. It was significantly lower in the placebo group than in the diclofenac group after four years ($P<0.05$).</p>
<p>Holzer et al⁴¹</p> <p>Ketorolac 0.5% 1 drop in the affected eye(s) QID starting 24 hours after surgery for 1 week, then 1 drop in the affected eye(s) BID for 3 weeks</p> <p>vs</p> <p>loteprednol 0.5% 1 drop in the affected eye(s) QID starting 24 hours after surgery for 1 week, then 1 drop in the affected eye(s) BID for 3 weeks</p> <p>Each patient also received ofloxacin 0.3% one drop in the affected eye(s) QID starting three days before surgery, one drop perioperatively and at completion of surgery, and one drop in the affected eye(s) QID beginning immediately after surgery.</p>	<p>DB, PRO, RCT</p> <p>Patients >18 years of age (mean age of 68 years) scheduled to have cataract extraction with posterior chamber intraocular lens implantation</p>	<p>N=60</p> <p>30 days</p>	<p>Primary: Signs and symptoms of inflammation documented by external slit-lamp examination, IOP, Kowa cell and flare measurements on days 1, 4, 7 and 30</p> <p>Secondary: Not reported</p>	<p>Primary: There was no statistically significant difference between the two treatment groups in any of the ocular symptoms including deep eye pain, photophobia, itching, foreign-body sensation, stinging and burning (P values not reported).</p> <p>There were no differences between ketorolac and loteprednol in terms of preoperative laser cell and flare meter evaluation of cells and flare ($P=0.83$ and $P=0.92$, respectively).</p> <p>The mean cell and flare values evaluated by laser cell and flare meter at day one was higher in the ketorolac group than the loteprednol group ($P=0.72$ and $P=0.67$, respectively).</p> <p>The mean cell and flare measurements, by laser cell and flare meter at week one, was 3.96 in the ketorolac and 4.89 in the loteprednol groups and 1.43 in the ketorolac and 0.94 in the loteprednol groups, respectively. However, the between-group difference in the measurements was not statistically different ($P=0.16$ and $P=0.61$, respectively).</p> <p>The mean IOP in both treatment groups ranged from 12 mmHg to 16 mmHg. Two patients in the loteprednol group had overall highest IOP one month postoperatively of 23 mmHg and 24 mmHg. However, these two patients had elevated IOP preoperatively of 25 mmHg and 24 mmHg, respectively (P values not reported).</p> <p>Secondary: Not reported</p>
<p>Solomon et al⁴²</p> <p>Ketorolac 0.5% 1 drop in</p>	<p>DB, PRO, RCT</p> <p>Patients >18 years</p>	<p>N=36</p> <p>30 days</p>	<p>Primary: Signs and symptoms of inflammation, IOP, visual</p>	<p>Primary: Subjective measurement of inflammation by slit-lamp measurements of cell and flare were not statistically significant between the two treatment</p>

<p>the affected eye(s) QID starting 24 hours after surgery for 1 week and then BID for remainder of study</p> <p>vs</p> <p>rimexolone 1% 1 drop in the affected eye(s) QID starting 24 hours after surgery for 1 week and then BID for remainder of study</p> <p>Each patient also received ofloxacin QID (duration not mentioned).</p>	<p>of age (mean age of 68 years) scheduled to undergo cataract extraction with posterior chamber intraocular lens implantation</p>		<p>acuity, slit-lamp cell and flare, and Kowa cell and flare measurements evaluated at 1, 4, 7, and 30 days postoperatively</p> <p>Secondary: Not reported</p>	<p>groups ($P=0.17$ and $P=0.48$, respectively).</p> <p>Objective measurement of cell and flare using Kowa cell and flare meter did not significantly differ between the two treatment groups ($P=0.17$ and $P=0.48$, respectively). The cell measurements at visit two (postoperative day one) in the ketorolac and rimexolone groups were 17.5 and 8.3, respectively ($P=0.28$). The flare measurements at visit two in the ketorolac and rimexolone groups were 18.3 and 4.7, respectively ($P=0.17$).</p> <p>There were no differences in IOP found over time or between groups (P values not reported).</p> <p>Visual acuity measurements at each visit and the overall improvement in visual acuity were similar in both groups (P values not reported).</p> <p>No statistical difference was found between the two treatment groups in terms of ocular symptom (P values not reported).</p> <p>Secondary: Not reported</p>
<p>Simone et al²³</p> <p>Ketorolac 0.5% 1 to 2 drops in the affected eye(s) per following schedule: QID on week 1, TID on week 2, BID on week 3 and once daily on week 4</p> <p>vs</p> <p>prednisolone acetate 1% 1 to 2 drops in the affected eye(s) per following schedule: QID on week 1, TID on week 2, BID on</p>	<p>DB, RCT, SC</p> <p>Patients (mean age of 74 years) who underwent extracapsular cataract extraction and posterior chamber intraocular lens implantation</p>	<p>N=59</p> <p>4 weeks</p>	<p>Primary: Intraocular anti-inflammatory efficacy (assessed by lid edema, lid injection, conjunctival injection, corneal edema, ciliary flush, and anterior chamber cells), analgesic efficacy (assessed by patient reported pain severity, pain frequency, total symptom sum, and overall global improvement)</p> <p>Secondary: Not reported</p>	<p>Primary: There were no statistically significant differences between the two treatment groups in any measure of anti-inflammatory efficacy, with the exception of anterior chamber cells. Prednisolone acetate had fewer cells in the anterior chamber than ketorolac at seven days after surgery ($P=0.0073$). This significance was lost by day 28 after surgery ($P=0.23$).</p> <p>Ketorolac reported less frequent and severe pain symptoms at day 28. The difference was not statistically significant (P value not reported).</p> <p>There were no statistically significant differences between the two treatment groups in terms of sum of symptoms, overall global improvement and IOP (P values not reported).</p> <p>There were no serious adverse events during the course of the study in either of the two treatment groups and no adverse event was considered to be treatment related (P values not reported).</p>

<p>week 3 and once daily on week 4</p> <p>Each patient also received ofloxacin one drop in the affected eye(s) QID for one week.</p>				<p>Secondary: Not reported</p>
<p>Guzey et al²⁴</p> <p>Ketorolac/tobramycin</p> <p>vs</p> <p>fluorometholone/tobramycin</p>	<p>PRO, RCT, SC</p> <p>Patients undergoing phacoemulsification cataract extract with sclera tunnel incision</p>	<p>N=60</p> <p>2 weeks</p>	<p>Primary: Burning/stinging sensation, blurred vision, ocular discomfort, conjunctival hyperemia, anterior chamber flare, and anterior chamber cells assessed preoperatively and postoperatively on days 1 (baseline), 2, 3, 7 and 14; findings were recorded in a 4-point (0 to 3) grading system</p> <p>Secondary: Not reported</p>	<p>Primary: There was no statistically significant difference between the two treatment groups in terms of ocular inflammation at any of the postoperative visits (<i>P</i> values not reported).</p> <p>The two treatment regimens were both well tolerated (<i>P</i> values not reported).</p> <p>Secondary: Not reported</p>
<p>El-Harazi et al²⁵</p> <p>Ketorolac 0.5% 1 drop in the affected eye(s) QID for 1 week, then 1 drop in the affected eye(s) BID for next 3 weeks</p> <p>vs</p> <p>diclofenac 0.1% 1 drop in the affected eye(s) QID for 1 week, then 1 drop in the affected eye(s) BID for</p>	<p>DB, RCT</p> <p>Patients undergoing phacoemulsification with posterior chamber intraocular lens implantation</p>	<p>N=58</p> <p>28 days</p>	<p>Primary: Flare, cells and IOP on postoperative days 1, 7 and 28</p> <p>Secondary: Medication-related complications</p>	<p>Primary: There were no statistically significant differences in flare or cell counts or in change in flare or cell counts from baseline between the three treatment groups (<i>P</i> values not reported).</p> <p>There were no statistically significant differences in IOP or in change in IOP from baseline between the three treatment groups (<i>P</i> values not reported).</p> <p>Secondary: There were no medication-related complications observed at any time during the course of study (<i>P</i> values not reported).</p>

<p>next 3 weeks</p> <p>vs</p> <p>prednisolone acetate 1% 1 drop in the affected eye(s) QID for 1 week, then 1 drop in the affected eye(s) BID for next 3 weeks</p>				
<p>Ostrov et al²⁶</p> <p>Ketorolac 0.5% 1 drop in the affected eye(s) TID starting 1 day before surgery to 4 weeks after surgery</p> <p>vs</p> <p>prednisolone acetate 1% 1 drop in the affected eye(s) TID starting 1 day before surgery to 4 weeks after surgery</p> <p>vs</p> <p>dexamethasone 0.1% 1 drop in the affected eye(s) TID starting 1 day before surgery to 4 weeks after surgery</p> <p>Seventy-nine percent of patients also received perioperative subconjunctival injections of a glucocorticosteroid</p>	<p>MC, RCT, SB</p> <p>Patients (mean age of 70 years) who underwent routine extracapsular cataract extraction or phacoemulsification and posterior chamber intraocular lens implantation</p>	<p>N=157</p> <p>6 weeks</p>	<p>Primary: Signs of anterior-segment inflammation-primarily cells and flare in the anterior chamber observed by slit-lamp biomicroscopy, fluorescein leakage across blood-aqueous barrier measured by fluorophotometry, rating of efficacy by investigator, IOP, visual acuity, and adverse events</p> <p>Secondary: Other clinical signs of inflammation (lid edema and hyperemia)</p>	<p>Primary: There were no statistically significant differences between the three treatment groups in terms of infiltration of cells into the anterior chamber on days one to two, day five, week two, week four, or week six ($P=0.59$, $P=0.51$, $P=0.08$, $P=0.32$ and $P=0.37$, respectively).</p> <p>There were no statistically significant differences between the three treatment groups in terms of anterior chamber flare on days one to two, day five, week two, week four or week six ($P=0.40$, $P=0.09$, $P=0.45$, $P=0.09$, and $P=0.70$, respectively).</p> <p>Postoperative elevations in fluorescein concentration was significantly less in the ketorolac group than the two corticosteroid groups at day five and week two ($P\leq 0.001$ and $P=0.016$, respectively). There were no differences between prednisolone acetate 1% and dexamethasone ($P=0.53$ and $P=0.77$ at day five and week two, respectively).</p> <p>Ketorolac, prednisolone acetate, and dexamethasone treatment groups had mean scores ranging from 86 to 91 for overall effectiveness ($P=0.32$) and 87 to 91 for overall acceptability ($P=0.46$).</p> <p>There were no significant differences between the three treatment groups at any visit with respect to IOPs and visual acuity tests ($P\geq 0.33$ for both endpoints).</p> <p>Two of the six adverse events were treatment-related; one patient in the dexamethasone group had a moderate allergic reaction at weeks two and four and one patient in the ketorolac group developed severe uveitis (P values not reported).</p>

(e.g., betamethasone or equivalent) and 82% patients received an antibiotic.				<p>Secondary: The ketorolac group had higher conjunctival hyperemia as compared to the prednisolone acetate group at week two ($P=0.04$ among groups).</p>
<p>Trinavarat et al²⁷</p> <p>Ketorolac 1 drop in the affected eye(s) QID</p> <p>vs</p> <p>prednisolone acetate 1 drop in the affected eye(s) QID</p> <p>vs</p> <p>fluorometholone(s) 1 drop in the affected eye QID</p>	<p>PRO, RCT, SB</p> <p>Patients undergoing phacoemulsification</p>	<p>N=120</p> <p>28 days</p>	<p>Primary: Visual acuity, IOP, slit-lamp biomicroscopy, grading of cells and flare in anterior chamber, ocular symptoms</p> <p>Secondary: Not reported</p>	<p>Primary: The number of eyes with a minimal amount of cells in the anterior chamber in the ketorolac group, was less than the prednisolone acetate group on day seven (11 vs 20; $P=0.008$) and day 14 (23 vs 31; $P=0.015$), and was less than fluorometholone group on day seven (11 vs 21; $P=0.011$).</p> <p>IOP was higher in the prednisolone acetate group than the ketorolac group on day 21 (14.6 vs 12.2 mmHg; $P=0.016$). One eye in prednisolone group had IOP of 32 mmHg.</p> <p>Burning sensation was reported frequently in the ketorolac group (P values not reported).</p> <p>Secondary: Not reported</p>
<p>Hirneiss et al²⁸</p> <p>Ketorolac 0.5% in the affected eye(s) per taper schedule as follows: 6 drops on days 1 to 3, then 5 drops on days 4 to 10, then 4 drops on days 11 to 14, then 3 drops on days 15 to 18, then 2 drops on days 19 to 21 and then 1 drop on days 22 to 28</p> <p>vs</p> <p>prednisolone acetate 1% in the affected eye(s) per taper schedule as follows:</p>	<p>DB, PRO, RCT, SC</p> <p>Patients ≥ 18 years of age (mean age of 68 years) who underwent elective, unilateral extracapsular cataract extraction using phacoemulsification and implantation of a posterior chamber intraocular lens with an uneventful surgery</p>	<p>N=45</p> <p>28 days</p>	<p>Primary: Conjunctival hyperemia (0=none to 3=marked diffuse injection), corneal edema (0=none to 3=severe) and assessment of best-corrected visual acuity, applanatory measurement of IOP, standardized slit-lamp examination of the anterior segment of the eye and cells and flare, stereoscopic dilated retinal examination with the biomicroscope, and report of patients' comfort</p>	<p>Primary: With regards to inflammation control, there was a statistically significant difference seen with aqueous flare in the anterior chamber. Overall aqueous flare was found to be lowest with ketorolac followed by prednisolone acetate and then rimexolone ($P=0.008$).</p> <p>Regarding conjunctival hyperemia, most hyperemia was observed with ketorolac, followed by rimexolone and then prednisolone acetate.</p> <p>The prednisolone acetate group had statistically significant lowest conjunctival hyperemia followed by the rimexolone and ketorolac groups had the most hyperemia ($P=0.002$ for overall group difference).</p> <p>Aqueous cells and corneal edema did not differ among the three treatment groups ($P=0.165$ and $P=0.311$, respectively).</p> <p>There were no significant differences in pre- and postoperative visual acuity measurements ($P=0.183$).</p>

<p>6 drops on days 1 to 3, then 5 drops on days 4 to 10, then 4 drops on days 11 to 14, then 3 drops on days 15 to 18, then 2 drops on days 19 to 21 and then 1 drop on days 22 to 28</p> <p>vs</p> <p>rimexolone 1% in the affected eye(s) per taper schedule as follows: 6 drops on days 1 to 3, then 5 drops on days 4 to 10, then 4 drops on days 11 to 14, then 3 drops on days 15 to 18, then 2 drops on days 19 to 21 and then 1 drop on days 22 to 28</p> <p>Patients received antibiotic eye drops containing polymyxin-B, neomycin and gramicidin one drop in the affected eye(s) QID for first 3 days after surgery.</p>			<p>or discomfort on postoperative days 1, 3, 5, 14 and 28</p> <p>Secondary: Not reported</p>	<p>The ketorolac group had statistically significant higher IOP values followed by the rimexolone group. Prednisolone acetate had the lowest IOP values of the three treatments ($P=0.030$ for overall group difference).</p> <p>Patients more frequently complained about stinging and itching associated with the application of drops in the ketorolac group than the rimexolone group. Patient comfort was highest with the prednisolone acetate group ($P=0.041$ for overall group difference).</p> <p>Secondary: Not reported</p>
<p>Corneal Refractive Surgery</p>				
<p>Narvaez et al⁴³</p> <p>Ketorolac 0.5% 1 drop in one eye every 4 hours while awake for 24 hours after surgery</p> <p>vs</p>	<p>DB, PRO, RCT, SC</p> <p>Patients undergoing elective, bilateral simultaneous radial keratotomy</p>	<p>N=30</p> <p>1 day</p>	<p>Primary: Postoperative ocular pain and discomfort recorded before and 15 minutes after instillation with a visual analog scale and a questionnaire</p> <p>Secondary:</p>	<p>Primary: Ketorolac and diclofenac were both highly effective in relieving pain (P value not reported).</p> <p>There was no significant difference in pain relief, or stinging on instillation between the two treatment groups ($P=0.29$).</p> <p>Secondary: Not reported</p>

diclofenac 0.1% 1 drop in the other eye every 4 hours while awake for 24 hours after surgery			Not reported	
Seitz et al ⁴⁴ Ketorolac 0.5% 1 drop in one eye every 5 minutes for a total of 7 drops and 1 drop of placebo in the other eye every 5 minutes for a total of 7 drops vs diclofenac 0.1% 1 drop in one eye every 5 minutes for a total of 7 drops and 1 drop of placebo in the other eye every 5 minutes for a total of 7 drops	DB, PG Patients 22 to 60 years of age	N=15 2 days	Primary: Assessment of corneal sensitivity before instillation, immediately after instillation, and after termination of drop application; subjective evaluation of burning sensation (0=none to 3=severe) after each drop application Secondary: Not reported	Primary: Ketorolac and diclofenac both significantly decreased corneal sensitivity compared to placebo ($P<0.01$ for both groups). Diclofenac was significantly more effective than ketorolac after controlling for the effects of time ($P<0.01$). Diclofenac decreased corneal sensitivity to a lower level (47.3 ± 0.7 mm) than ketorolac (51.0 ± 0.7 mm) after 30 minutes (P value not reported). The mean duration of decreased corneal sensitivity was significantly shorter in the ketorolac group than the diclofenac group ($P<0.01$). There was no significant difference between the two groups on subjective grading of perceived burning sensation ($P=0.12$). There was no trend of decreased burning sensation over time with either ketorolac or diclofenac ($P=0.12$ and $P=0.99$, respectively). Secondary: Not reported
Cystoid Macular Edema				
Rho DS ⁴⁵ Ketorolac 0.5% 1 drop in the affected eye(s) QID vs diclofenac 0.1% 1 drop in the affected eye(s) QID	PRO, RCT Patients with clinical cystoid macular edema after phacoemulsification cataract extraction with posterior chamber intraocular lens	N=34 26 weeks	Primary: Improvement in cystoid macular edema and visual acuity Secondary: Not reported	Primary: There was a significant reduction in cystoid macular edema and a significant improvement in visual acuity in both the treatment groups. Sixteen patients in the diclofenac group had a reduction in cystoid macular edema as compared to 14 patients in the ketorolac group within 26 weeks (89 vs 88%; $P=0.92$). Fourteen patients in the diclofenac group and 12 patients in the ketorolac group had eliminated cystoid macular edema within 26 weeks (78 vs 75%; $P=0.86$).

				<p>The mean time to initial cystoid macular edema reduction was 7.5 weeks with diclofenac and eight weeks with ketorolac ($P=0.41$).</p> <p>The mean time to cystoid macular edema resolution was 13.6 weeks with diclofenac and 12.8 weeks with ketorolac ($P=0.49$).</p> <p>Secondary: Not reported</p>
<p>Singal et al⁴⁶</p> <p>Ketorolac 0.5% and placebo</p> <p>vs</p> <p>ketorolac 0.5% and prednisolone acetate 1%</p>	<p>DB, PRO, RCT</p> <p>Patients with clinical cystoid macular edema occurring at least 6 weeks following cataract extraction</p>	<p>N=10</p> <p>90 days</p>	<p>Primary: Improvement in Early Treatment Diabetic Retinopathy Study Snellen equivalent vision and resolution of cysts on clinical examination</p> <p>Secondary: Not reported</p>	<p>Primary: There were no statistically significant differences between the two treatment groups in the outcomes measures at any visit (P values not reported).</p> <p>There were no significant differences between the two treatment groups in the subgroup analysis of patients with chronic cystoid macular edema (P values not reported).</p> <p>Secondary: Not reported</p>
<p>Miyake et al⁴⁷</p> <p>Diclofenac 0.1% 1 drop in the affected eye(s) 3 hours, 2 hours, 1 hour, and 30 minutes prior to surgery and TID for 8 weeks following surgery</p> <p>vs</p> <p>fluorometholone 0.1% 1 drop in the affected eye(s) 3 hours, 2 hours, 1 hour, and 30 minutes prior to surgery and TID for 8 weeks following surgery</p> <p>Each patient was also</p>	<p>MC, OL, PRO</p> <p>Patients between 60 and 70 years of age (mean age of 65 years) with indication for unilateral cataract surgery</p>	<p>N=106</p> <p>8 weeks</p>	<p>Primary: Visual acuity, IOP, amount of anterior chamber flare and cells measured by laser flare-cell photometry, severity of cystoid macular edema determined by fluorescein fundus angiography</p> <p>Secondary: Not reported</p>	<p>Primary: There was no significant difference between the two treatment groups in changes in visual acuity at any of the time points.</p> <p>Both treatment groups showed significantly lower IOP at three days, and one, two, five and eight weeks after surgery when compared with the preoperative values ($P<0.05$ to $P<0.001$).</p> <p>Fluorometholone showed a statistically significant increase in flare at three days, and one, two, five, and eight weeks after surgery ($P<0.01$ to $P<0.001$).</p> <p>Both treatment groups had a statistically significantly increase in flare at three days, and one, two, five, and eight weeks after surgery in eyes with cystoid macular edema ($P<0.001$).</p> <p>There was a statistically significant increase in flare in eyes with and without cystoid macular edema in the fluorometholone group ($P<0.05$ to $P<0.01$).</p>

<p>receiving oral and topical antimicrobial medications.</p>				<p>Fluorometholone group had a significantly greater number of cells at one and two weeks after surgery ($P<0.05$).</p> <p>More patients in the fluorometholone group than in the diclofenac group revealed cystoid macular formation (54.7 vs 5.7%; $P<0.001$).</p> <p>Secondary: Not reported</p>
<p>Heier et al⁴⁸</p> <p>Ketorolac 0.5% 1 drop in the affected eye(s) QID</p> <p>vs</p> <p>prednisolone acetate 1% 1 drop in the affected eye(s) QID</p> <p>vs</p> <p>ketorolac 0.5% and prednisolone acetate 1% 1 drop in the affected eye(s) QID</p> <p>Study medications were tapered at the rate of one drop per week when cystoid macular edema was resolved or for three months, whichever occurred first, on fundoscopic and angiographic examination.</p>	<p>DB, PRO, RCT</p> <p>Patients (mean age of 75 years) diagnosed with acute clinical cystoid macular edema occurring after phacoemulsification and posterior chamber intraocular lens implantation</p>	<p>N=28</p> <p>4 months</p>	<p>Primary: Snellen visual acuity, contrast sensitivity, Amsler grid, slit-lamp examination, dilated fundus examination, fluorescein angiography examined at monthly intervals with final examination occurring 1 month after discontinuation of medications</p> <p>Secondary: Not reported</p>	<p>Primary: There was a statistically significant difference between the prednisolone acetate group and the combined group at visits four ($P=0.006$) and five ($P=0.042$) (average of 1.1 vs 3.8 lines of improvement for the treatment group, respectively).</p> <p>There was no statistically significant difference in visual acuity between the ketorolac group and the combined group (P values not reported).</p> <p>Ketorolac and prednisolone acetate did not exhibit a mean change from baseline of two lines or more at any time during the study and at no time there was a statistically significant difference between the two groups (P values not reported). However, there was a significant difference for the combined group vs the prednisolone acetate group at visits two, three, four and five ($P=0.05$, $P=0.013$, $P=0.002$ and $P=0.004$ respectively) as well as for the combined group vs the ketorolac group at visits four and five ($P=0.017$ and $P=0.012$ respectively).</p> <p>Fifty percent of patients in the prednisolone acetate group, 67% of patients in the ketorolac group and 89% of patients in the combined group achieved a two-line or more improvement in Snellen acuity. A total of 61% of patients achieved the two-line improvement in Snellen acuity.</p> <p>Sixty five percent of patients had an improvement in contrast sensitivity at final visit when compared to baseline (50%, 55% and 89% in the prednisolone acetate, ketorolac, and combined groups, respectively; P values not reported).</p> <p>Most patients had an improvement in fluorescein angiography vs baseline</p>

				<p>(50%, 55% and 77% in the prednisolone acetate, ketorolac, and combined groups, respectively; <i>P</i> values not reported).</p> <p>Recurrence of cystoid macular edema was noted in two patients, one from the ketorolac group and the other from combined group, during the taper period after an initial two-line improvement in visual acuity.</p> <p>Secondary: Not reported</p>
<p>Wittpenn et al⁴⁹</p> <p>Ketorolac 0.4% and prednisolone acetate 1% 1 drop in the affected eye(s) QID for 4 weeks postoperatively (patients in this group also received ketorolac 0.4% 1 drop in the affected eye(s) QID for 3 days preoperatively)</p> <p>vs</p> <p>prednisolone acetate 1% 1 drop in the affected eye(s) QID for 4 weeks</p> <p>Each patient also received ketorolac 0.4% one drop in the affected eye(s) every 15 minutes for a total of four doses, one hour before surgery.</p>	<p>MC, PRO, RCT, SB</p> <p>Patients (mean age of 70 years) scheduled to undergo phacoemulsification with no recognized cystoid macular edema risks (diabetic retinopathy, retinal vascular disease, or macular abnormality)</p>	<p>N=546</p> <p>6 weeks</p>	<p>Primary: Cystoid macular edema incidence measured by slit-lamp biomicroscopy and optical coherence tomography</p> <p>Secondary: Retinal thickness as measured by optical coherence tomography, Snellen best-corrected visual acuity, contrast sensitivity and adverse events</p>	<p>Primary: Five patients in the prednisolone acetate group had clinically apparent cystoid macular edema compared to zero in the combined group based on slit-lamp biomicroscopy (<i>P</i>=0.032).</p> <p>Based on optical coherence tomography analysis, no patients in the combined group and six patients in the prednisolone acetate group developed definite or probable cystoid macular edema (<i>P</i>=0.018).</p> <p>Fewer patients in the combined group than in the prednisolone acetate group were identified with possible cystoid macular edema based on optical coherence tomography (2.2 vs 6.0%; <i>P</i>=0.037).</p> <p>Secondary: Mean retinal thickening in the combined group was less than that seen with the prednisolone acetate group (3.9 vs 9.6 μm; <i>P</i>=0.003).</p> <p>More patients in the prednisolone acetate group than in the combined group had >10 μm of retinal thickening on optical coherence tomography (49.0 vs 26.4%; <i>P</i><0.001).</p> <p>The prednisolone acetate group had a significantly higher incidence of retinal thickening \geq15 μm (<i>P</i><0.001).</p> <p>The incidence of thickening \geq25 μm and \geq40 μm was higher in the prednisolone acetate group than in the combined group, but it was not statistically significant (<i>P</i>=0.056 and <i>P</i>=0.069 for \geq25 μm and \geq40 μm respectively).</p>

				<p>In the combined group 1.3% of patients in the combined group had best-corrected visual acuity worse than 20/40 at week four compared to 2.5% of patients in the prednisolone acetate group ($P=0.360$).</p> <p>The difference in contrast sensitivity between the two treatment groups was not statistically significant ($P\geq 0.581$).</p> <p>Burning/stinging/tearing was the most commonly reported adverse event in the combined group, whereas, transient elevations in IOP were the most commonly reported adverse event in the prednisolone acetate group (4/268 and 3/278 respectively).</p> <p>There were two serious adverse events, both in the prednisolone acetate group. One patient developed endophthalmitis and the other patient died and the cause was determined to be unrelated to study medication.</p>
<p>Sivaprasad et al⁵⁰</p> <p>Diclofenac 0.1%</p> <p>vs</p> <p>fenoprofen 1%</p> <p>vs</p> <p>flurbiprofen 0.03%</p> <p>vs</p> <p>indomethacin 25 mg (oral)</p> <p>vs</p> <p>ketorolac 0.5%</p> <p>vs</p> <p>placebo</p>	<p>SR</p> <p>7 trials; 3 studied acute cystoid macular edema and 4 trials compared NSAIDs to placebo in chronic cystoid macular edema</p>	<p>N=266</p> <p>4 to 12 weeks</p>	<p>Primary:</p> <p>Improvement of 2 or more lines in Snellen visual acuity or equivalent at end of treatment, persistence of improvement of vision 1 month after discontinuation of treatment</p> <p>Secondary:</p> <p>Proportion of patients with improvement in leakage on fundus fluorescein angiography, proportion of participants with improved contrast sensitivity, quality of life</p>	<p>Primary:</p> <p>The mean time taken for a two line improvement in Snellen visual acuity and resolution of cystoid macular edema was found to be equally effective for diclofenac and ketorolac.</p> <p>There was minimal evidence of any difference between ketorolac and placebo in achieving a two-line improvement in Snellen visual acuity at the end of crossover period for treatment of acute cystoid macular edema.</p> <p>Study by Heier et al showed that ketorolac and prednisolone acetate combined is more effective than either of the agents alone for treatment of acute cystoid macular edema.</p> <p>There was a statistically significant benefit in using ophthalmic NSAIDs for chronic cystoid macular edema in two of the three studies for the improvement of visual acuity at the end of treatment (RR, 8.00; 95% CI, 1.16 to 55.20 and RR, 2.34; 95% CI, 1.25 to 4.40).</p> <p>There was a statistically significant benefit in using ophthalmic NSAIDs for chronic cystoid macular edema in one of the three studies for the improvement of visual acuity one month after treatment (RR, 3.37; 95% CI, 1.60 to 7.09).</p>

vs prednisolone acetate 1%				Secondary: Not reported
Intraoperative Miosis				
Roberts CW ⁵¹ Flurbiprofen 0.03% 1 drop in the affected eye(s) every 15 minutes for 4 doses beginning 1 hour before surgery vs diclofenac 0.1% 1 drop in the affected eye(s) every 15 minutes for 4 doses beginning 1 hour before surgery Each patient also received dilating drops along with the study medication.	RCT Patients undergoing cataract extraction by phacoemulsification	N=51 1 day	Primary: Horizontal and vertical diameters of the pupil measured just before the initial conjunctival incision (baseline) and then every 5 minutes during the procedure; at the beginning of capsulorhexis, the beginning of phacoemulsification, the end of phacoemulsification, the end of cortical cleanup, and before and after implantation of an intraocular lens Secondary: Not reported	Primary: There was no statistically significant difference between the two treatment groups in baseline pupil dilation (<i>P</i> values not reported). There were no statistically significant differences between the two treatment groups after start of surgery at any time, except at the start of phacoemulsification, when the flurbiprofen group had more dilation than the diclofenac group (<i>P</i> values not reported). Secondary: Not reported
Thaller et al ⁵² Flurbiprofen 0.03% vs diclofenac 0.1% vs vehicle	DB, RCT Patients undergoing extracapsular cataract extraction with lens implantation	N=52 Duration not specified	Primary: Change in pupil size (measured prior to the corneal section and after the completion of the operation), IOP, degree of inflammation (degree of pain, redness, flare and cells in the anterior chamber on day after surgery)	Primary: There was a smaller decrease in the diclofenac group compared with the flurbiprofen group in terms of change in pupil size (<i>P</i> values not reported). There was less reported postoperative redness in the diclofenac group compared with the other two groups (<i>P</i> =0.001). There were no significant differences found between the three treatment groups in terms of anterior chamber cells, flare or IOP change (<i>P</i> values not reported). Secondary:

Each patient also received balanced salt solution containing adrenaline.			Secondary: Not reported	Not reported
Solomon et al ⁵³ Flurbiprofen 0.03% 1 drop in the affected eye(s) every 15 minutes for 3 intervals beginning 1 hour prior to surgery vs ketorolac 0.5% 1 drop in the affected eye(s) every 15 minutes for 3 intervals beginning 1 hour prior to surgery	DB, PRO, RCT, SC Patients (mean age of 68 years) undergoing cataract extraction by phacoemulsification with posterior chamber intraocular lens insertion via scleral tunnel or clear corneal incision	N=118 1 day	Primary: Pupillary diameter measurements in the horizontal meridian at start of surgery, before phacoemulsification, before lens placement, and after lens placement Secondary: Not reported	Primary: Mean horizontal papillary diameter measurements for the two treatment groups were similar at baseline, at start of surgery. There were measurably larger pupils in the ketorolac group compared to the flurbiprofen group; however, the results were not statistically significant. The mean <i>P</i> values for intervals including start of surgery, before phacoemulsification, before lens placement, and after lens placement were <i>P</i> =0.80, <i>P</i> =0.27, <i>P</i> =0.26, and <i>P</i> =0.63 respectively. The ketorolac group had fewer miotic changes in the before phacoemulsification interval and greater mydriasis in the before and after lens placement intervals compared with the flurbiprofen group. However, these results were not statistically significant. The <i>P</i> values for change from baseline for the treatment comparisons were <i>P</i> =0.21, <i>P</i> =0.15, and <i>P</i> =0.67 respectively. Secondary: Not reported
Seasonal Allergic Conjunctivitis				
Tauber et al ⁵⁴ Ketorolac 0.5% 1 drop in each eye QID vs diclofenac 0.1% 1 drop in each eye QID	DB, MC, PG, PRO, RCT Patients (mean age of 40 years) clinically diagnosed with acute seasonal allergic conjunctivitis	N=60 14 days	Primary: Itching and bulbar conjunctival injection (0=absent, 1=mild, 2=moderate, and 3=severe, for both) at 30 minute, 7 day, and 14 day visits Secondary: Patient and physician's global improvement assessment with calculation of primary composite score (sum of	Primary: Significant clinical and statistical reductions from baseline were observed for primary and secondary composite scores for both treatment groups at 30 minute, seven day, and 14 day visits (<i>P</i> <0.001). The results were also significant for individual ocular itching and bulbar conjunctival injection (<i>P</i> <0.001). Secondary: There were no significant differences between the two treatment groups for the primary and secondary composite scores or for the individual parameters of itching and bulbar conjunctival injection. Treatment group differences were observed for pain/soreness score with an advantage observed for the diclofenac group at 30 minutes and at day seven (<i>P</i> =0.007 and <i>P</i> =0.039, respectively). There was a statistically

			<p>scores for ocular itching and bulbar conjunctival injection) and a secondary composite score (sum of remaining sign and symptom scores), safety parameters including visual acuity and intraocular pressure, occurrence of adverse events</p>	<p>significant advantage for the diclofenac group to be free of symptoms at day seven visit as compared to the ketorolac group (20.7 vs 3.2%; $P=0.049$). There was no significant treatment group difference observed at day 14 visit (P value not reported).</p> <p>There were no significant changes in visual acuity and IOP during the course of study (P values not reported).</p> <p>There were no serious adverse events reported with either of the treatment groups. Minor adverse events included burning and stinging on instillation of the medication, burning/stinging, irritation, discharge and one instance of corneal erosion in the diclofenac group and this was attributed to eye rubbing due to itching.</p>
<p>Yaylali et al⁵⁵</p> <p>Olopatadine 0.1% one eye BID and placebo other eye BID</p> <p>vs</p> <p>ketorolac 0.5% one eye QID and placebo other eye QID</p>	<p>PC, PG, RCT, SC</p> <p>Patients with seasonal allergic conjunctivitis, average age 19 years</p>	<p>N=40</p> <p>15 days</p>	<p>Primary: Hyperemia and itching at 30 minutes then at 2, 7, and 15 days</p> <p>Secondary: Not reported</p>	<p>Primary: Hyperemia and itching were improved significantly in eyes treated with olopatadine and ketorolac compared to placebo at all control examinations (all $P<0.05$).</p> <p>The mean score of hyperemia was found to be lower in the olopatadine group compared to the ketorolac group, but the difference was not statistically significant ($P>0.05$). However, the itching score was significantly lower in the olopatadine group compared to the ketorolac group from the second day through to the end of the study ($P<0.05$).</p> <p>Secondary: Not reported</p>
<p>Discepola et al⁵⁷</p> <p>Emedastine 0.05% 1 eye and placebo in other eye one time only</p> <p>vs</p> <p>ketorolac 0.5% in 1 eye and placebo in the other</p>	<p>DB, PC, RCT, SC, XO</p> <p>Patients (age not reported) with a history of allergic conjunctivitis, study used conjunctival allergen challenge model</p>	<p>N=36</p> <p>4 weeks</p>	<p>Primary: Ocular itching and redness at 3, 10, and 20 minutes post challenge; discomfort</p> <p>Secondary: Not reported</p>	<p>Primary: Emedastine significantly inhibited ocular itching and redness in vascular beds following ocular administration ($P<0.05$). In contrast, ketorolac failed to significantly inhibit ocular itching or redness in this study (P value not reported).</p> <p>Patient assessment of comfort indicated emedastine was significantly more comfortable than ketorolac upon topical ocular administration ($P<0.05$).</p>

<p>eye one time only</p> <p>About 14 days later, patients received the alternate treatment in one eye and placebo in the contralateral eye.</p>				<p>Secondary: Not reported</p>
<p>Shulman et al⁵⁸</p> <p>Study 1 (n=45): cromolyn 4% vs pemirolast 0.1% vs ketorolac 0.5% given bilaterally one time only (3 visits XO)</p> <p>Study 2 (n=48): nedocromil 2% vs pemirolast 0.1% given contralaterally one time only (1 visit)</p>	<p>DB, PG, PRO, RCT, SC</p> <p>Healthy adult volunteers, mean age 36 years in Study 1 and 34 years in Study 2</p>	<p>N=93</p> <p>Study 1: 7 days (3 visits)</p> <p>Study 2: 1 day</p>	<p>Primary: Overall ocular discomfort</p> <p>Secondary: Ocular burning/stinging, foreign-body sensation, tearing, photophobia, tolerability</p>	<p>Primary: Overall ocular discomfort was significantly lower with pemirolast than with cromolyn ($P=0.001$), ketorolac ($P<0.001$), and nedocromil ($P<0.001$).</p> <p>Secondary: Burning/stinging and tearing were significantly lower with pemirolast than cromolyn and nedocromil (all $P<0.05$). Foreign body sensation was also significantly lower with pemirolast than nedocromil ($P<0.05$). There were no significant differences in photophobia between treatment groups.</p> <p>No notable differences were found in the incidence of adverse events between treatment groups (P values not reported).</p>

*Agent not available in the United States.

Drug regimen abbreviations: BID=twice daily, QID=four times daily, TID=three times daily

Study abbreviations: CI=confidence interval, DB=double-blind, IOP=intraocular pressure, MC=multicenter, NSAID=nonsteroidal anti-inflammatory drug, OL=open label, PC=placebo-controlled, PG=parallel group, PRO=prospective, RCT=randomized controlled trial, RR=relative risk, SB=single blind, SC=single center, SR=systematic review, XO=cross over

Special Populations**Table 4. Special Populations²⁻¹²**

Generic Name	Population and Precaution				
	Elderly/Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Bromfenac sodium	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy have not been established in patients younger than 18 years of age.	Not reported	Not reported	C	Use with caution.
Diclofenac sodium	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy have not been established in pediatric patients.	Not reported	Not reported	C	Has not been established.
Flurbiprofen sodium	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy have not been established in pediatric patients.	Not reported	Not reported	C	Has not been established.
Ketorolac tromethamine	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy have not been established in patients younger than 3 years of age.	Not reported	Not reported	C	Use with caution.
Nepafenac	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.	Not reported	Not reported	C	Use with caution.

Generic Name	Population and Precaution				
	Elderly/Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	Safety and efficacy have not been established in patients younger than 10 years of age.				

*Use during late pregnancy should be avoided because of the known effects of prostaglandin biosynthesis-inhibiting drugs on the fetal cardiovascular system (closure of ductus arteriosus).

Adverse Drug Events

The most common adverse reactions seen with ophthalmic non-steroidal agents are transient burning and stinging, keratitis, lacrimation, ocular irritation and corneal adverse effects.

Table 5. Adverse Drug Events (%)^{2-12,59-63}

Adverse Event(s)	Bromfenac Sodium	Diclofenac Sodium	Flurbiprofen Sodium	Ketorolac Tromethamine	Nepafenac
Cardiovascular					
Facial edema	-	≤3	-	-	-
Hypertension	-	-	-	-	1 to 4
Central Nervous System					
Fever	-	≤3	-	-	-
Headache	2 to 7	≤3	-	≤1 ⁺ , 1 to 5 [†] , 1 to 6 [‡]	1 to 4
Insomnia	-	≤3	-	-	-
Pain	-	≤3	-	-	-
Gastrointestinal					
Abdominal pain	-	≤3	-	-	-
Nausea	-	≤3	-	-	1 to 4
Vomiting	-	≤3	-	-	1 to 4
Musculoskeletal					
Pain	-	≤3	-	-	-
Weakness	-	≤3	-	-	-
Ocular					
Abnormal sensation	2 to 7	-	-	-	5 to 10
Abnormal vision	-	5	-	≤1 ⁺ , 1 to 6 [‡]	5 to 10
Allergy	-	5	-	-	-
Bleeding of ocular tissues during ocular surgery	-	-	✓	-	-
Capsular opacity	-	-	-	-	5 to 10
Conjunctival edema	-	-	-	-	1 to 5
Conjunctival hyperemia	2 to 7	-	-	1 to 5 [†] , 1 to 6 [‡]	1 to 5
Conjunctivitis	-	5	-	-	-
Corneal deposits	-	5	-	1 to 5 [†]	-
Corneal edema	-	5	-	1 to 10 [†] , 1 to 6 [‡]	1 to 5
Corneal erosion	✓	✓	-	✓ ^{†,‡}	-
Corneal infiltrates	-	✓	-	≤1 ⁺ , 1 to 5 [†]	-
Corneal lesions	-	5	-	-	-
Corneal opacity	-	5	-	-	-
Corneal perforation	✓	✓	-	✓ ^{†,‡}	-
Corneal thinning	✓	✓	-	✓ ^{†,‡}	-

Adverse Event(s)	Bromfenac Sodium	Diclofenac Sodium	Flurbiprofen Sodium	Ketorolac Tromethamine	Nepafenac
Corneal ulceration	-	✓	-	≤1*	-
Discharge	-	5	-	-	-
Dry eye	-	-	-	≤1 ^{†,‡}	1 to 5
Edema	-	-	-	1 to 5 [†]	-
Epithelial breakdown	✓	✓	-	✓ ^{†,‡}	-
Eyelid swelling	-	5	-	-	-
Fibrosis	-	-	✓	-	-
Infection	-	5	-	1 to 10 ^{†,‡}	-
Inflammation	-	-	-	1 to 10 ^{†,‡}	-
Intraocular pressure increased	-	15	-	1 to 6 [‡]	5 to 10
Iritis	2 to 7	5	-	1 to 10 ^{†,‡}	-
Irritation	2 to 7	5	✓	1 to 10 ^{†,‡}	1 to 5
Keratitis	-	28	-	-	-
Lacrimation	-	30	-	1 to 6 [‡]	1 to 5
Lid margin crusting	-	-	-	-	1 to 5
Miosis	-	-	✓	-	-
Mydriasis	-	-	✓	-	-
Pain	2 to 7	-	-	1 to 10 [†] , 1 to 6 [‡]	1 to 5
Photophobia	-	-	-	-	1 to 5
Pruritus	2 to 7	5	✓	-	1 to 5
Redness	2 to 7	-	-	-	-
Superficial keratitis	-	✓	-	1 to 10 ^{†,‡}	-
Transient burning/stinging	2 to 7	15	✓	40 ^{†,‡} , 20 to 40 [†]	-
Vitreous detachment	-	-	-	-	1 to 5
Other					
Allergic reaction	-	-	-	1 to 10 ^{†,‡}	1 to 10
Viral infection	-	≤3	-	-	-
Respiratory					
Rhinitis	-	≤3	-	-	-
Sinusitis	-	-	-	-	1 to 4

✓ Percent not specified.

-Not reported or incidence <1%.

*Ketorolac tromethamine 0.5%.

†Ketorolac tromethamine 0.4%.

‡Ketorolac tromethamine 0.45%.

Contraindications/Precautions

Ophthalmic nonsteroidal anti-inflammatory drugs (NSAIDs) are contraindicated in patients with known hypersensitivity to any active or inactive ingredients in the formulation. Ophthalmic bromfenac sodium contains sodium sulfite and is contraindicated in patients with sulfite hypersensitivity.¹⁻¹²

All ophthalmic NSAIDs contain similar class warnings which include the potential for prolonged bleeding times due to interference with thrombocyte aggregation. These patients have a potential for increased risk of developing bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery. There is also a potential for cross-sensitivity with acetylsalicylic acid and other NSAIDs with these agents.

Ophthalmic NSAIDs and ophthalmic corticosteroids slow or delay the process of healing. Patients should be monitored closely if these agents are used concomitantly as it may increase the risk of developing healing problems. Ophthalmic NSAIDs may cause keratitis. Continued use of ophthalmic NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation

in certain patients. NSAIDs should be discontinued immediately and patients should be monitored closely when there is evidence of corneal epithelial breakdown.¹⁻¹²

Postmarketing evidence with these agents suggest that patients experiencing complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis or frequent ocular surgeries within a short period of time may be at an increased risk of developing corneal adverse events. Ophthalmic NSAIDs should not be used more than one day prior to surgery or use beyond 14 days after surgery to decrease the risk of developing corneal adverse events.¹⁻¹²

Ophthalmic formulations of bromfenac sodium, ketorolac tromethamine and nepafenac should not be administered while wearing contact lenses. Ophthalmic diclofenac sodium, with the exception of the use of bandage hydrogel soft contact lens during the first 3 days following refractive surgery, should not be administered while wearing soft contact lenses.^{2-4,7-9,11,12}

Drug Interactions

Due to limited systemic absorption with ophthalmic nonsteroidal anti-inflammatory agents (NSAIDs), drug interactions with other topical ophthalmic agents and systemically absorbed agents have not been fully investigated. Although clinical and animal studies have revealed no interference, acetylcholine chloride and carbachol have reportedly been ineffective when used in patients treated with ophthalmic flurbiprofen sodium.²⁻¹²

Some ophthalmic NSAIDs have shown to be safe when administered with other ophthalmic agents. Ophthalmic formulations of ketorolac tromethamine and nepafenac may be administered in conjunction with ophthalmic formulations of beta blockers, carbonic anhydrase inhibitors, cycloplegics and mydriatics. Ophthalmic ketorolac tromethamine may also be administered with ophthalmic antibiotics and ophthalmic nepafenac has been safely given with ophthalmic alpha-agonists.^{2-12,64}

Dosage and Administration

Table 6. Dosing and Administration²⁻¹²

Generic Name	Adult Dose	Pediatric Dose	Availability
Bromfenac sodium	<u>Treatment of postoperative patients who have undergone cataract extraction:</u> Instill 1 drop into affected eye(s) once daily, beginning 24 hours after cataract surgery, continued through the first 2 weeks of the postoperative period	Safety and efficacy have not been established in patients younger than 18 years of age.	Ophthalmic solution: 0.09% (2.5 mL, 5 mL)
Diclofenac sodium	<u>Treatment of postoperative patients who have undergone cataract extraction:</u> Instill 1 drop into affected eye(s) four times a day, beginning 24 hours after cataract surgery, continued through the first 2 weeks of the postoperative period <u>Temporary relief of pain and photophobia in patients undergoing corneal refractive surgery:</u> Instill 1 or 2 drops into affected eye(s) within 1 hour prior to surgery, then 1 or 2 drops within 15 minutes after surgery, then 1 or 2 drops four times a day for up to 3 days	Safety and efficacy have not been established in pediatric patients.	Ophthalmic solution: 0.1% (2.5 mL, 5 mL)

Flurbiprofen sodium	<u>Inhibition of intraoperative miosis:</u> Instill 1 drop into affected eye(s) every 30 minutes for a total of 4 drops beginning 2 hours before surgery	Safety and efficacy have not been established in pediatric patients.	Ophthalmic solution: 0.03% (2.5 mL)
Ketorolac tromethamine	<u>Treatment of pain and inflammation associated with cataract surgery:</u> 0.45%: Instill 1 drop into affected eye(s) two times a day, beginning 1 day prior to surgery, continued on the day of surgery, and through the first 2 weeks of the postoperative period 0.5%: Instill 1 drop into affected eye(s) four times a day, beginning 24 hours after cataract surgery, continued through the first 2 weeks of the postoperative period <u>Reduction of ocular pain and burning/stinging following corneal refractive surgery:</u> 0.4%: Instill 1 drop into affected eye(s) four times a day as needed for up to 4 days <u>Temporary relief of ocular itching due to seasonal allergic conjunctivitis:</u> 0.5%: Instill 1 drop four times a day	Safety and efficacy have not been established in patients younger than 3 years of age.	Ophthalmic solution: 0.4% (5 mL) 0.45% (0.4 mL single-use vials in package of 30) 0.5% (3 mL, 5 mL, 10 mL)
Nepafenac	<u>Treatment of pain and inflammation associated with cataract surgery:</u> Instill 1 drop into affected eye(s) three times a day, beginning 1 day prior to surgery, continue on the day of surgery, and through the first 2 weeks of the postoperative period	Safety and efficacy have not been established in patients younger than 10 years of age.	Ophthalmic suspension: 0.1% (3 mL)

Clinical Guidelines

Table 7. Clinical Guidelines

Clinical Guideline	Recommendations
American Academy of Ophthalmology: Preferred Practice Pattern: Cataract in the Adult Eye (2006) ²⁹	<ul style="list-style-type: none"> • Postoperative regimens of topically applied antibiotics, corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs) vary among practitioners. • No controlled investigations establish optimal regimens for the use of topical agents. • The operating surgeon is responsible for making the decision whether to use any or all of the topical products singly or in combination. <p><u>Cystoid macular edema</u></p> <ul style="list-style-type: none"> • Topical anti-inflammatory agents are used in an attempt to reduce the inflammatory response to cataract surgery and to treat established cystoid macular edema. • There is evidence that topically applied NSAIDs alone or in combination with corticosteroids is more effective than topical corticosteroids alone in preventing and treating cystoid macular edema.
American Optometric Association: Care of the Adult Patient with Cataract (2004) ³⁰	<ul style="list-style-type: none"> • A combination of topical and oral antiglaucoma, antibiotic and anti-inflammatory medications may be administered to the patient before, during and after an operation. • Topical corticosteroids may be used to suppress inflammation associated

Clinical Guideline	Recommendations
	<p>with cataract surgery.</p> <ul style="list-style-type: none"> To control inflammation associated with anterior uveitis, topical corticosteroids such as prednisolone acetate 1% may be used every 2-4 hours depending on the degree of inflammation.
<p>American Academy of Ophthalmology: Preferred Practice Pattern: Refractive Errors and Refractive Surgery (2009)⁶⁴</p>	<p><u>Photorefractive keratectomy</u></p> <ul style="list-style-type: none"> Topical antibiotics are administered to minimize the risk of postoperative infection. Topical corticosteroids are generally started immediately after surgery and tapered over a period of days to weeks, and sometimes months. If corticosteroid treatment is prolonged, the intraocular pressure should be monitored. Although postoperative pain may be reduced by the use of a bandage, contact lens, and NSAIDs drops, patients may still require prescription oral analgesics. Since NSAID drops may delay corneal epithelialization, they should be applied judiciously. Sterile corneal infiltrates associated with the use of NSAID drops without the concomitant use of topical corticosteroids have been described. Periodic examinations are necessary to monitor ocular status and to check for corticosteroid-related side effects such as elevated intraocular pressure. <p><u>Laser in situ keratomileusis (LASIK)</u></p> <ul style="list-style-type: none"> Topical antibiotics are administered to minimize the risk of postoperative infection. Corticosteroids are generally used for a short time postoperatively. Frequent lubrication is recommended in the postoperative period. Diffuse lamellar keratitis is a noninfectious aggregation of inflammatory cells and treatment is commonly guided by the severity of the inflammation. Increasing frequency of topical corticosteroid administration with a closer follow-up is practiced by most surgeons.
<p>American Academy of Ophthalmology: Preferred Practice Pattern: Conjunctivitis (2008)⁶⁵</p>	<p><u>Seasonal allergic conjunctivitis</u></p> <ul style="list-style-type: none"> Treat mild allergic conjunctivitis with an over-the-counter (OTC) antihistamine/vasoconstrictor or second-generation topical histamine H₁-receptor antagonist. The guideline does not give preference to one OTC antihistamine/vasoconstrictor or antihistamine versus another. The guideline does not address the role of prescription vasoconstrictors in the management of allergic conjunctivitis. If the condition is frequently recurrent or persistent, use mast-cell stabilizers. The guideline does not give preference to one mast-cell stabilizer versus another. Medications with antihistamine and mast-cell stabilizing properties may be utilized for either acute or chronic disease. The guideline does not give preference to one antihistamine/mast-cell stabilizer versus another. If the symptoms are not adequately controlled, a brief course (1-2 weeks) of low-potency topical corticosteroid may be added to the regimen. The lowest potency and frequency of corticosteroid administration that relieves the patient's symptoms should be used. Ketorolac, a NSAID, is also Food and Drug Administration (FDA) approved for the treatment of allergic conjunctivitis. Additional measures include allergen avoidance and using cool compresses, oral antihistamines, and artificial tears, which dilute

Clinical Guideline	Recommendations
	<p>allergens and treat coexisting tear deficiency. Frequent clothes washing and bathing before bedtime may also be helpful.</p> <ul style="list-style-type: none"> • Consultation with an allergist or dermatologist may be helpful for patients with disease that cannot be adequately controlled with topical medications and oral antihistamines. <p><u>Vernal/atopic conjunctivitis</u></p> <ul style="list-style-type: none"> • General treatment measures include modifying the environment to minimize exposure to allergens or irritants, and using cool compresses and ocular lubricants. Topical and oral antihistamines and topical mast-cell stabilizers may be beneficial in maintaining comfort. • For acute exacerbations, topical corticosteroids are usually necessary to control severe symptoms. The minimal amount of corticosteroid should be used based on patient response and tolerance. Topical cyclosporine is effective as adjunctive therapy to reduce the amount of topical corticosteroid used to treat severe atopic keratoconjunctivitis. For entities such as vernal keratoconjunctivitis, which may require repeat short-term therapy with topical corticosteroid, patients should be informed about potential complications of corticosteroid therapy and general strategies to minimize corticosteroid use should be discussed. • For severe sight-threatening atopic keratoconjunctivitis that is not responsive to topical therapy, systemic immunosuppression may be warranted. Eyelid involvement may be treated with pimecrolimus or tacrolimus. Patients should be told to keep these medications away from the conjunctival and corneal surface, and from the tear film. Both agents are rarely associated with the development of skin cancer and lymphoma. • Frequency of follow-up visits is based on the severity of disease presentation, etiology, and treatment. Consultation with a dermatologist is often helpful. If corticosteroids are prescribed, baseline and periodic measurement of intraocular pressure and papillary dilation should be performed to evaluate for glaucoma and cataract(s).
<p>American Optometric Association: Optometric Clinical Practice Guideline: Care of the Patient With Conjunctivitis (2002)⁶⁶</p>	<p><u>Allergic conjunctivitis (includes atopic keratoconjunctivitis, simple allergic conjunctivitis, seasonal or perennial conjunctivitis, and vernal conjunctivitis)</u></p> <ul style="list-style-type: none"> • The treatment of allergic conjunctivitis is based upon identification of specific antigens and elimination of specific pathogens, when practical, and upon the use of medications that decrease or mediate the immune response. The use of supportive treatment, including unpreserved lubricants and cold compresses, may provide symptomatic relief. • The following agents are useful in treating allergic conjunctivitis: topical corticosteroids (numerous products listed), vasoconstrictors/antihistamines (specific products not listed), antihistamines (azelastine, emastadine, and levocabastine*), NSAIDs (ketorolac), mast-cell stabilizers (cromolyn, lodoxamide, nedocromil, and pemirolast), antihistamines/mast-cell stabilizers (ketotifen and olopatadine), and immunosuppressants; and systemic immunosuppressants and antihistamines. • Topical corticosteroids are effective in relieving the acute symptoms of allergy; however, their use should be limited to the acute suppression of symptoms because of the potential for adverse side effects with their protracted use (e.g., cataract formation and elevated intraocular pressure). • Topical vasoconstrictors/antihistamines cause vascular constriction,

Clinical Guideline	Recommendations
	<p>decrease vascular permeability, and reduce ocular itching by blocking histamine H₁ receptors. The guideline does not address the role of prescription vasoconstrictors in the management of allergic conjunctivitis.</p> <ul style="list-style-type: none"> • Topical antihistamines competitively bind with histamine receptor sites and reduce itching and vasodilation. Azelastine, emedastine, and levocabastine* are effective in reducing the symptoms of allergic conjunctivitis, and emedastine may be more efficacious than levocabastine*. • Topical diclofenac and ketorolac, which are both NSAIDs, are effective in reducing the signs and symptoms associated with allergic conjunctivitis, although only ketorolac is FDA approved for this indication. • Nedocromil, an effective treatment for seasonal allergic conjunctivitis, is more effective than cromolyn (2%[†]) in treating vernal conjunctivitis. Nedocromil was less effective than fluorometholone in treating severe vernal keratoconjunctivitis but has fewer side effects. Lodoxamide has demonstrated a greater improvement in the signs and symptoms of allergic eye disease, including vernal keratoconjunctivitis, than cromolyn (2%[†] or 4%). Pemirolast has FDA approval as a treatment to relieve (to prevent) itching associated with allergic conjunctivitis. • Ketotifen and olopatadine are selective histamine H₁-receptor antagonists that also have mast-cell stabilizing properties. Olopatadine may be more effective than other mast-cell stabilizing agents in targeting the subtype of mast cell found in the conjunctiva. Compared with ketorolac or ketotifen, olopatadine is more effective in relieving the itching and redness associated with acute allergic conjunctivitis. • Systemically administered cyclosporine may be an effective treatment for patients with severe atopic keratoconjunctivitis. Topical cyclosporine is an alternative to topical corticosteroids for treatment of patients with severe atopic keratoconjunctivitis. Topical cyclosporine may also be beneficial in patients with vernal keratoconjunctivitis who have failed conventional therapy. • Systemic antihistamines are useful when the allergic response is associated with lid edema, dermatitis, rhinitis, or sinusitis. They should be used with caution because of the sedating and anticholinergic effects of some first-generation antihistamines. Newer antihistamines are much less likely to cause sedation, but their use may result in increased ocular surface dryness.
<p>American Academy of Ophthalmology (AAO): Preferred Practice Pattern Guidelines: Blepharitis (2008)⁶⁷</p>	<ul style="list-style-type: none"> • There is insufficient evidence to make definitive recommendations for the treatment of blepharitis, and cure is not possible in most cases. • Treatments that are helpful include the following: <ul style="list-style-type: none"> ○ Warm compresses. ○ Eyelid hygiene. ○ Antibiotics (topical and/or systemic). ○ Ophthalmic anti-inflammatory agents (e.g., corticosteroids). • These treatment options are often used in combination. • Eyelid hygiene is especially useful for anterior blepharitis, and warm compresses are especially helpful for posterior blepharitis. • Optimal treatment regimens often require a trial and error approach. • An ophthalmic antibiotic ointment such as ophthalmic bacitracin or ophthalmic erythromycin can be prescribed and applied on the eyelid margins one or more times daily or at bedtime for 1 or more weeks. The frequency and duration of treatment should be guided by the severity of

Clinical Guideline	Recommendations
	<p>the blepharitis and response to treatment.</p> <ul style="list-style-type: none"> • For patients with meibomian gland dysfunction, whose chronic signs and symptoms are not adequately controlled with eyelid hygiene, an oral tetracycline can be prescribed. Macrolide antibiotics also have anti-inflammatory activity. • Treatments can be intermittently discontinued and reinstated, based on the severity of the patient's blepharitis and tolerance for the medication, and to allow re-colonization of normal flora. • Ophthalmic corticosteroid eye drops or ointments are typically applied several times daily to the eyelids or ocular surface. • Once the inflammation is controlled, the ophthalmic corticosteroid can be tapered and discontinued and then used intermittently to maintain patient comfort. • The minimal effective dose of ophthalmic corticosteroid should be utilized, and long-term ophthalmic corticosteroid therapy should be avoided if possible. • Potential adverse effects of ophthalmic corticosteroid use, including the risk for developing increased intraocular pressure and cataracts may be minimized by using a site-specific ophthalmic corticosteroid such as ophthalmic loteprednol etabonate and ophthalmic corticosteroids with limited ocular penetration, such as ophthalmic fluorometholone. • Artificial tears may improve symptoms when used as an adjunct to eyelid hygiene and medications. If used more than four times per day, non-preserved tears should be used to avoid preservative toxicity.
<p>AAO: Preferred Practice Pattern Guidelines: Bacterial Keratitis (2008)⁶⁸</p>	<p><u>Initial treatment</u></p> <ul style="list-style-type: none"> • Ophthalmic antibiotic eye drops are the preferred method of treatment in most cases of bacterial keratitis. • Ophthalmic ointments may be useful at bedtime in less severe cases and also may be useful for adjunctive therapy. • Ophthalmic broad-spectrum antibiotics are used initially in the empiric treatment of bacterial keratitis. • The recommended ophthalmic empiric treatments include: <ul style="list-style-type: none"> ○ No organism identified or multiple types of organisms: ophthalmic cefazolin sodium (with gentamicin sulfate or tobramycin) or ophthalmic fluoroquinolones (fewer gram-positive cocci are resistant to gatifloxacin and moxifloxacin hydrochloride than other fluoroquinolones). ○ Gram-positive cocci: ophthalmic cefazolin sodium, vancomycin (for resistant <i>Enterococcus</i> and <i>Staphylococcus</i> species and penicillin allergy), ophthalmic bacitracin (for resistant <i>Enterococcus</i> and <i>Staphylococcus</i> species and penicillin allergy), or ophthalmic fluoroquinolones (fewer gram-positive cocci are resistant to ophthalmic gatifloxacin and moxifloxacin hydrochloride than other ophthalmic fluoroquinolones). ○ Gram-negative rods: ophthalmic formulations of tobramycin or gentamicin sulfate, ceftazidime, or fluoroquinolones. ○ Gram-negative cocci: ophthalmic ceftazidime, ceftriaxone sodium, or fluoroquinolones (systemic therapy is necessary for suspected gonococcal infection). ○ Nontuberculous mycobacteria: ophthalmic amikacin sulfate, azithromycin, clarithromycin, or fluoroquinolones. ○ Nocardia: ophthalmic amikacin sulfate, sulfacetamide sodium, or

Clinical Guideline	Recommendations
	<p>trimethoprim/sulfamethoxazole.</p> <ul style="list-style-type: none"> • Single-drug therapy using an ophthalmic fluoroquinolone has been shown to be as effective as combination therapy with ophthalmic antibiotics that are fortified by increasing their concentration over commercially available topical antibiotics. • Some pathogens (e.g., <i>Streptococci</i>, anaerobes) reportedly have variable susceptibility to ophthalmic fluoroquinolones and the prevalence of resistance to fluoroquinolones appears to be increasing • Combination fortified-antibiotic therapy is an alternative to consider for severe infection and for eyes unresponsive to initial treatment. • Treatment with more than one agent may be necessary for nontuberculous mycobacteria; infection with this pathogen has been reported in association with LASIK. • Methicillin-resistant <i>Staphylococcus aureus</i> (MRSA) has been isolated with increasing frequency from patients with bacterial keratitis and has been reported following kerato-refractive surgery. Ophthalmic fluoroquinolones are generally poorly effective against MRSA ocular isolates. MRSA isolates are generally sensitive to ophthalmic vancomycin. • Systemic antibiotics are rarely needed, but they may be considered in severe cases where the infectious process has extended to adjacent tissues (e.g., the sclera) or when there is impending or frank perforation of the cornea. • Systemic therapy is necessary in cases of gonococcal keratitis. <p><u>Modification of therapy</u></p> <ul style="list-style-type: none"> • Efficacy of the regimen is judged primarily by clinical response. The results of cultures and sensitivity testing may have an impact on therapeutic decision making, especially if the patient is not responding to initial therapy. • Dual antibiotic treatment designed to achieve broad-spectrum coverage may become unnecessary once the causative organism has been isolated. • The initial therapeutic regimen should be modified (change in type, concentration or frequency of antibiotic) when the eye shows a lack of improvement or stabilization within 48 hours. • Most antibiotic eye drops should not be tapered below three to four times a day, because low doses are sub-therapeutic and may increase the risk of developing antibiotic resistance. <p><u>Corticosteroid therapy</u></p> <ul style="list-style-type: none"> • Ophthalmic corticosteroid therapy may have a beneficial role in treating some cases of infectious keratitis due to the probable suppression of inflammation, which may reduce subsequent corneal scarring and associated visual loss. • Potential disadvantages of ophthalmic corticosteroid use include infection reoccurrence, local immunosuppression, inhibition of collagen synthesis predisposing to corneal melting, and increased intraocular pressure. • There is no conclusive evidence that ophthalmic corticosteroids alter clinical outcome. • Despite risks involved, it is believed that sensible use of ophthalmic corticosteroids can reduce morbidity.

Clinical Guideline	Recommendations
	<ul style="list-style-type: none"> • Patients being treated with ophthalmic corticosteroids at the time of presentation of suspected bacterial keratitis should have their ophthalmic corticosteroid regimen reduced or eliminated until the infection has been controlled. • Inflammation may temporarily increase as ophthalmic corticosteroids are reduced. • The minimum amount of ophthalmic corticosteroid required should be used to achieve control of inflammation. • Ophthalmic corticosteroids should not be part of initial treatment of presumed bacterial ulcers, and ideally they should not be used until the organism has been determined by cultures. • The use of ophthalmic corticosteroids in the initial treatment of corneal ulcers has been determined to be a risk factor for requiring a penetrating keratoplasty. • Ophthalmic antibiotics, which are generally administered more frequently than ophthalmic corticosteroids during treatment of active infection, are continued at high levels and tapered gradually. • Patient compliance is essential, intraocular pressure must be monitored frequently, and the patient should be examined within 1 to 2 days after initiation of ophthalmic corticosteroid therapy.

*Product is not available in the United States.

†Cromolyn 4% but not 2% is available in the United States. The concentrations of cromolyn that were used in the original clinical studies are noted in this table.

Conclusions

There are currently seven ophthalmic nonsteroidal anti-inflammatory drugs (NSAIDs) available in the United States including bromfenac sodium (Bromday[®]), diclofenac sodium (Voltaren[®]), flurbiprofen sodium (Ocufen[®]), ketorolac tromethamine (Acular[®], Acular LS[®], Acuvail[®]) and nepafenac (Nevanac[®]).¹⁻¹² Ketorolac is available in various strengths, including the original 0.5% formulation, the preservative free 0.45% formulation and the lower strength 0.4% formulation. Ophthalmic formulations of diclofenac sodium, flurbiprofen sodium and ketorolac tromethamine 0.4% and 0.5% are available generically. A generic formulation of bromfenac sodium became available in May 2011, and is only approved for twice-daily dosing (Xibrom[®]), and not once-daily administration (Bromday[®]). Ophthalmic NSAIDs exert their anti-inflammatory activity primarily by nonselective inhibition of cyclooxygenase-1 and cyclooxygenase-2 enzymes. FDA-approved for various non-infectious ocular conditions including management of pain and inflammation following cataract and corneal refractive surgeries, inhibition of intraoperative miosis and relief of ocular itching due to seasonal allergic conjunctivitis. The twice-daily bromfenac sodium formulation (Xibrom[®]) was discontinued in February 2011, following the approval of once-daily bromfenac sodium (Bromday[®]). The 0.45% strength of ketorolac tromethamine is dosed twice daily, nepafenac is dosed three times daily and all others agents are dosed four times daily. Diclofenac sodium and ketorolac tromethamine 0.45% are the only ophthalmic NSAIDs that are preservative-free.

In placebo-controlled trials, ophthalmic NSAIDs have shown to be safe and effective in inhibiting intraoperative miosis, reducing postoperative inflammation and pain associated with cataract surgery, relieving pain and photophobia following corneal refractive surgery and relieving seasonal allergic conjunctivitis symptoms. Although not Food and Drug Administration-approved, there is some evidence to support the use of most ophthalmic NSAIDs for preventing or treating cystoid macular edema and for reducing pain associated with various other refractive surgeries. The once-daily bromfenac sodium product has only been compared to its vehicle (placebo) for its FDA-approved indication. In these trials, patients who received once-daily dosing with bromfenac sodium were more likely to be clear of ocular inflammation by day 15 compared to placebo (46 to 51% vs 26 to 29%; $P < 0.001$). In head-to-head studies comparing the agents in the class, no one agent was consistently more efficacious than any other for a given indication. With regard to safety, no one agent was consistently reported to be better tolerated than

another across trials, although there is some evidence that the preservative-free products may be less irritating to patients.⁵⁶ Corneal complications have been reported to occur with all of the agents in the class and available evidence does not support a greater risk with one agent versus another.

Consensus guidelines established by the American Academy of Ophthalmology and the American Optometric Association recommend the use of topical NSAIDs for preventing and treating cystoid macular edema due to cataract surgery. There is no recommendation for use of one ophthalmic NSAID over another.^{29,30}

Appendix I: Utilization Within This Drug Class for DVHA: April 1, 2011 to September 30, 2011

Medication	# of Rx's	Market Share (%)	Plan Cost \$	Avg \$/Rx
Acular LS	88	59.06%	\$10,758.95	\$122.26
Acular	54	36.24%	\$6,616.96	\$122.54
Flurbiprofen	5	3.36%	\$58.34	\$11.67
Ketorolac	2	1.34%	\$149.50	\$74.75
Class Total:	149	100%	\$17,583.75	\$118.01

Recommendations

No changes to the current Department of Vermont Health Access (DVHA) approval criteria for ophthalmic NSAIDs (below) are proposed.

Acuvail®

- The patient has had a documented side effect, allergy, or treatment failure to Acular® or Acular LS®
- OR**
- The patient has a documented hypersensitivity to the preservative benzalkonium chloride.

Bromfenac, Diclofenac, Nevanac®, Voltaren®, Xibrom®

- The patient has had a documented side effect, allergy, or treatment failure to Acular® or Acular LS®. In addition, if a product has an AB rated generic, there must have also been a trial of the generic formulation.

Ketorolac 0.4 %/0.5 %

- The patient has had a documented intolerance to brand Acular®/Acular LS® ophthalmic solution.

Ocufen®

- The patient has had a documented intolerance to generic flurbiprofen ophthalmic solution.

Bromday (bromfenac 0.09%) ophthalmic solution is currently coded as a new-to-market agent and as such is not included in the DVHA preferred drug list. However, in recognition of its cost and the availability of a generic alternative product, it is recommended to move Bromday to PA required with the following approval criteria:

- The patient has had a documented side effect, allergy, or treatment failure to Acular® or Acular LS®. In addition, if a product has an AB rated generic, there must have also been a trial of the generic formulation.

References

1. Drug Facts and Comparisons 4.0 [database on the Internet]. St. Louis: Wolters Kluwer Health, Inc.; 2011 [cited 2011 Oct 29]. Available at: <http://online.factsandcomparisons.com>.
2. Bromday[®] [package insert]. Irvine (CA): ISTA Pharmaceuticals, Inc.; 2011 Aug.
3. Voltaren[®] [package insert]. Duluth (GA): Novartis Ophthalmics; 2011 Apr.
4. Diclofenac [package insert]. Lake Forest (IL): Akorn Inc.; 2008 Sep.
5. Ocufer[®] [package insert]. Irvine (CA): Allergan, Inc.; 2003 Feb.
6. Flurbiprofen [package insert]. Tampa (FL): Bausch & Lomb Inc.; 2008 Mar.
7. Acuvail[®] [package insert]. Irvine (CA): Allergan, Inc.; 2009 Jul.
8. Acular[®] [package insert]. Irvine (CA): Allergan, Inc.; 2004 Jan.
9. Acular LS[®] [package insert]. Irvine (CA): Allergan, Inc.; 2011 May.
10. Nevanac[®] [package insert]. Fort Worth (TX): Alcon Laboratories, Inc.; 2011 Jul.
11. Ketorolac tromethamine 0.5% [package insert]. Lake Forest (IL): Akorn, Inc.; 2009 Oct.
12. Ketorolac tromethamine 0.4% [package insert]. Lake Forest (IL): Akorn, Inc.; 2009 Oct.
13. Micromedex[®] Healthcare Series [database on the Internet]. Greenwood Village (CO): Thomson Micromedex; 2011 [cited 2011 Oct 29]. Available from: <http://www.thomsonhc.com/>.
14. Mylan Launches First Generic Version of Xibrom[®] Ophthalmic Solution [press release on the Internet]. Canonsburgh (PA): 2011 May 16 [cited 2011 Oct 29]. Available from: <http://investor.mylan.com/releasedetail.cfm?ReleaseID=577501>.
15. Drugs@FDA [database on the Internet]. Rockville (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2011 [cited 2011 Oct 29]. Available from: <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>.
16. Cho H, Wolf KJ, Wolf EJ. Management of ocular inflammation and pain following cataract surgery: focus on bromfenac ophthalmic solution. *Clin Ophthalmol*. 2009;3:199-210.
17. Ahuja M, Dhake AS, Sharma SK, Majumdar DK. Topical ocular delivery of NSAIDs. *AAPS J*. 2008;10(2):229-41.
18. Gaynes BI, Fiscella R. Topical nonsteroidal anti-inflammatory drugs for ophthalmic use: a safety review. *Drug Saf*. 2002;25(4):233-50.
19. Colin J. The role of NSAIDs in the management of postoperative ophthalmic inflammation. *Drugs*. 2007;67(9):1291-308.
20. Roberts CW, Brennan KM. A comparison of topical diclofenac with prednisolone for postcataract inflammation. *Arch Ophthalmol*. 1995;113(6):725-7.
21. Reddy MS, Suneetha N, Thomas RK, Battu RR. Topical diclofenac sodium for treatment of postoperative inflammation in cataract surgery. *Indian J Ophthalmol*. 2000;48(3):223-6.
22. Laurell CG, Zetterstrom C. Effects of dexamethasone, diclofenac, or placebo on the inflammatory response after cataract surgery. *Br J Ophthalmol*. 2002;86:1380-4.
23. Simone JN, Pendelton RA, Jenkins JE. Comparison of the efficacy and safety of ketorolac tromethamine 0.5% and prednisolone acetate 1% after cataract surgery. *J Cataract Refract Surg*. 1999;25(5):699-704.
24. Guzey M, Karadede S, Dogan Z, Satici A. Ketorolac-tobramycin combination vs fluorometholone-tobramycin combination in reducing inflammation following phacoemulsification cataract extraction with scleral tunnel incision [abstract]. *Ophthalmic Surg Lasers*. 2000;31:451-6.
25. El-Harazi SM, Ruiz RS, Feldman RM, Villanueva G, Chuang AZ. A randomized double-masked trial comparing ketorolac tromethamine 0.5%, diclofenac sodium 0.1%, and prednisolone acetate 1% in reducing post-phacoemulsification flare and cells [abstract]. *Ophthalmic Surg Lasers*. 1998;29(7):539-44.
26. Ostrov CS, Sirkin SR, Deutsch WE, Masi RJ, Chandler JW, Lindquist TD. Ketorolac, prednisolone, and dexamethasone for postoperative inflammation. *Clin Ther*. 1997;19(2):259-72.
27. Trinavarat A, Atchaneeyasakul LO, Surachatkumtonekul T, Kosrirukvongs P. Comparison of topical prednisolone acetate, ketorolac tromethamine and fluorometholone acetate in reducing inflammation after phacoemulsification [abstract]. *J Med Assoc Thai*. 2003;86(2):143-50.
28. Hirneiss C, Neubauer AS, Kampik A, Schonfeld CL. Comparison of prednisolone 1%, rimexolone 1% and ketorolac tromethamine 0.5% after cataract extraction: a prospective, randomized, double-masked study. *Graefes Arch Clin Exp Ophthalmol*. 2005;43(8):768-73.

29. American Academy of Ophthalmology Preferred Practice Patterns Committee. Preferred Practice Pattern Guidelines. Cataract in the adult eye [guideline on the Internet]. 2006 [cited 2011 Oct 28]. Available from: <http://one.aao.org/asset.axd?id=821cecfb-85c5-400d-a65f-7a9a727bc163>.
30. American Optometric Association. Care of the adult patient with cataract [guideline on the Internet]. 2004 [cited 2011 Oct 28]. Available from: <http://www.aoa.org/documents/CPG-8.pdf>.
31. Silverstein SM, Cable MG, Sadri E, Peace JH, Fong R, Chandler SP, et al. Once daily dosing of bromfenac ophthalmic solution 0.09% for postoperative ocular inflammation and pain. *Curr Med Res Opin*. 2011 Sep;27(9):1693-703.
32. Henderson BA, Gayton JL, Chandler SP, Gow JA, Klier SM, McNamara TR, et al. Safety and Efficacy of Bromfenac Ophthalmic Solution (Bromday) Dosed Once Daily for Postoperative Ocular Inflammation and Pain. *Ophthalmology*. 2011 Ophthalmology. 2011 Jul 16. [Epub ahead of print]
33. Donnenfeld ED, Holland EJ, Stewart RH, Gow JA, Grillone LR. Bromfenac ophthalmic solution 0.09% (Xibrom) for postoperative ocular pain and inflammation. *Ophthalmology*. 2007;114(9):1653-62.
34. Stewart RH, Grillone LR, Shiffman ML, Donnenfeld ED, Gow JA. The systemic safety of bromfenac ophthalmic solution 0.09%. *J Ocul Pharmacol Ther*. 2007;23(6):601-12.
35. Lane SS, Modi SS, Lehmann RP, Holland EJ. Nepafenac ophthalmic suspension 0.1% for the prevention and treatment of ocular inflammation associated with cataract surgery. *J Cataract Refract Surg*. 2007;33(1):53-8.
36. Maxwell WA, Reiser HJ, Stewart RH, Cavanagh HD, Walters TR, Sager DP, et al. Nepafenac dosing frequency for ocular pain and inflammation associated with cataract surgery. *J Ocul Pharmacol Ther*. 2008;24(6):593-9.
37. Duong HVQ, Westfield KC, Chalkley TH. Ketorolac tromethamine LS 0.4% versus nepafenac 0.1% in patients having cataract surgery. Prospective randomized double-masked clinical trial. *J Cataract Refract Surg*. 2007;33(11):1925-9.
38. Flach AJ, Dolan BJ, Donahue ME, Faktorovich EG, Gonzalez GA. Comparative effects of ketorolac 0.5% or diclofenac 0.1% ophthalmic solutions on inflammation after cataract surgery. *Ophthalmology*. 1998;105(9):1775-9.
39. Koçak I, Yalvaç IS, Koçak A, Nurözler A, Unlü N, Kasim R, Duman S. Comparison of the anti-inflammatory effects of diclofenac and flurbiprofen eye drops after cataract extraction. *Acta Ophthalmol Scand*. 1998;76(3):343-5.
40. Sandoval HP, De Castro LE, Vroman DT, Solomon KD. Evaluation of 0.4% ketorolac tromethamine ophthalmic solution versus 0.5% ketorolac tromethamine ophthalmic solution after phacoemulsification and intraocular lens implantation. *J Ocul Pharmacol Ther*. 2006;22(4):251-7.
41. Holzer MP, Solomon KD, Sandoval HP, Vroman DT. Comparison of ketorolac tromethamine 0.5% and loteprednol etabonate 0.5% for inflammation after phacoemulsification: prospective randomized double-masked study. *J Cataract Refract Surg*. 2002;28(1):93-9.
42. Solomon KD, Vroman DT, Barker D, Gehlken J. Comparison of ketorolac tromethamine 0.5% and rimexolone 1% to control inflammation after cataract extraction. Prospective randomized double-masked study. *J Cataract Refract Surg*. 2001;27(8):1232 to 7.
43. Narváez J, Krall P, Tooma TS. Prospective, randomized trial of diclofenac and ketorolac after refractive surgery [abstract]. *J Refract Surg*. 2004;20(1):76-8.
44. Seitz B, Sorken K, LaBree L, Garbus J, McDonnell P. Corneal sensitivity and burning sensation: comparing topical ketorolac and diclofenac. *Arch Ophthalmol*. 1996;114(8):921-4.
45. Rho DS. Treatment of acute pseudophakic cystoid macular edema: diclofenac versus ketorolac [abstract]. *J Cataract Refract Surg*. 2003;29(12):2378-84.
46. Singal N, Hopkins J. Pseudophakic cystoid macular edema: ketorolac alone vs ketorolac plus prednisolone [abstract]. *Can J Ophthalmol*. 2004;39:245-50.
47. Miyake K, Masuda K, Shirato S, Oshika T, Eguchi K, Hoshi H, et al. Comparison of diclofenac and fluorometholone in preventing cystoid macular edema after small incision cataract surgery: a multicentered prospective trial. *Jpn J Ophthalmol*. 2000;44:58-67.
48. Heier JS, Topping TM, Baumann W, Dirks MS, Chern S. Ketorolac versus prednisolone versus combination therapy in the treatment of acute pseudophakic cystoid macular edema. *Ophthalmology*. 2000;107:2034-8.

49. Wittpenn JR, Silverstein S, Heier J, Kenyon KR, Hunkeler JD, Earl M; Acular LS for Cystoid Macular Edema (ACME) Study Group. A randomized, masked comparison of topical ketorolac 0.4% plus steroid vs steroid alone in low-risk cataract surgery patients. *Am J Ophthalmol*. 2008;146(4):554-60.
50. Sivaprasad S, Bunce C, Wormald R. Non-steroidal anti-inflammatory agents for cystoid macular oedema following cataract surgery: a systematic review. *Br J Ophthalmol*. 2005;89(11):1420-2.
51. Roberts CW. Comparison of diclofenac sodium and flurbiprofen for inhibition of surgically induced miosis [abstract]. *J Cataract Refract Surg*. 1996;22(1):780-7.
52. Thaller VT, Kulshrestha MK, Bell K. The effect of pre-operative topical flurbiprofen or diclofenac on pupil dilatation [abstract]. *Eye (Lond)* 2000;14(4):642-5.
53. Solomon KD, Turkalj JW, Whiteside SB, Stewart JA, Apple DJ. Topical 0.5% ketorolac vs 0.03% flurbiprofen for inhibition of miosis during cataract surgery. *Arch Ophthalmol*. 1997;115(9):1119-22.
54. Tauber J, Raizman MB, Ostrov CS, Laibovitz RA, Abelson MB, Betts JG, et al. A multicenter comparison of the ocular efficacy and safety of diclofenac 0.1% solution with that of ketorolac 0.5% solution in patients with acute seasonal allergic conjunctivitis. *J Ocul Pharmacol Ther*. 1998;14(2):137-45.
55. Yaylali V, Demirelenk I, Tatlipinar S. Comparative study of 0.1% olopatadine hydrochloride and 0.5% ketorolac tromethamine in the treatment of seasonal allergic conjunctivitis. *Acta Ophthalmol Scand*. 2003;81:378-82.
56. Maca SM, Amon M, Findl O, Kahraman G, Barisani-Asenbauer T. Efficacy and tolerability of preservative-free and preserved diclofenac and preserved ketorolac eye drops after cataract surgery. *Am J Ophthalmol*. 2010 May;149(5):777-84.
57. Discepolo M, Deschenes J, Abelson M. Comparison of the topical ocular antiallergic efficacy of emedastine 0.05% ophthalmic solution to ketorolac 0.5% ophthalmic solution in a clinical model of allergic conjunctivitis. *Acta Ophthalmol Scand Suppl*. 1999;(228):43-6. [abstract]
58. Shulman DG, Amdahl L, Washington C, Graves A. A combined analysis of two studies assessing the ocular comfort of antiallergy ophthalmic agents. *Clin Ther*. 2003 Apr;25(4):1096-106.
59. Bromfenac: drug information. In: Basow D (Ed). UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2011 [cited 2011 Oct 28]. Available from: <http://www.utdol.com/utd/index.do>.
60. Diclofenac: drug information. In: Basow D (Ed). UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2011 [cited 2011 Oct 28]. Available from: <http://www.utdol.com/utd/index.do>.
61. Flurbiprofen: drug information. In: Basow D (Ed). UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2011 [cited 2011 Oct 28]. Available from: <http://www.utdol.com/utd/index.do>.
62. Ketorolac: drug information. In: Basow D (Ed). UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2011 [cited 2011 Oct 28]. Available from: <http://www.utdol.com/utd/index.do>.
63. Nepafenac: drug information. In: Basow D (Ed). UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2011 [cited 2011 Oct 28]. Available from: <http://www.utdol.com/utd/index.do>.
64. American Academy of Ophthalmology Preferred Practice Patterns Committee. Preferred Practice Pattern Guidelines. Refractive errors and refractive surgery [guideline on the Internet]. 2008 [cited 2011 Oct 28]. Available from: http://one.aao.org/CE/PracticeGuidelines/PPP_Content.aspx?cid=e6930284-2c41-48d5-afd2-631dec586286.
65. American Academy of Ophthalmology Cornea/External Disease Panel. Preferred Practice Pattern Guidelines. Conjunctivitis. [guideline on the Internet]. 2008 [cited 2011 Oct 28]. Available from: <http://one.aao.org/CE/PracticeGuidelines/PPP.aspx>.
66. American Optometric Association. Optometric Clinical Practice Guideline. Care of the patient with conjunctivitis. [guideline on the Internet]. 2002 [cited 2011 Oct 28]. Available from: <http://www.aao.org/ppp>.
67. American Academy of Ophthalmology Preferred Practice Patterns Committee. Preferred Practice Pattern Guidelines. Blepharitis [guideline on the Internet]. 2008 [cited 2011 Oct 28]. Available from: http://one.aao.org/CE/PracticeGuidelines/PPP_Content.aspx?cid=080ac46b-ea4d-4556-893a-2a63ba87ffcd. Accessed April 2010.
68. American Academy of Ophthalmology Preferred Practice Patterns Committee. Preferred Practice Pattern Guidelines. Bacterial Keratitis [guideline on the Internet]. 2008 [cited 2011 Oct 28]. Available

at: http://one.aao.org/CE/PracticeGuidelines/PPP_Content.aspx?cid=1d56d934-c309-4072-b6b5-0698559a3b47. Accessed April 2010.