

**Month/Year of Review:** May 2014  
**PDL Classes:** BPH

**Date of Last Review:** November 2012  
**Source Document:** OSU College of Pharmacy

**Current Status of PDL Class:**

- Preferred Agents: DOXAZOSIN MESYLATE, FINASTERIDE, TAMSULOSIN HCL, TERAZOSIN HCL
- Non-Preferred Agents: ALFUZOSIN HCL, SILODOSIN (RAPAFLO), DUTASTERIDE (AVODART), TADALAFIL (ADCIRCA), PRAZOSIN (MINIPRESS), DOXAZOSIN ER (CARDURA XL), DUTASTERIDE/TAMSULOSIN (JALYN)

**Previous Conclusions and Recommendation:**

- Evidence does not support a difference in efficacy/effectiveness
- Evidence does not support a difference in harms/adverse events
- Tadalafil demonstrated improvements in urinary symptoms compared to placebo in patients with lower urinary tract symptoms, but demonstrated no difference in post void residual volume or urinary flow rate.
- Tadalafil is also indicated for patients with concurrent BPH and erectile dysfunction. Erectile dysfunction is not a covered diagnosis under the Oregon Health Plan.
- There is insufficient evidence to demonstrate superiority of tadalafil over standard treatment.
- Recommend including at least one Alpha-Blocker and one Alpha Reductase Inhibitor as preferred on the PDL.
- Consider PA criteria to limit cosmetic use

**Prior Authorization Criteria:** PA criteria are in place to ensure medications are prescribed for OHP covered diagnosis. BPH with urinary obstruction treatment is covered by OHP only when post-void residuals are at least 150 ml (Appendix 1).

**Conclusions and Recommendations:**

- No further review or research needed at this time
- Evaluate comparative costs in executive session.

**Methods:**

A Medline OVID search was conducted with the following search terms: doxazosin mesylate, finasteride, tamsulosin HCl, terazosin HCl, alfuzosin HCl, silodosin, dutasteride, tadalafil, BPH, benign prostatic hypertension. The search was limited to English language articles of controlled trials conducted on humans published from 2010 to February week four 2014.

The Cochrane Collection, Dynamed and Medline OVID were searched for high quality systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts. Finally, a search for new or updated guidelines was conducted at the AHRQ National Guideline Clearinghouse (NGC).

**New Systematic Reviews:**

Filson et al conducted a meta-analysis and systematic review to compare the efficacy of treating benign prostatic hyperplasia with alpha blockers and anticholinergics with alpha blocker monotherapy. Seven studies were included with a total of 3629 participants. The primary endpoint was improvement in International Prostate Symptom Score (IPSS) and urinary frequency. Secondary outcomes included maximal flow rate and incidence of urinary retention. Alpha blockers studied were tamsulosin or doxazosin. Anticholinergics included tolterodine, oxybutynin, solifenacin, and fesoterodine. Combination alpha blocker and anticholinergic treatment significantly improved IPSS compared with alpha blocker therapy alone (mean difference -0.73, 95%CI -1.09 to -0.37). Combination therapy also had a significant

decrease in voiding frequency (mean difference -0.69 voids, 95%CI -0.97 to -0.41), a greater reduction in maximal flow rate (mean difference -0.59 mL/s, 95%CI -1.04 to -0.14) and an increase in post-void residual urinary volume (mean difference 11.60 mL, 95%CI 8.50 to 14.70). All studies included were randomized control trials and were analyzed for quality by the authors based on inclusion of allocation concealment, randomization, and blinding methodology. The authors also looked for any evidence of selective reporting, rates of completion of intervention, and what group was used for final analysis. None of the information regarding individual trial quality was published in the review; instead, the authors stated the studies included were deemed as high quality based on their criteria.<sup>1</sup>

Gacci et al performed a meta-analysis and systematic review to compare the effectiveness of combination phosphodiesterase-five inhibitors (PDE5-I) and alpha blockers with alpha blocker monotherapy for improvement in lower urinary tract symptoms in benign prostatic hyperplasia. Trials were included with active or placebo control. In total 12 trials were pooled: seven trials (n=3214) with placebo control and five (n=216) with an alpha blocker combination comparator. The primary endpoint was improvement in the International Index of Erectile Function (IIEF) score, the International Prostate Symptom Score (IPSS) and maximum flow rate. When compared with placebo, subjects on a phosphodiesterase inhibitor showed significant improvement in IIEF (mean difference 5.5, p<0.0001) and IPSS (mean difference -2.8, p<0.0001). There was no difference between placebo and PDE5-I groups in change in maximal flow rate. When combination alpha blocker and PDE5-I therapy was compared with alpha blocker monotherapy, the combination cohort had significantly improved IIEF score (mean difference 3.6, p<0.0001), IPSS (mean difference -1.8, p=0.05) and flow rate (mean difference Qmax1.5, p<0.0001). The strength of evidence from this meta-analysis could not be determined as individual trial quality was not assessed in the review.<sup>2</sup>

Ding et al conducted a systematic review to compare the efficacy of silodosin with placebo or tamsulosin for treatment of lower urinary tract symptoms in benign prostatic hyperplasia. Four trials (n=2504) were included; three of which included a tamsulosin cohort. All trials were of 12 week duration. The primary outcome was change from baseline in International Prostate symptom Score (IPSS), improvement in quality of life (QoL), and maximum urine flow. When compared with placebo, the silodosin group had a significantly improved IPSS (mean difference -2.78, p<0.00001), QoL score (mean difference -0.42, p=0.004) and maximum flow rate (mean difference Qmax 1.17 mL/s, p<0.00001). Silodosin was also had significant improvement in IPSS (mean difference -1.14, p=0.02) and QoL score (mean difference -0.26, p=0.02) when compared with tamsulosin. Silodosin was not superior to tamsulosin in improvement in urinary flow rate (mean difference -0.85 mL/s, p=0.01). Individual trial quality was measured by the transparency of the allocation concealment, randomization and blinding methodology; as well as the presence of incomplete outcome data, selective outcome reporting and any other sources of bias. By these standards, all four included trials were considered poor quality with unclear sequence generation, allocation concealment, selective outcome reporting and other sources of bias. All four also reported incomplete outcome data.<sup>3</sup>

Yuan et al performed a systematic review to evaluate the safety and efficacy of alpha blockers for benign prostatic hyperplasia (BPH). Fifteen systematic reviews studying five medications (alfuzosin, doxazosin, tamsulosin, terazosin, and naftopidil) were included in the analysis. Primary outcomes were improvement in urinary symptoms using the International Prostate Symptoms Score (IPSS) or Boyarsky scale and improvement in urinary flow rate. Alfuzosin did not show improvement over doxazosin (mean difference 1.7, 95%CI 0.76 to 1.64) or tamsulosin (mean difference 0.30, 95% CI 0.21 to 0.39) in improvement from baseline in urinary symptoms. Terazosin also did not show improvement in symptom score when compared with tamsulosin (0.72, 95% CI -1.51 to 2.94). There was no statistical difference between alfuzosin and terazosin in change of symptom score. Doxazosin significantly improved symptom score when compared with tamsulosin (mean difference -1.60, 95% CI -1.80 to -1.40) but there was no difference between doxazosin and terazosin. Doxazosin showed significant improvement in urinary flow rate compared with tamsulosin (mean difference 0.9 mL/s, p<0.05). All other alpha blocker comparisons demonstrated no statistical difference in change in flow rate. There were no significant differences in alpha blockers in total adverse events or rates of withdrawal with the exception of terazosin which had higher adverse event rates (18.00 RR, 95% CI 2.5 to 129.6) and total withdrawals (1.82 RR, 95% CI 1.00 to 3.32) than tamsulosin. Individual systematic reviews were analyzed for

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quality using the Assessment of Multiple Systematic Reviews (AMSTAR) and evidence for primary outcomes was evaluated using the GRADE system and presented as high, moderate, and low. All evidence presented between direct comparisons of alpha blockers was graded low or moderate.<sup>4</sup>

### Guidelines:

In 2013, the European Association of Urology published updated guidelines regarding the treatment and follow-up of non-neurogenic male lower urinary tract symptoms including benign prostatic obstruction. Recommendations were graded for the strength of the evidence source: an A grade was based on randomized clinical trials, a B on well-conducted but not randomized clinical trials, and a C grade was made despite the absence of directly applicable clinical studies. Recommendations were further classified by quality of evidence. Recommendations derived from evidence from a meta-analysis were given the ranking 1a. 1b recommendations were from evidence from at least one randomized control trial. 2a and 2b recommendations were based on evidence from well-designed nonrandomized clinical trials, or other quasi-experimental studies respectively. Level 3 recommendations were based on well-designed non-experimental studies, such as comparative or correlation studies and case reports and level 4 recommendations were based on expert opinion or clinical experience.<sup>5</sup>

- $\alpha$ 1-Blockers can be offered to men with moderate-to-severe LUTS. Recommendation 1a A
- 5 $\alpha$ -Reductase inhibitors can be offered to men who have moderate-to-severe LUTS and an enlarged prostate (>40 ml). 5 $\alpha$ -Reductase inhibitors can prevent disease progression with regard to acute urinary retention and need for surgery. Recommendation 1b A
- Muscarinic receptor antagonists may be used in men with moderate-to-severe LUTS who have predominantly bladder storage symptoms. Recommendation 1b B
- Phosphodiesterase type 5 inhibitors reduce moderate-to-severe (storage and voiding) LUTS in men with or without erectile dysfunction. Recommendation 1b A
- Combination treatment with an  $\alpha$ 1-blocker together with a 5 $\alpha$ -reductase inhibitor can be offered to men with bothersome moderate-to-severe LUTS, enlarged prostates, and reduced Qmax (men likely to develop disease progression). Recommendation 1b A
- Combination treatment with an  $\alpha$ 1-blocker together with a muscarinic receptor antagonist may be used in patients with bothersome moderate-to-severe LUTS if relief of storage symptoms has been insufficient with the monotherapy of either drug. Recommendation 1b B

The American Urological Association updated its guidelines in 2012 for the management of benign prostatic hyperplasia. Recommendations were based on outcomes data from current clinical literature and by opinion derived from clinical experience of an expert panel. All guideline statements were classified into one of three levels with respect to the degree of flexibility in their application. A "**standard**" had the least flexibility as a treatment policy. A guideline statement was a standard if: the health outcomes of the alternative interventions were sufficiently well known to permit meaningful decisions and there was virtual unanimity about which intervention was preferred. A "**recommendation**" had significantly more flexibility; and an "**option**" was even more flexible. A guideline statement was a recommendation if: the health outcomes of the alternative intervention were sufficiently well known to permit meaningful decisions, and an appreciable but not unanimous majority agrees on which intervention was preferred. A guideline statement was an option if: the health outcomes of the interventions were not sufficiently well known to permit meaningful decisions, or preferences were unknown or equivocal. Options may exist because of insufficient evidence or because patient preferences are divided and may/should influence choices made.<sup>6</sup>

- **Option:** Alfuzosin, doxazosin, tamsulosin, and terazosin are appropriate and effective treatment alternatives for patients with bothersome, moderate to severe LUTS secondary to BPH (AUA-SI score  $\geq 8$ ). Although there are slight differences in the adverse events profiles of these agents, all four appear to have equal clinical effectiveness. As stated in the 2003 Guideline, the effectiveness and efficacy of the four alpha blockers under

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consideration appear to be similar. Although studies directly comparing these agents are currently lacking, the available data support this contention.

- **Option:** The older, less costly, generic alpha blockers remain reasonable choices. These require dose titration and blood pressure monitoring. [Based on Panel consensus]
- **Recommendation:** As prazosin and the nonselective alpha-blocker phenoxybenzamine were not reviewed in the course of this Guideline revision, the 2003 Guideline statement indicating that the data were insufficient to support a recommendation for the use of these two agents as treatment alternatives for LUTS secondary to BPH has been maintained. [Based on Panel consensus]
- **Option:** The combination of an alpha-blocker and a 5-alpha reductase inhibitor (5-ARIs) (combination therapy) is an appropriate and effective treatment for patients with LUTS associated with demonstrable prostatic enlargement based on volume measurement, prostate-specific antigen (PSA) level as a proxy for volume, and/or enlargement on digital rectal exam (DRE). [Based on review of the data and Panel consensus]
- **Option:** Finasteride is an appropriate and effective treatment alternative in men with refractory hematuria presumably due to prostatic bleeding (i.e., after exclusion of any other causes of hematuria). A similar level of evidence concerning dutasteride was not reviewed; it is the expert opinion of the Panel that dutasteride likely functions in a similar fashion. [Based on review of the data and Panel consensus]
- **Option:** Anticholinergic agents are appropriate and effective treatment alternatives for the management of LUTS secondary to BPH in men without an elevated post-void residual and when LUTS are predominantly irritative. [Based on Panel consensus]
- **Recommendation:** Prior to initiation of anticholinergic therapy, baseline PVR urine should be assessed. Anticholinergics should be used with caution in patients with a post-void residual greater than 250 to 300 mL. [Based on Panel consensus]

**New drugs:**

None

**New Formulations/Indications:**

None

**New FDA safety alerts:**

None

**New Trials (Appendix 2):**

A total of 196 citations resulted from the initial Medline search. Articles were excluded due to the wrong study design (observational), comparator (placebo), or outcome (non-clinical). After a review of titles and abstracts for inclusion, five relevant head-to-head clinical trials were identified and are discussed below. Please see Appendix 1 for the full abstracts.

Haillet et al performed a post hoc analysis of the combination of Avodart and tamsulosin (CombAT) trial focusing solely on the European subgroup. Male subjects with a diagnosis of benign prostatic hypertrophy were randomized to daily tamsulosin 0.4 mg (n=972), dutasteride 0.5 mg (n=970), or both (n=983) and followed for four years. The primary endpoint was time to acute urinary retention (AUR) or BPH-related surgery. Secondary outcomes included BPH progression, symptoms, or maximum urinary flow rate. At the end of study, AUR or BPH-related surgery had occurred in 3.5% of combination, 11.9% of tamsulosin, and 5.5% of dutasteride subjects. Combination therapy significantly reduced the risk of AUR or BPH-related surgery compared with tamsulosin (RR 72%; 95% CI 58.9 to 80.9%) or dutasteride monotherapy (RR 39.6%; 95% CI 7.6 to 60.6%). When the two primary endpoints were examined separately combination therapy still significantly reduced the risk of AUR compared with tamsulosin (RR 70.3; p <0.001) but not dutasteride (RR 30.1%; p= 0.23). Combination therapy significantly reduced the risk of BPH-surgery compared with both tamsulosin (RR 76%; p<0.001) and dutasteride monotherapy (RR 47.5%; p= 0.018). Combination therapy was

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significantly more effective at decreasing BPH clinical progression than tamsulosin (RR 43%; 95% CI 27.7 to 55.1%) or dutasteride (RR 32.1%; 95% 13.2 to 46.9%). Subject symptoms were tracked and measured using the International Prostate Symptom Score (IPSS) tool. Again subjects on the combination therapy experienced a significantly greater decrease in BPH symptoms than either tamsulosin or dutasteride (both  $p < 0.01$ ). Combination therapy significantly increased the urinary flow rate (Qmax) from baseline when compared with tamsulosin (2.5 mL/s vs. 0.8 mL/s;  $p < 0.001$ ) but not with dutasteride (2.5 mL/s vs. 2.2 mL/s;  $p = 0.25$ ). Methodology from the CombAT trial was not reported; trial quality was not able to be assessed.<sup>7</sup>

Yu et al examined whether silodosin was inferior to tamsulosin in treatment of lower urinary tract symptoms related to benign prostatic hyperplasia (BPH). Subjects ( $n = 209$ ) were randomized to either silodosin 4 mg twice daily or tamsulosin 0.2 mg once daily for 3 months. The primary endpoint was the mean change from baseline in the International Prostate Symptom Score (IPSS) tool. For silodosin to be determined noninferior to tamsulosin, the noninferiority margin for change an IPSS was set at 1.0. Change in maximum urinary flow rate was a secondary endpoint. The difference between the silodosin and tamsulosin groups in change in IPSS score was not significant; 86.2% of silodosin and 81.9% of tamsulosin subjects had a  $>25\%$  decrease in IPSS score from baseline. The mean difference in IPSS change from baseline was  $-0.60$  (95% CI  $-2.15$  to  $0.95$ ) between silodosin and tamsulosin. As this was below the set 1.0, silodosin was found to be noninferior to tamsulosin. There was no difference in change in Qmax between tamsulosin and silodosin (mean change  $-0.74$ ; 95% CI  $-2.01$  to  $0.74$ ). This was a poor quality trial; blinding, randomization and allocation concealment methodology were not described. Tamsulosin dosing was below the standard dose of 0.4 mg while the silodosin dose was the FDA approved daily maintenance dose of 8 mg.<sup>8</sup>

Oelke et al compared the efficacy of tadalafil or tamsulosin with placebo to improve lower urinary tract symptoms in benign prostatic hyperplasia. Male subjects with BPH were randomized to placebo ( $n = 172$ ), tamsulosin 0.4 mg ( $n = 168$ ), or tadalafil 5 mg ( $n = 171$ ) once daily for 12 weeks. The primary outcome was improvement in International Prostate Symptom Score (IPSS) from baseline. Improvement in urinary flow rate as measured by Qmax was a secondary endpoint. Both treatments showed significant improvement in IPSS mean change from baseline compared with placebo (tadalafil  $-2.1$ ,  $p < 0.001$ ; tamsulosin  $-1.5$ ,  $p = 0.023$ ). Qmax was also significantly improved in both tamsulosin (2.2 mL/s,  $p = 0.014$ ) and tadalafil (2.4 mL/s,  $p = 0.009$ ) compared with placebo. No comparison was made between treatment groups. This was a fair quality trial but without direct comparison between treatments it does not add any new information.<sup>9</sup>

Chung et al conducted a post hoc analysis of the Combination of Avodart and tamsulosin (CombAT) trial to compare any differences in treatment in the subpopulation of Asian ( $n = 325$ ) men. CombAT subjects were randomized to either once daily tamsulosin 0.4 mg ( $n = 112$ ), dutasteride 0.5 mg ( $n = 106$ ), or both ( $n = 107$ ), and followed for four years. The primary endpoint was time to acute urinary retention (AUR) or BPH-related surgery. Secondary outcomes included BPH progression, symptoms, or maximum urinary flow rate. Although rates of AUR or BPH-related surgery varied greatly between tamsulosin (10.7%) and dutasteride (1.9%), the difference for each was nonsignificant when compared with combination therapy (6.5%, both  $p > 0.05$ ). Symptom progression was significantly improved with combination therapy (18.7%) compared with tamsulosin monotherapy (33%,  $p < 0.05$ ) but not with dutasteride (17.9%). Combination therapy subjects had a significantly greater improvement in IPSS from baseline when compared with tamsulosin ( $-6.4$  vs.  $-2.2$ ,  $p < 0.05$ ) subjects. There was no significant difference between combination and dutasteride ( $-6.4$  vs.  $-4.9$ ,  $p > 0.05$ ). Improvement in urinary flow rate was significantly improved with combination therapy (1.9 mL/s) compared with tamsulosin monotherapy (0.3 mL/s,  $p < 0.05$ ) but not with dutasteride (1.6 mL/s). Methodology from the CombAT trial was not reported; trial quality was not able to be assessed.<sup>10</sup>

Yokoyama et al compared the efficacy of tadalafil with tamsulosin and placebo in improving lower urinary tract symptoms in benign prostatic hyperplasia. Asian men were randomized to either placebo ( $n = 154$ ), tadalafil 2.5 mg ( $n = 151$ ), tadalafil 5 mg ( $n = 155$ ), or tamsulosin 0.2 mg ( $n = 152$ ) for 12 weeks. The primary outcome was improvement from baseline in the International Prostate Symptom Score (IPSS) for tadalafil compared with tamsulosin. Both doses of

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tadalafil had significant improvement in IPSS from baseline compared with placebo (for 2.5 mg: -4.8 vs. -3.0,  $p = 0.003$ ; for 5 mg -4.7 mg vs. -3.0,  $p = 0.004$ ). Tamsulosin had an improvement in baseline score of -5.5, but this was not statistically compared with placebo or either tadalafil dose. This was a poor quality trial; no description of blinding, randomization or allocation concealment was provided. Tamsulosin was included in the trial as an active comparator but was not compared with tadalafil or placebo. In addition, tamsulosin was suboptimally dosed.<sup>11</sup>

1. Filson CP, Hollingsworth JM, Clemens JQ, Wei JT. The Efficacy and Safety of Combined Therapy with  $\alpha$ -Blockers and Anticholinergics for Men with Benign Prostatic Hyperplasia: A Meta-Analysis. *The Journal of Urology*. 2013;190(6):2153-2160. doi:10.1016/j.juro.2013.05.058.
2. Gacci M, Corona G, Salvi M, et al. A Systematic Review and Meta-analysis on the Use of Phosphodiesterase 5 Inhibitors Alone or in Combination with  $\alpha$ -Blockers for Lower Urinary Tract Symptoms Due to Benign Prostatic Hyperplasia. *European Urology*. 2012;61(5):994-1003. doi:10.1016/j.eururo.2012.02.033.
3. Ding H, Du W, Hou Z-Z, Wang H-Z, Wang Z-P. Silodosin is effective for treatment of LUTS in men with BPH: a systematic review. *Asian Journal of Andrology*. 2013;15(1):121-128. doi:10.1038/aja.2012.102.
4. Yuan J, Liu Y, Yang Z, Qin X, Yang K, Mao C. The efficacy and safety of alpha-1 blockers for benign prostatic hyperplasia: an overview of 15 systematic reviews. *Current Medical Research and Opinion*. 2013;29(3):279-287. doi:10.1185/03007995.2013.766594.
5. Oelke M, Bachmann A, Descasez A, et al. EAU Guidelines on the Treatment and Follow-up of Non-neurogenic Male Lower Urinary Tract Symptoms Including Benign Prostatic Obstruction. *European Urology*. 2013;64(1):118-140. doi:10.1016/j.eururo.2013.03.004.
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7. Hailot O, Fraga A, Maciukiewicz P, et al. The effects of combination therapy with dutasteride plus tamsulosin on clinical outcomes in men with symptomatic BPH: 4-year post hoc analysis of European men in the CombAT study. *Prostate Cancer and Prostatic Diseases*. 2011;14(4):302-306. doi:10.1038/pcan.2011.13.
8. Yu H-J, Lin AT-L, Yang SS-D, et al. Non-inferiority of silodosin to tamsulosin in treating patients with lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH): EFFICACY AND SAFETY OF SILODOSIN VS TAMSULOSIN FOR BPH. *BJU International*. 2011;108(11):1843-1848. doi:10.1111/j.1464-410X.2011.10233.x.
9. Oelke M, Giuliano F, Mirone V, Xu L, Cox D, Viktrup L. Monotherapy with Tadalafil or Tamsulosin Similarly Improved Lower Urinary Tract Symptoms Suggestive of Benign Prostatic Hyperplasia in an International, Randomised, Parallel, Placebo-Controlled Clinical Trial. *European Urology*. 2012;61(5):917-925. doi:10.1016/j.eururo.2012.01.013.
10. Chung B-H, Lee SH, Roehrborn CG, et al. Comparison of the response to treatment between Asian and Caucasian men with benign prostatic hyperplasia: Long-term results from the combination of dutasteride and tamsulosin study: BPH treatment in Asian and Caucasian men. *International Journal of Urology*. 2012;19(11):1031-1035. doi:10.1111/j.1442-2042.2012.03091.x.
11. Yokoyama O, Yoshida M, Kim SC, et al. Tadalafil once daily for lower urinary tract symptoms suggestive of benign prostatic hyperplasia: A randomized placebo- and tamsulosin-controlled 12-week study in Asian men: Tadalafil for BPH-LUTS in Asian men. *International Journal of Urology*. 2013;20(2):193-201. doi:10.1111/j.1442-2042.2012.03130.x.

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**Appendix 1: Prior Authorization Criteria:**

**Benign Prostatic Hypertrophy (BPH) Medications**

**Goal(s):**

- BPH with urinary obstruction treatment is covered by OHP only when post-void residuals are at least 150ml.
- Cosmetic use for baldness is NOT covered.
- Erectile dysfunction is NOT covered.

\* Note: Finasteride is also available as Propecia®, which is FDA-approved for alopecia/male pattern baldness. Alopecia and male pattern baldness are not approvable diagnoses for 5-Alpha Reductase (5AR) Inhibitors.

**Length of Authorization: 1 year**

**Preferred Alternatives:** All preferred alternatives on PDL list:

<http://www.dhs.state.or.us/policy/healthplan/guides/pharmacy/pdl.pdf>

**Requires PA: Non-preferred drugs**

Approval Criteria		
1. What is the diagnosis?	Record ICD9 code.	
2. Is the request for a phosphodiesterase type 5 inhibitor (e.g. tadalafil or sildenafil)?	<b>Yes:</b> Go to #3	<b>No:</b> Go to #5
3. Is the diagnosis pulmonary arterial hypertension (PAH)?	<b>Yes:</b> Go to Pulmonary arterial hypertension PA criteria	<b>No:</b> Go to #4
4. Is the diagnosis erectile dysfunction?	<b>Yes:</b> Pass to RPh; Deny (not covered by OHP).	<b>No:</b> Go to #5
5. Will the prescriber consider a change to a preferred product?  Message: <ul style="list-style-type: none"> <li>• Preferred products do not require a PA.</li> <li>• Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Health Resource Commission (HRC). Reports are available at:  <a href="http://pharmacy.oregonstate.edu/drug_policy/index.php">http://pharmacy.oregonstate.edu/drug_policy/index.php</a> </li> </ul>	<b>Yes:</b> Inform Provider of covered alternatives in class. <a href="http://www.dhs.state.or.us/policy/healthplan/guides/pharmacy/pdl.pdf">http://www.dhs.state.or.us/policy/healthplan/guides/pharmacy/pdl.pdf</a>	<b>No:</b> Go to #6
6. Is the request for renewal of current therapy?	<b>Yes:</b> Go to "Renewal Therapy"	<b>No:</b> Go to #7
7. Is the request for an alpha blocker, and does client have a diagnosis related to functional and mechanical disorders of the genitourinary system including bladder outlet obstruction? (592.1, 595.1, 596.0, 596.3-596.5, 596.54, 596.7-596.9, 598, 599.82-	<b>Yes:</b> Go to #8	<b>No:</b> Go to #9

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599.89)		
<b>8.</b> Has the client tried and failed a 2-month trial of a covered alternative alpha blocker (terazosin, doxazosin, prazosin, tamsulosin)?	<b>Yes:</b> Approve an alpha blocker only for 1 year	<b>No:</b> Deny until client has tried and failed a covered alternative
<b>9.</b> Does client have a diagnosis of BPH (Benign Prostatic Hypertrophy) or enlarged prostate with obstruction? (600.01, 600.11, 600.21, and 600.91; 788.2 + 600.xx see RPH notes)	<b>Yes:</b> Approve for the shorter of 1 year or length of the prescription	<b>No:</b> Go to #10
<b>10.</b> Does client have a diagnosis of unspecified urinary obstruction or benign prostatic hyperplasia without obstruction? ( <b>599.6, 600.00, 600.10, 600.20, and 600.90</b> )	<b>Yes:</b> Pass to RPH; Deny, (Not Covered by the OHP)	<b>No:</b> Pass to RPH; Go to #11
<p><b>11. RPH Notes only</b> - All other indications need to be evaluated to see if they are above or below the line:</p> <p><b>Above the line</b> covered diagnoses related to prostate may be approved for 1 year</p> <p><b>Below the line</b> diagnoses (e.g. Hair growth, erectile dysfunction) should be denied (Not Covered by the OHP).</p> <p>Alpha Blockers and 5-alpha reductase inhibitors (ARI) may be used concurrently for BPH up to 1 year. Alpha-blockers may be discontinued once prostate is reduced to normal size.</p> <ul style="list-style-type: none"> <li>788.2 (retention of urine, obstructive); Ask for more specific diagnosis. If along with 600.01, 600.11, 600.21 or 600.91, then may approve.</li> </ul> <p>Refer questions of coverage to DMAP.</p>		

## Renewal Therapy

<b>1.</b> Is the request for an alpha blocker, and does client have a diagnosis related to functional and mechanical disorders of the genitourinary system including bladder outlet obstruction? (592.1, 595.1, 596.0, 596.3-596.5, 596.54, 596.7-596.9, 598, 599.82-599.89)	<b>Yes:</b> Go to #2	<b>No:</b> Go to #3
<b>2.</b> Has the patient also been taking a 5-alpha reductase inhibitor for the last year?	<b>Yes:</b> Recommend against combination therapy exceeding 1 year	<b>No:</b> Approve for the shorter of 1 year or length of the prescription
<b>3.</b> Does client have a diagnosis of BPH (Benign Prostatic Hypertrophy) or enlarged prostate with obstruction? (600.01, 600.11, 600.21, and 600.91; 788.2 + 600.xx see RPH notes)	<b>Yes:</b> Approve for 1 year	<b>No:</b> Go to #4
<b>4.</b> Does client have a diagnosis of unspecified urinary obstruction or	<b>Yes:</b> Pass to RPH;	<b>No:</b> Pass to RPH;

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benign prostatic hyperplasia without obstruction? <b>(599.6, 600.00, 600.10, 600.20, and 600.90)</b>	Deny, (Not Covered by the OHP)	Go to #5
<p><b>5. RPH only</b> All other indications need to be evaluated as to whether they are above the line or below the line diagnosis.</p> <ul style="list-style-type: none"> <li>Alpha Blockers and 5-alpha reductase inhibitors (ARI) may be used concurrently for BPH up to 1 year. Alpha-blockers may be discontinued once prostate is reduced to normal size.</li> <li>788.2 (retention of urine, obstructive); Ask for more specific diagnosis. If along with 600.01, 600.11, 600.21 or 600.91, then may approve.</li> </ul>	<p><b>If above the line or clinic provides supporting literature:</b> approve for one year.</p>	<p><b>If below the line:</b> Deny, (Not Covered by the OHP).</p>

DUR Board Action: 9/16/10 (KS), 3/18/10(KK), 5-22-08, 2-23-06  
Revision(s): 11/29/12 (MH), 1/1/11, 4/20/10, 5-22-08 (Aebi), 7-1-06, 9-30-05  
Effective: 10-14-04 (previously excluded)

DRAFT

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## Appendix 2: Abstracts of Randomized Controlled Trials:

**Hailott O, Fraga A, Maciukiewicz P, et al. The effects of combination therapy with dutasteride plus tamsulosin on clinical outcomes in men with symptomatic BPH: 4-year post hoc analysis of European men in the CombAT study. *Prostate Cancer and Prostatic Diseases*. 2011;14(4):302-306.** CombAT (Combination of Avodart and Tamsulosin) was a randomised, double-blind study in men (n=4844) aged > 50 years with a clinical diagnosis of BPH. Patients were randomised to daily tamsulosin 0.4 mg, dutasteride 0.5 mg or both for 4 years. The primary endpoint was time to acute urinary retention (AUR) or BPH-related surgery. Secondary endpoints included BPH clinical progression, symptoms and maximum urinary flow rate. A post hoc analysis of data from the European subgroup was conducted. A total of 2925 men were randomised to treatment in Europe as part of CombAT (tamsulosin, n=972; dutasteride, n=970; combination, n=983). Combination therapy significantly reduced the relative risk of AUR or BPH-related surgery compared with either monotherapy at 4 years, and also significantly reduced the risk of BPH clinical progression. Combination therapy also provided significantly greater symptom improvement than either monotherapy at 4 years. Safety and tolerability of dutasteride plus tamsulosin was consistent with previous experience of this combination and with the monotherapies. These data provide further evidence to support the use of long-term combination therapy (dutasteride plus tamsulosin) in men with moderate-to-severe lower urinary tract symptoms because of BPH and prostatic enlargement. The results in the European subgroup are generally consistent with those in the overall study population.

**Yu H-J, Lin AT-L, Yang SS-D, et al. Non-inferiority of silodosin to tamsulosin in treating patients with lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH): EFFICACY AND SAFETY OF SILODOSIN VS TAMSULOSIN FOR BPH. *BJU International*. 2011;108(11):1843-1848**

**OBJECTIVE** To test the hypothesis that the efficacy of silodosin would not be inferior to tamsulosin in treating patients with lower urinary tract symptoms associated with benign prostate hyperplasia (BPH).

**PATIENTS AND METHODS** At nine medical centres, 209 patients with an International Prostate Symptom Score (IPSS) of  $\geq 13$  were randomized to silodosin (4 mg twice daily) or tamsulosin (0.2 mg once daily) for 12 weeks. The primary efficacy measure was the mean change from baseline to endpoint in IPSS. The non-inferiority margin of the IPSS change was set at 1.0. Secondary efficacy measures included change in maximal urinary flow rate (Q max) and health-related quality of life (HRQL) score.

**RESULTS** Of the 170 (81.3%) patients who completed the study, 86.2% in the silodosin group vs 81.9% in the tamsulosin group achieved a  $\geq 25\%$  decrease in IPSS ( $=0.53$ ). The mean difference (silodosin minus tamsulosin) in IPSS change from baseline was  $-0.60$  (95% confidence interval  $-2.15, 0.95$ ), inferring the non-inferiority of silodosin to tamsulosin. The mean changes in the Q max and HRQL score from baseline were comparable between the groups (both,  $P > 0.05$ ). Although patients receiving silodosin had a significantly higher incidence of abnormal ejaculation (9.7% vs tamsulosin 1.0%,  $P=0.009$ ), only 1.9% discontinued treatment. Tamsulosin treatment resulted in a significant reduction in mean systolic blood pressure ( $-4.2$  mmHg, within-group  $P=0.004$ ) relative to the negligible change of silodosin ( $-0.1$  mmHg, within-group  $P=0.96$ )

**CONCLUSION** The trial shows the non-inferiority of silodosin 4 mg twice daily to tamsulosin 0.2 mg once daily in patients with symptoms of BPH.

**Oelke M, Giuliano F, Mirone V, Xu L, Cox D, Viktrup L. Monotherapy with Tadalafil or Tamsulosin Similarly Improved Lower Urinary Tract Symptoms Suggestive of Benign Prostatic Hyperplasia in an International, Randomised, Parallel, Placebo-Controlled Clinical Trial. *European Urology*. 2012;61(5):917-925.**

Background: Tadalafil improved lower urinary tract symptoms (LUTS) suggestive of benign prostatic hyperplasia (BPH; LUTS/BPH) in clinical studies but has not been evaluated together with an active control in an international clinical study.

Objective: Assess tadalafil or tamsulosin versus placebo for LUTS/BPH. Design, setting, and participants: A randomised, double-blind, international, placebo-controlled, parallel-group study assessed men  $\geq 45$  yr of age with LUTS/BPH, International Prostate Symptom Score (IPSS)  $\geq 13$ , and maximum urinary flow rate (Qmax)  $\leq 4$  to  $\leq 15$  ml/s. Following screening and washout, if needed, subjects completed a 4-wk placebo run-in before randomisation to placebo (n = 172), tadalafil 5 mg (n = 171), or tamsulosin 0.4 mg (n = 168) once daily for 12 wk.

Measurements: Outcomes were assessed using analysis of covariance (ANCOVA) or ranked analysis of variance (ANOVA) (continuous variables) and Cochran-Mantel-Haenszel test or Fisher exact test (categorical variables).

Results and limitations: IPSS significantly improved versus placebo through 12 wk with tadalafil ( $\geq 2.1$ ;  $p = 0.001$ ; primary efficacy outcome) and tamsulosin ( $\geq 1.5$ ;  $p = 0.023$ ) and as early as 1 wk (tadalafil and tamsulosin both  $\geq 1.5$ ;  $p < 0.01$ ). BPH Impact Index significantly improved versus placebo at first assessment (week 4) with tadalafil ( $\geq 0.8$ ;  $p < 0.001$ ) and tamsulosin ( $\geq 0.9$ ;  $p < 0.001$ ) and through 12 wk (tadalafil  $\geq 0.8$ ,  $p = 0.003$ ; tamsulosin  $\geq 0.6$ ,  $p = 0.026$ ). The IPSS Quality-of-Life Index and the Treatment Satisfaction Scale-BPH improved significantly versus placebo with tadalafil (both  $p < 0.05$ ) but not with tamsulosin (both  $p > 0.1$ ). The International Index of Erectile Function-Erectile Function domain improved versus placebo with tadalafil (4.0;  $p < 0.001$ ) but not tamsulosin ( $\geq 0.4$ ;  $p = 0.699$ ). Qmax increased significantly versus placebo with both tadalafil (2.4 ml/s;  $p = 0.009$ ) and tamsulosin (2.2 ml/s;  $p = 0.014$ ). Adverse event profiles were consistent with previous reports. This study was limited in not being powered to directly compare tadalafil versus tamsulosin.

Conclusions: Monotherapy with tadalafil or tamsulosin resulted in significant and numerically similar improvements versus placebo in LUTS/BPH and Qmax. However, only tadalafil improved erectile dysfunction.

**Chung B-H, Lee SH, Roehrborn CG, et al. Comparison of the response to treatment between Asian and Caucasian men with benign prostatic hyperplasia: Long-term results from the combination of dutasteride and tamsulosin study: BPH treatment in Asian and Caucasian men. *International Journal of Urology*. 2012;19(11):1031-1035.**

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The Combination of Avodart and Tamsulosin study was a 4-year, randomized, double-blind study of the efficacy and safety of dutasteride and tamsulosin, alone or in combination, in men with moderate-to-severe benign prostatic hyperplasia. In this post-hoc investigation, we analyzed primary and secondary end-points from the Combination of Avodart and Tamsulosin study in Asian ( $n = 325$ ) and Caucasian men ( $n = 4259$ ). The incidence of acute urinary retention or benign prostatic hyperplasia-related surgery did not differ significantly between treatment groups in the Asian subpopulation. In Caucasian men, the incidence of acute urinary retention/benign prostatic hyperplasia-related surgery was significantly lower in the combination therapy group compared with the tamsulosin monotherapy group ( $P < 0.001$ ), but not compared with dutasteride monotherapy. Combination therapy significantly increased the time to benign prostatic hyperplasia clinical progression and resulted in improved International Prostate Symptom Score, maximum urinary flow rate, quality of life, and reduced prostate volume in Asian and Caucasian men who received combination therapy compared with tamsulosin monotherapy. Combination therapy also significantly improved ( $P < 0.05$ ) time to benign prostatic hyperplasia clinical progression, International Prostate Symptom Score, maximum urinary flow rate and quality of life versus dutasteride in the Caucasian subpopulation. The adverse-event profile was comparable between subpopulations. In conclusion, Asian and Caucasian men respond similarly to these treatments, despite apparent racial differences in 5 $\alpha$ -reductase activity.

**Yokoyama O, Yoshida M, Kim SC, et al. Tadalafil once daily for lower urinary tract symptoms suggestive of benign prostatic hyperplasia: A randomized placebo- and tamsulosin-controlled 12-week study in Asian men: Tadalafil for BPH-LUTS in Asian men. *International Journal of Urology*. 2013;20(2):193-201.**

**Objectives:** To examine the efficacy and safety of tadalafil in Asian men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia.

**Methods:** Asian men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia were randomized to once-daily placebo ( $n = 154$ ), tadalafil 2.5 mg ( $n = 151$ ), tadalafil 5.0 mg ( $n = 155$ ) or tamsulosin 0.2 mg (active control,  $n = 152$ ) for 12 weeks.

**Results:** Total International Prostate Symptom Score least-squares mean changes from baseline to end-point significantly improved with tadalafil 2.5 mg ( $-4.8$ ,  $P = 0.003$ ) and 5 mg ( $-4.7$ ,  $P = 0.004$ ) versus placebo ( $-3.0$ ). Significant improvement in the International Prostate Symptom Score versus placebo was observed earlier (week 2) for tadalafil 5.0 mg than for tadalafil 2.5 mg (week 8). Significant improvements ( $P < 0.05$ ) in both tadalafil groups versus placebo were observed for the International Prostate Symptom Score voiding subscore, International Prostate Symptom Score Quality of Life, and for Patient and Clinician Global Impressions of Improvement. Significant improvements versus placebo were observed in the International Prostate Symptom Score storage subscore for tadalafil 5.0 mg ( $-1.7$ ,  $P = 0.021$ ), but not tadalafil 2.5 mg ( $-1.5$ ,  $P = 0.072$ ). No significant improvements in benign prostatic hyperplasia Impact Index or improvements in peak urinary flow rates were observed with tadalafil 2.5 mg or 5.0 mg versus placebo. Tamsulosin treatment resulted in significant improvements versus placebo across all efficacy parameters, except for peak urinary flow rates. Safety results were consistent with the known tadalafil and tamsulosin safety profiles.

**Conclusions:** Tadalafil once daily represents an effective and well tolerated medical treatment for Asian men presenting with lower urinary tract symptoms suggestive of benign prostatic hyperplasia.

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