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

Therapeutic Class:

Ophthalmic Mast Cell Stabilizers and Eye Antihistamines

Overview:

Common allergic ophthalmologic conditions include seasonal allergic conjunctivitis (SAC), vernal keratoconjunctivitis (VKC), vernal keratitis, and vernal conjunctivitis. Many of these diseases are present for 6 weeks or longer. The ophthalmic preparations used in the treatment of ocular allergic diseases are mast cell stabilizers, antihistamines, or products with both mast cell stabilizing and antihistaminic properties.

Cromolyn (Crolom[®]), lodoxamide (Alomide[®]), nedocromil (Alocril[®]), and pemirolast (Alamast[™]) are all mast cell stabilizers. Mast cell stabilizers primarily work at the surface of the mast cell to inhibit its degranulation. This, in turn, prevents the release of histamine and slow-reacting substance of anaphylaxis (SRS-A), which are mediators of type I allergic reactions. These agents also decrease activation of eosinophils. Cromolyn and lodoxamide are indicated for the treatment of vernal keratoconjunctivitis, vernal conjunctivitis, and vernal keratitis. Nedocromil is indicated for the treatment of itching associated with allergic conjunctivitis and pemirolast is indicated for the prevention of itching associated with allergic conjunctivitis. Nedocromil is administered twice daily, while the cromolyn, lodoxamide, and pemirolast are administered four times daily. Emedastine (Emadine[®]) is an ocular antihistamine and is an antagonist at histamine H₁-receptors.

Emedastine and levocabastine are indicated for the relief of signs and symptoms associated with allergic conjunctivitis. Azelastine (Optivar[®]), bepotastine (Bepreve[™]), epinastine (Elestat[™]), ketotifen (Zaditor[®], Alaway[™]), and olopatadine (Patanol[®], Pataday[™]) are both mast cell stabilizers and antihistamines. Azelastine and bepotastine are indicated for the treatment of allergic conjunctivitis, ketotifen and olopatadine are indicated for the temporary prevention of itching of the eye due to allergic conjunctivitis, and epinastine is indicated for the prevention of itching associated with allergic conjunctivitis. Of note, ketotifen is available over the counter.

In clinical studies comparing the efficacy of ophthalmic mast cell stabilizers and eye antihistamines, lodoxamide was statistically superior to cromolyn 4% and nedocromil was statistically superior to cromolyn 2% in the treatment of VKC. Only cromolyn 4% is available in the United States. In the treatment of SAC, olopatadine was statistically superior to cromolyn 2%, emedastine was statistically superior to levocabastine, pemirolast was equivalent to nedocromil²⁶, and azelastine was equivalent to levocabastine. The clinical significance of these differences is unknown. Adverse events consisted of mild ocular irritations and were similar among the agents. Epinastine was approved by the Food and Drug Administration in October of 2003 and has not been



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studied in head to head trials with other agents. Among the mast cell stabilizers, patients using pemirolast experienced significantly less ocular discomfort compared to patients using nedocromil or cromolyn.

The majority of the studies comparing these agents used the conjunctival allergen challenge model. In these studies, olopatadine has demonstrated statistical superiority to azelastine, nedocromil, and ketotifen. Emedastine demonstrated equivalence to ketotifen; nedocromil demonstrated equivalence to levocabastine, which is no longer available. Ketotifen was statistically superior to nedocromil. Clinical significance, other than comparing an active treatment to placebo, was demonstrated only when olopatadine was compared to nedocromil.

Subclass	Generic Name	Brand Name	Manufacturer	Generic Availability
Mast Cell Stabilizers	Cromolyn	Crolom [®]	Dura, Various	Y
	Lodoxamide	Alomide [®]	Alcon	N
	Nedocromil	Alocril [®]	Allergan	N
	Pemirolast	Alamast [™]	Santen	N
Antihistamines	Emedastine	Emadine [®]	Alcon	N
Mast Cell Stabilizers and Antihistamines	Azelastine	Optivar [®]	MedPointe Healthcare	N
	Bepotastine	Bepreve [™]	ISTA / Bausch and Lomb	N
	Epinastine	Elestat [™]	Allergan	N
	Ketotifen	Zaditor [®] , Alaway [™]	CIBA Vision, Bausch and Lomb, various	Y
	Olopatadine	Patanol [®] , Pataday [™]	Alcon	N

Summary:

Olopatadine appears to have superior efficacy to other agents in this class. Lodoxamide and cromolyn are unique in their indications. Cromolyn and ketotifen are available generically. Selection of an agent for the preferred drug list should be based upon drug utilization and total cost impact to the program.