

Ophthalmic Anti-Inflammatories Review

02/28/2011

Copyright © 2004 - 2011 by Provider Synergies, L.L.C. All rights reserved.
Printed in the United States of America.

All rights reserved. No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording, digital scanning, or via any information storage and retrieval system without the express written consent of Provider Synergies, L.L.C.

All requests for permission should be mailed to:

*Attention: Copyright Administrator
Intellectual Property Department
Provider Synergies, L.L.C.
10101 Alliance Road, Ste 201
Cincinnati, Ohio 45242*

The materials contained herein represent the opinions of the collective authors and editors and should not be construed to be the official representation of any professional organization or group, any state Pharmacy and Therapeutics committee, any state Medicaid Agency, or any other clinical committee. This material is not intended to be relied upon as medical advice for specific medical cases and nothing contained herein should be relied upon by any patient, medical professional or layperson seeking information about a specific course of treatment for a specific medical condition. All readers of this material are responsible for independently obtaining medical advice and guidance from their own physician and/or other medical professional in regard to the best course of treatment for their specific medical condition. This publication, inclusive of all forms contained herein, is intended to be educational in nature and is intended to be used for informational purposes only. Send comments and suggestions to PSTCReDitor@magellanhealth.com.



Together, we can do more.

Ophthalmic Anti-Inflammatories Review

FDA-Approved Indications

Drug	Manufacturer	Indication(s)
Corticosteroids		
dexamethasone (Maxidex®) ¹	Alcon	<ul style="list-style-type: none"> • Treatment of inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe • Corneal injury
dexamethasone (Ozurdex™) ²	Allergan	<ul style="list-style-type: none"> • Treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO)
dexamethasone sodium phosphate (Ak-Dex, Dexasol) ³	generic	<ul style="list-style-type: none"> • Treatment of inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe • Corneal injury
difluprednate (Durezol™) ⁴	Sirion	<ul style="list-style-type: none"> • Treatment of inflammation and pain associated with ocular surgery
fluocinolone (Retisert™) ⁵	Bausch & Lomb	<ul style="list-style-type: none"> • Treatment of chronic non-infectious uveitis affecting the posterior segment of the eye
fluorometholone (FML®) ⁶	generic	<ul style="list-style-type: none"> • Treatment of inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe
fluorometholone (FML Forte®) ⁷	Allergan	<ul style="list-style-type: none"> • Treatment of corticosteroid-responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe
fluorometholone (FML S.O.P.®) ⁸	Allergan	<ul style="list-style-type: none"> • Treatment of corticosteroid-responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe
fluorometholone acetate (Flarex®) ⁹	Alcon	<ul style="list-style-type: none"> • Treatment of corticosteroid-responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe
loteprednol (Lotemax™) ¹⁰	Bausch & Lomb	<ul style="list-style-type: none"> • Treatment of corticosteroid-responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe • Treatment of post-operative inflammation following ocular surgery
prednisolone acetate (Econopred® Plus, Omnipred™, Pred Forte) ^{11,12,13}	generic	<ul style="list-style-type: none"> • Treatment of corticosteroid-responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe • Treatment of corneal injury
prednisolone acetate (Pred Mild) ¹⁴	Allergan	<ul style="list-style-type: none"> • Treatment of inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe • Corneal injury
prednisolone sodium phosphate (Prednisol) ¹⁵	generic	<ul style="list-style-type: none"> • Treatment of inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe • Corneal injury

FDA-Approved Indications (continued)

Drug	Manufacturer	Indication(s)
rimexolone (Vexol [®]) ¹⁶	Alcon	<ul style="list-style-type: none"> • Treatment of anterior uveitis • Treatment of post-operative inflammation after ocular surgery
triamcinolone acetonide (Triesence [™]) ¹⁷	Alcon	<ul style="list-style-type: none"> • Treatment of sympathetic ophthalmia, temporal arteritis, uveitis, and ocular inflammatory conditions unresponsive to topical corticosteroids • Visualization during vitrectomy
NSAIDs		
bromfenac (Bromday [™] , Xibrom [™]) ^{18,19}	Ista	<ul style="list-style-type: none"> • Treatment of post-operative inflammation and reduction of ocular pain secondary to cataract extraction
diclofenac (Voltaren [®]) ²⁰	generic	<ul style="list-style-type: none"> • Treatment of post-operative inflammation secondary to cataract extraction • Temporary relief of pain and photophobia in patients undergoing corneal refractive surgery
flurbiprofen (Ocufen [®]) ²¹	generic	<ul style="list-style-type: none"> • Inhibition of intraoperative miosis
ketorolac (Acular LS [®]) ²²	generic	<ul style="list-style-type: none"> • Reduction of ocular pain, burning, and stinging after corneal refractive surgery
ketorolac (Acuvail [®]) ²³	Allergan	<ul style="list-style-type: none"> • Treatment of pain and inflammation following cataract surgery.
nepafenac (Nevanac [™]) ²⁴	Alcon	<ul style="list-style-type: none"> • Treatment of pain and inflammation associated with cataract surgery

Ketorolac (Acular[®]) is indicated for treatment of post-operative inflammation secondary to cataract extraction and temporary relief from ocular itching related to seasonal allergic conjunctivitis.²⁵ As of July 2009, Ketorolac PF (Acular PF[®]) is no longer available.

Overview

A wide variety of conditions, including trauma, surgery and infection, can cause ocular inflammation. Local application of anti-inflammatory medications can decrease inflammation with minimal systemic adverse effects. Ophthalmic anti-inflammatories are also used post-operatively to control inflammation related to cataract surgery. Persistent inflammation or cystoid macular edema following cataract surgery occurs occasionally despite the initial post-operative use of an ophthalmic anti-inflammatory.²⁶ Another post-operative complication of cataract surgery is the development of elevated intraocular pressure (IOP) that may be due to the use of topical anti-inflammatories.

Ophthalmic anti-inflammatories include corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs). The main use of ophthalmic NSAIDs is for ophthalmic surgery.²⁷ These agents reduce inflammation in the cornea and conjunctiva in refractive surgery and are effective at reducing pain both during and after the procedure. During cataract surgery, ophthalmic NSAIDs are utilized to control pain, but more importantly, ophthalmic NSAIDs help maintain papillary dilatation during cataract surgery. Ophthalmic NSAIDs also control inflammation during the first few days following the procedure.

Pharmacology

Topical corticosteroids exert an anti-inflammatory action. Aspects of the inflammatory process such as edema, fibrin deposition, capillary dilation, leukocyte migration, capillary proliferation, deposition of collagen, scar formation, and fibroblastic proliferation are suppressed. Topical corticosteroids are effective in acute inflammatory conditions of the conjunctiva, sclera, cornea, lids, iris, and anterior segment of the globe as well as in ocular allergic conditions. In ocular disease, route of administration depends on the site and extent of the condition being treated.

Ophthalmic NSAIDs have analgesic and anti-inflammatory activity. The mechanism of action is thought to be through the inhibition of cyclooxygenase enzymes, which are essential in prostaglandin production. Prostaglandins disrupt the blood-aqueous humor barrier, produce vasodilation, and increase vascular permeability, leukocytosis, and intraocular pressure (IOP).

Prostaglandins also appear to play a role in the miotic response produced during ocular surgery by constricting the iris sphincter independently of cholinergic mechanisms. These agents inhibit the miosis induced during the course of cataract surgery and have no significant effect on IOP.

Pharmacokinetics

Due to the topical nature of this drug class, systemic absorption for most products is below detectable levels. For those that do have appreciable levels, no clinical impact results from the systemic exposure. Ketorolac (Acular, Acular LS, Acuvail) does achieve measurable systemic levels, but there is no clinical impact.^{28,29,30} Nepafenac (Nevanac) is a prodrug that is metabolized via ocular tissue hydrolases to the active NSAID, amfenac.³¹ Low systemic levels of nepafenac and amfenac have been observed after topical administration to the eye. Nepafenac has been shown to penetrate the cornea more rapidly and provides more complete (80 percent versus 50 percent) and longer lasting inhibition of prostaglandin synthesis (greater than six hours versus three hours) and vascular permeability (eight hours versus four hours) than diclofenac (Voltaren).^{32,33} After topical instillation, systemic levels of bromfenac (Bromday, Xibrom) and diclofenac remain below the level of detection.^{34,35,36}

Contraindications/Warnings^{37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58}

The topical corticosteroids are contraindicated in patients with epithelial herpes simplex keratitis, vaccinia, varicella and most other viral infections of the cornea or conjunctiva, mycobacterial or fungal infections of the eye, and other infections. Prolonged use of ophthalmic corticosteroids may cause ocular hypertension and/or glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision, posterior subcapsular cataract formation, and secondary ocular infections. Perforations have occurred in patients with thinning of the cornea or sclera.

Bromfenac (Xibrom, Bromday) contains sodium sulfite and is contraindicated in patients with sulfite hypersensitivity.

As with all the NSAIDs, cross-hypersensitivity in patients with aspirin and other NSAID-hypersensitivities is possible; caution should be used in such patients.

Refractive stability undergoing corneal refractive procedures and diclofenac (Voltaren) usage has not been well established. Monitoring of visual acuity is recommended.

Ophthalmic Anti-Inflammatories

There may be ocular surgical complications when implanting fluocinolone (Retisert). Following implantation, patients will experience an immediate and temporary decrease in visual acuity lasting one to four weeks post-operatively.

Intravitreal injections, such as dexamethasone (Ozurdex), have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments.

Triamcinolone (Triesence) is contraindicated in patients with systemic fungal infections.

Precautions

NSAIDs may cause keratitis. In some patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration, or corneal perforation.⁵⁹ These events may be sight-threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs and should be closely monitored. Patients who might be at risk for complications include those with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time. Using ophthalmic NSAIDs beyond the 14 days may increase a patient's risk of severe corneal adverse events.

Ketorolac (Acular LS) and nepafenac (Nevanac) should not be administered while wearing contact lenses.

All topical NSAIDs may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.

Bromfenac (Bromday, Xibrom), Ketorolac (Acular, Acular LS, Acuvail) and nepafenac (Nevanac) should not be administered while wearing contact lenses.^{60,61,62,63,64} Except for the use of a bandage hydrogel soft contact lens during the first three days following refractive surgery, diclofenac 0.1% solution should not be used by patients currently wearing soft contact lenses.⁶⁵

Drug Interactions^{66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85}

Due to the topical nature of these anti-inflammatories, drug interaction studies have not been systematically performed. Nepafenac (Nevanac) has been investigated for potential impact on the cytochrome P450 system; no potential impact was identified.

Ketorolac ophthalmic products (Acular, Acular LS, Acuvail) have been safely given with ophthalmic antibiotics, beta blockers, carbonic anhydrase inhibitors, cycloplegics, and mydriatics.

Nepafenac ophthalmic suspension may be administered in conjunction with other topical ophthalmic medications such as beta-blockers, carbonic anhydrase inhibitors, alpha-agonists, cycloplegics, and mydriatics.

Adverse Effects

Drug	Transient burning/stinging	Ocular irritation	Corneal edema	Vision change
Corticosteroids				
dexamethasone (Maxidex) ⁸⁶	nr	nr	nr	reported
dexamethasone (Ozurdex) ⁸⁷	nr	7	nr	nr
dexamethasone sodium phosphate (Ak-Dex, Dexasol) ⁸⁸	reported	reported	nr	reported
difluprednate (Durezol) ⁸⁹	<1	<1	5-15	1-5
fluocinolone (Retisert) ⁹⁰	10-40	10-40	5-9	10-40
fluorometholone (FML) ⁹¹	reported	reported	nr	reported
fluorometholone (FML Forte) ⁹²	reported	reported	nr	reported
fluorometholone (FML S.O.P.) ⁹³	nr	reported	nr	nr
fluorometholone acetate (Flarex) ⁹⁴	nr	nr	nr	reported
loteprednol (Lotemax) ⁹⁵	5-15	<5	nr	5-15
prednisolone acetate (Econopred Plus, Omnipred, Pred Forte) ^{96,97,98}	nr	reported	nr	nr
prednisolone acetate (Pred Mild) ⁹⁹	nr	nr	nr	reported
prednisolone sodium phosphate (Prednisol) ¹⁰⁰	nr	nr	nr	reported
rimexolone (Vexol) ¹⁰¹	1-5	1-5	<1	1-5
triamcinolone acetonide (Triesence) ¹⁰²	nr	<2	nr	<2
NSAIDs				
bromfenac (Bromday, Xibrom) ^{103, 104}	2-7	2-7	nr	nr
diclofenac (Voltaren) ¹⁰⁵	15	<5	<5	<5
flurbiprofen (Ocufen) ¹⁰⁶	reported	reported	nr	nr
ketorolac (Acular LS) ¹⁰⁷	20-40	1-10	1-10	nr
ketorolac (Acuvail) ¹⁰⁸	nr	1-6	1-6	1-6
nepafenac (Nevanac) ¹⁰⁹	reported	1-5	1-5	5-10

Adverse effects are reported as a percentage. Adverse effects data are obtained from prescribing information and are not meant to be comparative or all inclusive. nr = not reported.

Ophthalmic Anti-Inflammatories

The following products contain the preservative benzalkonium chloride: bromfenac (Xibrom), dexamethasone (Maxidex), dexamethasone sodium phosphate (Ak-Dex, Dexasol), fluorometholone (FML, FML Forte), fluorometholone acetate (Flarex), loteprednol (Lotemax), ketorolac (Acular, Acular LS), nepafenac (Nevanac), prednisolone (Econopred Plus, Omnipred), prednisolone acetate (Pred Mild), prednisolone sodium phosphate (Prednisol), and rimexolone (Vexol).^{110,111,112,113} Flurbiprofen (Ocufen) contains thimerosal.¹¹⁴ Sorbic acid is the preservative in difluprednate (Durezol). Fluorometholone (FML S.O.P.) uses phenylmercuric acetate. Ketorolac (Acuvail) does not contain any preservative.

Results from clinical studies indicate that ophthalmic NSAIDs have no significant effect upon intraocular pressure; however, changes in intraocular pressure may occur following cataract surgery. In clinical studies with diclofenac (Voltaren), elevated intraocular pressure following cataract surgery was reported in approximately 15 percent of patients undergoing cataract surgery. Studies reported increased ocular pressure following cataract surgery in five to ten percent of patients treated with nepafenac 0.1% suspension (Nevanac).¹¹⁵

Special Populations

Pediatrics

Safety and effectiveness of fluocinolone (Retisert) have not been established in patients 12 years and younger. Fluorometholone (FML, FML Forte, FML S.O.P.) has been studied in children ages two years and older.¹¹⁶ The safety and efficacy of other products in this class have not been studied, but dexamethasone and prednisolone are reportedly safe in children, in general.¹¹⁷

Safety and effectiveness in pediatric patients have not been established in children for bromfenac (Bromday, Xibrom), diclofenac (Voltaren), flurbiprofen sodium (Ocufen), and ketorolac tromethamine 0.45% solution (Acuvail).^{118,119,120,121, 122} Nepafenac (Nevanac) has not been studied in children less than ten years of age.¹²³ Ketorolac products (Acular, Acular LS) have been approved for use in children age three years and older.^{124,125}

rimexolone (Vexol) versus fluorometholone

In 54 children who underwent surgery for bilateral symmetric strabismus, rimexolone and fluorometholone were compared for anti-inflammatory efficacy and ocular hypertension.¹²⁶ One eye was randomized to receive rimexolone 1% and the other eye received fluorometholone 0.1%; both medications were administered four times daily for four weeks. IOP increased significantly in both treatment groups, but the mean peak IOP was significantly higher with rimexolone than fluorometholone (19.7 mm Hg versus 17.6 mm Hg, respectively; $p < 0.001$). More in the rimexolone group had no conjunctival erythema on days 13 and 20 ($p = 0.03$). Authors concluded that IOP should be monitored in children receiving rimexolone therapy on a regular basis.

Pregnancy

With the exception of triamcinolone (Triesence), which is Pregnancy Category D, agents in this class are Pregnancy Category C. Due to the known effects of NSAIDs and the prostaglandin biosynthesis-inhibiting drugs on the fetal cardiovascular system, including the closure of ductus arteriosus, the use of many of these ophthalmic NSAIDs during late pregnancy should be avoided.

Dosages

Drug	Dosage	Availability
Corticosteroids		
dexamethasone 0.1% suspension (Maxidex) ¹²⁷	Apply one to two drops to the conjunctival sac of the affected eye(s) every four to six hours (may be used hourly in severe disease)	5, 15 mL
dexamethasone (Ozurdex) ¹²⁸	Implanted intravitreally by healthcare provider	0.7 mg implant
dexamethasone sodium phosphate 0.1% solution (Ak-Dex, Dexasol) ¹²⁹	Apply one to two drops to the conjunctival sac of the affected eye(s) every hour during the day and every two hours at night; reduce frequency to every four hours once a favorable response occurs	5 mL
difluprednate 0.05% emulsion (Durezol) ¹³⁰	Apply one to two drops to the conjunctival sac of the affected eye(s) four times daily for two weeks post-op, then twice daily for another week, then taper	5 mL
fluocinolone (Retisert) ¹³¹	Surgically implanted into posterior segment of the affected eye(s); designed to release drug over 30 months	0.59 mg implant
fluorometholone 0.1% suspension (FML) ¹³²	Apply one drop to the conjunctival sac of the affected eye(s) two to four times daily (may be used every four hours during initial 24-48 hours)	5, 10, 15 mL
fluorometholone 0.25% solution (FML Forte) ¹³³	Apply one drop to the conjunctival sac of the affected eye(s) two to four times daily	5, 10, 15 mL
fluorometholone 0.1% ointment (FML S.O.P.) ¹³⁴	Apply half-inch ribbon to the conjunctival sac of the affected eye(s) one to three times daily (may be used every four hours during initial 24-48 hours)	3.5 g tube
fluorometholone acetate 0.1% solution (Flarex) ¹³⁵	Apply one to two drops to the conjunctival sac of the affected eye(s) four times daily (may be used as two drops every two hours during initial 24-48 hours)	5 mL
loteprednol 0.5% solution (Lotemax) ¹³⁶	Anti-inflammatory: Apply one to two drops four times daily (up to every hour during the first week if necessary) Cataract surgery: Apply one to two drops four times a day starting 24 hours after surgery for two weeks	2.5, 5, 10, 15 mL
prednisolone acetate 1% solution (Econopred Plus, Omnipred, Pred Forte) ^{137, 138, 139}	Apply two drops to the conjunctival sac of the affected eye(s) four times daily	1, 5, 10, 15 mL
prednisolone acetate 0.12% solution (Pred Mild) ¹⁴⁰	Apply one to two drops to the conjunctival sac of the affected eye(s) every hour during the day and every two hours at night; reduce frequency once a favorable response occurs	5, 10 mL
prednisolone sodium phosphate 1% solution (Prednisol) ¹⁴¹	Apply one to two drops to the conjunctival sac of the affected eye(s) every hour during the day and every two hours at night; reduce frequency once a favorable response occurs	5, 10, 15 mL

Dosages (continued)

Drug	Dosage	Availability
rimexolone 1% solution (Vexol) ¹⁴²	Anti-inflammatory: One to two drops every hour (while awake) for one week, then every two hours for the second week, then taper off until resolved Cataract surgery: Two drops four times a day starting 24 hours after surgery for a duration of two weeks	5, 10 mL
triamcinolone acetonide (Triesence) ¹⁴³	Inflammation: 4 mg intravitreally Visualization: 1-4 mg intravitreally	40 mg/mL vial
NSAIDs		
bromfenac 0.09% solution (Xibrom) ¹⁴⁴	Cataract surgery: One drop twice daily starting 24 hours post-op for two weeks	2.5, 5 mL
bromfenac 0.09% solution (Bromday) ¹⁴⁵	Cataract surgery: One drop once daily to affected eye(s) starting one day prior to surgery, continued on the day of surgery and through the first 14 days post-op	1.7 mL
diclofenac 0.1% solution (Voltaren) ¹⁴⁶	Cataract surgery: One drop four times daily starting 24 hours post-op for two weeks Refractive surgery: One to two drops within one hour prior to surgery, then one to two drops 15 minutes post-op, then one to two drops four times a day for up to three days	2.5, 5 mL
flurbiprofen sodium 0.03% solution (Ocufen) ¹⁴⁷	Intraoperative use: Beginning two hours before surgery, instill one drop every 30 minutes for a total of four drops	2.5 mL
ketorolac tromethamine 0.4% solution (Acular LS) ¹⁴⁸	Refractive surgery: One drop four times a day for up to four days as needed for burning or stinging following refractive surgery	5 mL
ketorolac tromethamine 0.45% solution (Acuvail) ¹⁴⁹	Cataract surgery: One drop twice daily beginning one day prior to surgery and continuing through the first two weeks post-op	0.4 mL single use vials
nepafenac 0.1% suspension (Nevanac) ¹⁵⁰	Cataract surgery: One drop three times daily beginning one day prior to surgery; continue on the day of surgery, and through the first two weeks post-op	3 mL

Clinical Trials

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the ophthalmic use of all drugs in this class. Randomized controlled comparative trials for ophthalmic FDA-approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including

Ophthalmic Anti-Inflammatories

those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance. Several studies were performed in the perioperative setting which is not applicable to the outpatient utilization. These studies were excluded from this review.

bromfenac (Xibrom) versus placebo

Two Phase III, randomized, double-blind studies evaluated bromfenac 0.09% in the treatment of post-operative inflammation and reduction of ocular pain in patients undergoing cataract surgery.¹⁵¹ Bromfenac 0.09% (n=356) or vehicle (n=171) was instilled twice daily for 14 days followed by a 14-day evaluation period. The primary endpoint was cleared ocular inflammation as measured by the summed ocular inflammation score (SOIS), defined as less than five cells and absence of flare after 14 days of treatment. Bromfenac 0.09% was superior to vehicle in reducing ocular inflammation after cataract surgery at day 15 (64 percent versus 43.3 percent; $p<0.0001$). The effect of bromfenac on clearance of ocular inflammation was observed as early as day three after initiation of treatment (8.4 percent versus 1.2 percent for placebo, $p=0.0012$). Bromfenac 0.09% reduced median time to resolution of ocular pain to two days, compared with five days for vehicle ($p<0.0001$). Most commonly reported adverse effects included eye irritation, burning and stinging, and photophobia; all of these adverse effects were reported more frequently with placebo. No clinically significant systemic adverse events or changes in liver enzymes were reported with bromfenac.¹⁵²

bromfenac once daily dosing (Bromday) versus placebo

In two double-masked, placebo-controlled trials subjects requiring cataract surgery were randomized to bromfenac ophthalmic solution or placebo.¹⁵³ Patients were dosed with 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. An additional efficacy endpoint was the number of patients who were pain free on day-1 after cataract surgery. Bromfenac had statistically significant higher incidence of completely clearing inflammation (46-47 versus 25-29 percent) and also had a statistically significant higher incidence of subjects that were pain free at day-1 post cataract surgery (83-89 versus 51-71 percent).

diclofenac (Voltaren) versus flurbiprofen (Ocufen)

In a double-blind trial, 43 patients undergoing cataract extraction were randomized to diclofenac sodium 0.1% or flurbiprofen 0.03%.¹⁵⁴ The assigned medication was instilled every six hours for three doses prior to surgery, then four drops over 90 minutes just prior to surgery. After surgery, patients administered the assigned medication four times daily for three to six weeks. Patients were examined one, three, and six weeks post-operatively. There were no statistically significant differences between the treatment groups for conjunctival hyperemia, corneal surface changes, IOP, or anterior chamber inflammation.

diclofenac (Voltaren) versus ketorolac (Acular)

In a double-masked, randomized trial during the post-operative period of cataract extraction and implantation of an intraocular lens, a total of 120 patients were treated with either diclofenac 0.1% solution or ketorolac tromethamine 0.5% solution four times daily for 30 days.¹⁵⁵ Treatment began the first post-operative day after surgery. Objective measurements of

inflammation and toxicity were made at three post-operative visits. The anti-inflammatory effects were similar at all three post-operative visits. Both treatments were equally tolerated.

In a long-term follow-up to the above study, the primary endpoint was to evaluate the incidence of post-operative posterior opacification.¹⁵⁶ Patients were followed for three years and received yttrium-aluminum-garnet (YAG) laser capsulotomies and were evaluated for any existing post-operative posterior opacification. The incidence of post-operative posterior opacification and YAG capsulotomies were similar (12 percent in each treatment group). Adverse effects from therapy were also similar in both groups.

In a double-blind, randomized study, diclofenac 0.1% solution and ketorolac 0.5% solution were compared in 30 patients for efficacy in relieving corneal pain after refractive surgery.¹⁵⁷ Patients underwent radial keratotomy and were monitored for post-operative pain and instillation comfort. Both diclofenac and ketorolac were similarly effective in reducing ocular pain and had similar comfort on instillation ($p=0.29$).

diclofenac (Voltaren) versus nepafenac 0.1% (Nevanac) versus nepafenac 0.03%

In a randomized, double-blind, parallel-group trial, nepafenac 0.03% and 0.1% ophthalmic suspensions and diclofenac 0.1% were compared in 60 patients undergoing excimer photoreactive keratectomy (PRK).¹⁵⁸ On surgery day, two drops were given one hour prior to surgery, two drops within one hour after surgery, then one drop four and eight hours after the post-operative dose. The day after surgery, patients instilled one drop of the assigned medication four times daily, then therapy was discontinued. Patients recorded pain (0 to 9 on visual analog scale) and photophobia (0=none and 3=severe). On surgery day, there were no significant differences between groups except that, at three hours, the nepafenac 0.03% group had significantly higher pain scores than the nepafenac 0.1% group (mean score, 4.0 versus 3.0; $p<0.038$). On day two, the nepafenac 0.1% group had less pain at bedtime compared to the diclofenac group (1.9 versus 3.1; $p<0.024$). Less morning photophobia was recorded in the nepafenac 0.1% group compared to the diclofenac group (1.2 versus 1.8; $p<0.023$). No significant differences in the rate of corneal re-epithelialization existed among the three groups. Adverse events were infrequently reported. Nepafenac is not indicated for the treatment of pain and inflammation following PRK.

ketorolac 0.4% (Acular LS) versus nepafenac 0.1% (Nevanac)

Ketorolac 0.4% ophthalmic solution and nepafenac 0.1% ophthalmic suspension were compared in a randomized, double-blind study in 132 patients undergoing cataract extraction.¹⁵⁹ Patients were given ketorolac 0.4% or nepafenac 0.1% four times daily for two days before cataract extraction. The primary outcome measures in the study were the level of prostaglandin E(2) [PGE(2)] in the treated eyes and aqueous concentration of the active drug therapy in the treated eyes. Significantly more ketorolac eyes (61.9 percent) had PGE(2) levels below the level of detection than did the eyes receiving nepafenac (17.5 percent, $p<0.001$). Mean aqueous concentrations of active drug were significantly higher with ketorolac (1,079 ng/mL) than with nepafenac (353 ng/mL), the active form of nepafenac. The mean level of inactive nepafenac was 588 ng/mL ($p<0.001$ versus ketorolac).

Nepafenac 0.1% and ketorolac 0.4% were compared for effects on corneal re-epithelialization and pain after PRK in 40 adults.¹⁶⁰ In the double-blind, randomized trial, nepafenac 0.1% and ketorolac 0.4% were administered in the contralateral eyes as one drop three times daily for three days after bandage contact lens insertion. Patients were evaluated on days one, three,

Ophthalmic Anti-Inflammatories

four, five, and seven. Pain and comfort upon eyedrop instillation were assessed at each visit. The epithelial defect was assessed starting on day three and was found to be similar with both treatments at each post-operative visit ($p>0.05$). The average time of healing was 4.18 days with nepafenac and 4.0 days with ketorolac ($p=0.3134$). Mean post-operative pain scores were similar between the two drugs. Nepafenac patients had lower mean sensation scores for instillation pain ($p=0.009$), irritation ($p=0.0007$), and burning and stinging ($p=0.0003$) compared to ketorolac. Overall comfort score was also in favor of nepafenac (7.43 versus 6.41, $p<0.0001$). Nepafenac is not indicated for the treatment of pain and inflammation following PRK.

ketorolac 0.5% (Acular) versus ketorolac 0.4% (Acular LS)

The two formulations of ketorolac tromethamine 0.4% and 0.5% ophthalmic solutions were compared for effectiveness and patient tolerance in 40 patients undergoing phacoemulsification and lens implantation.¹⁶¹ In a double-masked study, patients were randomized to receive one of the two strengths of ketorolac starting 15 minutes prior to surgery. After surgery, patients administered one drop four times daily for one week, then twice daily for three weeks. Patients were examined on day one, seven, and 30. On day one, more patients reported foreign body sensation or stinging and burning in the ketorolac 0.5% group (70 percent) than the ketorolac 0.4% group (40 percent; $p<0.05$). 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.

ketorolac (Acular) versus loteprednol (Lotemax)

In a randomized, double-blind trial looking at controlling inflammation after cataract surgery, 60 patients were randomized to receive ketorolac tromethamine 0.5% or loteprednol etabonate 0.5% four times a day starting 24 hours after surgery.¹⁶² There was no statistically significant difference in any measurement of post-operative inflammation between the two groups measured by external slit-lamp examination on post-operative days one, four, seven, and 30.

ketorolac (Acular) versus prednisolone acetate

In a double-blind trial, 59 patients requiring cataract extraction were randomized to receive either ketorolac tromethamine 0.5% solution or prednisolone acetate 1%.¹⁶³ Treatment was administered according to the following schedule: one to two drops four times daily for one week; three times daily for the second week; two times daily for the third week; and once daily for the fourth week. At day 28, both treatments produced comparable reductions in intraocular inflammation and pain after cataract surgery and were well tolerated by patients. No adverse events were reported.

ketorolac (Acular) versus rimexolone (Vexol)

Ketorolac tromethamine 0.5% and rimexolone 1% were compared in two small studies evaluating the control of inflammation following cataract surgery in 36 patients.¹⁶⁴ Patients were randomized to either agent in a double-blind manner, and the assigned drops were administered four times daily starting 24 hours post-operatively. No difference was found between the two agents for the post-operative inflammation at any time period. No difference was noted in the IOP between the groups.

loteprednol (Lotemax) versus prednisolone acetate

In two studies of acute anterior uveitis, loteprednol 0.5% was compared to prednisolone acetate 1% for reduction in ocular signs and symptoms. Both studies were parallel, randomized, double-blind, active controlled comparisons.¹⁶⁵ In the first study, treatment was administered

eight times daily and lasted for 42 days in 70 patients. The second study was 28 days in duration with initial treatment given 16 times daily in 175 patients. At the end of the first trial, 74 percent of loteprednol patients and 88 percent of prednisolone patients achieved resolution. The difference was not significant. In the second study, the two groups were not different with resolution rates of 72 percent for loteprednol and 87 percent for prednisolone groups. Elevated IOP was observed more frequently in the prednisolone group. This difference in resolution rates between loteprednol and prednisolone acetate appears in the prescribing information for loteprednol. The use of a more potent corticosteroid than loteprednol such as prednisolone acetate 1% is suggested for the treatment of anterior uveitis.¹⁶⁶

rimexolone (Vexol) versus prednisolone acetate

Rimexolone 1% suspension and prednisolone acetate 1% were compared in 48 patients undergoing cataract extraction with phacoemulsification followed by posterior chamber intraocular lens implantation in a randomized, double-blind trial.¹⁶⁷ Both therapies were administered four times daily for 15 days. Patients were examined on day one, three, seven, and 15. Efficacy was similar in both groups as defined by anterior chamber cells, anterior chamber flare, and conjunctival hyperemia. IOP measurements were similar in both groups.

Two multicenter studies compared the efficacy and safety of rimexolone 1% suspension and prednisolone acetate 1% in patients with uveitis.¹⁶⁸ Administration of each drug was every two hours initially with a gradual taper over four weeks. No significant differences in response rates were found between the two groups at the various evaluation periods or at the end of treatment. Prednisolone patients were found to have a higher likelihood of elevation of IOP in both studies.

In a randomized, triple-blinded, parallel comparison was completed evaluating rimexolone 1% and prednisolone 1% in 78 patients with acute, chronic or recurrent anterior uveitis.¹⁶⁹ Patients instilled one or two drops of the assigned drug hourly while awake for the first week, then every two hours during the second week, then four times daily in the third week, then following a taper to complete four weeks of therapy. Anterior chamber cells and flare reactions were monitored periodically during the study. Overall clinical efficacy was similar between the two treatments. The IOP was also similar during the study, however three patients receiving rimexolone 1% and one patient receiving prednisolone 1% had elevated IOP during the study.

Summary

Ophthalmic corticosteroids have long been used as first-line therapy for the treatment of ophthalmic inflammatory conditions prior to the increased use of ophthalmic NSAIDs. The ophthalmic NSAIDs offer equivalent anti-inflammatory efficacy for post-operative inflammation. Ophthalmic corticosteroids have the potential for long-term adverse events such as increased IOP, but studies comparing ophthalmic corticosteroids to ophthalmic NSAIDs have not shown clinical differences in adverse event profiles when treatment duration is 30 days or less. There are no data to suggest a significant advantage for any one product in either subclass in terms of clinical effectiveness or adverse effect profile, nor are there data that show a difference between agents in different subclasses.

Products with invasive administration (Retisert, Triesence, Ozurdex) are typically administered when topical therapy fails.

References

- ¹ Maxidex [package insert] Fort Worth, TX; Alcon; August 2008.
- ² Ozurdex [package insert] Irvine, CA; Allergan; June 2009.
- ³ Available at: <http://www.clinicalpharmacology.com>. Accessed February 28, 2011.
- ⁴ Durezol [package insert] Tampa, FL; Sirion; June 2008.
- ⁵ Retisert [package insert] Rochester, NY; Bausch & Lomb; August 2008.
- ⁶ FML [package insert] Irvine, CA; Allergan; June 2003.
- ⁷ FML Forte [package insert] Irvine, CA; Allergan; June 2004.
- ⁸ FML S.O.P. [package insert] Irvine, CA; Allergan; July 1997.
- ⁹ Flarex [package insert] Fort Worth, TX; Alcon; April 2004.
- ¹⁰ Lotemax [package insert] Tampa, FL; Bausch & Lomb; April 2006.
- ¹¹ Econopred Plus [package insert] Fort Worth, TX; Alcon; August 2002.
- ¹² Omnipred [package insert] Fort Worth, TX; Alcon; June 2006.
- ¹³ Lotemax [package insert] Tampa, FL; Bausch & Lomb; April 2006.
- ¹⁴ Available at: <http://www.clinicalpharmacology.com>. Accessed February 28, 2011.
- ¹⁵ Available at: <http://www.clinicalpharmacology.com>. Accessed February 28, 2011.
- ¹⁶ Vexol [package insert] Fort Worth, TX; Alcon; 2007.
- ¹⁷ Triesence [package insert] Fort Worth, TX; Alcon; November 2007.
- ¹⁸ Xibrom [package insert]. Irvine, CA; Ista Pharmaceuticals; December 2008.
- ¹⁹ Bromday [package insert]. Irvine, CA; Ista Pharmaceuticals; September 2010.
- ²⁰ Voltaren [package insert]. Duluth, GA; Novartis; July 2009.
- ²¹ Ocufen [package insert]. Irvine, CA; Allergan; May 2004.
- ²² Acular LS [package insert]. Irvine, CA; Allergan; December 2008.
- ²³ Acuvail [package insert]. Irvine, CA; Allergan; October 2009.
- ²⁴ Nevanac [package insert]. Fort Worth, TX; Alcon; May 2008.
- ²⁵ Acular [package insert]. Irvine, CA; Allergan; January 2004.
- ²⁶ McColgin AZ, Heier JS. Control of intraocular inflammation associated with cataract surgery. *Curr Opin Ophthalmol.* 2000; 11:3-6.
- ²⁷ Lindstrom R. The pharmacologic and pathophysiologic rationale for using NSAIDs in ocular inflammatory disease and ocular surgery. *Int Ophthalmol Clin.* 2006; 46(4):7-11.
- ²⁸ Acular [package insert] Irvine, CA; Allergan; January 2004.
- ²⁹ Acular LS [package insert]. Irvine, CA; Allergan; May 2003.
- ³⁰ Acuvail [package insert]. Irvine, CA; Allergan; July 2009.
- ³¹ Nevanac [package insert]. Fort Worth, TX; Alcon; September 2007.
- ³² Kapin Yanni JM, Brady MT, et al. Inflammation-mediated retinal edema in the rabbit is inhibited by topical nepafenac. *Inflammation.* 2003; 27(5):281-291.
- ³³ Gamache DA, Graff G, Brady MT, et al. Nepafenac, a unique nonsteroidal prodrug with potential utility in the treatment of trauma-induced ocular inflammation. I. Assessment of anti-inflammatory efficacy. *Inflammation.* 2000; 24(4):357-370.
- ³⁴ Bromday [package insert]. Irvine, CA; Ista Pharmaceuticals; September 2010.
- ³⁵ Xibrom [package insert]. Irvine, CA; Ista Pharmaceuticals; July 2006.
- ³⁶ Voltaren [package insert]. Duluth, GA; Novartis; March 2008.
- ³⁷ Maxidex [package insert] Fort Worth, TX; Alcon; August 2008.
- ³⁸ Available at: <http://www.clinicalpharmacology.com>. Accessed February 28, 2011.
- ³⁹ Durezol [package insert] Tampa, FL; Sirion; June 2008.
- ⁴⁰ Retisert [package insert] Rochester, NY; Bausch & Lomb; August 2008.
- ⁴¹ FML [package insert] Irvine, CA; Allergan; June 2003.
- ⁴² FML Forte [package insert] Irvine, CA; Allergan; June 2004.
- ⁴³ FML S.O.P. [package insert] Irvine, CA; Allergan; July 1997.
- ⁴⁴ Flarex [package insert] Fort Worth, TX; Alcon; April 2004.
- ⁴⁵ Lotemax [package insert] Tampa, FL; Bausch & Lomb; April 2006.
- ⁴⁶ Econopred Plus [package insert] Fort Worth, TX; Alcon; August 2002.
- ⁴⁷ Omnipred [package insert] Fort Worth, TX; Alcon; June 2006.
- ⁴⁸ Lotemax [package insert] Tampa, FL; Bausch & Lomb; April 2006.
- ⁴⁹ Vexol [package insert] Fort Worth, TX; Alcon; 2007.
- ⁵⁰ Triesence [package insert] Fort Worth, TX; Alcon; November 2007.
- ⁵¹ Xibrom [package insert]. Irvine, CA; Ista Pharmaceuticals; December 2008.
- ⁵² Voltaren [package insert]. Duluth, GA; Novartis; July 2009.
- ⁵³ Ocufen [package insert]. Irvine, CA; Allergan; May 2004.
- ⁵⁴ Acular LS [package insert]. Irvine, CA; Allergan; December 2008.
- ⁵⁵ Nevanac [package insert]. Fort Worth, TX; Alcon; May 2008.
- ⁵⁶ Ozurdex [package insert] Irvine, CA; Allergan; June 2009.
- ⁵⁷ Acuvail [package insert]. Irvine, CA; Allergan; October 2009.
- ⁵⁸ Bromday [package insert]. Irvine, CA; Ista Pharmaceuticals; September 2010.
- ⁵⁹ Gaynes BI, Fiscella R. Topical nonsteroidal anti-inflammatory drugs for ophthalmic use: a safety review. *Drug Saf.* 2002; 25(4):233-250.
- ⁶⁰ Bromday [package insert]. Irvine, CA; Ista Pharmaceuticals; September 2010.
- ⁶¹ Xibrom [package insert]. Irvine, CA; Ista Pharmaceuticals; July 2006.

- ⁶² Acular LS [package insert]. Irvine, CA; Allergan; May 2003.
- ⁶³ Nevanac [package insert]. Fort Worth, TX; Alcon; September 2007.
- ⁶⁴ Acuvail [package insert]. Irvine, CA; Allergan; July 2009.
- ⁶⁵ Voltaren [package insert]. Duluth, GA; Novartis; March 2008.
- ⁶⁶ Maxidex [package insert] Fort Worth, TX; Alcon; August 2008.
- ⁶⁷ Available at: <http://www.clinicalpharmacology.com>. Accessed February 28, 2011.
- ⁶⁸ Durezol [package insert] Tampa, FL; Sirion; June 2008.
- ⁶⁹ Retisert [package insert] Rochester, NY; Bausch & Lomb; August 2008.
- ⁷⁰ FML [package insert] Irvine, CA; Allergan; June 2003.
- ⁷¹ FML Forte [package insert] Irvine, CA; Allergan; June 2004.
- ⁷² FML S.O.P. [package insert] Irvine, CA; Allergan; July 1997.
- ⁷³ Flarex [package insert] Fort Worth, TX; Alcon; April 2004.
- ⁷⁴ Lotemax [package insert] Tampa, FL; Bausch & Lomb; April 2006.
- ⁷⁵ Econopred Plus [package insert] Fort Worth, TX; Alcon; August 2002.
- ⁷⁶ Omnipred [package insert] Fort Worth, TX; Alcon; June 2006.
- ⁷⁷ Lotemax [package insert] Tampa, FL; Bausch & Lomb; April 2006.
- ⁷⁸ Vexol [package insert] Fort Worth, TX; Alcon; 2007.
- ⁷⁹ Triesence [package insert] Fort Worth, TX; Alcon; November 2007.
- ⁸⁰ Xibrom [package insert]. Irvine, CA; Ista Pharmaceuticals; December 2008.
- ⁸¹ Voltaren [package insert]. Duluth, GA; Novartis; July 2009.
- ⁸² Ocufen [package insert]. Irvine, CA; Allergan; May 2004.
- ⁸³ Acular LS [package insert]. Irvine, CA; Allergan; December 2008.
- ⁸⁴ Nevanac [package insert]. Fort Worth, TX; Alcon; May 2008.
- ⁸⁵ Acuvail [package insert]. Irvine, CA; Allergan; October 2009.
- ⁸⁶ Maxidex [package insert] Fort Worth, TX; Alcon; August 2008.
- ⁸⁷ Ozurdex [package insert] Irvine, CA; Allergan; June 2009.
- ⁸⁸ Available at: <http://www.clinicalpharmacology.com>. Accessed February 28, 2011.
- ⁸⁹ Durezol [package insert] Tampa, FL; Sirion; June 2008.
- ⁹⁰ Retisert [package insert] Rochester, NY; Bausch & Lomb; August 2008.
- ⁹¹ FML [package insert] Irvine, CA; Allergan; June 2003.
- ⁹² FML Forte [package insert] Irvine, CA; Allergan; June 2004.
- ⁹³ FML S.O.P. [package insert] Irvine, CA; Allergan; July 1997.
- ⁹⁴ Flarex [package insert] Fort Worth, TX; Alcon; April 2004.
- ⁹⁵ Lotemax [package insert] Tampa, FL; Bausch & Lomb; April 2006.
- ⁹⁶ Econopred Plus [package insert] Fort Worth, TX; Alcon; August 2002.
- ⁹⁷ Omnipred [package insert] Fort Worth, TX; Alcon; June 2006.
- ⁹⁸ Lotemax [package insert] Tampa, FL; Bausch & Lomb; April 2006.
- ⁹⁹ Available at: <http://www.clinicalpharmacology.com>. Accessed February 28, 2011.
- ¹⁰⁰ Available at: <http://www.clinicalpharmacology.com>. Accessed February 28, 2011.
- ¹⁰¹ Vexol [package insert] Fort Worth, TX; Alcon; 2007.
- ¹⁰² Triesence [package insert] Fort Worth, TX; Alcon; November 2007.
- ¹⁰³ Xibrom [package insert]. Irvine, CA; Ista Pharmaceuticals; December 2008.
- ¹⁰⁴ Bromday [package insert]. Irvine, CA; Ista Pharmaceuticals; September 2010.
- ¹⁰⁵ Voltaren [package insert]. Duluth, GA; Novartis; July 2009.
- ¹⁰⁶ Ocufen [package insert]. Irvine, CA; Allergan; May 2004.
- ¹⁰⁷ Acular LS [package insert]. Irvine, CA; Allergan; December 2008.
- ¹⁰⁸ Acuvail [package insert]. Irvine, CA; Allergan; October 2009.
- ¹⁰⁹ Nevanac [package insert]. Fort Worth, TX; Alcon; May 2008.
- ¹¹⁰ Acular LS [package insert]. Irvine, CA; Allergan; December 2008.
- ¹¹¹ Acular [package insert] Irvine, CA; Allergan; January 2004.
- ¹¹² Nevanac [package insert]. Fort Worth, TX; Alcon; May 2008.
- ¹¹³ Xibrom [package insert]. Irvine, CA; Ista Pharmaceuticals; December 2008.
- ¹¹⁴ Ocufen [package insert]. Irvine, CA; Allergan; May 2004.
- ¹¹⁵ Nevanac [package insert]. Fort Worth, TX; Alcon; September 2007.
- ¹¹⁶ Available at: <http://www.clinicalpharmacology.com>. Accessed February 28, 2011.
- ¹¹⁷ Available at: <http://www.clinicalpharmacology.com>. Accessed February 28, 2011.
- ¹¹⁸ Bromday [package insert]. Irvine, CA; Ista Pharmaceuticals; September 2010.
- ¹¹⁹ Xibrom [package insert]. Irvine, CA; Ista Pharmaceuticals; July 2006.
- ¹²⁰ Ocufen [package insert]. Irvine, CA; Allergan; February 2003.
- ¹²¹ Voltaren [package insert]. Duluth, GA; Novartis; March 2008.
- ¹²² Acuvail [package insert]. Irvine, CA; Allergan; July 2009.
- ¹²³ Nevanac [package insert]. Fort Worth, TX; Alcon; September 2007.
- ¹²⁴ Acular [package insert] Irvine, CA; Allergan; January 2004.
- ¹²⁵ Acular LS [package insert]. Irvine, CA; Allergan; December 2008.
- ¹²⁶ Fan DS, Yu CB, Chiu TY, et al. Ocular-hypertensive and anti-inflammatory response to rimexolone therapy in children. Arch Ophthalmol. 2003; 121(12):1716-1721.
- ¹²⁷ Maxidex [package insert] Fort Worth, TX; Alcon; August 2008.
- ¹²⁸ Ozurdex [package insert] Irvine, CA; Allergan; June 2009.
- ¹²⁹ Available at: <http://www.clinicalpharmacology.com>. Accessed February 28, 2011.

- ¹³⁰ Durezol [package insert] Tampa, FL; Sirion; June 2008.
- ¹³¹ Retisert [package insert] Rochester, NY; Bausch & Lomb; August 2008.
- ¹³² FML [package insert] Irvine, CA; Allergan; June 2003.
- ¹³³ FML Forte [package insert] Irvine, CA; Allergan; June 2004.
- ¹³⁴ FML S.O.P. [package insert] Irvine, CA; Allergan; July 1997.
- ¹³⁵ Flarex [package insert] Fort Worth, TX; Alcon; April 2004.
- ¹³⁶ Lotemax [package insert] Tampa, FL; Bausch & Lomb; April 2006.
- ¹³⁷ Econopred Plus [package insert] Fort Worth, TX; Alcon; August 2002.
- ¹³⁸ Omnipred [package insert] Fort Worth, TX; Alcon; June 2006.
- ¹³⁹ Lotemax [package insert] Tampa, FL; Bausch & Lomb; April 2006.
- ¹⁴⁰ Available at: <http://www.clinicalpharmacology.com>. Accessed February 28, 2011.
- ¹⁴¹ Available at: <http://www.clinicalpharmacology.com>. Accessed February 28, 2011.
- ¹⁴² Vexol [package insert] Fort Worth, TX; Alcon; 2007.
- ¹⁴³ Triescence [package insert] Fort Worth, TX; Alcon; November 2007.
- ¹⁴⁴ Xibrom [package insert]. Irvine, CA; Ista Pharmaceuticals; December 2008.
- ¹⁴⁵ Bromday [package insert]. Irvine, CA; Ista Pharmaceuticals; September 2010.
- ¹⁴⁶ Voltaren [package insert]. Duluth, GA; Novartis; July 2009.
- ¹⁴⁷ Ocufer [package insert]. Irvine, CA; Allergan; May 2004.
- ¹⁴⁸ Acular LS [package insert]. Irvine, CA; Allergan; December 2008.
- ¹⁴⁹ Acuvail [package insert]. Irvine, CA; Allergan; October 2009.
- ¹⁵⁰ Nevanac [package insert]. Fort Worth, TX; Alcon; May 2008.
- ¹⁵¹ Donnerfeld ED, Holland EJ, Stewart RH, et al for the Bromfenac Ophthalmic Solution 0.09% (Xibrom) Study Group. Bromfenac ophthalmic solution 0.09% (Xibrom) for postoperative ocular pain and inflammation. *Ophthalmology*. 2007; 114(9):1653-62.
- ¹⁵² Stewart RH, Grillone LR, Shiffman ML, et al for the Bromfenac Ophthalmic Solution 0.09% Study Group. The systemic safety of bromfenac ophthalmic solution 0.09%. *J Ocul Pharmacol Ther*. 2007; 23(6):601-12.
- ¹⁵³ Bromday [package insert]. Irvine, CA; Ista Pharmaceuticals; September 2010.
- ¹⁵⁴ Kocak I, Yalvac IS, Kocak A, et al. Comparison of the anti-inflammatory effects of diclofenac and flurbiprofen eye drops after cataract extraction. *Acta Ophthalmol Scand*. 1998; 76(3):343-345.
- ¹⁵⁵ Flach AJ, Dolan BJ, Donahue ME, et al. Comparative effects of ketorolac 0.5% or diclofenac 0.1% ophthalmic solutions on inflammation after cataract surgery. *Ophthalmology*. 1998; 105(9):1775-1779.
- ¹⁵⁶ Flach AJ, Dolan BJ. Incidence of postoperative posterior opacification following treatment with diclofenac 0.1 percent and ketorolac 0.5 percent ophthalmic solutions: 3-year randomized, double-masked, prospective clinical investigation. *Trans Am Ophthalmol Soc*. 2000; 98:101-105.
- ¹⁵⁷ Narvaez J, Krall P, Tooma TS. Prospective, randomized trial of diclofenac and ketorolac after refractive surgery. *J Refract Surg*. 2004; 20(1):76-78.
- ¹⁵⁸ Colin J, Paquette B. Comparison of the analgesic efficacy and safety of nepafenac ophthalmic suspension compared with diclofenac ophthalmic solution for ocular pain and photophobia after excimer laser surgery: a phase II, randomized, double-masked trial. *Clin Ther*. 2006; 28(4):527-536.
- ¹⁵⁹ Bucci FA Jr, Waterbury LD, Amico LM, et al. Prostaglandin E2 inhibition and aqueous concentration of ketorolac 0.4% (Acular LS) and nepafenac 0.1% (Nevanac) in patients undergoing phacoemulsification. *Am J Ophthalmol*. 2007; 144(1):146-147.
- ¹⁶⁰ Donnerfeld ED, Holland EJ, Durrie DS, et al. Double-masked study of the effects of nepafenac 0.1% and ketorolac 0.4% on corneal epithelial wound healing and pain after photorefractive keratectomy. *Adv Ther*. 2007; 24(4):852-862.
- ¹⁶¹ Sandoval HP, De Castro LE, Vroman DT, et al. 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):251-257.
- ¹⁶² Holzer MP, Solomon KD, Sandoval HP, et al. 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):93-99.
- ¹⁶³ 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.
- ¹⁶⁴ Solomon KD, Vroman DT, Barker D, et al. Comparison of ketorolac tromethamine 0.5 percent and rimexolone 1 percent to control inflammation after cataract extraction. Prospective randomized double-masked study. *J Cataract Refract Surg*. 2001; 27(8):1232-1237.
- ¹⁶⁵ Controlled evaluation of loteprednol etabonate and prednisolone acetate in the treatment of acute anterior uveitis. Loteprednol Etabonate US Uveitis Study Group. *Am J Ophthalmol*. 1999; 127(5):537-544.
- ¹⁶⁶ Lotemax [package insert]. Tampa, FL; Bausch and Lomb; May 2005.
- ¹⁶⁷ Yaylali V, Ozbay D, Tatlipinar S, et al. Efficacy and safety of rimexolone 1% versus prednisolone acetate 1% in the control of postoperative inflammation following phacoemulsification cataract surgery. *Int Ophthalmol*. 2004; 25(1):65-68.
- ¹⁶⁸ Foster CS, Alter G, De Barge LR, et al. Efficacy and safety of rimexolone 1% ophthalmic suspension vs. 1% prednisolone acetate in the treatment of uveitis. *Am J Ophthalmol*. 1996; 122(2):171-182.
- ¹⁶⁹ Biswas J, Ganeshbabu TM, Raghavendran SR, et al. Efficacy and safety of 1% rimexolone versus 1% prednisolone acetate in the treatment of anterior uveitis--a randomized triple masked study. *Int Ophthalmol*. 2004; 25(3):147-153.