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

Therapeutic Class:

Miotics/Other Intraocular Pressure Reducers

Overview:

Glaucoma is an optic neuropathy that will eventually lead to visual field loss and blindness. The most common type of glaucoma is primary open-angle glaucoma. Based on data extrapolated from the Baltimore Eye Survey, about 2.5 million Americans have primary open-angle glaucoma. In the United States, more than 7 million office visits occur per year for the primary purpose of monitoring patients with glaucoma and patients at risk for developing glaucoma.²⁵ The major risk factor for glaucoma is elevated intraocular pressure (IOP). The reduction of intraocular pressure can be achieved by decreasing the amount of aqueous humor produced by the ciliary body or by increasing its outflow. There are five classes of drugs used for the long-term management of glaucoma: beta-blockers, prostaglandin analogues, sympathomimetics, carbonic anhydrase inhibitors, and direct/indirect cholinergic agonists.

Topical beta-blockers are usually given to patients as first line therapy. Because the formation of aqueous humor in the ciliary body is mediated by sympathetic stimulation, beta-blockers inhibit this stimulation and produce substantial reduction of aqueous humor. The first ophthalmic beta-blocker, timolol, came to the market in 1978. There are five commercially available beta-blockers. Even with topical application, beta-blockers may still have systemic side effects on cardiovascular and pulmonary systems. Betaxolol is the only beta-1 selective beta-blocker, and it has a lower tendency than non-beta-1 selective beta-blockers to cause bronchospasm in patients with pulmonary problems. However, betaxolol is less effective in lowering IOP when compared with other nonselective beta-blockers for the first month of treatment. Few ocular side effects are seen with topical beta-blockers. All ophthalmic beta-blockers require twice daily applications except timolol gel-solution (Timoptic XE[®]), which can be used once a day.

Prostaglandin F_{2α}, at a low concentration, reduces IOP by increasing the outflow of aqueous humor without causing ocular inflammation. The systemic side effects are uncommon because the amount of prostaglandin analogue that reaches the circulation is very small compared with endogenous prostaglandin. The most common ocular side effects are conjunctival hyperemia, eyelash changes, and irreversible discoloration of the iris. The first prostaglandin analogue, latanoprost, was introduced in 1996. Since then, three additional prostaglandin analogues have come to the market: travoprost, bimatoprost, and unoprostone. Prostaglandin analogues were traditionally used as a second-line or adjunct therapy. However, latanoprost and bimatoprost have received FDA approval for first line therapy. Based on the results of clinical trials, all the prostaglandin analogues are at least as effective, if not more effective, in lowering IOP than timolol.^{21,24} In some studies, bimatoprost and travoprost have been shown to be

more effective than latanoprost in lowering IOP^{24,27}; however, other studies have demonstrated equivalent efficacy among the prostaglandin analogs.¹⁹ Latanoprost appears to be less frequently associated with conjunctival hyperemia than the other agents, but more commonly associated with increased iris pigmentation.^{1,9,13,16,19,24,27}

Sympathomimetic agents decrease the production of aqueous humor and increase aqueous humor outflow. Epinephrine was the first agent introduced in this class, but it has many systemic and ocular side effects. Dipivefrin is an epinephrine prodrug, which is inactive until it reaches the corneal enzyme. Therefore, the systemic side effects of dipivefrin are very limited. Apraclonidine and brimonidine were derived from clonidine. Brimonidine has less ocular side effects than apraclonidine. However, brimonidine crosses the blood-brain barrier and can cause mild systemic hypotension and lethargy.

Carbonic anhydrase inhibitors decrease bicarbonate production. Therefore, they decrease the flow of bicarbonate, sodium, and water into the posterior chamber. There are two brand name topical carbonic anhydrase inhibitors, dorzolamide, and brinzolamide. They have fewer side effects compared with traditional oral carbonic anhydrase inhibitors. The efficacy of the carbonic anhydrase inhibitors in treating ocular hypertension is less than that of the prostaglandin analogues.²⁰

Cholinergic agonists are the oldest antiglaucoma agents. By stimulating parasympathetic receptors, these agents increase aqueous outflow of the eye. This class consists of two groups. Carbachol and pilocarpine are direct cholinergic agonists. Demecarium, echothiopate, and physostigmine are cholinesterase inhibitors, which are indirect cholinergic agonists. Because the cholinesterase inhibitors are more potent than the direct cholinergic agonists, most patients will gain additional IOP reduction when switching from direct agent to indirect agent.²⁶ Pilocarpine is the most commonly used direct cholinergic agonist and it is available generically. Among the cholinesterase inhibitors, echothiopate iodine is more commonly used.

The combined effect of timolol and dorzolamide administered together twice daily results in additional intraocular pressure reduction compared with either agent administered alone, but the reduction is not as great as when dorzolamide 3 times daily and timolol twice daily are administered concomitantly. The IOP-lowering of brimonidine tartrate and timolol maleate combined together and dosed twice a day was slightly less than that seen with the concomitant administration of 0.5% timolol maleate ophthalmic solution dosed twice a day and 0.2% brimonidine tartrate ophthalmic solution dosed three times per day.

Therapeutic Class	Generic Name	Brand Name	Manufacturer	Generic Availability
Beta Blockers	Betaxolol HCL	Betoptic®	Alcon, various	Y
		Betoptic-S®		N
	Levobunolol HCL	Betagan®	Allergan, various	Y
	Timolol Maleate	Timoptic® Timoptic XE® Betimol® Istalol™	Merck, various	Y
				Y
				N
Carteolol	Ocupress®	Novartis Ophthalmic, various	Y	
Metipranolol	OptiPranolol®	Bausch & Lomb, various	Y	
Prostaglandin Analogue	Latanoprost	Xalatan®	Pfizer	N
	Travoprost	Travatan®	Alcon	N
		Travatan Z™		N
Bimatoprost	Lumigan™	Allergan	N	
Sympathomimetics	Apraclonidine HCL	Iopidine®	Alcon	Y
	Brimonidine Tartrate	Alphagan®	Allergan	Y
		Alphagan P®		N
	Epinephrine	Epifrin®	Allergan, various	Y
Glaucan®		Y		
Dipivefrin	Propine®	Allergan, various	Y	
Carbonic Anhydrase Inhibitors	Dorzolamide HCL	Trusopt®	Merck, various	Y
	Brinzolamide	Azopt®	Alcon	N
Miotics, Cholinergic Agonists	Physostigmine Sulfate	Isopto-Eserine®	Novartis	Y



	Echothiophate Iodide	Phospholine Iodide®	Wyeth-Ayerst	N
	Carbachol	Miostat®	Alcon	N
	Pilocarpine HCL	Isopto-Carpine® Pilocar® Pilopine-HS®	Novartis, Alcon, Alza	Y Y N
Combination Therapy	Timolol Maleate/ Dorzolamide	Cosopt®	Merck, various	Y
	Brimonidine Tartrate/Timolol Maleate	Combigan™	Allergan	N

Summary:

Selection of agents for the preferred drug list for the treatment of glaucoma should take into consideration the morbidity associated with glaucoma and subsequent blindness if the disease is not treated properly. Many agents in the beta-blocker, miotic, and sympathomimetic classes are generically available. Current utilization, efficacy, safety, and cost should be considered when selecting agents for preferred drug list inclusion.