



# Ophthalmic Anti-Inflammatories

## Therapeutic Class Review (TCR)

March 27, 2013

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## FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication(s)
<b>Corticosteroids</b>		
dexamethasone (Maxidex®) <sup>1</sup>	Alcon	<ul style="list-style-type: none"> <li>▪ Treatment of inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe</li> <li>▪ Corneal injury</li> </ul>
dexamethasone (Ozurdex™) <sup>2</sup>	Allergan	<ul style="list-style-type: none"> <li>▪ Treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO)</li> <li>▪ Treatment of non-infectious uveitis affecting the posterior segment of the eye</li> </ul>
dexamethasone sodium phosphate (Ak-Dex, Dexasol) <sup>3</sup>	generic	<ul style="list-style-type: none"> <li>▪ Treatment of inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe</li> <li>▪ Corneal injury</li> </ul>
difluprednate (Durezol™) <sup>4</sup>	Sirion	<ul style="list-style-type: none"> <li>▪ Treatment of inflammation and pain associated with ocular surgery</li> <li>▪ Treatment of endogenous anterior uveitis</li> </ul>
fluocinolone (Retisert™) <sup>5</sup>	Bausch & Lomb	<ul style="list-style-type: none"> <li>▪ Treatment of chronic non-infectious uveitis affecting the posterior segment of the eye</li> </ul>
fluorometholone (FML®) <sup>6</sup>	generic	<ul style="list-style-type: none"> <li>▪ Treatment of inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe</li> </ul>
fluorometholone (FML Forte®) <sup>7</sup>	Allergan	<ul style="list-style-type: none"> <li>▪ Treatment of corticosteroid-responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe</li> </ul>
fluorometholone (FML S.O.P.®) <sup>8</sup>	Allergan	<ul style="list-style-type: none"> <li>▪ Treatment of corticosteroid-responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe</li> </ul>
fluorometholone acetate (Flarex®) <sup>9</sup>	Alcon	<ul style="list-style-type: none"> <li>▪ Treatment of corticosteroid-responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe</li> </ul>
loteprednol solution (Lotemax™) <sup>10</sup>	Bausch & Lomb	<ul style="list-style-type: none"> <li>▪ Treatment of corticosteroid-responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe</li> <li>▪ Treatment of post-operative inflammation following ocular surgery</li> </ul>
loteprednol ointment, gel (Lotemax™) <sup>11,12</sup>	Bausch & Lomb	<ul style="list-style-type: none"> <li>▪ Treatment of post-operative inflammation and pain following ocular surgery</li> </ul>
prednisolone acetate (Econopred® Plus, Omnipred™, Pred Forte) <sup>13,14,15</sup>	generic	<ul style="list-style-type: none"> <li>▪ Treatment of corticosteroid-responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe</li> <li>▪ Treatment of corneal injury</li> </ul>
prednisolone acetate (Pred Mild) <sup>16</sup>	Allergan	<ul style="list-style-type: none"> <li>▪ Treatment of inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe</li> <li>▪ Corneal injury</li> </ul>
prednisolone sodium phosphate (Prednisol) <sup>17</sup>	generic	<ul style="list-style-type: none"> <li>▪ Treatment of inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe</li> <li>▪ Corneal injury</li> </ul>

**FDA-Approved Indications (continued)**

Drug	Manufacturer	Indication(s)
rimexolone (Vexol <sup>®</sup> ) <sup>18</sup>	Alcon	<ul style="list-style-type: none"> <li>▪ Treatment of anterior uveitis</li> <li>▪ Treatment of post-operative inflammation after ocular surgery</li> </ul>
triamcinolone acetonide (Triesence <sup>™</sup> ) <sup>19</sup>	Alcon	<ul style="list-style-type: none"> <li>▪ Treatment of sympathetic ophthalmia, temporal arteritis, uveitis, and ocular inflammatory conditions unresponsive to topical corticosteroids</li> <li>▪ Visualization during vitrectomy</li> </ul>
<b>NSAIDs</b>		
bromfenac (Bromday <sup>™</sup> , Prolensa <sup>™</sup> ) <sup>20,21</sup>	generic	<ul style="list-style-type: none"> <li>▪ Treatment of post-operative inflammation and reduction of ocular pain secondary to cataract extraction</li> </ul>
diclofenac (Voltaren <sup>®</sup> ) <sup>22</sup>	generic	<ul style="list-style-type: none"> <li>▪ Treatment of post-operative inflammation secondary to cataract extraction</li> <li>▪ Temporary relief of pain and photophobia in patients undergoing corneal refractive surgery</li> </ul>
flurbiprofen (Ocufer <sup>®</sup> ) <sup>23</sup>	generic	<ul style="list-style-type: none"> <li>▪ Inhibition of intraoperative miosis</li> </ul>
ketorolac (Acular LS <sup>®</sup> ) <sup>24</sup>	generic	<ul style="list-style-type: none"> <li>▪ Reduction of ocular pain, burning, and stinging after corneal refractive surgery</li> </ul>
ketorolac (Acuvail <sup>®</sup> ) <sup>25</sup>	Allergan	<ul style="list-style-type: none"> <li>▪ Treatment of pain and inflammation following cataract surgery.</li> </ul>
nepafenac (Ilevro <sup>™</sup> , Nevanac <sup>™</sup> ) <sup>26,27</sup>	Alcon	<ul style="list-style-type: none"> <li>▪ Treatment of pain and inflammation associated with cataract surgery</li> </ul>

Ketorolac (Acular<sup>®</sup>) is indicated for treatment of post-operative inflammation secondary to cataract extraction and temporary relief from ocular itching related to seasonal allergic conjunctivitis.<sup>28</sup> As of July 2009, Ketorolac PF (Acular PF<sup>®</sup>) is no longer available. Bromfenac (Xibrom<sup>™</sup>) was removed from the market in February 2011.

**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.<sup>29</sup> 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.<sup>30</sup> 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<sup>31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53</sup>

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<sup>54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76</sup>

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.<sup>77, 78, 79</sup> Nepafenac (Ilevro, Nevanac) is a prodrug that is metabolized via ocular tissue hydrolases to the active NSAID, amfenac.<sup>80</sup> 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).<sup>81, 82</sup> After topical instillation, systemic levels of bromfenac (Bromday, Prolensa) and diclofenac remain below the level of detection.<sup>83, 84</sup>

## CONTRAINDICATIONS/WARNINGS<sup>85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107</sup>

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.

Dexamethasone intravitreal implant (Ozurdex) is contraindicated in who have aphakic eyes an anterior chamber or intraocular lens (ACIOL), each with rupture of the posterior lens capsule.

Bromfenac (Bromday, Prolensa) contains sodium sulfite which may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes, particularly in those with asthma.

As with all the NSAIDs, cross-hypersensitivity in patients with aspirin and other NSAID-hypersensitivities is possible; caution should be used in such patients. There have been reports of bronchospasm or exacerbation of asthma associated with the use of ketorolac tromethamine ophthalmic solution in patients who either have a known hypersensitivity to aspirin/NSAID or a past medical history of asthma.

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

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 implants, such as dexamethasone (Ozurdex) and fluocinolone (Retisert) have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments. The dexamethasone implant may migrate to the anterior chamber if the posterior lens capsule is not intact; the fluocinolone implant has been associated with separation of implant components.

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.<sup>108</sup> 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.

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.

There have been reports that ocularly applied NSAIDs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery. Use with caution in patients at increased risk of bleeding.

Bromfenac (Bromday, Prolensa), Ketorolac (Acular, Acular LS, Acuvail) and nepafenac (Ilevro, Nevanac) should not be administered while wearing contact lenses.<sup>109, 110, 111, 112</sup> 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.<sup>113</sup>

Use of the same bottle of rimexolone (Vexol) for both eyes is not recommended with topical eye drops that are used in association with surgery.

Precautions for triamcinolone intravitreal suspension include elevated blood pressure, salt and water retention, hypokalemia, gastrointestinal perforation, behavioral and mood disturbances, decreased bone density, and weight gain.

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## **DRUG INTERACTIONS**<sup>114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133</sup>

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, alpha-agonists, beta blockers, carbonic anhydrase inhibitors, cycloplegics, and mydriatics. Drops should be administered at least five minutes apart.

Nepafenac ophthalmic suspension (Ilevro, Nevanac) may be administered in conjunction with other topical ophthalmic medications such as beta-blockers, carbonic anhydrase inhibitors, alpha-agonists, cycloplegics, and mydriatics. Medications should be administered at least five minutes apart.

## ADVERSE EFFECTS

Drug	Transient burning/stinging	Ocular irritation	Corneal edema	Vision change
<b>Corticosteroids</b>				
dexamethasone (Maxidex) <sup>134</sup>	nr	nr	nr	reported
dexamethasone (Ozurdex) <sup>135</sup>	nr	7	nr	nr
dexamethasone sodium phosphate (Ak-Dex, Dexasol) <sup>136</sup>	reported	reported	nr	reported
difluprednate (Durezol) <sup>137</sup>	nr	1-5	2-5	1-5
fluocinolone (Retisert) <sup>138</sup>	nr	10-40	50-90	10-40
fluorometholone (FML) <sup>139</sup>	reported	reported	nr	reported
fluorometholone (FML Forte) <sup>140</sup>	reported	reported	nr	reported
fluorometholone (FML S.O.P.) <sup>141</sup>	nr	reported	nr	nr
fluorometholone acetate (Flarex) <sup>142</sup>	nr	nr	nr	reported
loteprednol gel (Lotemax) <sup>143</sup>	nr	nr	nr	nr
loteprednol ointment (Lotemax) <sup>144</sup>	nr	nr	4-5	nr
loteprednol suspension (Lotemax) <sup>145</sup>	5-15	<5	<5	5-15
prednisolone acetate (Econopred Plus, Omnipred, Pred Forte) <sup>146, 147, 148</sup>	nr	reported	nr	nr
prednisolone acetate (Pred Mild) <sup>149</sup>	nr	nr	nr	reported
prednisolone sodium phosphate (Prednisol) <sup>150</sup>	nr	nr	nr	reported
rimexolone (Vexol) <sup>151</sup>	1-5	1-5	<1	1-5
triamcinolone acetonide (Triesence) <sup>152</sup>	nr	<2	nr	<2

**Adverse Effects (continued)**

Drug	Transient burning/stinging	Ocular irritation	Corneal edema	Vision change
<b>NSAIDs</b>				
bromfenac 0.07% (Prolensa) <sup>153</sup>	nr	nr	nr	3-8
bromfenac 0.09% (Bromday) <sup>154</sup>	2-7	2-7	nr	nr
diclofenac (Voltaren) <sup>155</sup>	15	<5	<5	<5
flurbiprofen (Ocufen) <sup>156</sup>	reported	reported	nr	nr
ketorolac (Acular LS) <sup>157</sup>	20-40	1-10	1-10	nr
ketorolac (Acuvail) <sup>158</sup>	nr	1-6	1-6	1-6
nepafenac (Ilevro, Nevanac) <sup>159, 160</sup>	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.

The most common ocular adverse event reported in clinical studies for loteprednol ointment was anterior chamber inflammation at a rate of approximately 25 percent. In studies with loteprednol gel, this was reported in five percent of subjects.<sup>161</sup>

The following products contain the preservative benzalkonium chloride: dexamethasone (Maxidex), dexamethasone sodium phosphate (Ak-Dex, Dexasol), fluorometholone (FML, FML Forte), fluorometholone acetate (Flarex), loteprednol (Lotemax suspension, gel), ketorolac (Acular, Acular LS), nepafenac (Ilevro, Nevanac), prednisolone (Econopred Plus, Omnipred), prednisolone acetate (Pred Mild), prednisolone sodium phosphate (Prednisol), and rimexolone (Vexol).<sup>162, 163, 164</sup> Flurbiprofen (Ocufen) contains thimerosal.<sup>165</sup> Sorbic acid is the preservative in difluprednate (Durezol). Fluorometholone (FML S.O.P.) uses phenylmercuric acetate. Ketorolac (Acuvail) does not contain any preservative.

The most commonly adverse reactions following use of bromfenac 0.07% (Prolensa), reported in three to eight percent of patients include anterior chamber inflammation, foreign body sensation, eye pain, and photophobia.<sup>166</sup>

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).<sup>167</sup>

## SPECIAL POPULATIONS

### Pediatrics

In a three-month, double-masked trial a similar safety profile was observed for difluprednate (Durezol) and prednisolone acetate ophthalmic suspension 1%, in 79 pediatric patients, zero to three years of age, in the treatment of inflammation following cataract surgery.<sup>168</sup>

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.<sup>169</sup> 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.<sup>170</sup>

Safety and effectiveness in pediatric patients have not been established in children for bromfenac (Bromday, Prolensa), diclofenac (Voltaren), flurbiprofen sodium (Ocufen), ketorolac tromethamine 0.45% solution (Acuvail), and loteprednol (Lotemax gel, ointment, suspension).<sup>171,172,173,174,175,176</sup> Nepafenac (Ilevro, Nevanac) has not been studied in children less than ten years of age.<sup>177</sup> Ketorolac products (Acular, Acular LS) have been approved for use in children age three years and older.<sup>178, 179</sup>

### 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.<sup>180</sup> 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<sup>181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203</sup>

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
<b>Corticosteroids</b>		
dexamethasone 0.1% suspension (Maxidex) <sup>204</sup>	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). <b>In severe disease, may administer drops hourly, tapering to discontinuation as the inflammation subsides.</b>	5, 15 mL
dexamethasone (Ozurdex) <sup>205</sup>	Implanted intravitreally by healthcare provider	0.7 mg implant
dexamethasone sodium phosphate 0.1% solution (Ak-Dex, Dexasol) <sup>206</sup>	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) <sup>207</sup>	<b>Inflammation and pain with ocular surgery:</b> 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 <b>Endogenous anterior uveitis:</b> Apply one drop to the conjunctival sac of the affected eye four times daily for 14 days followed by tapering as clinically indicated	5 mL
fluocinolone (Retisert) <sup>208</sup>	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) <sup>209</sup>	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) <sup>210</sup>	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.) <sup>211</sup>	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) <sup>212</sup>	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
<b>loteprednol 0.5% gel (Lotemax)<sup>213</sup></b>	<b>Apply one to two drops into the conjunctival sac of the affected eye(s) four times daily starting 24 hours after surgery for two weeks.</b>	<b>5 g</b>
loteprednol 0.5% ointment (Lotemax) <sup>214</sup>	Apply half-inch ribbon into the conjunctival sac of the affected eye(s) four times daily starting 24 hours after surgery for two weeks.	3.5 g tube
loteprednol 0.5% solution (Lotemax) <sup>215</sup>	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) <sup>216, 217, 218</sup>	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) <sup>219</sup>	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

**Dosages (continued)**

Drug	Dosage	Availability
prednisolone sodium phosphate 1% solution (Prednisol) <sup>220</sup>	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
rimexolone 1% solution (Vexol) <sup>221</sup>	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) <sup>222</sup>	Inflammation: 4 mg intravitreally Visualization: 1-4 mg intravitreally	40 mg/mL vial
NSAIDs		
bromfenac 0.07% solution (Prolensa) <sup>223</sup>	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	1.6 mL, 3 mL
bromfenac 0.09% solution	Cataract surgery: One drop to affected eye(s) twice daily starting 24 hours post-op for two weeks	2.5, 5 mL
bromfenac 0.09% solution (Bromday) <sup>224</sup>	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) <sup>225</sup>	Cataract surgery: One drop to affected eye(s) 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 (Ocufer) <sup>226</sup>	Intraoperative use: Beginning two hours before surgery, instill one drop to affected eye(s) every 30 minutes for a total of four drops	2.5 mL
ketorolac tromethamine 0.4% solution (Acular LS) <sup>227</sup>	Refractive surgery: One drop to affected eye(s) 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) <sup>228</sup>	Cataract surgery: One drop to affected eye(s) twice daily beginning one day prior to surgery and continuing through the first two weeks post-op	0.4 mL single use vials
nepafenac 0.3% suspension (Ilevro) <sup>229</sup>	Cataract surgery: One drop to affected eye(s) once daily beginning one day prior to surgery; continue on the day of surgery, and through the first two weeks post-op. Administer an additional drop 30 to 120 minutes prior to surgery	1.7 mL
nepafenac 0.1% suspension (Nevanac) <sup>230</sup>	Cataract surgery: One drop to affected eye(s) 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 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 0.07% once daily dosing (Prolensa) versus placebo**

In two double-masked, parallel-group trials patients were randomized to bromfenac 0.07% or vehicle for the treatment of postoperative inflammation and reduction of ocular pain.<sup>231</sup> Patients self-administered bromfenac or vehicle once daily, beginning 1 day prior to surgery, continuing on the morning of surgery and for 14 days after surgery. The primary efficacy endpoint was the proportion of subjects who had complete clearance of ocular inflammation by day 15, as measured by slit lamp biomicroscopy. Bromfenac 0.07% was superior in complete clearance of inflammation compared to vehicle. In addition, proportion of patients who self-reported as pain-free was significantly greater for bromfenac versus vehicle.

### **bromfenac 0.09% once daily dosing (Bromday) versus placebo**

In two double-masked, placebo-controlled trials subjects requiring cataract surgery were randomized to bromfenac 0.09% ophthalmic solution or placebo.<sup>232</sup> 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%.<sup>233</sup> 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.<sup>234</sup> 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.<sup>235</sup> 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.<sup>236</sup> 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).<sup>237</sup> 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.

### **difluprednate 0.05% (Durezol) versus prednisolone acetate 1%**

In a multicenter, randomized, contralateral-eye, double-masked trial, the effects of difluprednate 0.05% and prednisolone acetate 1% on corneal thickness and visual acuity after cataract surgery were compared on fifty-two patients (104 eyes) that underwent bilateral phacoemulsification.<sup>238</sup> For each patient, the first eye randomly received difluprednate 0.05% or prednisolone acetate 1%; the other eye received the alternative. Before surgery, seven doses were administered over two hours; three additional doses were given after surgery, before discharge. For the remainder of the day, corticosteroids were administered every two hours, then four times daily during week one and twice daily during week two. On day one corneal thickness was 33  $\mu\text{m}$  less in difluprednate-treated eyes ( $p=0.026$ ), uncorrected and best corrected visual acuity were significantly better with difluprednate than prednisolone by 0.093 logMAR lines ( $p=0.041$ ) and 0.134 logMAR lines ( $p<0.001$ ), respectively.

Endothelial cell density was 195.52 cells/mm<sup>2</sup> higher in difluprednate-treated eyes at day 30 ( $p<0.001$ ). Retinal thickness at day 15 was 7.74  $\mu\text{m}$  less in difluprednate-treated eyes ( $p=0.011$ ).

### **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.<sup>239</sup> 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.<sup>240</sup> 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, 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.<sup>241</sup> 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 suspension (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% suspension four times a day starting 24 hours after surgery.<sup>242</sup> 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%.<sup>243</sup> 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.<sup>244</sup> 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 suspension (Lotemax) versus prednisolone acetate**

In two studies of acute anterior uveitis, loteprednol 0.5% suspension was compared to prednisolone acetate 1% for reduction in ocular signs and symptoms. Both studies were parallel, randomized, double-blind, active controlled comparisons.<sup>245</sup> 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.<sup>246</sup>

### **nepafenac 0.3% (Ilevro) versus nepafenac 0.1% (Nevanac) versus placebo**

In two double-masked, randomized clinical trials, nepafenac ophthalmic suspension 0.3% and 0.1% was compared to vehicle dosed daily starting one day prior to cataract surgery, continued on the day of surgery, and for the first two weeks postoperatively.<sup>247</sup> Nepafenac suspension showed better clinical efficacy compared to its vehicle. In the first study, inflammation resolved at postoperative day 14 in 65 percent of nepafenac ophthalmic suspension 0.3% patients (n=851), in 32 percent of vehicle patients (n=211), and in 67 percent of nepafenac ophthalmic suspension 0.1% patients (n=845) (95% CI, 33% [26-40] for nepafenac ophthalmic suspension 0.3% and vehicle). Ocular pain at day 14 resolved in 86 percent of nepafenac 0.3% patients, 46 percent of placebo patients, and 87 percent of nepafenac 0.1% patients (95% CI 40% [32-47] for nepafenac ophthalmic suspension 0.3% and vehicle). In the second study, nepafenac 0.3% (n=540) resolved pain (postoperative day 14) versus vehicle (n=268) in 61 and 24 percent of patients, respectively. Ocular pain resolved in 84 and 38 percent, of nepafenac 0.3% and vehicle groups, respectively.

## 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.<sup>248</sup> 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.<sup>249</sup> 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.<sup>250</sup> 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 intraocular pressure (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.

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