



Alfuzosin HCl (Uroxatral®): An Extended-Release Alpha₁-Adrenergic Receptor Antagonist for Benign Prostatic Hyperplasia

Michelle Gonzales, PharmD, and Deidree Edwards, PharmD

INTRODUCTION

Benign prostatic hyperplasia (BPH) is the most common non-neoplastic disorder of aging American men.¹ The prevalence of BPH increases from 8% in men between 31 and 40 years of age to 50% in men between 51 and 60 years of age to more than 80% in men older than 80 years of age.^{2,3}

Although the exact etiologic mechanism of BPH is unknown, hormonal changes involving the accumulation of dihydrotestosterone (DHT) promote both prostate enlargement and growth.⁴ As the prostate increases in size, pressure is exerted on the lumen of the urethra, causing obstruction of urinary flow.^{2,5} Enlargement of the prostate gland also correlates with excessive alpha-adrenergic tone, resulting in contraction of the prostate gland and narrowing of the urethral lumen.⁶

Symptoms associated with BPH include urinary hesitancy, a weak urine stream, increased urinary frequency or urgency, nocturia, incontinence, and painful urination. Untreated BPH is associated with lower urinary tract symptoms such as gross hematuria, repeated urinary tract infections, and obstructive uropathy.⁴ Standard treatments include

watchful waiting in patients with mild symptomatic BPH, pharmacological treatment with alpha-adrenergic antagonists and 5-alpha reductase inhibitors in patients with moderate-to-severe symptomatic BPH, and surgery in patients with severe symptomatic BPH.¹

Three generations of alpha-adrenergic antagonists have been used to treat BPH:^{1,6}

- First-generation agents antagonize both prostatic and vascular alpha₁-adrenergic and alpha₂-adrenergic receptors.
- Second-generation agents selectively antagonize alpha₁-adrenergic receptors.
- Third-generation agents competitively antagonize prostatic alpha_{1a}-adrenergic receptors.

Because of first dose-related cardiac side effects (i.e., as reflex tachycardia, syncope, and cardiac arrhythmias), the first-generation alpha-adrenergic antagonists have been replaced by second-generation and third-generation alpha-adrenergic antagonists.^{1,6} The four second-generation agents used in the treatment of BPH are (1) terazosin, (2) doxazosin, (3) prazosin, and (4) alfuzosin (Uroxatral®, Sanofi-Synthelabo).

Although alfuzosin HCl has been commercially available in Europe since 1987, it is the first uroselective second-generation alpha-adrenergic antagonist to be marketed in the U.S.⁷ The U.S. Food and Drug Administration (FDA) approved this drug on June 12, 2003, to treat patients with signs and symptoms of BPH. The use of alfuzosin for the treatment of hypertension is not indicated.⁸

CHEMISTRY AND PHARMACOLOGY

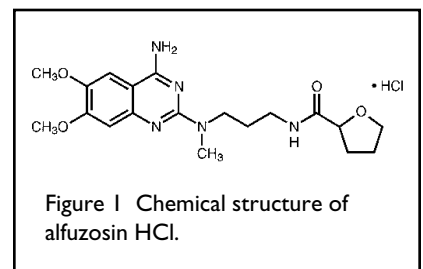
Alfuzosin HCl is a quinazoline derivative. It is chemically designated as (R,S)-N-[3-[(4-amino-6,7-dimethoxy-2-quinazolyl) methylamino] propyl] tetrahydro-2-furancarboxamide HCl.⁸ Its empirical formula is C₁₉H₂₇N₅O₄ HCl, and its molecular weight is 425.9. It is a white to off-white crystalline powder that is freely soluble in water (Figure 1).⁹

Alfuzosin HCl relaxes the tone of the prostate smooth muscle, prostate capsule, bladder neck, and proximal urethra.⁷ It competitively and selectively binds to the postsynaptic alpha₁-adrenergic receptors in the lower urinary tract.^{1,3,9,10} Alfuzosin also relaxes sympathetic nervous stimulation, reduces resting urethral pressure, and inhibits urethral hypertonia-induced sympathetic nervous stimulation.³

As a uroselective agent, alfuzosin preferentially binds to prostatic alpha₁-receptors. Blockade of these receptors results in reduction of BPH symptoms, improvement of urine flow, and a decreased potential for hypertensive events.¹²

PHARMACOKINETICS

The pharmacokinetic profile of extended-release (ER) alfuzosin HCl has been investigated in healthy volunteers and patients with renal impairment.^{1,2,9,14} The ER formulation is composed of a three-layered matrix. The active drug is



At the time of this writing, Dr. Gonzales was a Pharmacy Practice Resident at the Veterans Affairs Medical Center in Miami, Florida. She is now with the VA Medical Center in Hampton, Virginia. Dr. Edwards is a Clinical Pharmacy Specialist in the Department of Internal Medicine at the VA Medical Center in Miami. Drug Forecast is a regular department coordinated by Alan Caspi, PhD, PharmD, MBA, President of Caspi & Associates in New York.

embedded in a hydrophilic core between two impermeable layers.^{1,2,9,14} Upon contact with fluid, the hydrophilic layer expands and the impermeable layers control the rate of drug release from the core, thereby slowing absorption and continually releasing alfuzosin over the dosage interval.¹⁵

ER alfuzosin is absorbed slowly, with a mean maximum plasma concentration (C_{max}) of 16.6 mcg/liter at approximately nine hours.¹³ Because the extent of absorption is decreased by 50% in fasting conditions, ER alfuzosin should be taken immediately after a meal.⁹ The agent's oral bioavailability is 49%, and the mean area-under-the-plasma concentration curve over 24 hours (AUC_{24}) is 238 mcg · hour/liter.¹⁵ In healthy volunteers, the volume of distribution is between 2.5 and 3.2 liters/kg; 90% of the drug is protein-bound.⁹

ER alfuzosin undergoes extensive hepatic metabolism that primarily involves cytochrome P450 isoenzyme CYP3A4.⁹ Although the agent is pharmacologically inactive, 75% to 91% of metabolites are eliminated through the feces and 11% are excreted unchanged in the urine.^{9,16} The mean elimination half-life of alfuzosin is approximately nine hours in healthy volunteers.^{13,16}

Marbury et al. evaluated the pharmacokinetic properties of alfuzosin in patients with renal impairment.¹⁴ No significant changes in half-life were observed for subjects with mild or moderate renal impairment, compared with patients who had normal renal function. Therefore, dosage adjustment is not necessary for

patients with renal insufficiency. However, ER alfuzosin is contraindicated in patients with moderate-to-severe (Child-Pugh class B and C) hepatic insufficiency.¹⁰

A complete pharmacokinetic comparison of the second-generation α_1 -adrenergic receptor antagonists that have been approved to treat BPH is presented in Table 1.^{8,17-19}

CLINICAL TRIALS

The FDA's approval of alfuzosin was based on a reasonable amount of clinical data about the product's immediate-release (IR) and ER formulations. Various investigators have compared the efficacy of alfuzosin with that of placebo as well as with that of other α_1 -adrenergic antagonists.

Comparisons with Placebo

The BPH-ALF Trial³

Jardin et al. evaluated the efficacy of alfuzosin in symptomatic patients with BPH. A total of 518 patients were randomly assigned to receive alfuzosin 7.5 or 10 mg daily for six months. According to the Boyarsky scale, obstructive and irritative symptoms significantly improved in the alfuzosin group compared with the placebo group ($P = .0004$). There was an increase in the dropout rate because of acute urinary retention in the placebo patients, compared with patients receiving alfuzosin (14.6% vs. 6.8%; $P = .004$). For the patients receiving alfuzosin, the urinary flow rate was increased ($P < .05$) and the urinary residual volume was decreased ($P = .017$).

Buzelin et al.²⁰

Buzelin and associates conducted a multicenter trial to assess the efficacy and safety of sustained-release (SR) alfuzosin in the treatment of benign prostatic obstruction. Patients were randomly selected to receive 5 mg of SR alfuzosin twice daily or placebo for one month or three months. Treatment groups were well matched in terms of demographics and baseline disease characteristics. The primary measurement outcomes were symptomatic improvements according to Boyarsky scores and changes in the maximum urinary flow rate (Q_{max}).

From the first month, 42% of patients receiving SR alfuzosin, compared with 32% of patients receiving placebo, demonstrated symptom improvement of greater than 25% ($P = .002$). The treated group had a Q_{max} increase of greater than 29%; the placebo group's rate was 13% ($P < .001$).

The ALFUS²¹ and ALFORTI Trials²²

In the ALFUS and the ALFORTI trials, investigators compared the efficacy of the prolonged-release formulation of alfuzosin in patients with symptomatic BPH with that of placebo.

In the ALFUS study, the primary endpoints included the International Prostate Symptom Score (IPSS), the Q_{max} , and the Quality-of-Life (QOL) Index. The mean changes from baseline to endpoint for the IPSS were -3.6 for alfuzosin 10 mg ($P = .001$), -3.4 for alfuzosin 15 mg ($P = .004$), and -1.6 for placebo. The mean changes in Q_{max} from baseline were +1.7 ml/second for alfu-

Table 1 Pharmacokinetic Parameters of Second-Generation α_1 -Adrenergic Antagonists

Pharmacokinetic Parameters	Prazosin*	Doxazosin†	Terazosin‡	Alfuzosin§
Peak concentration (hours)	1-3	2-5	1-2	8
Bioavailability (%)	48-68	62-69	90	49
Protein binding (%)	92-97	98-99	90-94	90
Liver metabolism	0-demethylation	0-demethylation Hydroxylation	0-demethylation N-dealkylation Hydrolysis	0-demethylation N-dealkylation Oxidation
Excretion in urine (%)	<10	9	40	11
Half-life (hours)	2-4	8.8-22	9-12	9

* Data from Ivax Pharmaceuticals, package insert.¹⁷

† Data from Mylan Pharmaceuticals, package insert.¹⁸

‡ Data from Geneva Pharmaceuticals, package insert.¹⁹

§ Data from Drugdex System, Drug Evaluations. Micromedex Healthcare Series, Vol 121.⁹

zosin 10 mg ($P = .004$), +0.9 ml/second for alfuzosin 15 mg ($P = 0.12$) and +0.2 ml/second for placebo. In addition, both the 10- and 15-mg prolonged-release formulations demonstrated an improved QOL Index mean change from baseline (-0.7 for both groups) compared with placebo (-0.3; $P = .002$).

Similarly, in the ALFORTI trial,²² 40% of patients in the SR and IR alfuzosin groups experienced symptomatic improvements, compared with 28% of patients in the placebo group ($P = .005$). The QOL Index also significantly improved with both IR and SR alfuzosin doses compared with placebo: -1.1 for alfuzosin 10 mg once daily, -1.0 for alfuzosin 2 mg three times daily, and -0.6 for placebo.

McNeill et al.²³

McNeill and colleagues conducted a prospective, placebo-controlled study to investigate the efficacy of SR alfuzosin in patients with acute urinary retention without catheterization. Eighty-one patients were randomly assigned to receive SR alfuzosin or placebo twice daily for 48 hours. The primary outcome measurement was successful voiding after catheter removal. Significantly more patients in the treatment group (55%) reported successful voiding in contrast to patients in the placebo group (29%; $P = .034$).

Comparison with Other Alpha₁-Adrenergic Blockers

McNeill et al.²⁴

In a three-week clinical trial, the efficacy of alfuzosin was compared with that of prazosin in the symptomatic treatment of BPH. A total of 103 patients were assigned to take alfuzosin 2.5 mg three times daily or prazosin 2 mg twice daily, at a gradual dose increase within the first week. After three weeks, voiding symptoms, according to Boyarsky scores and urination diaries, improved in the two groups, revealing similar increases in peak and mean urinary flow rates. Peak flow rates for alfuzosin were 2.6 ± 0.6 ml/second, and those for prazosin were 2.9 ± 0.7 ml/second. The alfuzosin group demonstrated a greater increase in the mean flow rate and voided volume (30% and 22.2%, respectively), compared with the prazosin group (20.6% and 6.5%).

Buzelin et al.²⁵

Buzelin et al. conducted another study

Table 2 Adverse Events Associated with Immediate-Release Alfuzosin Therapy After Six Months of Therapy (The Benign Prostatic Hyperplasia–Alfuzosin Study)

Adverse Event	Alfuzosin (n = 251) (%)	Placebo (n = 267) (%)
Vasodilator effects		
Dizziness	7.2	5.2
Headache	6.4	4.9
Hypotension	1.9	1.2
Tachycardia	1.6	<1
Gastrointestinal effects		
Diarrhea	2.8	<1
Nausea	2.4	<1
Vomiting	1.6	1.9
Miscellaneous		
Skin rash	4.4	5.2
Dry mouth	4.4	2.6
Asthenia	2.0	3.8
Chest pain	2.0	<1
Impotence	<1	2.3

to review the efficacy of tamsulosin (Flomax®, Boehringer Ingelheim) with alfuzosin in the treatment of men with lower urinary tract symptoms suggestive of bladder obstruction. Patients were randomly selected to receive 0.4 mg of tamsulosin daily or 2.5 mg of alfuzosin three times daily over 12 weeks. Both agents were comparable in improvements of urinary flow rate and in Boyarsky symptom scores. There was a mean increase in maximum urinary flow rate of 1.6 ml/second for both groups with a reduction of Boyarsky symptom scores in the tamsulosin and alfuzosin groups of 4.1 and 3.8, respectively. Tamsulosin and alfuzosin were equally effective in increasing peak urinary flow rates (11.6 and 11.5 ml/second, respectively).

ADVERSE DRUG EVENTS

Alfuzosin was well tolerated in clinical trials. The most commonly reported vasodilator side effects included orthostatic hypotension, headache, dizziness, and tachycardia. At the end of six months in the BPH-ALF trial,³ most patients in the alfuzosin group (8.4%) experienced vasodilator effects during the first two weeks of treatment. Vasodilator and other side effects associated with IR alfuzosin therapy are shown in Table 2.³

Although dizziness and orthostatic hypotension are common adverse drug

events (ADEs) reported with most alpha₁-adrenergic antagonists, the improved pharmacokinetic profile of prolonged-release alfuzosin formulations are associated with fewer vasodilator ADEs. In the ALFORTI trial,²² the incidence of dizziness was comparable between the SR alfuzosin 10-mg group (2.1%) and the placebo group (1.3%). Although no reduction in blood pressure was reported in the placebo group, the incidence of hypotension was less with the prolonged-release alfuzosin formulation (0.7%) than with the IR alfuzosin formulation (1.3%). In the ALFUS trial, however,²¹ dizziness was the most common side effect reported in patients receiving prolonged-release alfuzosin 10 or 15 mg once daily (7.4% and 9.0%, respectively) compared with those receiving placebo (2.9%).

Buzelin et al.²⁰ also found the incidence of ADEs relating to SR alfuzosin (18.5%) to be similar to that of placebo (15.8%). Discontinuation of therapy owing to ADEs was reported more frequently with the placebo group (5.7%) than with the SR alfuzosin group (3.4%).

After a one-year follow-up (by Lukacs et al.) of 2,829 patients with lower urinary tract symptoms, hypotension (n = 47; 1.6%) was one of the most frequently reported cardiovascular events occurring during the first month of alfuzosin therapy.²⁶ However, average systolic and dia-

stolic blood pressure changes between baseline and 24 months were -3.1 mm Hg and -1.4 mm Hg, respectively, representing no significant change overall.

DRUG INTERACTIONS

Because alfuzosin is metabolized by the liver, enzyme inhibitors and inducers affect its metabolism.¹ For instance, when it is administered together with inhibitors of CYP3A4, the C_{max} and AUC of alfuzosin increase, resulting in elevated serum concentrations.⁷⁻⁹ The concomitant use of potent CYP3A4 inhibitors (i.e., ketoconazole, itraconazole, and ritonavir) can result in prolonged alfuzosin exposure and is therefore contraindicated.

With the coadministration of atenolol (e.g., Tenormin®, AstraZeneca), the C_{max} and AUC of alfuzosin increase by 28% and 21%, respectively.⁸ Similarly, with the concomitant use of diltiazem (e.g., Cardizem®, Biovail), the C_{max} and AUC of alfuzosin are elevated by 1.5-fold and 1.3-fold, respectively.⁸ Because alfuzosin has been shown to increase serum concentrations of both atenolol and diltiazem and to result in hypotension, caution is recommended with its coadministration.^{1,9,10,15}

The concomitant use of alfuzosin with warfarin (Coumadin®, Bristol-Myers Squibb), hydrochlorothiazide, and digoxin (Lanoxin®, GlaxoSmithKline) does not result in clinically relevant drug-drug interactions.^{9,10,15}

Clinicians should take precautions when administering drugs that cause changes in the QT interval with alfuzosin because of the increased potential for QT prolongation.

Both tadalafil (Cialis®, Eli Lilly) and vardenafil (Levitra®, Bayer/GlaxoSmithKline) are contraindicated for use with alfuzosin. The FDA has not yet determined the safety of using ER alfuzosin with sildenafil (Viagra®, Pfizer).¹

DOSAGE AND ADMINISTRATION

The recommended dose of alfuzosin is 10 mg once daily taken orally after a meal.⁷⁻⁹ No dosage adjustment is needed for elderly patients or patients with renal insufficiency.

CONTRAINDICATIONS

Alfuzosin is contraindicated in patients with moderate-to-severe hepatic impairment. The dose should be adjusted for those with mild hepatic insufficiency.⁷⁻⁹

Coadministration with potent CYP3A4 inhibitors is contraindicated because of increased alfuzosin serum concentrations.⁷⁻⁹

COST

According to retail pharmacies nationwide, the cost of 30 days of treatment with 10 mg of once-daily alfuzosin is \$55.87.⁸

CONCLUSION

Alfuzosin, a second-generation α_1 -adrenergic antagonist, is used to treat BPH. Although it is comparable to other α_1 blockers in relieving lower urinary tract symptoms relating to benign prostatic obstruction, its pharmacokinetic properties allow for once-daily dosing and titration is not required. The extended-release formulation is associated with limited cardiovascular side effects and minimal drug interactions.

REFERENCES

- Lee M. Alfuzosin HCl for the treatment of benign prostatic hyperplasia. *Am J Health Syst Pharm* 2003;60:1426-1439.
- McKeage L, Plosker GL. Alfuzosin: A review of therapeutic use of the prolonged-release formulation given once daily in the management of benign prostatic hyperplasia. *Drugs* 2002;60(4):633-653.
- Jardin A, Bensadoun H, Delauche-Cavallier MC, Attali P. Alfuzosin for the treatment of benign prostatic hypertrophy. BPH-ALF Group. *Lancet* 1991;337:1457-1461.
- McConnell JD. Epidemiology, etiology, pathophysiology, and diagnosis of benign prostatic hyperplasia. In: Walsh PA, Retik AB, Vaughan ED Jr, et al., eds. *Campbell's Urology*, 7th ed. Philadelphia, PA: WB Saunders Company; 1998:1429-1452.
- U.S. National Library of Medicine and National Institutes of Health. Available at: www.nlm.nih.gov/medlineplus/prostatediseases.html. August 31, 2004.
- Lee M. Management of benign prostatic hyperplasia. In: DiPiro JT, Talbert RL, Yee GC, et al, eds. *Pharmacotherapy: A Pathophysiologic Approach*, 5th ed. New York: McGraw-Hill; 2002:1533-1542.
- Alfuzosin (Uroxatral): Another α_1 -blocker for benign prostatic hyperplasia. *Med Lett Drugs Ther* 2004;46(1173)1-2.
- FDA. Available at www.fda.gov/cder/foi/label/2003/21287_uroxatral_ibl.pdf.
- Alfuzosin. Drugdex System, Drug Evaluations; Micromedex Healthcare Series, Vol 121. Available at: [vaww.visn8.med.va.gov](http://www.visn8.med.va.gov).
- Uroxatral® (alfuzosin), product information. New York: Sanofi-Synthelabo; issued July 2003, reviewed December 2003.
- Lefevre-Borg F, O'Connor SE, Schoemaker H, Hicks PE. Alfuzosin, a selective α_1 -adrenoreceptor antagonist in the lower urinary tract. *Br J Pharmacol* 1993; 109:1282-1289.
- Martin DJ, Angel I, Arbillia S. Functional

- uroselectivity. *Eur Urol* 1998;33(Suppl 2): 12-18.
- Ahtoy P, Chretien P, Dupain T, et al. Alfuzosin, an α_1 -adrenoreceptor antagonist, for the treatment of benign prostatic hyperplasia: Once daily versus three times daily dosing in healthy subjects. *Int J Clin Pharmacol Ther* 2002; 40:289-294.
- Marbury TC, Blum RA, Ruach C, Pinquier JL. Pharmacokinetics and safety of a single oral dose of once-daily alfuzosin, 10 mg, in male subjects with mild to severe renal impairment. *J Clin Pharmacol* 2002;42:1311-1317.
- Rauch C, Ahtoy P, Pinquier JL, et al. Bioequivalence of a new once-a-day controlled-release alfuzosin formulation with the immediate-release alfuzosin (Abstract). *Eur J Urol* 2000(163 Suppl):306.
- Wilde MI, Fitton A, McTavish D, et al. Alfuzosin: A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in benign prostatic hyperplasia. *Drugs* 1993;45:410-429.
- Prazosin package insert. Miami, Florida: Ivax Pharmaceuticals, Inc; 2002.
- Doxazosin package insert. Morgantown, WV: Mylan Pharmaceuticals, Inc; 2002.
- Terazosin package insert. Broomfield, CO: Geneva Pharmaceuticals, Inc; 2002.
- Buzelin JM, Delauche-Cavallier MC, Roth S. Clinical uroselectivity: Evidence from patients treated with slow-release alfuzosin for symptomatic benign prostatic obstruction. *Br J Urol* 1997;79: 898-906.
- Roehrborn CGI. 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. ALFUS Study Group. *Urology* 2001;58(6):953-959.
- van Kerrebroeck P, Jardin A, Lavall KU, et al. 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. ALFORTI Study Group. *Eur Urol* 2000;37:306-313.
- McNeill SA, Daruwala PD, Mitchell ID, et al. Sustained-release alfuzosin and trial without catheter after acute urinary retention. *Br J Urol Int* 1999;84:622-627.
- Buzelin JM, Herbert M, Blondin P, et al. Alpha-blocking treatment with alfuzosin in symptomatic benign prostatic hyperplasia: Comparative study with prazosin. *Br J Urol* 1993;72:922-927.
- Buzelin JM, Fonteyne E, Kontturi M, et al. Comparison of tamsulosin with alfuzosin in the treatment of patients with lower urinary tract symptoms suggestive of bladder outlet obstruction. European Tamsulosin Group. *Br J Urol* 1997; 80: 597-605.
- Lukacs B, Grange JC, Comet D. One-year follow-up of 2829 patients with moderate to severe lower urinary tract symptoms treated with alfuzosin in general practice according to IPSS and a health-related quality-of-life questionnaire. BPM Group in General Practice. *Urology* 2000;55: 540-546.