



Class Update: Benign Prostatic Hyperplasia (BPH)

Month/Year of Review: November 2012

Date of Last Review: September 2010

PDL Classes: Benign Prostatic Hyperplasia

Source Document: Provider Synergies

Current Status of PDL Class:

- Preferred Agents:
 - Alpha-Blockers: DOXXAZOSIN, TAMSULOSIN HCL, TERAZOSIN HCL
 - 5-Alpha Reductase Inhibitors: FINASTERIDE
- Non Preferred Agents:
 - Alpha-Blockers: ALFUZOSIN (UROXATRAL®), SILODOSIN (RAPAFLO®), PRAZOSIN (MINIPRESS®), DOXAZOSIN ER (CARDURA XL®), PHENOXYBENZAMINE (DIBENZYLINE®), INDORAMIN (BARATOL®)
 - 5-Alpha Reductase Inhibitors: DUTASTERIDE (AVODART®)
 - Combination: DUTASTERIDE/TAMSULOSIN (JALYN ®)

Research Questions:

- Is there any new evidence of superiority in efficacy or safety of one agent for BPH over another?
- Is there any new relevant evidence to change current policy?

Conclusions:

- There is no new evidence suggesting superiority of one of the newer alpha-blockers or 5-alpha reductase inhibitors over another in efficacy or safety.
- 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 (ED). ED is not a covered diagnosis under the Oregon Health Plan.
- There is insufficient evidence to demonstrate superiority of tadalafil over standard treatment (alpha-blockers).

Recommendations:

- Maintain at least one alpha-blocker and one 5-alpha reductase inhibitor as preferred on the PDL.
- Recommend making tadalafil non-preferred for the treatment of BPH. Because medications to treat impotency or erectile dysfunction are not covered by the Oregon Health Plan, update PA criteria for indication of tadalafil for the simultaneous occurrence of BPH and erectile dysfunction.
- Continue to require prior authorization in accordance with the Oregon Health Plan list of prioritized health services and to limit cosmetic use.

Previous Recommendations:

- Previous evidence does not support a difference in efficacy or effectiveness between different BPH medications.
- According to prior evidence, no differences were found between medications in terms of harms and adverse events.
- It is recommended that at least one Alpha-blocker and one 5-Alpha Reductase Inhibitor be included on the preferred drug list (PDL).
- Consider prior authorization criteria to limit cosmetic use.

Background:

In BPH, the enlarged gland contributes to lower urinary tract symptoms (LUTS) through direct bladder outlet obstruction and increased smooth muscle tone and resistance.¹ The main causes of LUTS include abnormalities of the bladder, prostate, urethra, or sphincters.² The primary treatment goal has been to alleviate inconvenient LUTS and more recently to address the prevention of disease progression. LUTS includes storage and/or voiding disturbances common in aging men due to structural or functional abnormalities.¹ The American Urological Association (AUA) guidelines on the management of BPH recommend alpha-blockers for patients with bothersome, moderate to severe LUTS and they have equal clinical effectiveness with slight differences in adverse event profiles.¹ The combination of an alpha-blocker with a 5-alpha-reductase inhibitor is recommended when the LUTS is associated with prostatic enlargement and 5-alpha reductase inhibitors should not be used when BPH is not associated with prostate enlargement.¹ Guidelines from the National Institute for Health and Clinical Excellence recommend an alpha blocker (afuzosin, doxazosin, tamsulosin, or terazosin) to men with moderate to severe LUTS, an anticholinergic to men with the symptoms of overactive bladder, and a 5-alpha reductase inhibitor to men who have prostates to be larger than 30g or a PSA level greater than 1.4ng/ml and who are considered to be at high risk for progression.² The Oregon Health Plan (OHP) only covers BPH with urinary obstruction when post void residuals are at least 150 cc's and unspecified urinary obstruction and BPH with obstruction is an unfunded diagnosis.³ Current prior authorization criteria for the BPH medications are found in Appendix 1.

Methods:

A MEDLINE OVID search was conducted using all included drugs with benign prostatic hyperplasia and limits for humans, English language, and controlled clinical trials or randomized controlled trials from 2010 to current. The Cochrane Collection, PubMed Health, DynaMed, the Canadian Agency for Drug and Technologies in Health (CADTH), and the Centre for Reviews and Dissemination (DARE) were searched for high quality systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) and the American Urological Association (AUA) were searched for updated and recent evidence-based guidelines.

New Trials:

A total of 43 citations resulted from the initial MEDLINE search and after review for inclusion, 15 potentially relevant clinical trials were identified (Appendix 2). The other trials were excluded due to lack of relevant outcomes, comparisons to other non-pharmacological treatments and/or no head-to-head studies. These trials are briefly described in Table 1.

Table 1: Study details

| Study | Comparison | Population | Primary Outcome | Results | | | | | | | | | | | | | | | | | |
|--|---|--|---|---|---|-------|----------------|------------|---------|--------|----------------|----------------|-------|-------|----------------|----------------|-------|---------|----------------|----------------|--------|
| | | | | Before switch(Success rate) | After switch(Improvement) | | | | | | | | | | | | | | | | |
| Karadag, et al. ⁴ Randomized crossover comparison study | Tamsulosin(10mg) to Alfuzosin(0.4mg) vs. Alf to Tam | Men with BPH admitted with lower urinary tract symptoms (LUTS) | Effectiveness of switching alpha blockers based on improvement in IPSS, QoL, average flow rate and voided urine volume. | Tam to Alf: 42% Tam Alf to Tam: 47% Alf | 27.5% Alf 14% Tam | | | | | | | | | | | | | | | | |
| Chung, et al. ⁵ Multicentre, prospective, randomized study | Doxazosin-gastrointestinal therapeutic system GITS 4mg vs. Tamsulosin 0.2mg | Male ambulatory patients over 50 years of age with LUTS. | Comparison of early onset (over a 12 week period) efficacy between the two drugs using IPSS scores. | <u>Improvement in total IPSS score from baseline</u> <table border="1"> <thead> <tr> <th>Visit</th> <th>Doxazosin-GITS</th> <th>Tamsulosin</th> <th>p value</th> </tr> </thead> <tbody> <tr> <td>Week 1</td> <td>(-7.62),-37.5%</td> <td>(-5.02),-27.5%</td> <td>0.021</td> </tr> <tr> <td>Week4</td> <td>(-8.56),-42.2%</td> <td>(-6.34),-34.8%</td> <td>0.030</td> </tr> <tr> <td>Week 12</td> <td>(-9.27),-45.6%</td> <td>(-5.48),-27.3%</td> <td>0.0005</td> </tr> </tbody> </table> | | Visit | Doxazosin-GITS | Tamsulosin | p value | Week 1 | (-7.62),-37.5% | (-5.02),-27.5% | 0.021 | Week4 | (-8.56),-42.2% | (-6.34),-34.8% | 0.030 | Week 12 | (-9.27),-45.6% | (-5.48),-27.3% | 0.0005 |
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| Week 12 | (-9.27),-45.6% | (-5.48),-27.3% | 0.0005 | | | | | | | | | | | | | | | | | | |
| Yu, et al. ⁶ RCT, double-blind, multicentre | Silodosin 4mg bid vs. tamsulosin 0.2mg qam + placebo qpm | Men with BPH aged ≥ 40 years with an IPSS of ≥ 13 | Mean change from baseline to endpoint in IPSS. | <u>Decrease in IPSS ($\geq 25\%$)</u> S: 86.2% T: 81.9% P=0.53 | <u>Mean difference in IPSS change</u> -0.60, 95% CI (-2.15,0.95) | | | | | | | | | | | | | | | | |
| Zhang, et al. ⁷ Prospective, multicenter, randomized, open, parallel study | Doxazosin-GITS 4mg vs. Tasmulosin 0.2mg | Chinese men aged ≥ 50 years with LUTS/BPH. | Change from baseline in self-reported nocturia according to the IPSS and FVC, quality of sleep and quality of life. | <u>Reduction from baseline in mean nocturia (FVC/IPSS)</u> Week 4: D: 1.7, T: 1.3(P=0.001) / D: 1.5, T: 1.1(P=0.001) Week 8: D: 2.1, T: 1.7(P=0.001) / D: 2.0, T: 1.6(P<0.001) <u>Percentage reported improved sleep</u> Week 4: D: 43.6%, T: 27.4% (P=0.020) Week 8: D: 81.9%, T: 67.4% (P=0.022) <u>Improvement in quality of life(Lower number=better QoL)</u> Week 4: D: 2.5, T: 2.8 (P=0.001) Week 8: D: 2.1, T: 2.5 (P<0.001) | | | | | | | | | | | | | | | | | |
| Nickel, et al. ⁸ RCT, double-blind, double-dummy, multicentre | Dutasteride 0.5mg vs. Finasteride 5mg | Men aged >50 years with a clinical diagnosis of BPH | Change in prostate volume | <u>Mean percent reduction in prostate volume</u> 3 months: F: 18.5%, D: 18.3% (P=0.76) 12 months: F: 26.7%, D: 26.3% (P=0.65, CI 1.4-2.3) <u>Reduction in prostate volume at 12 months</u> $\geq 40\text{cm}^3$ baseline: F: 27.7%, D: 27.6% (P=0.90) $< 40\text{cm}^3$ baseline: F: 24.2%, D: 22.6% (P=0.37) | | | | | | | | | | | | | | | | | |

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|--|---|--|--|---|
| Watanabe, et al. ⁹ RCT, crossover, comparative, open-label | Tamsulosin (0.2mg) to Silodosin (4mg) vs. Silo to Tam | Untreated Japanese men diagnosed with LUTS/BPH and an IPSS \geq 8 and IPSS-QoL score \geq 2 | Patient-reported preferred drug for treatment continuation at 8 weeks | <u>Patient preferred Drug</u> Tamsulosin: 59/84 (70.2%) Silodosin: 18/84 (21.4%) P=NS |
| Montorsi, et al. ¹⁰ post hoc analysis | Dutasteride 0.5mg vs Tamsulosin 0.4mg vs. combination | Men \geq 50 years with moderate-to-severe LUTS due to BPH at risk of disease progression | Mean changes from baseline in IPSS. | <u>Mean changes from baseline in IPSS at 4 years</u> Combination: -6.3 Dutasteride: -5.3 Tamsulosin: -3.8 P<0.001 |
| Roehrborn, et al. ¹¹ Post hoc analysis | Dutasteride 0.5mg vs. tamsulosin 0.4mg vs. combined therapy | Men aged \geq 50 years with diagnosis of BPH | Time to first AUR or BPH-related surgery | Combined therapy (dutasteride + tamsulosin) was statistically better than tamsulosin alone in reducing the risk of AUR or BPH-related surgery (P \leq 0.001). The incidence of surgery was higher with tamsulosin than in dutasteride or combined therapy (P \leq 0.001). |
| Miyakita, et al. ¹² RCT, crossover | Silodosin (4mg) to Tamsulosin (0.2mg) vs. Tam to Sil | BPH patients complaining of LUTS | Change in total IPSS from baseline | <u>Change in IPSS total score after first drug</u> S: -7.7 \pm 5.9, T: -4.6 \pm 5.4 (P<0.05) <u>Change in IPSS after crossover</u> S: -2.6 \pm 3.8, T: 0.3 \pm 4.3 (P<0.01) |
| Montorsi, et al. ¹³ Post hoc analysis | Dutasteride 0.5mg vs. tamsulosin 0.4mg vs. combined therapy | Men age \geq 50 years with moderate-to-severe symptoms of BPH | Change from baseline in IPSS and BII scores with combination vs. monotherapy | <u>Mean change in IPSS from baseline</u> Combo: -1.5, D: -1.3, T: -1.1 (P<0.001) <u>Mean change from baseline in BII scores</u> Combo: -2.2, D: -1.8, T: -1.2 (P<0.001) |
| Yanqun, et al. ¹⁴ RCT, DB, parallel group, placebo controlled with an open label extension | Dutasteride (D/D) 0.5mg vs. placebo (6 months) to dutasteride (P/D) | Chinese men aged \geq 50 years with diagnosis of BPH | Percentage change in total prostate volume (TPV) from baseline at 6 months | <u>Mean reduction in TPV at 6 months</u> D/D: 17.14% P/D: 3.71% P<0.05 |
| Shin, et al. ¹⁵ Retrospective study | Alpha blocker vs. combination (alpha blocker + 5-alpha reductase inhibitor) | Patients \geq 40 years with an IPSS of \leq 7 and previously treated for BPH without AUR or BPH-related surgery. | Difference in incidences of AUR and BPH-related surgeries between the two groups | <u>Incidence in AUR</u> Alpha blocker: 50/368 (13.6%) Combination: 7/252 (2.8%) P<0.001 <u>Incidence of BPH-related surgeries</u> Alpha blocker: 31/368 (8.4%) Combination: 8/252 (3.2%) P=0.008 |
| Kruep, et al. ¹⁶ Retrospective study | 5-alpha reductase inhibitor early (within 30 days of | Men \geq 50 years of age with BPH or an enlarged prostate | AUR, prostate surgery, and clinical progression (combination of the two | <u>Percentage of patients with AUR</u> Early: 10.2%, Late: 13.8% P<0.0001 |

| | starting an alpha blocker) vs. delayed therapy (30-180 days after starting alpha blocker) | | above) | <u>Percentage of patients who underwent surgery</u> Early: 5%, Late: 7% P=0.0002 <u>Percentage of patients with clinical progression</u> Early: 12.8%, Late:17.4% P<0.0001 <u>Mean values after treatment of the two groups</u> | | | | | | | | | | | | | | | | |
|------------------------------|---|--|---|---|--|---------|------|---------|------|------------|-----------|-------|-----|-----------|----------|-------|------|-----------|-----------|-------|
| Madani, et al. ¹⁷ | Standard treatment + tadalafil 10mg vs. standard treatment alone (placebo) | Patients with obstructive and irritative urinary tract symptoms due to BPH, IPSS≥8 | Differences in IPSS, Qmax and QoL after 3 months between groups | <table border="1"> <thead> <tr> <th></th> <th>Placebo</th> <th>Drug</th> <th>P-value</th> </tr> </thead> <tbody> <tr> <td>IPSS</td> <td>11.37±3.64</td> <td>7.66±3.99</td> <td>0.001</td> </tr> <tr> <td>QoL</td> <td>2.19±0.53</td> <td>1.8±0.98</td> <td>0.036</td> </tr> <tr> <td>Qmax</td> <td>8.73±2.22</td> <td>9.99±4.76</td> <td>0.066</td> </tr> </tbody> </table> | | Placebo | Drug | P-value | IPSS | 11.37±3.64 | 7.66±3.99 | 0.001 | QoL | 2.19±0.53 | 1.8±0.98 | 0.036 | Qmax | 8.73±2.22 | 9.99±4.76 | 0.066 |
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| Qmax | 8.73±2.22 | 9.99±4.76 | 0.066 | | | | | | | | | | | | | | | | | |
| Oelke, et al. ¹⁸ | Tadalafil 5mg vs. Tamsulosin 0.4mg vs. placebo | Men ≥45 years of age with LUTS/BPH | Efficacy based on IPSS and BPH Impact Index (BII) | <u>IPSS mean difference from placebo</u> Tadalafil: -2.1 (95%CI -3.3 to -0.8, p=0.001) Tamsulosin: -1.5 (95%CI -2.8 to -0.2, p=0.023) <u>BII mean difference from placebo</u> Tadalafil: -0.8 (95%CI -1.3 to -0.3, p=0.003) Tamsulosin: -0.6 (95%CI -1.1 to -0.1, p=0.026) | | | | | | | | | | | | | | | | |

IPSS= International Prostate Symptom Score; FVC= frequency volume chart; AUR= Acute urinary retention; QoL=quality of life

New drugs:

The FDA approved tadalafil (Cialis®) in October of 2011 to treat the signs and symptoms of BPH and for the treatment of simultaneous occurrence of BPH and erectile dysfunction.^{17,18} In two clinical trials, men with BPH on standard treatment (alpha-blockers) were compared to standard treatment in addition to 5 mg of tadalafil on reduction of symptoms. The mean change in the International Prostate Symptom Score (IPSS) from baseline to endpoint for tadalafil versus placebo was -5.00 versus -2.67. According to the AUA guidelines, a 3-point improvement in IPSS was suggested as the minimum perceived by patients.¹⁹ However, it failed to show a significant improvement in maximal urinary flow rate (Qmax) or post void residual urine volume. There was no significant difference in serious adverse events. A recent systematic review found that tadalafil or other phosphodiesterase-5 inhibitors could significantly improve symptoms in patients with comorbid BPH and ED, however in those without ED there was no sufficient data to prove superiority to alpha-blockers for first-line treatment.¹⁹

New Combination Products:

The FDA approved the combination of dutasteride and tamsulosin hydrochloride (Jalyn) in June 2010 for the treatment of BPH. The labeling has then been revised to include the risk of high-grade prostate cancer due to dutasteride, its effects on serum prostate specific antigen, and information regarding male breast cancer.^{16,17}

New Formulations/Indications:

The FDA approved generic alfuzosin hydrochloride 10mg extended-release tablets in July of 2011. The Division of Bioequivalence has determined that the 10mg dose is therapeutically equivalent to Uroxatral 10mg extended-release tablets.

The FDA also approved generic dutasteride capsules 0.5mg in December 2010. The Division of Bioequivalence determined that the 0.5mg dutasteride capsule is therapeutically equivalent and bioequivalent to Avodart capsules 0.5mg.

New FDA safety alerts:

There was a new FDA drug safety communication in June of 2011 regarding the increased risk of being diagnosed with a more serious form of prostate cancer (high-grade prostate cancer) with the use of 5-alpha reductase inhibitors. The risk appears to be low, but healthcare professionals should weigh the known benefits against the potential risk when deciding to start or continue treatment with these agents in men.¹⁸

New Systematic Reviews (Appendix 3):

Two recent systematic reviews were published evaluating the new indication of phosphodiesterase-5 (PDE-5) inhibitors for BPH as monotherapy and combination.

A review by Liu et al., included a total of 5 studies (2054 participants) and assessed the efficacy and safety of PDE-5 inhibitors for treating LUTS secondary to BPH.¹⁹ The primary outcomes included changes in the IPSS and maximal urinary flow rate (Qmax) after treatment with PDE-5 inhibitors. Three of the 5 studies investigated tadalafil versus placebo (1499 patients with BPH alone), and vardenafil and sildenafil were evaluated in the other two studies. Their pooled mean change in IPSS from baseline was -5.24 for PDE-5 inhibitors vs. -2.64 for placebo, which demonstrated a statistically significant difference in favor of the PDE-5 inhibitor (95% CI -3.12,-2.07; P<0.00001). The 5 studies then investigated the change in the Qmax from baseline and found that the PDE-5 inhibitors and placebo had a similar effect (95% CI -0.21, 0.64; P=0.32). Even though PDE-5 inhibitors showed an improvement in IPSS, they failed to result in significant improvement in Qmax.¹⁹ The study did not mention a protocol and even though it stated the publication bias was evaluated using a funnel plot, it did not show or discuss the results. Overall, this was a good systematic review and its results can be extrapolated due to the thorough discussion of the studies limitations and that all other data was reported.

In the review by Gacci et al., 12 studies were assessed which looked at use of PDE5-inhibitors alone or in combination with alpha blockers in patients with LUTS/BPH.²⁰ Studies comparing the effect of PDE5-inhibitors alone vs. placebo included a total of 3,214 patients. These studies found that PDE-5 inhibitors significantly improve IPSS (-2.8; p <0.0001), but not Qmax when compared with placebo (-0.00; p=not significant). These studies also found that 16% of men taking the PDE-5 inhibitor had adverse effects versus 6% of men taking placebo. The studies that compared the effect of alpha blockers alone vs. the combination of alpha blockers and PDE-5 inhibitors included 216 patients. The combination of the two medications significantly improved IPSS (-1.8; p=0.05) and IIEF score (+3.6; p<0.0001) as well as Qmax (+1.5; p<0.0001) when compared to alpha blockers alone. The reported adverse events in the combination therapy group were 6.8% and 5.1% in the group treated with alpha blocker alone.²⁰ This was a well done systematic review with proper data and results provided, but it lacked the principal summary measures and risk of bias across each study.

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Appendix 1: Current PA 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 by OHP

* 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.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

Requires PA: Non-preferred drugs

| Approval Criteria | | |
|--|--|-----------------------|
| 1. What is the diagnosis? | Record ICD9 code. | |
| 2. Will the prescriber consider a change to a preferred product? Message: <ul style="list-style-type: none"> • Preferred products do not require a PA. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Health Resource Commission (HRC). Reports are available at: http://www.oregon.gov/OHPPR/HRC/Evidence_Based_Reports.shtml. | Yes: Inform Provider of covered alternatives in class. http://www.oregon.gov/DHS/healthplan/tools_prov/dl.shtml . | No: Go to #3 |
| 3. 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) | Yes: Go to #4 | No: Go to #5 |
| 4. Has the client tried and failed a 2-month trial of a covered alternative | Yes: Approve an alpha | No: Deny until |

| | | |
|---|---|---|
| alpha blocker (terazosin, doxazosin, prazosin, tamsulosin)? | blocker only for 1 year | client has tried and failed a covered alternative |
| 5. 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) | Yes: Approve for the shorter of 1 year or length of the prescription | No: Go to #6 |
| 6. Does client have a diagnosis of unspecified urinary obstruction or benign prostatic hyperplasia without obstruction? (599.6, 600.00, 600.10, 600.20, and 600.90) | Yes: Pass to RPH; Deny, (Not Covered by the OHP) | No: Pass to RPH; Go to #7 |
| <p>7. RPH Notes only - All other indications need to be evaluated to see if they are above or below the line:</p> <p>Above the line covered diagnoses related to prostate may be approved for 1 year</p> <p>Below the line 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"> 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. <p>Refer questions of coverage to DMAP.</p> | | |

| Renewal Therapy | | |
|--|----------------------|---------------------|
| 1. 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) | Yes: Go to #2 | No: Go to #3 |

| | | |
|---|---|---|
| <p>2. Has the patient also been taking a 5-alpha reductase inhibitor for the last year?</p> | <p>Yes: Recommend against combination therapy exceeding 1 year</p> | <p>No: Approve for the shorter of 1 year or length of the prescription</p> |
| <p>3. 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)</p> | <p>Yes: Approve for 1 year</p> | <p>No: Go to #4</p> |
| <p>4. Does client have a diagnosis of unspecified urinary obstruction or benign prostatic hyperplasia without obstruction? (599.6, 600.00, 600.10, 600.20, and 600.90)</p> | <p>Yes: Pass to RPH; Deny, (Not Covered by the OHP)</p> | <p>No: Pass to RPH; Go to #5</p> |
| <p>5. RPH only 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"> • 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. • 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. | <p>If above the line or clinic provides supporting literature: approve for one year.</p> | <p>If below the line: 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): 1/1/11, 4/20/10, 5-22-08 (Aebi), 7-1-06, 9-30-05
Effective: 10-14-04 (previously excluded)

Appendix 2: New Trial Abstracts

- 1. Karadag E, Oner S, Budak Y, Atahan O. Randomized crossover comparison of tamsulosin and alfuzosin in patients with urinary disturbances caused by benign prostatic hyperplasia. *International Urology & Nephrology*. 2011;43(4):949–54.**

OBJECTIVE: To compare the efficacy and safety of alfuzosin (Alf) and tamsulosin (Tam) in patients with lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH). METHODS: One hundred men were enrolled in this randomized cross-over study. During enrollment, a detailed medical history was recorded, and International Prostate Symptom Score (IPSS), digital rectal exam, urinary ultrasound, prostate specific antigen (PSA) level, and uroflowmetry were determined. Those with IPSS greater than 8 and a maximum urinary flow rate (Qmax) lower than 15ml/s were randomly divided into either Alf-Tam group or Tam-Alf group (taking each medication for 8 weeks) with no washout period between switching drugs. RESULTS: During the first 8 weeks, each drug significantly improved IPSS and Qmax. After the crossover, both groups continued to have improvement in IPSS and Qmax. Both drugs significantly lowered IPSS and increase Qmax from baseline ($P<0.001$). Neither drug affected the serum PSA levels. CONCLUSION: Similar favorable outcomes were associated with Tam and Alf. When one alpha blocker does not provide a desired effect in the treatment of BPH, switching to another in the class seems to be beneficial.

- 2. Chung M, Lee S, Park K, Yoo S, Chung B. Comparative rapid onset of efficacy between doxazosin gastrointestinal therapeutic system and tamsulosin in patients with lower urinary tract symptoms from benign prostatic hyperplasia: a multicentre, prospective, randomised study. *Journal of Clinical Practice*. 2011;65(11):1193–9.**

OBJECTIVE: To compare the rapidity of improvement in lower urinary tract symptoms (LUTS) for the doxazosin gastrointestinal therapeutic system (GITS) and tamsulosin in BPH patients. METHODS: There were 207 patients randomized for a 12-week daily treatment with either doxazosin-GITS 4 mg or tamsulosin 0.2mg. The primary outcome was to compare the early onsets of efficacy between the two drugs. This was done by analyzing the changes from baseline IPSS. The secondary outcomes included comparing improvements in obstructive/irritative subcore and quality of life (QoL) between the groups, and to evaluate adverse events with the drugs. RESULTS: Both groups showed significant improvements in IPSS scores after the 12 weeks of treatment ($p<0.0001$). The doxazosin-GITS group showed significantly greater improvements in total IPSS and obstructive subscore than the tamsulosin group during the beginning of the trial ($p<0.05$). Improvements in irritative subscore and QoL score did not show significant differences between the two groups. The groups had similar adverse events incidences. CONCLUSION: Doxazosin-GITS showed significantly more rapid onset of efficacy and similar adverse events when compared with tamsulosin. This may help improve patient compliance. Further studies need to be conducted with a larger population and longer follow-up period to confirm the findings of this study.

- 3. Yu H, Lin A, Yang S, et al. Non-inferiority of silodosin to tamsulosin in treating patients with lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH). *BJU International*. 2011;108(11):1843–8.**

OBJECTIVE: To test the hypothesis that the efficacy of silodosin would not be inferior to tamsulosin in treating patients with LUTS/BPH. METHODS: The study was conducted at 9 medical centres with a total of 209 patients with an IPSS of ≥ 13 . The patients were randomized to either silodosin 4mg twice daily or tamsulosin 0.2mg once daily for 12 weeks. The primary outcome was the mean change in IPSS from baseline to endpoint. The secondary outcomes measured change in Qmax and QoL score. RESULTS: Of the patients who completed the study 86.2% taking silodosin vs. 81.9% taking tamsulosin achieved a $\geq 25\%$ decrease in IPSS ($P=0.53$). The mean difference in IPSS change from baseline was -0.60 (95%CI -2.15, 0.95),

inferring non-inferiority of silodosin to tamsulosin. The mean changes in the Qmax and QoL score from baseline were comparable between groups ($P>0.05$). **CONCLUSION:** This study shows the non-inferiority of silodosin 4 mg twice daily to tamsulosin 0.2mg once daily in patients with BPH.

4. Zhang K, Yu W, Jin J, et al. Effect of doxazosin gastrointestinal therapeutic system 4 mg vs tamsulosin 0.2 mg on nocturia in Chinese men with lower urinary tract symptoms: a prospective, multicenter, randomized, open, parallel study. *Urology*. 2011;78(3):636–40.

OBJECTIVE: To compare the efficacy of doxazosin-GITS 4mg and tamsulosin 0.2mg on nocturia in Chinese men with LUTS/BPH. **METHODS:** The study is a prospective, multicenter, randomized, open, parallel study of Chinese men aged 50-84 years with LUTS/BPH. Two hundred patients were randomized to receive either 4mg doxazosin-GITS or 0.2mg tamsulosin for 8 weeks. The IPSS-question 7 and frequency volume chart (FVC) were used to assess nocturia at weeks 4 and 8. Patients also self-reported quality of sleep and quality of life. **RESULTS:** The reduction in mean nocturia from baseline was greater with doxazosin-GITS than tamsulosin by the FVC ($P=0.001$) and IPSS-question 7 ($P<0.001$). There were more patients on doxazosin-GITS who reported improved quality of sleep than patients taking tamsulosin ($P=0.020$ at 4 weeks; $P=0.022$ at 8 weeks) and similar results were seen with reports of QoL ($P=0.001$ at 4 weeks; $P<0.001$ at 8 weeks). **CONCLUSION:** Chinese men with LUTS/BPH have shown a slightly better response in reduction of frequency of nocturia with doxazosin-GITS than tamsulosin.

5. Nickel J, Gillig P, Tammela T, Morrill B, Wilson T, Rittmaster R. Comparison of dutasteride and finasteride for treating benign prostatic hyperplasia: the Enlarged Prostate International Comparator Study (EPICS). *BJU International*. 2011;108(3):388–94.

OBJECTIVE: To assess the efficacy and safety of dutasteride compared with finasteride in treating men with symptomatic BPH for 12 months. **METHODS:** The study was a multicenter, randomized, double-blind, 12-month, parallel group study. The participants were men aged ≥ 50 years with a clinical diagnosis of BPH. The participants either received once-daily treatment with dutasteride 0.5mg or finasteride 5 mg. Patients underwent a 4-week placebo run-in period and then were randomized to one of the two groups for 48 weeks, followed by an optional 24 month, open-label phase where the patients received dutasteride 0.5mg once daily. The primary outcome was change in prostate volume. The secondary endpoints include improvement in Qmax, symptom scores, and safety in the 24 month open-label phase. **RESULTS:** Both dutasteride and finasteride were effective at reducing prostate volume with no significant difference between the two. Similar percentage of adverse events was experienced in both treatment groups. **CONCLUSION:** For the 12 months that dutasteride and finasteride were administered, they showed similar effectiveness in reducing prostate volume and improving Qmax and urinary symptoms.

6. Watanabe T, Ozono S, Kageyama S. A randomized crossover study comparing patient preference for tamsulosin and silodosin in patients with lower urinary tract symptoms associated with benign prostatic hyperplasia.[Erratum appears in *J Int Med Res*. 2011;39(3):1122]. *Journal of International Medical Research*. 2011;39(1):129–42.

OBJECTIVE: To compare patient preference for tamsulosin and silodosin in patient with LUTS/BPH. **METHODS:** The study was a randomized, crossover, comparative, open-label study. The study included Japanese patients with LUTS associated with BPH and had an IPSS ≥ 8 and a QoL score ≥ 2 . They randomly assigned the patients to either a Tam-Sil or Sil-Tam for a total of 8 weeks. The primary outcome was the preferred drug for treatment continuation at 8 weeks, according to the patient-report questionnaire. **RESULTS:** There were a total of 102 patients who enrolled in the study and 82 completed the 8 weeks. There was a significant difference between the patients who preferred tamsulosin (59/84; 70.2%) and those

that preferred silodosin (18/84; 21.4%). Incidence of adverse effects was significantly lower with tamsulosin (3/91; 3.3%) than with silodosin (25/88).
CONCLUSION: The findings of the study indicate that tamsulosin is very effective for BPH, has few adverse effects and is patient-preferred.

7. Montorsi F, Roehrborn C, Garcia-Penit J, et al. The effects of dutasteride or tamsulosin alone and in combination on storage and voiding symptoms in men with lower urinary tract symptoms (LUTS) and benign prostatic hyperplasia (BPH): 4-year data from the Combination of Avodart and Tamsulosin (CombAT) study. *BJU International*. 2011;107(9):1426–31.

OBJECTIVE: To assess the effects of combination therapy with dutasteride and tamsulosin on voiding and storage symptoms with those of dutasteride or tamsulosin alone. METHODS: The study included men aged ≥ 50 years with moder-to-severe LUTS due to BPH, a prostate volume of >30 mL, and a PSA of 1.50-10ng/mL. This was a post hoc analysis of a multicenter, double-blind, parallel group study. Patients received either oral dutasteride 0.5mg or tamsulosin 0.4mg alone or in combination for 4 years. The outcomes analyzed included mean changes from baseline in storage and voiding symptoms at 4 years, which were assessed using the IPSS. RESULTS: The mean reduction in the storage subscore was significantly greater in the combined group versus the dutasteride and tamsulosin monotherapy groups ($P<0.001$). The mean reduction in the voiding subscore was significantly greater in the combination group versus the dutasteride and tamsulosin monotherapy group ($P<0.001$). CONCLUSION: It appeared that combined therapy with dutasteride plus tamsulosin provided better long-term control of storage and voiding compared to tamsulosin monotherapy in men with a prostate volume of ≥ 30 mL. Combined therapy was also better than dutasteride monotherapy in men with prostate volumes of ≥ 30 and <58 mL, but not in men with a prostate volume of ≥ 58 mL.

8. Roehrborn C, Barkin J, Siami P, et al. Clinical outcomes after combined therapy with dutasteride plus tamsulosin or either monotherapy in men with benign prostatic hyperplasia (BPH) by baseline characteristics: 4-year results from the randomized, double-blind Combination of Avodart and Tamsulosin (CombAT) trial. *BJU International*. 2011;107(6):946–54.

OBJECTIVE: To investigate the influence of baseline variables on the acute urinary retention (AUR), BPH-related surgery and overall clinical progression over a 4-year period in men treated with tamsulosin, dutasteride, or combination therapy. METHODS: A post hoc analysis of a multicenter, randomized, double-blind, parallel group study in men aged ≥ 50 years with symptomatic BPH. The primary endpoint was time to first AUR or BPH-related surgery. The secondary endpoints included clinical progression of BPH and symptoms. Baseline prostate volumes (PV) and prostate specific antigen (PSA) levels were measured. RESULTS: There were 4844 men participating in the study. Combined therapy was statistically better than tamsulosin alone in reducing the risk of AUR or BPH-related surgery in subgroups of baseline $PV \geq 42$ mL and in all subgroups of baseline PSA levels ($P<0.001$). Combined therapy reduced the relative risk (RR) of clinical progression compared with tamsulosin alone across all baseline subgroups. CONCLUSION: Men with baseline PV of >40 mL and any baseline PSA level of >1.5 ng/mL had greater reductions in the RR of AUR or BPH-related surgery and greater reduction in the RR of clinical progression and symptom deterioration on combined therapy or dutasteride monotherapy than on tamsulosin monotherapy. This supports the long-term use of combined therapy with dutasteride plus tamsulosin in moderate-to-severe BPH.

9. Miyakita H, Yokoyama E, Onodera Y, et al. Short-term effects of crossover treatment with silodosin and tamsulosin hydrochloride for lower urinary tract symptoms associated with benign prostatic hyperplasia. *Journal of Urology*. 2010;17(10):869–75.

OBJECTIVE: To compare the efficacy and safety of silodosin and tamsulosin in patients with LUTS/BPH. **METHODS:** This randomized crossover study analyzes BPH patients with the complaint of LUTS. The patients are randomly divided into either a silodosin-preceding group (4 weeks of twice daily silodosin 4mg) followed by 4 weeks of once daily tamsulosin at 0.2mg or a tamsulosin preceding group followed by a silodosin group. No drug withdrawal period occurred when switching the drugs. **RESULTS:** Both drugs significantly improved the IPSS score, but the improvement by silodosin was significantly superior to that by tamsulosin. After the crossover treatment, significant improvement was observed only with silodosin treatment. Silodosin also significantly improved QoL score in both treatment periods, while tamsulosin only significantly improved QoL score in the first treatment period. **CONCLUSION:** Silodosin exhibits better efficacy in improving subjective symptoms in both initial and crossover treatment, and it appears to improve the QoL of patients than tamsulosin.

10. Montorsi F, Henkel T, Geboers A, et al. Effect of dutasteride, tamsulosin and the combination on patient-reported quality of life and treatment satisfaction in men with moderate-to-severe benign prostatic hyperplasia: 4-year data from the CombAT study. *Journal of Clinical Practice*. 2010;64(8):1042–51.

OBJECTIVE: To investigate the effects of combination therapy (dutasteride plus tamsulosin) compared with each monotherapy in men with moderate-to-severe LUTS due to BPH. **METHODS:** Subjects were randomized to receive either dutasteride 0.5mg, tamsulosin 0.4mg or a combination of the two for 4 years. The primary outcome at 4 years was the time to event and proportion of subjects with acute urinary retention or BPH-related surgery. Secondary endpoints measures BPH Impact Index (BII), IPSS question 8, and Patient Perception of Study Medication (PPSM) questionnaire. **RESULTS:** Combination therapy resulted in significantly superior improvements from baseline in BII and IPSS question 8 than either monotherapy. The PPSM questionnaire showed that a significantly higher proportion of patients were satisfied and requested the combination therapy for treatment compared to either monotherapy. **CONCLUSION:** Combination therapy provides significantly superior improvements in patient-reported QoL and treatment satisfaction than either monotherapy at 4 years in men with moderate-to-severe BPH symptoms.

11. Na Y, Ye Z, Zhang S. Efficacy and safety of dutasteride in Chinese adults with symptomatic benign prostatic hyperplasia: a randomized, double-blind, parallel-group, placebo-controlled study with an open-label extension. *Clin Drug Investig*. 2012;32(1):29–39.

OBJECTIVE: To evaluate the efficacy and safety of dutasteride in Chinese adults with symptomatic BPH. **METHODS:** This was a randomized, double-blind, parallel-group, placebo-controlled study which took place over 6 months and was followed by an open-label extension of 12 months. Patients were randomized to receive either dutasteride 0.5mg/day orally or matching placebo treatment. After 6 months, eligible participants enter the open-label extension all receiving dutasteride 0.5mg/day orally. The changes in total prostate volume (TPV), Qmax, and American Urology Association Symptom Index (AUA-SI) were evaluated. **RESULTS:** Dutasteride significantly reduced mean TPV compared with placebo at 3 and 6 months ($P < 0.05$). Higher improvements in Qmax and AUA-SI were observed in the dutasteride group, but no statistical significance between groups was found. **CONCLUSION:** Dutasteride was effective compared with placebo in the treatment of symptomatic BPH among Chinese men.

12. Shin TJ, Kim CI, Park CH, Kim BH, Kwon YK. α -Blocker Monotherapy and α -Blocker Plus 5-Alpha-Reductase Inhibitor Combination Treatment in Benign Prostatic Hyperplasia; 10 Years' Long-Term Results. *Korean J Urol*. 2012;53(4):248–252.

OBJECTIVE: To compare the effects of alpha blocker monotherapy with combination therapy containing an alpha blocker and 5-alpha reductase inhibitor on BPH progression for over 10 years. **METHODS:** A total of 520 patients received alpha blocker monotherapy or combination therapy as their initial treatment. The incidences of acute urinary retention (AUR) and BPH-related surgery were compared between groups. **RESULTS:** The incidence of AUR was 13.6% in the alpha blocker group and 2.8% in the combination group ($P<0.001$). A total of 8.4% and 3.2% of patients underwent BPH-related surgery in the alpha blocker and combination groups, respectively ($P=0.008$). **CONCLUSION:** Long-term combination therapy with alpha blocker and 5-alpha reductase inhibitor can suppress the progression of BPH more efficiently than alpha blocker monotherapy (which showed the better effects in patients with $PSA>2\text{ng/mL}$ or $PV>35\text{mL}$).

13. Kruep EJ, Hogue SL, Eaddy MT, Chandra MD. Clinical and economic impact of early versus delayed 5-alpha reductase inhibitor therapy in men taking alpha blockers for symptomatic benign prostatic hyperplasia. *P T*. 2011;36(8):493–507.

OBJECTIVE: To assess the clinical and economic impact of early versus delayed 5-alpha reductase inhibitor (5-ARI) therapy in patients treated with alpha blocker for BPH. **METHODS:** This is a retrospective database analysis that included men ≥ 50 years of age who were treated with BPH. The primary outcome was to evaluate patients using 5-ARI early (within 30 days of starting an alpha blocker) compared with those using delayed 5-ARI therapy (between 30 and 180 days starting the alpha blocker). Acute urinary retention (AUR) and BPH-related surgery were assessed (clinical progression). **RESULTS:** Patients who started 5-ARI early were less likely than those receiving delayed treatment (12.8% vs. 17.4%, $p<0.0001$) to have clinical progression, AUR (10.2% vs. 13.8%, $p<0.0001$), and prostate surgery (5% vs. 7%, $p=0.0002$). The early group also acquired lower BPH-related medical costs (\$572 vs. \$730, $p<0.0001$). **CONCLUSION:** The results suggest that early 5-ARI therapy for men with symptomatic BPH who are receiving an alpha blocker may significantly reduce the risk of clinical progression over the next 12 months as well as lower BPH-related costs.

14. Madani AH, Afsharimoghaddam A, Roushani A, Farzan A, Asadollahzade A, Shakiba M. Evaluation of Tadalafil effect on lower urinary tract symptoms of benign prostatic hyperplasia in patients treated with standard medication. *Int Braz J Urol*. 2012;38(1):33–39.

OBJECTIVE: To evaluate safety and efficacy of tadalafil on lower urinary tract symptoms related to benign prostatic hyperplasia. **METHODS:** This is a case-controlled randomized clinical trial, from November 2008 to August 2009. The study selected 132 patients with obstructive and irritative urinary tract symptoms due to BPH, $IPSS \geq 8$, no indication for surgical intervention and that reached plateau levels of response to treatment. The treatment group received standard treatment of BPH and tadalafil 10mg nightly and the placebo group received only standard treatment of BPH. The primary outcome assessed IPSS, maximum urinary flow rate (Q_{\max}) and quality of life before and after a 3-month period of study. **RESULTS:** Before treatment, mean IPSS, Q_{\max} and QoL values in the treatment and placebo groups were 13.06 ± 4.37 and 13.66 ± 4.25 , 8.92 ± 2.96 mL/s and 9.09 ± 2.91 , 2.93 ± 0.86 and 2.66 ± 0.78 mL/s, respectively. After treatment, mean IPSS, Q_{\max} , and QoL values in treatment group were 7.66 ± 3.99 , 9.99 ± 4.76 and 1.80 ± 0.98 mL/s, respectively. These findings were compared to corresponding values of the placebo group (11.37 ± 3.64 , 8.73 ± 2.22 and 2.19 ± 0.53 mL/s, respectively). IPSS and quality of life were significantly different but Q_{\max} didn't show a significant change. **CONCLUSION:** Tadalafil improves quality of life and urinary symptoms in patients with LUTS suggestive of BPH, but doesn't have any significant effect on Q_{\max} . Therefore, this drug may be effectively used in combination with standard medical therapies for BPH.

15. 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.

OBJECTIVE: To assess tadalafil or tamsulosin versus placebo for LUTS/BPH. METHODS: This is a randomized, double-blind, international, placebo-controlled, parallel-group study assessing men >45 years of age with LUTS/BPH, International Prostate Symptom Score (IPSS) ≥ 13 , and maximum urinary flow rate (Qmax) ≥ 4 to ≤ 15 ml/s. Following screening and washout, if needed, subjects completed a 4-wk placebo run-in before randomization to placebo (n = 172), tadalafil 5 mg (n = 171), or tamsulosin 0.4 mg (n = 168) once daily for 12 wk. The primary outcome assessed efficacy based on IPSS and BPH Impact Index (BII). RESULTS: IPSS significantly improved versus placebo through 12 wk with tadalafil (-2.1; p = 0.001; primary efficacy outcome) and tamsulosin (-1.5; p = 0.023) and as early as 1 wk (tadalafil and tamsulosin both -1.5; p < 0.01). BPH Impact Index significantly improved versus placebo at first assessment (week 4) with tadalafil (-0.8; p < 0.001) and tamsulosin (-0.9; p < 0.001) and through 12 wk (tadalafil -0.8, p = 0.003; tamsulosin -0.6, p = 0.026). Qmax increased significantly versus placebo with both tadalafil (2.4 ml/s; p = 0.009) and tamsulosin (2.2 ml/s; p = 0.014). CONCLUSION: Monotherapy with tadalafil or tamsulosin resulted in significant and numerically similar improvements versus placebo in LUTS/BPH and Qmax.

Appendix 3: Abstracts of systematic reviews

1. Liu L, Zheng S, Han P, Wei Q. Phosphodiesterase-5 inhibitors for lower urinary tract symptoms secondary to benign prostatic hyperplasia: a systematic review and meta-analysis. *Urology*. 2011;77(1):123–129.

OBJECTIVE: To evaluate the efficacy and safety of phosphodiesterase-5 (PDE-5) inhibitors for treating lower urinary tract symptoms secondary to benign prostatic hyperplasia. METHODS: Randomized controlled trials were identified and extracted from MEDLINE, Embase, Cochrane Central, and relevant reference lists. The database search, quality assessment, and data extraction were independently performed by 2 reviewers. Heterogeneity was analyzed using the chi-square test and I^2 test. If lacking of heterogeneity, fixed-effects models were used for the meta-analysis, otherwise random-effects models were used. RESULTS: Five studies were identified. PDE-5 inhibitors showed significant improvement in the IPSS (P<0.00001) when compared with placebo. No statistically significant difference was found in maximal urinary flow rate and postvoid residual urine volume. No statistically significant difference was found between the 2 groups in the incidence of serious adverse events. CONCLUSION: PDE-5 inhibitors are effective and safe for LUTS/BPH. It could be considered first line treatment in the future as well as for patient with comorbid BPH and erectile dysfunction.

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 α -Blockers for Lower Urinary Tract Symptoms Due to Benign Prostatic Hyperplasia. *European Urology*. 2012;61(5):994–1003.

OBJECTIVE: To analyze the available studies on the use of PDE-5 inhibitors alone or in combination with alpha adrenergic blockers in LUT/BPH patients. METHODS: A systematic search was performed using the Medline, Embase, and Cochrane Library databases through September 2011 including the combination of the following terms: *LUTS, BPH, PDE5-Is, sildenafil, tadalafil, vardenafil, udenafil, α -blockers, and $\alpha 1$ -adrenergic blocker*. The meta-analysis was conducted according to the guidelines for observational studies in epidemiology. RESULTS: The use of PDE-5 inhibitors alone

was associated with a significant improvement of the IPSS (-2.8, $p < 0.0001$), but not Qmax compared to placebo at the end of the study. CONCLUSION: The data suggests that PDE-5 inhibitors can significantly improve LUTS/BPH in men with or without erectile dysfunction.