Alfuzosin Hydrochloride

Fozal®

10 mg Modified-Release Tablet
α-Adrenergic Blocking Agent

℞

FORMULATION
Each modified-release tablet contains:
Alfuzosin hydrochloride ..... 10 mg

PRODUCT DESCRIPTION
Alfuzosin hydrochloride (Fozal®) 10 mg Modified-Release Tablet is a white to off-white uncoated, round, biconvex tablet debossed with "RY 10" on one side.

PHARMACODYNAMICS
Alfuzosin hydrochloride is an α_1-adrenergic blocking agent that exhibits selectivity for α_1- adrenergic receptors in the lower urinary tract (bladder base, bladder neck, prostate, prostatic capsule, prostatic urethra). Relaxation of smooth muscle in the bladder neck and prostate, which improves urine flow and reduces symptoms of benign prostatic hyperplasia (BPH), result from blockade of these adrenoceptors. Alfuzosin hydrochloride relieves moderate to severe irritative and obstructive urinary symptoms of BPH including frequency of urination, urinary urgency, nocturia, hesitancy, interrrupted or weak stream , sensation of incomplete bladder emptying and straining. These effects are generally achieved with alfuzosin hydrochloride doses without clinically important effects on blood pressure or heart rate.

PHARMACOKINETICS
Alfuzosin hydrochloride 10 mg modified-release tablet has an absolute bioavailability of about 49% under fed conditions. It exhibits linear kinetics following single and multiple dosing of up to 30 mg.

The pharmacokinetics of a single dose alfuzosin hydrochloride 10 mg modified-release tablet was evaluated in healthy male adult subjects under fed and fasted conditions. The following are the important pharmacokinetic parameters of the said studies.

Pharmacokinetic Parameters	Alfuzosin hydrochloride 10 mg modified-release tablet	
	Fed Condition	Fasted Condition
1. T_{max} (hour)	7.089	5.284
2. C_{max} ng/mL	15.485	9.229
3. KELM	0.089	0.073
4. $T_{1/2}$ (hour)	8.565	11.298

T_{max} = time the drug reached its maximum concentration in the blood
C_{max} = maximum plasma concentration of the drug at the peak time
KELM = elimination rate constant
$T_{1/2}$ (hour) = half-life

The extent of absorption is decreased by about 50 % under fasting conditions, thus, it is recommended that Alfuzosin hydrochloride modified-release tablet should be taken immediately after a meal. (See **DOSAGE AND ADMINISTRATION**)

Alfuzosin hydrochloride is about 90% bound to plasma proteins and is rapidly and extensively distributed to tissues; its volume of distribution is about 2.5L/kg.

Alfuzosin hydrochloride is extensively metabolized with about 11% of a dose excreted unchanged in the urine. It undergoes metabolism to form inactive metabolites mainly through the liver under oxidation. *O*-demethylation, and/or *N*-dealkylation primarily through cytochrome P-450 (CYP) 3A4. It is not an inhibitor of CYP isoenzymes 1A2, 2A6, 2C9, 2C19, 2D6 or 3A4, it is also not an inducer of CYP isoenzymes 1A, 2A6, or 3A4. Alfuzosin's apparent half-life following oral administration of a 10 mg modified-release tablet is approximately 10 hours. After 7 days, 69% and 24% of the orally administered dose of ^{14}C-labelled alfuzosin solution were recovered in the feces and urine, respectively.

Hepatic Insufficiency
The AUC is increased and elimination half-life of alfuzosin hydrochloride is prolonged in patients with moderate to severe hepatic impairment. This results in approximately one-third to one-fourth higher plasma concentrations of alfuzosin in these patients compared to patients with normal liver function. Alfuzosin hydrochloride's pharmacokinetics has not been studied in patients with mild hepatic insufficiency.

Renal Insufficiency
Systemic alfuzosin hydrochloride exposure may increase by about 50% in patients with renal insufficiency (CL_{CR} <80 mL/minute); safety profile appears to be the same in patients with mild (CL_{CR} 60-80 mL/minute) or moderate (CL_{CR} 30-59 mL/minute) renal impairment and in patients with normal renal function. Experience in patients with severe renal insufficiency is limited.

INDICATIONS
- Treatment of signs and symptoms of benign prostatic hyperplasia (BPH)
- As an adjunct therapy with urethral catheterization for Acute Urinary Retention related to BPH and management following catheter removal.

Note: Alfuzosin hydrochloride is not indicated for the treatment of hypertension.

DOSAGE AND ADMINISTRATION
The modified-release tablet should be swallowed whole. Do not chew or crush or divide the modified-release tablet since this may cause inappropriate release and absorption of the drug that may lead to early adverse reactions.

Usual dose for BPH: Orally, 10 mg (1 tablet) once daily immediately after the same meal every day.

Acute Urinary Retention: Orally, 10 mg (1 tablet) once daily immediately after a meal to be taken on the first day of catheterization and continue beyond catheter removal unless there is a relapse of acute urinary retention or disease progression.

Or. as prescribed by a physician.

CONTRAINDICATIONS
- Hypersensitivity to alfuzosin hydrochloride or to any ingredient in the product
- Moderate or severe hepatic insufficiency
- Orthostatic hypotension
- Co-administration with potent CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, ritonavir, erythromycin and clarithromycin)
- Co-administration with other alpha blockers including antihypertensive α_1-blockers.

WARNINGS AND PRECAUTIONS

Postural Hypotension
Postural hypotension with or without symptoms such as dizziness, fatigue and sweating may occur within a few hours after alfuzosin hydrochloride administration. There is also a potential for syncope. Advise patients to avoid situations where injury could result should syncope occur. There maybe an increased risk of hypotension/postural hypotension and syncope when taking alfuzosin hydrochloride concomitantly with anti-hypertensive medication or nitrates. Administer alfuzosin hydrochloride with caution in patients with symptomatic hypotension or patients who have had a hypotensive response to other medications.

Coronary insufficiency
Discontinue alfuzosin hydrochloride treatment if symptoms of angina pectoris should appear or worsen.

Patients with Congenital or Acquired QT Prolongation
Alfuzosin hydrochloride may cause prolongation of QT interval which should be considered in clinical decisions when prescribing alfuzosin hydrochloride in patients with known history of QT prolongation or patients who are taking medications which prolong QT interval. No signs of *torsades de pointes* have been seen in post-marketing experience with alfuzosin hydrochloride.

Prostatic Carcinoma
Carcinoma of the prostate and BPH have similar symptoms and these two diseases frequently co-exist. Evaluate patients prior to starting alfuzosin hydrochloride treatment to rule out the presence of carcinoma of the prostate.

Interoperative Floppy Iris Syndrome (IFIS)
IFIS has been reported during cataract surgery in some patients on or previously treated with alpha-1 blockers. IFIS, a variant of small pupil syndrome, manifests as a combination of a flaccid iris that billows in response to intraoperative irrigation currents, progressive intraoperative miosis even with preoperative dilation with standard mydriatic drugs and potential prolapse of the iris towards the phacoemulsification incisions. Modifications of surgical technique such as utilization of iris hooks, iris dilator rings, or viscoelastic substance may be used by the patient's opthalmologist. There appears to be no benefit when α_1-blocker therapy is stopped before cataract surgery.

Hepatic Insufficiency
Do not use alfuzosin hydrochloride in patients with moderate or severe hepatic insufficiency since alfuzosin blood levels are increased in these patients (see **CONTRAINDICATIONS, PHARMACOKINETICS**)

Renal Insufficiency
Exercise caution when alfuzosin hydrochloride is administered to patients with renal insufficiency. (**See PHARMACOKINETICS**)

Effects on Ability to Drive or Use Machines
Advice patients to avoid hazardous tasks including driving and operating machinery since alfuzosin hydrochloride may potentially cause vertigo, dizziness and asthenia.

INTERACTION WITH OTHER MEDICAMENTS
Drugs Affecting Hepatic Microsomal Enzymes: Pharmacokinetic interaction (may increase plasma alfuzosin hydrochloride concentration) with inhibitors of CYP3A4 isoenzyme (e.g. itraconazole, ketoconazole, ritonavir, erythromycin, and clarithromycin). Concomitant use of alfuzosin hydrochloride with these medications is contraindicated (See **CONTRAINDICATIONS).**

Drugs that Prolong the QT Interval: Potential pharmacologic interaction (additive prolongation of QT interval). (See **WARNINGS AND PRECAUTIONS**).

α_1-Adrenergic Blocking Agents: Potential pharmacologic interaction (may cause additive cardiovascular effects). Use of alfuzosin hydrochloride with these medications is not recommended.

Antihypertensive Agents and Nitrates: May cause additive antihypertensive effect and increase risk of orthostatic hypotension.

Atenolol: Potential pharmacologic (additive cardiovascular effects) and pharmacokinetic (may increase plasma concentrations of alfuzosin hydrochloride and atenolol).

Diltiazem: Potential pharmacologic (additive cardiovascular effects) and pharmacokinetic (may increase plasma concentrations of alfuzosin hydrochloride and diltiazem).

Cimetidine: Pharmacokinetic interaction (increase both alfuzosin hydrochloride C_{max} and AUC values by 20%).

Sildenafil: Concomitant administration of alfuzosin hydrochloride and sildenafil showed a prolonged QT effect compared with administration of either drug alone.

Verdenafil: Potential drug interaction was not studied in a clinical trial.

General Anesthetics: The use of general anesthesia in patients on alfuzosin therapy resulted in profound hypotension. It is therefore recommended that alfuzosin hydrochloride be withdrawn 24 hours before surgery.

No pharmacokinetic interaction has been observed in clinical trials using alfuzosin hydrochloride and the following drugs: Warfarin, digoxin, hydrochlorothiazide and tadalafil.

Effects on Laboratory Tests: No clinically significant changes in urinalysis, the routine biochemical and hematologic tests as well as prostate specific antigen (PSA) have been observed up to 12 months of treatment with alfuzosin.

STATEMENT OF USAGE IN HIGH-RISK GROUPS

Pregnancy and Lactation

Pregnancy Category B
Alfuzosin hydrochloride is not indicated for use in women. There is no human data on the effects of alfuzosin hydrochloride in pregnancy. It is not known whether alfuzosin hydrochloride is excreted in breast milk.

Pediatrics
Alfuzosin hydrochloride is not indicated for use in children.

Geriatrics
Alfuzosin hydrochloride's pharmacokinetics does not appear to be significantly affected by old age. No overall differences in the safety or efficacy of alfuzosin hydrochloride is observed between the elderly (65 years and older) and younger patients.

UNDESIRABLE EFFECTS

CNS:
Dizziness/faintness, headache, vertigo, malaise, drowsiness

Respiratory:
Upper respiratory tract infection, bronchitis, sinusitis, rhinitis, and laryngitis, pharyngitis, influenza-like symptoms

Gastrointestinal:
Abdominal pain, dyspepsia, constipation, nausea, vomiting, diarrhea, and dry mouth

Musculoskeletal:
Pain, asthenia, back pain, neuralgia, neuropathy, and lumbar disc lesion, joint disorders including arthritis, arthrosis, arthropathy, arthralgia, and bursitis

Hepatobiliary Disorders:
Hepatocellular and cholestatic liver injury (including cases with jaundice leading to drug discontinuation)

Reproductive System Disorders:
Impotence, priapism, ejaculation disorders

Skin and subcutaneous tissue disorders:
Rash, urticaria, angioedema, pruritus

Cardiovascular:
Tachycardia, palpitations, chest pain, angina pectoris in patients with pre-existing coronary artery disease, and other symptoms associated with orthostasis such as hypotension or postural hypotension and syncope. Isolated spontaneous cases of QT interval prolongation, ventricular arrhythmias, including *torsades de pointes*, ventricular tachycardia, and fibrillation

Eye Disorders:
IFIS during cataract surgery in some patients on or previously treated with α1-blockers. (See **WARNINGS AND PRECAUTIONS**), abnormal vision

Others:
Fatigue, edema, flushing, bite, inflicted injury, pain

OVERDOSE AND TREATMENT
Support of the cardiovascular system is of primary importance should hypotension result from alfuzosin hydrochloride overdosage. Patients may be kept in supine position to restore blood pressure and normalize heart rate. Consider administration of intravenous fluids if this measure is inadequate. Use vasopressors when necessary, monitor and support renal function as needed. Dialysis may not be of benefit.

STORAGE CONDITION
Store at temperatures not exceeding 25°C.

CAUTION
Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

AVAILABILITY
Alfuzosin hydrochloride (Fozal®), in blister pack x 10's (box of 30 tablets).

ADVERSE DRUG REACTION REPORTING STATEMENT
For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph **AND** Unilab at (+632) 858-1000 or productsafety@unilab.com.ph. By reporting undesirable effects, you can help provide more information on the safety of this medicine.

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