National PBM Drug Monograph
Alfuzosin (UroXatral®)
January 2004

Monograph Summary

- **Indication:** Alfuzosin is a selective alpha$_1$-adrenergic receptor blocker approved for the treatment of signs and symptoms of benign prostatic hyperplasia (BPH).

- **Efficacy:** Treatment with alfuzosin 10mg extended-release once daily has been shown to be effective in reducing the symptoms associated with BPH [determined by a statistically significant decrease in International Prostate Symptom Score (IPSS)] and by resulting in a statistically significant increase in peak urinary flow rate (Qmax) compared to placebo. There was also a statistically significant improvement in the Quality of Life (QOL) index with alfuzosin vs. placebo.

- **Safety:** Alfuzosin appears to be well tolerated with the incidence of adverse effects slightly higher than seen with placebo. The most common reported adverse effect is dizziness (5.7% vs. 2.8% with placebo). Hypotension or postural hypotension was reported in 0.4% of patients on alfuzosin 10mg qd and syncope in 0.2%, with none reported in patients on placebo. Slightly greater decreases in blood pressure were seen with alfuzosin 10mg qd, although this was reported not to be significantly different compared to placebo. Impotence was reported in 1.5% of patients on alfuzosin and 0.6% in patients receiving placebo. Ejaculation disorders were reported in 0.6% of patients on alfuzosin. Alfuzosin should not be prescribed in patients receiving potent CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, ritonavir) or in patients with moderate to severe hepatic insufficiency, and should be used with caution in patients with severe renal impairment. The effect of alfuzosin on the QT interval should be considered in patients with a history of QT prolongation or who are taking medications that result in prolongation of the QT interval.

- **Dose:** Alfuzosin is available as a 10mg extended-release tablet that is to be administered immediately after the same meal once daily.

- **Comparison with other treatments for BPH:** Comparison trials of alfuzosin with other alpha$_1$-adrenergic blockers are limited with the extended-release preparation at a dose of 10mg qd. According to meta-analyses, alfuzosin appears similar in efficacy and safety to other alpha$_1$-adrenergic blockers. One meta-analysis reported tamsulosin to have less of an effect on blood pressure compared to alfuzosin (2.5mg tid). Reports of orthostatic hypotension were approximately 1% with alfuzosin and tamsulosin (comparable to placebo) and 2-8% with doxazosin and terazosin. According to another meta-analysis, tamsulosin appears to have a higher probability of ejaculatory dysfunction compared to other alpha$_1$-adrenergic blockers, although a comparative trial with alfuzosin and tamsulosin did not report ejaculatory dysfunction for either treatment.

- **Cost:** At this time, alfuzosin is competitively priced compared to treatment with tamsulosin, but is substantially higher than the price for treatment with the three alpha$_1$-adrenergic blockers listed on the VA National Formulary (VANF).

- **Recommendations:** It is recommended that alfuzosin not be added to the VANF or to VISN formularies at this time. Selection of a preferred clinically uroselective alpha$_1$-adrenergic receptor blocker for the treatment of symptomatic BPH should be considered. Criteria for non-formulary use established for tamsulosin should also include recommendations for alfuzosin.

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Introduction[1-3]

Alfuzosin (Uroxatral®, Sanofi-Synthelabo) received FDA approval for marketing in the U.S. on June 16, 2003. Alfuzosin is a selective alpha$_1$-adrenergic receptor blocker approved for the treatment of signs and symptoms of benign prostatic hyperplasia (BPH).

According to the American Urological Association (AUA) practice guidelines on the diagnosis and treatment of BPH published in 2003, patients with BPH and mild symptoms (AUA Symptom Score $\leq$ 7) or moderate or severe symptoms (AUA Symptom Score $\geq$ 8) that are not bothersome to the patient, watchful waiting is recommended as initial therapy. Pharmacologic therapy may be considered in patients with bothersome moderate to severe symptoms. Additional treatment options including watchful waiting, and minimally invasive or surgical therapies should also be discussed with the patient. Pharmacologic management of BPH includes the alpha-adrenergic blockers, 5 alpha-reductase inhibitors, or the two drugs in combination.

The selective alpha$_1$-adrenergic blockers doxazosin, prazosin, and terazosin are listed on the VA National Formulary (VANF) and can be used for the treatment of patients with symptomatic BPH and as combination therapy in the management of hypertension. These agents may be useful in patients with concomitant BPH and hypertension, although monotherapy with an alpha$_1$-adrenergic blocker for the treatment of hypertension is not recommended. Tamsulosin, another selective alpha$_1$-adrenergic receptor blocker approved for BPH, is currently not on the VANF and is restricted to criteria for use (http://www.vapbm.org/criteria/tamsulosincriteria.pdf).

Pharmacology[1-7]

Alfuzosin works by selectively blocking the alpha$_1$-adrenergic receptors in the lower urinary tract system resulting in smooth muscle relaxation in the bladder neck and prostate thereby relieving bladder outlet obstruction and reducing symptoms associated with BPH.

Unlike tamsulosin that is reported to have a high affinity for the alpha$_{1A}$-adrenoreceptor[4] (predominately in the stromal compartment of the prostate), alfuzosin is considered a nonspecific alpha$_1$-adrenoreceptor antagonist, having a higher concentration in the prostate compared to plasma.[5] Since receptor subtype affinity may not correlate with uroselectivity, it has been suggested that *clinical* uroselectivity (i.e., adverse effects) be used to differentiate between the alpha$_1$-adrenergic blockers.[6,7]

Pharmacokinetics[1]

Absorption	Bioavailability: 49%, fasting decreases extent of absorption by 50%; T_{max}: 8 hrs; C_{max}: 13.6 ng/mL; AUC_{0-24}: 194 ng.h/mL
Protein Binding	Moderately bound (82-90%) to plasma proteins
Half-life	Elimination half-life 10hrs
Metabolism	Extensively metabolized (oxidation, O-demethylation, N-dealkylation), metabolites not pharmacologically active; metabolism by CYP3A4
Elimination	Primarily in feces; 11% unchanged drug found in urine

FDA Approved Indications and Off-label Uses[1]

Alfuzosin HCl extended-release tablets are indicated for the treatment of signs and symptoms of BPH.

Dosage and Administration[1]

Alfuzosin is available as a 10mg extended-release tablet that is to be administered with food, immediately after the same meal once daily. The tablets should be swallowed whole and not chewed or crushed.

Adverse Events (Safety Data)[1, 8-12]

Adverse Drug Event (ADE)	Placebo N=678 (%)	Alfuzosin N=473 (%)
ADEs in ≥ 2% patients and > placebo		
Dizziness	19 (2.8)	27 (5.7)
Upper respiratory tract infection	4 (0.6)	14 (3.0)
Headache	12 (1.8)	14 (3.0)
Fatigue	12 (1.8)	13 (2.7)
Symptoms possibly associated w/orthostasis*		
Hypotension or postural hypotension	0	2 (0.4)
Syncope	0	1 (0.2)
Withdrawal due to ADEs	(3)	(4)

* Approximately 20-30% were taking antihypertensive agents

ADEs in 1-2% of patients on alfuzosin and > placebo: pain, abdominal pain, dyspepsia, constipation, nausea, impotence, bronchitis, sinusitis, pharyngitis.

ADEs in post-marketing experience: rash, tachycardia, chest pain, priapism. Case reports of drug-induced dermatomyositis and hepatotoxicity were reported in the literature.

A large phase IV observational study of 3,095 Spanish patients with symptomatic BPH treated with alfuzosin 5mg bid for 60 days reported 2.6% of adverse events as severe and 1.6% of patients dropped out of the study due to ADEs (0.5% related to vasodilation). Postural events occurred in 1.8% of patients. One patient reported sexual dysfunction (impotence) and none reported retrograde ejaculation. In 7,093 patients followed for 3 years on alfuzosin 2.5mg tid, 0.6-1.6% per month dropped out, 0.1-0.5% per month reported an ADE, 0.01-0.03% per month had acute urinary retention, and 0.1-0.3% per month had surgery. No retrograde ejaculation was reported.

The following changes in blood pressure (BP) or orthostatic hypotension (OH) were tested for in 3 placebo-controlled trials at days 14, 28, 56, and 84 (patients with a decrease in systolic BP of > 20 mm Hg from supine to standing for 2 minutes were excluded).

Adverse Event	Placebo N=674 (%)	Alfuzosin N=469 (%)
Definitions*		

Decreased systolic BP	0	1 (0.2)
Decreased diastolic BP	3 (0.4)	4 (0.9)
Orthostatic hypotension	52 (7.7)	31 (6.6)

*Positive for BP decrease:

- Supine systolic BP ≤ 90 mm Hg, with a decrease ≥ 20 mm Hg compared to baseline
- Supine diastolic BP ≤ 50 mm Hg, with a decrease ≥ 15 mm Hg compared to baseline

*Positive for orthostatic hypotension (OH):

- Decrease in systolic BP ≥ 20 mm Hg upon standing from a supine position

Results from pooled-analysis[8]

Mean BP (mm Hg)	Placebo	Alfuzosin
Overall	**N=478**	**N=469**
Baseline systolic BP	137.7 ± 16.9	136.3 ± 16.5
Baseline diastolic BP	82.6 ± 9.6	81.9 ± 9.8
Mean change	-1.3 ± 14.7/-2.0 ± 10.0	-2.1 ± 14.7/-0.9 ± 8.7
Asymptomatic OH	8 (1.7%)	10 (2.1%)
Elderly (≥ 65 years of age)	**N=209**	**N=224**
Baseline systolic BP	142.0 ± 16.9	138.2 ± 16.7
Baseline diastolic BP	82.7 ± 9.4	81.4 ± 9.9
Mean change	-1.7 ± 15.1/-0.2 ± 9.0	-1.3 ± 15.3/-1.4 ± 10.0
Asymptomatic OH	2 (1.0%)	5 (2.2%)
Hypertensive	**N=141**	**N=130**
Baseline systolic BP	147.2 ± 18.1	142.7 ± 15.8
Baseline diastolic BP	87.6 ± 10.7	85.5 ± 9.7
Mean change	-2.6 ± 17.0/-1.8 ± 9.1	-2.1 ± 17.6/-2.4 ± 10.4
Asymptomatic OH	5 (3.5%)	1 (0.8%)

Contraindications[1]

Alfuzosin is contraindicated in patients with moderate or severe hepatic insufficiency. It is also contraindicated in patients who are hypersensitive to alfuzosin or any of its components. Alfuzosin should not be administered to patients who are receiving concomitant therapy with a potent CYP3A4 inhibitor (e.g., ketoconazole, itraconazole, and ritonavir).

Warnings[1]

Postural hypotension may occur within a few hours after administration of alfuzosin. Syncope may also occur. Patients should be counseled to avoid activities that could result in injury if syncope were to occur. Use with caution in patients who have symptomatic hypotension or who have previously experienced a hypotensive response to other medications.

Precautions[1,2,13,14]

- *Prostatic carcinoma*: The manufacturer recommends that patients with BPH should be examined for prostatic carcinoma prior to being prescribed alfuzosin. However, the VA recommends screening for

prostate carcinoma, including use of the serum prostate-specific antigen (PSA) test be a shared decision with patient and clinician. The AUA recommends that PSA testing be offered to patients with at least a 10-year life expectancy and for whom knowledge of the presence of prostate cancer would change management.

- *Drug-drug interactions*: Alfuzosin should not be coadministered with other alpha-adrenergic blockers (see also Drug Interactions below).

- *Coronary insufficiency*: Alfuzosin should be discontinued if the patient presents with new or worsening angina symptoms.

- *Hepatic insufficiency*: Alfuzosin should not be prescribed in patients with moderate to severe hepatic insufficiency (the kinetics have not been studied in patients with mild hepatic insufficiency).

- *Renal insufficiency*: Pharmacokinetic studies showed that systemic exposure of alfuzosin increased by 50% in patients with mild, moderate, and severe renal insufficiency. Use caution in patients with severe renal insufficiency, as limited data are available in patients with a creatinine clearance < 30 mL/min.

- *Congenital or acquired QT prolongation*: Studies on the effect of alfuzosin on the QT interval were conducted as required by the FDA. The mean changes in corrected QT (i.e., Fridericia correction) from baseline were 4.9msec with alfuzosin 10mg, 7.7msec with alfuzosin 40mg (4 times the maximum dose), and 12.7msec with moxifloxacin 400mg (active control). According to reports from the FDA Cardio-Renal Committee discussion, the Committee voted 13 to zero (with one abstention) that the effect of alfuzosin on the QT interval was not "clinically relevant". It was reported that the effect on repolarization was acknowledged, and the risk vs. benefit should be taken into consideration for each patient. The manufacturer's product information states that the effect of alfuzosin on the QT interval should be considered in patients with a history of QT prolongation or who are taking medications that result in prolongation of the QT interval. It was noted that the manufacturer states that there have been no reports of torsade de pointes since the availability of alfuzosin in Europe in 1988.

- *Pregnancy Category B/Nursing Mothers*: Alfuzosin is not indicated for use in women.

Drug Interactions[1]

- *Potent CYP3A4 inhibitors*: Alfuzosin is principally metabolized by the CYP3A4 enzyme and should not be administered with potent CYP3A4 inhibitors including ketoconazole, itraconazole, and ritonavir. Coadministration with ketoconazole increased the Cmax of alfuzosin 2.3 fold and AUC 3.2 fold.

- *Moderate CYP3A4 inhibitors*: Concomitant administration with diltiazem increased the Cmax of alfuzosin 1.5 fold and AUC 1.3 fold, with an increase of 1.4 fold the Cmax and AUC of diltiazem, without any changes in blood pressure.

- *Other drug interactions*: There were no significant drug interactions noted with warfarin, digoxin, or hydrochlorothiazide. Cimetidine increased the Cmax and AUC of alfuzosin by 20%. Atenolol increased the Cmax of alfuzosin by 28% and the AUC by 21%. In addition, alfuzosin increased the Cmax of atenolol by 26% and the AUC by 14%, with a significant decrease in blood pressure and mean heart rate. Alfuzosin did not inhibit CYP 1A2, 2A6, 2C9, 2C19, 2D6, or 3A4 nor did it induce CYP 1A, 2A6, or 3A4.

Clinical Trials[15-17]

<table>
<tr><td>Citation[15]</td><td>Roehrborn CG, for the ALFUS Study Group. Efficacy and safety of once-daily alfuzosin in the treatment of lower urinary tract symptoms and clinical benign prostatic hyperplasia: a randomized, placebo-controlled trial. Urology 2001;58:953-9.</td></tr>
<tr><td>Study Goals</td><td>• To assess the safety and efficacy of alfuzosin once-daily in patients with lower urinary tract symptoms (LUTS) and symptomatic BPH
• To determine the optimal dosage of alfuzosin once-daily in the same patient population</td></tr>
<tr><td>Study Endpoints</td><td>Primary Endpoints
• International Prostate Symptom Score (IPSS)
• Maximum urinary flow rate (Qmax)

Secondary Endpoints
• Quality of Life (QOL) index</td></tr>
<tr><td>Methods</td><td>• Study Design
➢ Multi-center (32 urology centers in U.S. and Canada)
➢ Double-blind, placebo-controlled
➢ After a 4-week, single-blind, placebo run-in period, patients were randomly assigned to treatment with alfuzosin 10mg once daily (qd), alfuzosin 15mg once daily, or placebo for 12 weeks.
➢ Patient assessment occurred at screening, randomization (4 weeks later), and on days 28, 56, and 84 of treatment. Improvement in QOL and LUTS symptoms were assessed at each visit by QOL index and IPSS. Uroflowmetry was performed at screening, randomization, and on days 28 and 84 of treatment. Physical examination including supine blood pressure (BP) and upright after 5 minutes was conducted at each visit. Patients were assessed for prostate size by transrectal ultrasonography.
• Statistical Analysis
➢ Primary endpoint analysis was conducted in the intention-to-treat population. Repeated measures analysis with the last observation carried forward was also done. Analysis of variance was used to analyze the two primary efficacy variables, IPSS and Qmax. Improvement in QOL index was analyzed by chi-square or Fischer exact test. Analysis of safety was conducted in patients who received at least one dose of the medication and was evaluated by descriptive analysis. Patients were stratified by age (65 or greater and younger than 65 years) and hypertensive status at baseline.</td></tr>
<tr><td>Criteria</td><td>• Inclusion criteria
➢ Men age ≥ 50 years with a history of LUTS consistent with BPH for ≥ 6 months
➢ IPSS of ≥ 13 (0 to 35 point scale)
➢ Qmax between 5 and 12 mL/s (with a voided volume of ≥ 150mL)
➢ Residual urine volume ≤ 350mL
➢ QOL index of at least 3 points (0 to 6 point scale)
• Exclusion criteria
➢ Concomitant lower urinary tract disease
➢ Previous prostate surgery
➢ History of postural hypotension or syncope
➢ Concomitant use of medications with the potential to alter the voiding pattern
➢ Clinically relevant biochemical abnormalities
➢ Serum prostate-specific antigen > 10ng/mL (patients with a level of 4 to 10ng/mL required prostate cancer to be ruled-out)</td></tr>
<tr><td>Results</td><td>• Table 1. Efficacy
<table>
<tr><th>Efficacy (day 84)</th><th>Placebo (n=167)</th><th>Alfuzosin 10mg (n=170)</th><th>Alfuzosin 15mg (n=165)</th></tr>
<tr><td>IPSS (mean change from baseline)
IPSS (≥ 3 point ↓)</td><td>-1.6 ± 5.8
39%</td><td>-3.6 ± 4.8[a]
56%[b]</td><td>-3.4 ± 5.7[b]
52%[c]</td></tr>
<tr><td>Qmax (mean change from baseline)
Qmax (≥ 2 mL/sec ↑)</td><td>+0.2 ± 3.5
26%</td><td>+1.7 ± 4.2[d]
40%[f]</td><td>+0.9 ± 3.6[e]
41%[f]</td></tr>
</table>
[a] P=0.001 vs. placebo; [b] P=0.004 vs. placebo; [c] P=0.02 vs. placebo; [d] P=0.0004 vs. placebo; [e] P=0.12 vs. placebo; [f] P=0.008 vs. placebo
➢ Efficacy (as measured by IPSS) occurred at the first post-treatment assessment (day 28) and was maintained during the study
➢ Both voiding and filling IPSS subscores significantly improved with both doses vs. placebo; nocturia criterion significantly improved with alfuzosin 10mg vs. placebo (-0.4, P=0.02)
➢ Efficacy (as measured by Qmax) was optimal at the first post-treatment assessment (day 28) and was maintained with alfuzosin 10mg, but not alfuzosin 15mg vs. placebo
➢ When median changes in Qmax were analyzed, alfuzosin 10mg (+1.1 mL/sec) and 15mg (+1.0 mL/sec) had comparable changes from baseline that were statistically significant compared to placebo (P=0.0006)
• Quality of Life
➢ QOL index: improved significantly in both treatment groups compared to placebo [-0.7 ± 1.1 (10mg), -0.7 ±</td></tr>
</table>

<table>
<tr><td></td><td>
1.2 (15mg) vs. -0.3 ± 1.1 (placebo); P=0.002]
➢ Percent ≥ 2 points improvement in QOL index: significantly higher in both treatment groups compared to placebo (~21% vs. 12%; 10mg P=0.004, 15mg P=0.003)
• Safety
➢ Overall incidence of discontinuation due to adverse events was 3.7%
➢ Serious adverse events occurred in 8 (4.5%) and 6 (3.4%) patients on alfuzosin 10mg and 15mg, respectively, and in 5 (2.9%) patients on placebo
➢ Treatment related adverse events were reported in 52%, 43%, and 43% of patients on alfuzosin 10mg, 15mg, and placebo, respectively
➢ The most common adverse event was dizziness which was reported in 13 (7.4%) and 16 (9.0%) patients on alfuzosin 10mg and 15mg, respectively, and in 5 (2.9%) patients on placebo
➢ Patients in the older patient population (≥ 65 years) experienced a greater percentage of adverse events potentially related to vasodilation (17%) compared to the patients < 65 years (5%)
➢ One patient in each alfuzosin treatment group experienced temporary ejaculatory disorders reported not be related to the study drug
➢ Orthostatic hypotension was reported in 3.4% and 2.3% of patients on alfuzosin 10mg and 15mg, respectively, which was similar to 3.4% of patients on placebo; in patients ≥ 65 years of age, the incidence was 1.3% and 3.8% of patients on alfuzosin 10mg and 15mg, respectively, and 1.5% of patients on placebo; for patients with hypertension, the incidence was reported in 1.7% and 2.2% of patients on alfuzosin 10mg and 15mg, respectively, and 9.3% of patients on placebo
➢ Blood pressure changes were reported not to be significant vs. placebo
<table>
<tr><th>Blood Pressure Changes</th><th>Placebo</th><th>Alfuzosin 10mg</th><th>Alfuzosin 15mg</th></tr>
<tr><td>Supine SBP (mmHg)</td><td>-1.1 ± 15.0</td><td>-2.3 ± 14.6</td><td>-2.7 ± 13.6</td></tr>
<tr><td>Supine DBP (mmHg)</td><td>-0.8 ± 7.9</td><td>-1.5 ± 8.5</td><td>-2.1 ± 8.5</td></tr>
</table>
</td></tr>
<tr><td>Conclusions</td><td>
• Alfuzosin 10mg is safe and effective for the treatment of LUTS due to BPH (including patients ≥ 65 years of age and patients with hypertension); a dose of 15mg did not provide additional efficacy
• ARR=17%; NNT=5.9 patients with alfuzosin 10mg qd for 12 weeks to reduce IPSS ≥ 3 points
</td></tr>
<tr><td>Critique</td><td>
• Strengths
➢ Supported efficacy of alfuzosin 10mg extended-release formulation
➢ Reported orthostatic and blood pressure changes
➢ Randomized, placebo-controlled
• Limitations
➢ Only difference in baseline characteristics was a statistically significant higher prostate volume in the alfuzosin 10mg treatment group (P<0.05)
➢ Inclusion criteria not confirmed at second screening visit, leading to increased baseline variability and unilateral regression to the mean
➢ Thirteen percent of patients withdrew from the study, reasons not clearly specified
➢ First-dose syncope not evaluated
➢ Study concluded that alfuzosin 15mg did not provide additional efficacy although a statistical comparison of 10mg vs. 15mg was not conducted
➢ Details of QOL assessments were limited
</td></tr>
<tr><td>Sponsorship</td><td>
• Sponsored by Sanofi-Synthelabo
</td></tr>
</table>

<table>
<tr><td>Citation[16]</td><td>Van Kerrebroeck P, Jardin A, Laval KU, van Cangh P, and the ALFORTI Study Group. Efficacy and safety of a new prolonged release formulation of alfuzosin 10 mg once daily versus alfuzosin 2.5 mg thrice daily and placebo in patients with symptomatic benign prostatic hyperplasia. Eur Urol 2000;37:306-13.</td></tr>
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• IPSS

Secondary Endpoints
• Maximum urinary flow rate
• Residual urine volume
• QOL index</td></tr>
<tr><td>Methods</td><td>• Study Design
➢ Multi-center (48 urology centers in Europe)
➢ Double-blind, placebo-controlled
➢ After a 4-week, placebo-controlled run-in period, 447 patients were randomly assigned to treatment with alfuzosin 10mg once daily, alfuzosin 2.5mg three times daily (tid), or placebo for 12 weeks.
➢ Patient assessment occurred after 14, 28, 56, and 84 days of treatment. Improvement in QOL and LUTS were assessed at each visit by QOL index and IPSS. The primary endpoint was change from baseline in IPSS. Uroflowmetry and residual urine volume were performed at each assessment. Physical examination including supine systolic and diastolic BP and when upright, were conducted at each visit. Routine blood and chemistry tests were performed prior to inclusion and at the end of the study.
• Statistical Analysis
➢ Data were analyzed on the basis of an intention-to-treat population. The primary efficacy variable was IPSS. Endpoint analyses of mean changes from baseline were conducted. Repeated measures analysis with the last observation carried forward was also done. Secondary variables included change from baseline in maximum flow rate, residual urine volume, and QOL index. Safety and ADEs were assessed and patients were stratified into age subgroups (< 65 and ≥ 65 years) and according to BP (supine DBP < 90 mm Hg or ≥ 90 mm Hg at baseline).
➢ Analysis of variance was used to compare treatments for all quantitative criteria, a chi-square test for binary variables, and Cochran-Mantel-Haenszel test for ordinal categorial variables. The D_{end}-D_0 analysis was adjusted on the baseline value with an analysis of variance if there was a difference in baseline between groups.</td></tr>
<tr><td>Criteria</td><td>• Inclusion criteria
➢ Men age ≥ 50 years with micturition disorders related to BPH
➢ IPSS of ≥ 13
➢ Maximum flow rate between 5 and 12 mL/s (with a voided volume of ≥ 150mL)
➢ Residual urine volume ≤ 350mL
• Exclusion criteria
➢ Concomitant lower urinary tract disease
➢ Previous prostate surgery or other invasive procedures for treatment of BPH
➢ Associated severe visceral disease
➢ History of postural hypotension or syncope
➢ Concomitant use of medications with the potential to alter the voiding pattern
➢ Clinically relevant biological abnormalities
➢ Serum prostate-specific antigen > 10ng/mL
➢ α_1-blockers within 1 month prior to selection
➢ Androgen, antiandrogen, 5α-reductase inhibitors, or LHRH analogues within 3 months prior to selection</td></tr>
<tr><td>Results</td><td>• Table 1. Efficacy
<table>
<tr><th>Efficacy (3 months)</th><th>Placebo (n=152)</th><th>Alfuzosin 10mg qd (n=137)</th><th>Alfuzosin 2.5mg tid (n=165)</th></tr>
<tr><td>IPSS (baseline)</td><td>17.7 ± 4.1</td><td>17.3 ± 3.5</td><td>16.8 ± 3.7</td></tr>
<tr><td>IPSS (3 months)</td><td>12.8 ± 6.7</td><td>10.4 ± 4.7</td><td>10.5 ± 6.1</td></tr>
<tr><td>IPSS (absolute change)</td><td>-4.9 (28%)</td><td>-6.9 (40%)[a]</td><td>-6.4 (38%)[b]</td></tr>
</table>
[a] P=0.002 vs. placebo; [b] P=0.02 vs. placebo
➢ Symptom improvement (as measured by IPSS) was statistically significant with both treatments compared to placebo (refer to table above).
➢ Increases in peak flow rate (PFR) from baseline were statistically significantly higher with treatment [2.3ml/s alfuzosin 10mg qd (P=0.03); 3.2ml/s alfuzosin 2.5mg tid (P<0.0001); 1.4ml/s placebo] compared to placebo.
➢ Both voiding and filling IPSS subscores significantly improved with both doses vs. placebo.</td></tr>
</table>

- Quality of Life
  - Improvement in QOL index was statistically significant with both treatments compared to placebo [-1.1 alfuzosin 10mg (P=0.0008); -1.0 alfuzosin 2.5mg tid (P=0.005); -0.6 placebo].
- Safety
  - Forty (8.9%) patients discontinued the study with 4.5% due to adverse events
  - Overall, vasodilatory events occurred in 9 (6.3%), 14 (9.4%), and 4 (2.6%) of patients on alfuzosin 10mg qd, 2.5mg tid, and placebo, respectively. One patient discontinued the study due to syncope in the alfuzosin 2.5mg tid group; none of the patients in the other study groups were discontinued due to syncope. Vasodilatory adverse events did not differ in the subgroups according to age.
  - Other adverse events potentially related to treatment were reported as follows:

Adverse Event	Placebo (n=154)	Alfuzosin 10mg qd (n=143)	Alfuzosin 2.5mg tid (n=149)
Dizziness	2 (1.3%)	3 (2.1%)	7 (4.7%)
Headache	1 (0.6%)	2 (1.4%)	3 (2%)
Hypotension/postural hypotension	0 (0%)	1 (0.7%)	2 (1.3%)
Malaise	0 (0%)	2 (1.4%)	1 (0.7%)
Asthenia/fatigue	4 (2.6%)	5 (3.5%)	1 (0.7%)
Sexual dysfunction	2 (1.3%)	0 (0%)	1 (0.7%)

  - There were no reports of ejaculation disorders in any study group.
  - Serious adverse events occurred in 8 (4.5%) and 6 (3.4%) patients on alfuzosin 10mg and 15mg, respectively, and in 5 (2.9%) patients on placebo.
  - Blood pressure changes were reported not to be significant vs. placebo and were reported not to be clinically significant in the normotensive and hypertensive patient subgroups.

Mean BP Changes (mmHg)	Placebo*	Alfuzosin 10mg qd*	Alfuzosin 2.5mg tid*
Supine SBP			
Hypertensive	-4.3 ± 16.8 (54)	-4.5 ± 18.8 (49)	-5.4 ± 17.3 (63)
Normotensive	-0.5 ± 13.6 (99)	-0.4 ± 12.0 (94)	-0.9 ± 14.6 (84)
All patients	-1.2 ± 14.9 (153)	-1.3 ± 14.8 (143)	-2.8 ± 15.9 (147)
Supine DBP			
Hypertensive	-5.8 ± 9.6 (54)	-8.1 ± 11.7 (49)	-8.6 ± 9.7 (63)
Normotensive	2.2 ± 8.7 (99)	1.5 ± 8.5 (94)	1.1 ± 8.0 (84)
All patients	-0.6 ± 9.8 (153)	-1.8 ± 10.7 (143)	-3.1 ± 10.0 (147)
Standing SBP			
Hypertensive	-5.2 ± 18.8 (54)	-6.7 ± 19.6 (49)	-7.7 ± 15.1 (63)
Normotensive	0.4 ± 12.0 (99)	0.3 ± 10.9 (94)	-3.1 ± 15.0 (83)
All patients	-1.6 ± 15.0 (153)	-2.1 ± 14.8 (143)	-5.1 ± 15.2 (146)
Standing DBP			
Hypertensive	-5.0 ± 11.0 (54)	-8.1 ± 10.6 (49)	-8.1 ± 9.7 (63)
Normotensive	1.3 ± 8.0 (99)	-0.1 ± 8.7 (94)	-0.1 ± 8.2 (83)
All patients	-0.9 ± 9.6 (153)	-2.8 ± 10.2 (143)	-3.6 ± 9.7 (146)

*(n); 30% received antihypertensive treatment and 63% received at least one concomitant medication

Conclusions

- Treatment with alfuzosin 10mg qd and alfuzosin 2.5mg tid significantly improved the primary endpoint of mean change from baseline in IPSS compared to placebo.
- Treatment with alfuzosin was generally well tolerated and the once daily 10mg dose had less cardiovascular adverse events compared to 2.5mg tid or placebo.

Critique

- Strengths
  - Double-blind, randomized, multi-center, placebo-controlled trial for 3 months
  - Improvement in IPSS reflected in improvement in QOL index
  - Mean changes in BP reported in both hypertensive and normotensive subgroups
- Limitations
  - The authors concluded that alfuzosin 10mg qd provides a better cardiac safety profile compared to alfuzosin 2.5mg tid based on reported vasodilatory adverse events, although this did not include a statistical comparison. It was reported that there was not a statistically significant difference in supine systolic or diastolic BP reduction with alfuzosin 10mg qd compared to placebo, although results of a statistical analysis were not reported.
  - Secondary endpoint of residual urine volume not reported
  - Determination of filling and voiding subscores not adequately described
  - Baseline PFR was significantly lower in the alfuzosin 2.5mg tid treatment group
  - Determination of PFR obtained at trough with the 10mg dose and at peak with the 2.5mg dose

Sponsorship

- None reported.

Open-label Extension Study[17]	• Open-Label Extension Study ➢ Of 447 patients in the double-blind study, 311patients were placed on alfuzosin 10mg qd in the open-label extension study for 9 months ➢ At the end of the 9-month extension phase (i.e., month 12 of treatment), the decrease in IPSS from baseline was maintained and statistically significant compared to baseline in all three treatment groups (P<0.0001). Patients previously in the placebo group of the double-blind study had a statistically significant decrease in IPSS at month 13 compared to month 3, when the extension study began (P<0.0001). For all groups, the mean IPSS at baseline was 17.1 ± 3.6, and 10.9 ± 5.6 and 9.3 ± 5.5 at month 3 and month 12, respectively. ➢ There was a statistically significant difference in QOL index, with an improvement from a baseline of 3.3 ± 0.9, to 2.3 ± 1.1 at month 3 and 2.1 ± 1.2 at month 12 (P<0.0001). ➢ The increase in PFR at month 12 (11.3 ± 4.2 ml/s) was statistically significant compared to baseline (9.1 + 2.0ml/s) (P<0.0001). ➢ Data from 360 patients were used to evaluate safety and were similar to the double-blind study: asthenia/fatigue 3.6%, dizziness 2.5%, abdominal pain 2.2%, rhinitis 2.2%, diarrhea 1.4%, dyspepsia 1.4%, headache 1.4%, malaise 1.1%. Ejaculation disorders occurred in 2 patients (0.6%). Treatment was discontinued in 10 (5.6%) patients, with 4 (1.1%) discontinuing due to events related to vasodilation. Orthostatic hypotension, as defined by a decrease in SBP of > 20mmHg upon standing, occurred in 10 (2.8%) patients. These cases were reported to be asymptomatic. Mean decreases in SBP and DBP were 2.6 and 2.8 mm Hg, respectively, compared to baseline. ➢ The authors concluded that treatment with alfuzosin 10mg qd was well olerated and maintained clinical efficacy and improvement in QOL up to 12 months.

Trial Summary[15-17]

Trial	Baseline (mean)	Results (mean change endpoint vs. baseline)
ALFUS[15]	IPSS 21.4 Qmax 8.7ml/s QOL index 4.1	EP / Placebo / Alfuzosin 10mg qd / P value* / Alfuzosin 15mg qd / P value* N / 167 / 170 / / 165 / IPSS / -1.6 / -3.6 / <0.005 / -3.4 / <0.005 Qmax / 0.2 / 1.7 / <0.0005 / 0.9 / QOL / -0.3 / -0.7 / <0.005 / -0.7 / <0.005 * vs. Placebo
ALFORTI[16]	IPSS 17.3 Qmax 9.1ml/s QOL index 3.3	EP / Placebo / Alfuzosin 10mg qd / P value* / Alfuzosin 2.5mg tid / P value* N / 152 / 137 / / 147 / IPSS / -4.9 / -6.9 / <0.005 / -6.4 / <0.05 Qmax / 1.4 / 2.3 / <0.05 / 3.2 / <0.0005 QOL / -0.6 / -1.1 / <0.005 / -1.0 / <0.005 * vs. Placebo
ALFORTI Extension[17]	IPSS 17.3 Qmax 9.1ml/s QOL index 3.3	EP / Alfuzosin 10mg qd / P value N / 311 / IPSS / -7.8 / <0.0005 Qmax / 2.2 / <0.0005 QOL / -1.2 / <0.0005 * vs. Baseline

EP=endpoint; IPSS=International Prostate Symptom Score; Qmax=maximal urinary flow rate; QOL=Quality of Life

Pooled analyses[8,18]

Analysis	Patients/Methods	Results	Adverse Events
Roehrborn CG, et al.[8] 3 db, pc studies (refer to Clinical Trials for 2 of the studies[15,16])	Alfuzosin 10mg qd Placebo 12 weeks PEP: IPSS, PFR	PEP / Placebo N=482 / Alfuzosin N=473 / P value IPSS / -6.0 ± 5.1 / -4.2 ± 5.7 / < 0.005 PFR / +2.3 ± 3.8 / +1.1 ± 3.1 / < 0.001	Withdrawals: Placebo 8.7%; Alfuzosin 9.5% Dizziness: Placebo 2.9%; Alfuzosin 6.1% Impotence: Placebo 0.6%; Alfuzosin 1.5% Syncope: Placebo none; Alfuzosin 0.2% BP (Overall): Placebo -1.3/-2.0 (137.7/82.6); Alfuzosin -2.1/-0.9 (136.3/81.9). (HTN): Placebo -2.6/-1.8 (147.2/87.6); Alfuzosin -2.1/-2.4 (142.7/85.5). (Elderly): Placebo -1.7/-0.2 (142/82.7); Alfuzosin -1.3/-1.4 (138.2/81.4)

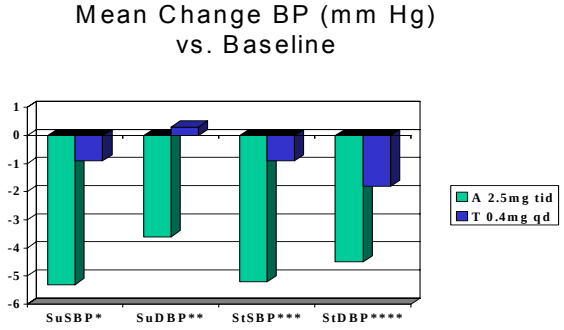
db=double-blind; HTN=patients with hypertension; IPSS=International Prostate Symptom Score; pc=placebo-controlled; PEP=primary endpoint; PFR=peak urinary flow rate

A pooled analysis of 11 studies showed treatment with alfuzosin to significantly decrease the post-void residual volume compared to placebo (P=0.01) however, treatment included alfuzosin at doses other than the approved 10mg extended-release qd.[18]

Comparison of alfuzosin to other alpha$_1$-adrenergic blockers[19-28]

Comparison trials of alfuzosin with other alpha$_1$-adrenergic blockers are limited with the extended-release preparation at a dose of 10mg qd. A meta-analysis of trials from a Medline search up to October 1998 included studies with alfuzosin (3 trials), doxazosin (6 trials), tamsulosin (5 trials), terazosin (7 trials), and 4 comparison trials (including alfuzosin vs. prazosin and alfuzosin vs. tamsulosin, both with alfuzosin 2.5mg tid). The meta-analysis evaluated efficacy (by AUA symptom score and Qmax) and tolerability (by withdrawal due to ADEs and ADEs due to vasodilation) in a total of 6,333 patients from the placebo-controlled studies and 507 patients from the comparative studies. The meta-analysis concluded that all agents evaluated produced comparable efficacy in improving LUTS and urinary flow. There was a 30-45% improvement in total symptom score (10-20% greater improvement compared to placebo) and a 15-30% improvement in Qmax (10-15% greater improvement compared to placebo). There was a difference in the tolerability of the agents with the uroselective agents (i.e., alfuzosin, tamsulosin) having less adverse effects compared to doxazosin and terazosin. Withdrawal rates with alfuzosin and tamsulosin were comparable to placebo (i.e., 4-10%) with an additional 4-10% of patients withdrawing in the trials with doxazosin or terazosin. Dizziness was slightly higher with alfuzosin and tamsulosin ($\leq$ 5%) compared to placebo (3-10%) whereas this side effect was more pronounced with doxazosin and terazosin (additional 5-20% vs. placebo). The meta-analysis reported tamsulosin to have less of an effect on blood pressure compared to alfuzosin and less orthostatic hypotension compared to treatment with terazosin during orthostatic stress testing. Reports of orthostatic hypotension were approximately 1% with alfuzosin and tamsulosin (comparable to placebo) and 2-8% with doxazosin and terazosin.[19] One direct comparison found a statistically significant difference in the blood pressure lowering effect (i.e., supine SBP and DBP, and standing DBP) with alfuzosin (2.5mg tid) compared with tamsulosin (0.4mg qd). This difference was reported to be more pronounced in older patients.[19,20]

The European Tamsulosin Study Group compared treatment with alfuzosin (2.5mg tid) vs. tamsulosin (0.4mg qd) for 12 weeks in 256 with LUTS suggestive of bladder outlet obstruction (BOO). Treatment with alfuzosin and tamsulosin statistically significantly improved the primary endpoint of Qmax and Boyarsky symptom score compared to baseline without a significant difference between treatment groups. Withdrawals due to adverse events were 4% (5 of 119) for alfuzosin and 8% (10 of 126) for tamsulosin. Treatment related adverse events that occurred in $\geq$ 3% of patients were not statistically significantly different between groups. Statistically significant changes in blood pressure were found between patients receiving alfuzosin vs. tamsulosin (refer to chart below).[20]



*P=0.019; **P=0.002; ***P=0.057; ****P=0.044
Mean baseline BP: Alfuzosin (A) 146.1/88.5 mm Hg; Tamsulosin (T) 141.0/88.0 mm Hg
Adapted from Buzelin JM et al. Br J Urol 1997;80:597-605.[20]

According to a subgroup analysis, the greater blood pressure reduction was greater in patients who were older (≥ 65 years of age) compared to younger patients (< 65 years of age) with a difference of approximately 9/5 mm Hg (P=0.016/0.007) between treatment groups in the older patient population. Patients were also classified into normotensive (DBP < 95 mm Hg) and hypertensive (DBP ≥ 95 mm Hg) with only the supine BP statistically significantly decreased in the normotensive group with alfuzosin vs. tamsulosin (refer to table below). The BP reductions in hypertensive patients were not statistically different between treatment groups.[20]

Patient Population	Normotensive		Hypertensive	
	Alfuzosin N=85	Tamsulosin N=103	Alfuzosin N=35	Tamsulosin N=24
Supine SBP/DBP				
Baseline	141.5/83.0	139.5/82.1	157.2/101.7	162.8/101.2
Mean change	-4.5/-1.7	-0.2/2.3	-7.0/-8.1	-3.8/-8.3
P value		0.029/0.002		0.685/0.879
Standing SBP/DBP				
Baseline	137.8/83.5	137.5/84.9	155.6/101.4	155.8/101.3
Mean change	-3.2/-2.3	-0.2/-0.2	-10.2/-9.9	-4.0/-8.6
P value		0.131/0.088		0.522/0.481

The results of these comparative trials are difficult to interpret, as they were not conducted with the currently available extended-release formulation of alfuzosin 10mg qd.

The AUA Practice Guidelines Committee Panel conducted a meta-analysis of the alpha$_1$-adrenergic blockers in placebo-controlled trials and concluded that doxazosin, terazosin, alfuzosin, and tamsulosin are similar in their effectiveness of partially relieving symptoms and improving the AUA Symptom Index an average of 4 to 6 points. By a similar comparison, the alpha$_1$-adrenergic blockers vary slightly in their adverse event profile, with tamsulosin appearing to have a slightly lower occurrence of orthostatic hypotension but a slightly higher probability of ejaculatory dysfunction compared to other alpha$_1$-adrenergic blockers. Ejaculatory dysfunction was reported as 1% for placebo, doxazosin, terazosin and 10% for tamsulosin (data not available for alfuzosin). There was also a significant difference in the rate of respiratory/nasal congestion, reported to be higher with tamsulosin vs. alfuzosin ($p<0.05$).[2,21]

A phase III placebo-controlled study of tamsulosin 0.4mg and 0.8mg reported abnormal ejaculation in 6% of patients on 0.4mg and 18% of patients on 0.8mg ($p<0.001$ vs. placebo).[22] In a 40-week extension study, the incidence increased to 10% and 26% in the 0.4mg and 0.8mg treatment groups, respectively.[23] In a second U.S. double-blind phase III clinical trial comparing tamsulosin 0.4mg, 0.8mg and placebo in 735 patients, abnormal ejaculation was reported in 11% of patients on 0.4mg and 18% on 0.8mg, compared with <1% on placebo ($p<0.01$ vs. placebo; $p\leq 0.05$ 0.4mg vs. 0.8mg).[24] Abnormal ejaculation was reported in 30% of patients in a U.S. extension study of an additional 64 weeks (combined data of 0.4mg and 0.8mg).[25] In a European three-year open-label extension study of tamsulosin 0.4mg in 355 patients, the treatment-emergent cumulative adverse events up to three years were 5.4% for abnormal ejaculation.[26] In the comparison trial of alfuzosin and tamsulosin discussed earlier, abnormal ejaculatory disorders were not reported.[20] In an evaluation of data from two placebo-controlled trials with tamsulosin 0.4mg qd and one comparative trial with tamsulosin 0.4mg qd and alfuzosin 2.5mg tid, the incidence of abnormal ejaculation (i.e., retrograde ejaculation or reduced volume) was reported to be 4.5% on tamsulosin vs. 1% on placebo (P=0.045). This adverse effect was reported within the first few weeks of therapy. Three (0.8%) patients withdrew due to sexual dysfunction in the tamsulosin group compared to 1 (0.5%) on placebo. It was reiterated that the comparison trial did not show a significant difference in reports of abnormal ejaculation between tamsulosin (0.8%) and alfuzosin (0%).[27] It is thought that the alpha-$_{1A}$ adrenoreceptor may be important in contraction of the vas deferens and the affinity of tamsulosin for this receptor subtype may contribute to ejaculatory dysfunction.[15] Others have questioned whether the difference in incidence of abnormal ejaculation is due to the potential difference in the mechanism of action of the drugs or the patient population studied.[28]

One trial compared alfuzosin with a 5α-reductase inhibitor and the combination in 1,051 patients with LUTS related to BPH, irrespective of prostate size. The improvement in IPSS was statistically significantly greater with alfuzosin 5mg bid alone (-6.3 ± 5.8) or in combination (-6.1 ± 5.6), compared to finasteride alone (-5.2 ± 5.7; p=0.01, p=0.03, respectively). The difference in Qmax was not statistically significant between treatment groups at 6 months. Withdrawals due to adverse events were similar in the three treatment groups. The incidence of postural hypotension or hypotension were not significantly different. Ejaculation failure was reported significantly more frequently in patients on combination therapy and finasteride monotherapy compared to alfuzosin alone (p=0.04). There was not a significant difference in mean blood pressure changes.[29] The AUA guidelines recommend that combination with a 5α-reductase inhibitor and alpha$_1$-adrenergic blocker may be considered in patients with LUTS associated with prostatic enlargement.[2]

Acquisition Cost

Drug	Dose	FSS Price/Dose	Drug Cost/Patient/Month*	Annual Drug Cost/Patient*
Alfuzosin	10mg qd	$1.0288	$30.86	$370.37
Tamsulosin	0.4mg qd	$1.1591	$34.77	$417.28

*Price for treatment with formulary alpha$_1$-adrenergic blockers range: $1.34-2.99/month or $16.08-35.86/year

Conclusions

Efficacy: Treatment with alfuzosin 10mg extended-release once daily has been shown to be effective in reducing the symptoms associated with BPH (i.e., statistically significant decrease in IPSS and increase in Qmax compared to placebo).

Safety: Alfuzosin has been available as three formulations, the first being a 2.5mg dose administered tid approved in Europe in 1988. The 10mg extended-release product is the first available formulation in the U.S. Alfuzosin appears to be well tolerated with the incidence of adverse effects slightly higher than seen with placebo. Hypotension or postural hypotension was reported in 0.4% of patients on alfuzosin 10mg qd and syncope in 0.2%, with none reported in patients on placebo. Slightly greater decreases in blood pressure were seen with alfuzosin 10mg qd, although this was reported not to be significantly different compared to placebo. Withdrawal rates due to adverse events were approximately 4% in two randomized controlled trials with alfuzosin 10mg qd for 3 months. An open-label extension study of 9 months duration reported that treatment with alfuzosin was discontinued in 5.6% of patients. Alfuzosin should not be prescribed in patients receiving potent CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, ritonavir) or in patients with moderate to severe hepatic insufficiency, and should be used with caution in patients with severe renal impairment. The effect of alfuzosin on the QT interval should be considered in patients with a history of QT prolongation or who are taking medications that result in prolongation of the QT interval.

Long-term outcomes: Outcomes of medical therapies are evaluated based on change in efficacy scores (IPSS, Qmax) as discussed above, and the impact on QOL measurements. Treatment with alfuzosin statistically significantly improves the QOL index compared to placebo. This measurement does not evaluate other QOL issues such as urinary retention or need for surgical intervention.

Comparison to other available agents in drug class: Comparison trials of alfuzosin with other alpha$_1$-adrenergic blockers are limited with the extended-release preparation at a dose of 10mg qd. According to meta-analyses, alfuzosin appears similar in efficacy and safety to other alpha$_1$-adrenergic blockers. One meta-analysis reported tamsulosin to have less of an effect on blood pressure compared to alfuzosin (2.5mg tid). Reports of orthostatic hypotension were approximately 1% with alfuzosin and tamsulosin (comparable to placebo) and 2-8% with doxazosin and terazosin. According to another meta-analysis, tamsulosin appears to have a higher probability of ejaculatory dysfunction compared to other alpha$_1$-adrenergic blockers, although a comparative trial with alfuzosin and tamsulosin did not report ejaculatory dysfunction for either treatment.

Cost: Treatment with alfuzosin is competitively priced compared to treatment with tamsulosin, another clinically uroselective agent for symptomatic BPH. Alfuzosin is substantially higher than treatment with the currently available alpha$_1$-adrenergic blockers, doxazosin, prazosin, and terazosin.

Recommendations

It is recommended that alfuzosin not be added to the VANF or to VISN formularies at this time. Selection of a preferred non-formulary clinically uroselective alpha$_1$-adrenergic receptor blocker for the treatment of symptomatic BPH should be considered. Criteria for non-formulary use established for tamsulosin should also include recommendations for alfuzosin.

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Appendix: Alpha-Blocker Utilization VISN Summary (3rd Quarter FY2003)

VISN	30 DAY EQUIV. RXS	*TERAZOSIN	*DOXAZOSIN	*PRAZOSIN	TAMSULOSIN	PREFERRED %
1	63,078	87.52%	1.80%	2.66%	8.02%	91.98%
2	33,949	90.73%	0.72%	1.91%	6.63%	93.37%
3	59,246	86.82%	1.26%	0.77%	11.16%	88.84%
4	83,960	87.33%	2.76%	6.14%	3.77%	96.23%
5	30,240	87.69%	1.36%	3.18%	7.76%	92.24%
6	66,239	88.61%	3.09%	1.87%	6.43%	93.57%

7	79,679	90.80%	2.17%	1.49%	5.54%	94.46%
8	147,909	91.76%	3.75%	1.81%	2.68%	97.32%
9	70,767	68.04%	14.21%	7.45%	10.31%	89.69%
10	48,658	84.57%	1.00%	8.72%	5.72%	94.28%
11	65,232	71.12%	2.80%	10.93%	15.15%	84.85%
12	62,900	84.86%	1.21%	4.46%	9.47%	90.53%
15	63,453	89.26%	2.39%	3.39%	4.97%	95.03%
16	125,363	80.60%	1.90%	3.57%	13.93%	86.07%
17	67,030	56.89%	27.39%	1.57%	14.15%	85.85%
18	63,422	76.94%	1.93%	12.07%	9.07%	90.93%
19	39,075	75.30%	8.65%	6.24%	9.81%	90.19%
20	46,453	50.66%	1.94%	27.04%	20.36%	79.64%
21	48,780	82.80%	2.05%	6.09%	9.05%	90.95%
22	64,815	76.43%	0.65%	10.25%	12.68%	87.32%
23	76,950	79.08%	4.71%	3.82%	12.39%	87.61%
NATIONAL	**1,407,198**	**81.12%**	**4.27%**	**5.43%**	**9.19%**	**90.81%**