

Indiana Medicaid Therapeutics Committee **Therapeutic Class Review Summary**

Therapeutic Class:

Ophthalmic NSAIDs

Overview:

The ophthalmic non-steroidal inflammatory drugs (NSAIDs) work by inhibiting cyclooxygenase (COX) and thus inhibiting prostaglandin synthesis. Endogenous prostaglandins can produce many pharmacological effects such as miosis, increased permeability of the blood-ocular barriers, conjunctival hyperemia and changes in intraocular pressure. Trauma from ocular surgical procedures like cataract and refractive surgery causes release of prostaglandins. Although advances in surgical procedures have resulted in decreased trauma to the eyes and lower amounts of prostaglandin release, postoperative inflammation continues to be a cause of patient discomfort, delayed recovery, and in some cases, less than expected visual results.

The first ophthalmic NSAID on the market was indomethacin; however, it is no longer available in the United States. Five ophthalmic NSAIDs are currently available with varying indications. Nepafenac and bromfenac, approved in 2005, are the most recently approved products in this therapeutic class. Flurbiprofen and ketorolac have been on the market since the 1990s while diclofenac has been on the market since the 1980's. Bromfenac is dosed twice daily and nepafenac is dosed three times a day; less frequent dosing is due to a theorized greater potency for inhibiting the COX-2 enzyme. Because most patients undergoing ocular surgery receive ophthalmic antibiotics dosed at four times daily, the convenience of these newer agents may be less important when compared to the other agents in this class dosed at four times per day.

The ophthalmic NSAIDs are effective for the prophylaxis and treatment of ocular conditions including: non-infectious inflammation, inhibition of intraoperative miosis, pain and healing following cataract and refractive surgery, and in the treatment of allergic conjunctivitis. Evidence also suggests the ophthalmic NSAIDs may be effective as primary or adjunctive therapy for the treatment of posterior segment disorders such as pseudophakic cystoid macular edema, an adverse event that occurs in 30% of post-cataract surgical cases. Four of the five ophthalmic NSAIDs are approved to reduce inflammation after cataract surgery, although it has become standard of care to use all of these preparations both pre- and post-operatively. Of note, flurbiprofen is the only agent indicated for inhibition of intraoperative



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miosis and ketorolac 0.5% solution is the only agent indicated for seasonal allergic conjunctivitis.

In general, the ophthalmic NSAIDs are well tolerated. Ketorolac 0.4% was brought to market due to its lower incidence of producing burning and stinging sensations upon instillation. Of note, diclofenac has a higher incidence of corneal adverse effects when compared to the other ophthalmic NSAIDs.

There are no large randomized, controlled trials comparing the efficacy of these agents. Studies comparing the ophthalmic NSAIDs have demonstrated differences in pain improvement and healing rates; however, these studies had small sample sizes and the data relied on patient reported scores. Other studies, also with small sample sizes, have shown comparable efficacy among these agents. A lack of well-designed studies comparing these agents makes assessing direct comparisons difficult.

Currently, diclofenac and flurbiprofen are the only ophthalmic NSAIDs available as generics.

GENERIC NAME	TRADE NAME	MANUFACTURER	GENERIC
Bromfenac	Xibrom [®]	Ista Pharmaceuticals	N
Diclofenac	Voltaren [®]	Novartis Pharmaceuticals, Akorn, Falcon Pharmaceuticals	Y
Flurbiprofen	Ocufen [®]	Allergan America, Bausch and Lomb Pharmaceuticals, Pacific Pharma LP	Y
Ketorolac tromethamine	Acular [®] Acular [®] PF Acular [®] LS Acuvail [™]	Allergan	Y (Acular, Acular LS)
Nepafenac	Nevanac [®]	Alcon	N

Summary:

The ophthalmic NSAIDs are effective for the prophylaxis and treatment of ocular conditions including: non-infectious inflammation, inhibition of intraoperative miosis, pain and healing following cataract and refractive surgery, and in the treatment of allergic conjunctivitis. Although each ophthalmic NSAID is chemically different, they all share the same mechanism of action, inhibiting the cyclooxygenase enzyme. Nepafenac and bromfenac offer improved dosing regimens over the other ophthalmic NSAIDs. Ketorolac 0.4% has been shown to have less burning and stinging sensations upon instillation when compared to ketorolac 0.5%. Diclofenac has a higher reported incidence of corneal adverse effects when compared to the other agents in this class. With the exception of flurbiprofen, only indicated for



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inhibition of intraoperative miosis, each ophthalmic NSAID has an indication for use following cataract surgery. Diclofenac and ketorolac also have indications for refractive ocular surgery. Within this therapeutic class, ketorolac 0.5% solution is the only agent approved for seasonal allergic conjunctivitis. Studies comparing the ophthalmic NSAIDs have demonstrated differences in pain improvement and healing rates; however, these studies had small sample sizes and the data relied on patient reported scores. Other studies, also with small sample sizes, have shown comparable efficacy among these agents. A lack of well-designed studies comparing these agents makes assessing direct comparisons difficult. The criteria for selection of an agent for the preferred drug list should include indications, dosing frequency, efficacy, safety and cost.