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

Therapeutic Class:

Agents to Treat Benign Prostatic Hyperplasia

Overview:

Benign prostatic hyperplasia (BPH) is present in more than 50% of men 60 years of age or older. Between 15% and 30% of these men have lower urinary tract symptoms. Pharmacological treatment, prostatectomy, and watchful waiting are the options for the lower urinary tract symptoms. Pharmacological options include alpha-1 adrenergic blockers and 5 α -reductase inhibitors. Alpha-1 adrenergic blockers improve urinary flow and have a rapid onset of action. 5 α -reductase inhibitors decrease prostate volume and prevent or delay the appearance of prostate cancer.

Alpha-1 adrenergic blockers competitively inhibit the sympathetic nervous system, which results in peripheral vasodilation and relaxation of the smooth muscles in the bladder neck and prostate. The first adrenergic blockers introduced to the US market were the nonselective agents indicated for the treatment of hypertension: prazosin (1976), terazosin (1987) and doxazosin (1990). Terazosin was the first alpha-blocker to obtain FDA approval for the treatment of BPH in 1993. It was followed by doxazosin in 1995. Extended release doxazosin was approved in 2005 and the newest alpha-1 receptor blocker, silodosin, was approved during October 2008. Tamsulosin was the first alpha-1a selective blocker marketed in the US with BPH as its sole indication. Alfuzosin, also selective for alpha-1a receptors, received final FDA approval for BPH in June 2003 and was launched in November 2003.

The nonselective alpha-blockers – prazosin in particular – are associated with a “first dose effect.” That is, marked hypotension, especially postural, and syncope with sudden loss of consciousness can occur with the first few doses. Initiating therapy with the lowest dose and administering the medication at bedtime may minimize this phenomenon. The selective alpha-blockers have a much lower affinity for the receptors in the vascular smooth muscle and do not appear to be associated with a first dose effect.

Finasteride and dutasteride, 5 α -reductase inhibitors, suppress the formation of dihydroxytestosterone (DHT) from testosterone. DHT is ten times more active than testosterone. Finasteride and dutasteride cause atrophy of the prostatic cells, which results in a reduction in volume. The onset of action of this class is slow (3-6 months) but long lasting. Finasteride is a selective type II 5 α -reductase inhibitor. The FDA approved finasteride (Proscar[®]) for the treatment of BPH in 1992. Finasteride in combination with doxazosin is indicated to reduce the risk of symptomatic progression of BPH (2004), while dutasteride in combination with tamsulosin is indicated to treat

symptomatic BPH in men with an enlarged prostate (2008). Another finasteride oral dosage form, Propecia®, was approved in 1997 for the treatment of male pattern baldness. The Prostate Cancer Prevention Trial showed that finasteride prevents or delays the appearance of prostate cancer. Dutasteride inhibits both type I and type II 5 α -reductase and was approved for the treatment of BPH in 2002.

	Generic Name	Brand Name	Manufacturer	Generic
<i>Alpha-1 Adrenergic Blockers</i>				
	Alfuzosin	UroXatral®	Sanofi-Synthelabo & SkyePharma PLC	N
	Doxazosin	Cardura®, Cardura® XL	Pfizer, various	Y N (XL)
	Prazosin	Minipress®	Pfizer, various	Y
	Silodosin	Rapaflo™	Watson Pharma, Inc.	N
	Tamsulosin	Flomax®	Boehringer Ingelheim	N
	Terazosin	Hytrin®	Abbott, various	Y
<i>5α-reductase inhibitors</i>				
	Dutasteride	Avodart®	GlaxoSmithKline	N
	Finasteride	Proscar®	Merck, various	Y

Summary:

The alpha antagonists appear to have equivalent efficacy in the treatment of symptomatic BPH. There have been some statistical differences in some studies, but no agent in the class has shown itself to be consistently superior to the other agents in terms of efficacy. The alpha-1a selective agents (tamsulosin, alfuzosin) do not appear to have the effect on blood pressure as do the older non-selective agents. These agents may offer an alternative for patients who are sensitive to blood pressure reduction and/or prone to postural hypotension, e.g., elderly patients and patients with impaired blood pressure regulation.

Finasteride and dutasteride are agents used to treat BPH by decreasing the formation of dihydroxytestosterone. Unlike alpha antagonists, the onset of action of finasteride or dutasteride is slow but the effect is long lasting. Finasteride is a selective type II 5 α -reductase inhibitor; whereas, dutasteride blocks both type I and type II 5 α -reductase. Additionally, finasteride in combination with doxazosin is indicated to reduce the risk of symptomatic progression of BPH, while dutasteride in combination with tamsulosin is indicated to treat symptomatic BPH in men with an enlarged prostate. Clinically,



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finasteride is indicated for BPH and alopecia; however, the Prostate Cancer Prevention Trial showed that finasteride also prevents or delays the appearance of prostate cancer.

Due to the different mechanism of actions, the preferred drug list should include at least one alpha-1a selective antagonist and one 5 α -reductase inhibitor.