For the use only of a Registered Medical Practitioner

Ranfuzosin

(Alfuzosin Hydrochloride Modified Release Tablets 10mg)

COMPOSITION

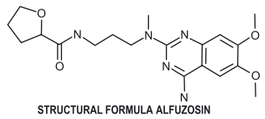
Each modified release tablet contains:
Alfuzosin Hydrochloride 10mg

PRODUCT DESCRIPTION

White to off-white, uncoated, round, biconvex tablets debossed with **'RY10'** on one side of the tablet.

DESCRIPTION

Ranfuzosin is a modified release formulation that contains alfuzosin hydrochloride as active ingredient, which is a selective peripherally acting antagonist of post-synaptic alpha1-adrerenoreceptors. Alfuzosin hydrochloride is chemically described as (R,S)-N-[3-[(4-amino-6,7-dimethoxy-2-quinazolinyl) methylamino] propyl] tetrahydro-2-furancarboxamide hydrochloride. The empirical formula of alfuzosin hydrochloride is C19H27N5O4HCl. The molecular weight of alfuzosin hydrochloride is 425.9.



STRUCTURAL FORMULA ALFUZOSIN

PHARMACODYNAMICS & PHARMACOKINETICS

Pharmacodynamics
Alfuzosin is an orally active quinazoline derivative. It is a selective peripherally acting antagonist of post-synaptic alpha1-adrerenoreceptors.

Selectivity of alfuzosin for the alpha-1-adrenoreceptors located in the prostate, bladder base and prostatic urethra have reported *in vitro*.
Clinical manifestations of Benign Prostatic Hypertrophy (BPH) are associated with infra vesical obstruction which is triggered by both anatomical (static) and functional (dynamic) factors. The functional component of obstruction arises from the tension of prostatic smooth muscle which is mediated by alpha-adrenoceptors. Activation of alpha-1-adrenoceptors stimulates smooth muscle contraction, thereby increasing the tone of the prostate, prostatic capsule, prostatic urethra and bladder base, and, consequently, increasing the resistance to bladder outflow. This in turn leads to outflow obstruction and possible secondary bladder instability.

Alpha-blockade decreases infra vesical obstruction via a direct action on prostatic smooth muscle.

It has been reported that alfuzosin decreases urethral pressure and therefore, resistance to urine flow during micturition in animal models. Moreover, alfuzosin inhibits the hypertonic response of the urethra more readily than that of vascular muscle and shows functional uroselectivity in conscious normotensive rats by decreasing urethral pressure at doses that do not affect blood pressure.

Alfuzosin improves voiding parameters in man by reducing urethral tone and bladder outlet resistance, and facilitates bladder emptying.

Significant increase in urine flow, significant decrease in detrusor pressure, significant increase the volume producing the sensation of the need to urinate and significant reduced residual urine volume have been reported in BPH patients receiving alfuzosin. These favourable urodynamic effects result in an improvement in the irritant and obstructive urinary symptoms.

Alfuzosin may cause moderate antihypertensive effects.

A lower frequency of acute urinary retention has been reported in patients receiving alfuzosin than untreated patients.

Pharmacokinetics
Alfuzosin HCl is approximately 90% bound to plasma proteins. Alfuzosin is extensively metabolized by the liver with excretion in the urine of only 11% of the unchanged compound. The majority of metabolites (which are inactive) are excreted in the faeces (75-90%). The pharmacokinetic profile of alfuzosin is not modified in the case of chronic cardiac insufficiency.

Modified release formulation: The mean value of relative bioavailability is 104.4% after administration of a dose of 10 mg, compared with that of the immediate-release formulation at a dosage of 7.5 mg (25 mg 3 times daily) in healthy volunteers of average age. The peak plasma concentration is reached 9 hrs after administration as against 1 hr for the immediate formulation.

The apparent elimination half-life is 9.1 hrs. Bioavailability is increased when the product is administered after a meal (see **DOSE/USE INSTRUCTION**).

The mean values of C_{max} and AUC are moderately increased in patients with moderate impairment of renal function (creatinine clearance ≥ 30 mL/min) without effect on the elimination half-life compared with patients with normal renal function. Dosage adjustment is not necessary in patients with impaired renal function with creatinine clearance >30 mL/min.

Special Populations

Geriatric: The pharmacokinetic properties (C_{max} and AUC) are not increased in elderly patients, compared with healthy volunteers of average age.

Renal Insufficiency
Relative to subjects with normal renal function (CL_{cr}>80 mL/min), the mean C_{max} and AUC values were increased by approximately 50% in patients with mild (CL_{cr} 60 to 80 mL/min), moderate (CL_{cr}30 to 59 mL/min), or severe (CL_{cr}30 mL/min), renal impairment. (See: **WARNINGS AND PRECAUTIONS**).

Hepatic Insufficiency
In clinical studies conducted by the innovator, in patients with moderate or severe hepatic insufficiency, plasma apparent clearance of alfuzosin hydrochloride was found to be reduced to about 1/3rd to 1/4th of that observed in healthy subjects. Therefore, alfuzosin is contraindicated in patients with moderate to severe hepatic impairment. In mild hepatic insufficiency, the pharmacokinetics of alfuzosin hydrochloride has not been studied.

INDICATIONS / USAGE

Treatment of functional symptoms of benign prostatic hypertrophy. Adjuvant treatment to a catheter in acute urinary retention related to benign prostatic hypertrophy.

DOSE/USE INSTRUCTION

The tablet must be swallowed whole with a glass of water.

The recommended dose is one 10mg tab daily to be taken immediately after the evening meal. The tablet must be swallowed whole.

Adjuvant treatment to a catheter in acute urinary retention related to benign prostatic hypertrophy: The recommended dosage is one 10 mg tab/day, to be taken after a meal, from the 1st day of catheterization onwards. The treatment is administered for 3-4 days, i.e. 2-3 days while the catheter is in place and 1 day after it is removed.

CONTRAINDICATIONS

Hypersensitivity to alfuzosin hydrochloride or any of excipients
History of orthostatic hypotension
Combination with other alpha-blockers
Hepatic insufficiency
Severe renal insufficiency (creatinine clearance <30 mL/min)
Use with potent CYP3A4 inhibitors such as ketoconazole, itraconazole and ritonavir, since it increases alfuzosin levels (see **DRUG INTERACTIONS).**

WARNINGS AND PRECAUTIONS

As with all alpha-1-blockers in some subjects, in particular patients receiving antihypertensive medications, postural hypotension with or without symptoms (dizziness, fatigue, sweating) may develop within a few hours following administration. In such cases, the patient should lie down until the symptoms have completely disappeared.

These effects are transient and do not usually prevent the continuation of treatment after adjustment of the dose. The patient should be warned of the possible occurrence of such events.

Treatment should be initiated gradually in patients with hypersensitivity to alpha-1-blockers. Alfuzosin should be administered carefully to patients being treated with antihypertensives. Blood pressure should be monitored regularly, especially at the beginning of treatment.

In patients with coronary insufficiency, anti-anginal therapy should be continued. However, if symptoms of angina pectoris newly develop, reappear or worsen, alfuzosin should be discontinued.

Carcinoma of the prostate and BPH cause many of the same symptoms. These two diseases frequently coexist. Therefore, patients thought to have BPH should be examined prior to starting therapy with alfuzosin to rule out the presence of carcinoma of the prostate.

The 'Intraoperative Floppy Iris Syndrome' (IFIS, a variant of small pupil syndrome) has been reported during cataract surgery in some patients on or previously treated with tamsulosin. Isolated reports have also been reported with other alpha-1 blockers and the possibility of a class effect cannot be excluded. As IFIS may lead to increased procedural complications during the cataract operation current or past use of alpha-1 blockers should be made known to the ophthalmic surgeon in advance of surgery.

The pharmacokinetic and pharmacodynamic interactions between alfuzosin and other alpha-blockers have not been reported. However, interactions may be expected, and alfuzosin should not be used in combination with other alpha-blockers.

Alfuzosin should not be given to patients with moderate or severe hepatic insufficiency (see: **CONTRAINDICATIONS**). The pharmacokinetics of alfuzosin have not been reported in patients with mild hepatic insufficiency

In patients with severe renal impairment (creatinine clearance below 30 mL/min), the use of alfuzosin is not advised (see: **CONTRAINDICATIONS**).

In patients with hypersensitivity to alpha-1 blockers, treatment with alfuzosin should be started gradually. Alfuzosin should be administered carefully to patients being treated with antihypertensives. Blood pressure should be monitored regularly, especially at the beginning of treatment.

Use with caution in patients with acquired or congenital QT prolongation or who are taking medications that prolong the QT interval.

This product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Patients should be warned that the tablet should be swallowed whole. Any other mode of intake such as crushing, crunching, chewing, grinding or pounding to powder should be prohibited. These actions may lead to inappropriate release and absorption of the drug and therefore possible early adverse reactions.

Effects on ability to drive and use machines: Particular caution must be exercised by drivers and machine operators because of the risk of orthostatic hypotension, particularly at the beginning of treatment with alfuzosin.

- **Pediatric Use**

Not indicated for use in children.

- **Geriatric Use**

In patients with BPH, there was no relationship reported between peak plasma concentrations of alfuzosin and age. However, trough levels were positively correlated with age. The concentration of the drug in subjects over 75 years of age have been reported to be about 35% higher than those below 65 years of age. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

DRUG INTERACTIONS

Inadvisable Combinations
- Alpha-1- receptor blockers (prazosin, urapidil, minoxidil): Enhanced hypotensive effect. Risk of severe orthostatic hypotension (See **CONTRAINDICATIONS).**
- Ketoconazole, itraconazole, ritonavir, clarithromycin, erythromycin: Risk of increased plasma alfuzosin concentrations and increased undesirable effects (See **CONTRAINDICATIONS)**.

Combination to be taken into account:
- Antihypertensive agents: Increased antihypertensive effect and risk of orthostatic hypotension (additive effect).
- Nitrates (see **WARNINGS AND PRECAUTIONS**).
- *PDE5 Inhibitors:* Caution is advised when alpha adrenergic blocking agents, including alfuzosin, are co-administered with PDE5 inhibitors. Alpha-adrenergic blockers and PDE5 inhibitors are both vasodilators that can lower blood pressure. Concomitant use of these two drug classes can potentially cause symptomatic hypotension.

The administration of general anaesthetics to patients on alfuzosin can cause profound hypotension. It is recommended that the tablet should be withdrawn 24 hours before surgery.

Other interactions
No pharmacodynamic or pharmacokinetic interaction has been reported in healthy volunteers between alfuzosin and the following drugs: warfarin, digoxin, hydrochlorothiazide and atenolol.

ADVERSE REACTIONS / SIDE EFFECTS

Expected frequencies are classified as under:
Very Common (>1/10), common (>1/100 to <1/10), uncommon (>1/1,000 to <1/100), rare (>1/10,000 to<1/1000), and very rare (<1/10,000) including isolated reports.

Nervous System:
Common: faintness/dizziness, headache
Uncommon: vertigo, malaise, drowsiness

Eye disorders
Uncommon: vision abnormal
Not known: intraoperative floppy iris syndrome (see **WARNINGS AND PRECAUTIONS**).

Cardiovascular System:
Uncommon: tachycardia, palpitations, hypotension (postural), syncope
Very rare: New Onset, aggravation or recurrence of angina pectoris in patients with pre-existing coronary artery disease

Gastro-intestinal System:
Common: nausea, abdominal pain,
Uncommon: diarrhoea, dry mouth, vomiting

Hepatobiliary disorders
Not known: hepatocellular injury, cholestatic liver disease
Skin and Subcutaneous Tissue Disorders:
Uncommon: rash, pruritus
Very rare: urticaria, angioedema

General Disorders:
Common: asthenia,
Uncommon: flushes, edema, chest pain,

Respiratory System:
Common: bronchitis, sinusitis, pharyngitis, rhinitis

In addition to the above following adverse events have also been reported: flushing, dyspepsia, constipation, pain, impotence, and priapism.

Post-Marketing Adverse Event Reports:
The following adverse reactions have been reported during post approval use of alfuzosin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency.
General disorders: edema
Cardiac disorders: tachycardia, chest pain, angina pectoris in patients with pre-existing coronary artery disease
Gastrointestinal disorders: diarrhea *Hepatobiliary disorders:* hepatocellular and cholestatic liver injury (including cases with jaundice leading to drug discontinuation)
Respiratory system disorders: rhinitis
Reproductive system disorders: priapism
Skin and subcutaneous tissue disorders: rash, pruritis, urticaria, angioedema
Vascular disorders: flushing

Laboratory test findings
No laboratory test interactions with alfuzosin tablets are known.

PREGNANCY AND LACTATION

Alfuzocin is not indicated for use in women. The safety of alfuzosin during the passage in the breast milk is not known.

OVERDOSE AND TREATMENT

In case of overdose of alfuzosin, maintenance of blood pressure is of prime importance, as it may present as hypotension. Keeping the patient in supine position can help restore blood pressure and normalize heart rate. Administration of intravenous fluids should be considered. Vasopressors may be required. Monitor renal function and give support as needed. Dialysis may not benefit as alfuzosin is 82-90% protein bound.

STORAGE
Store below 30°C, Protected from light and moisture.

KEEP ALL MEDICINES OUT OF REACH OF CHILDREN

SUPPLY
Blister pack of 10's. Packs of 3 x 10's

Date of revision: March 2016

5118914

Product Registration Holder:
RANBAXY (MALAYSIA) SDN. BHD.
(A Sun Pharma Company)
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PTT–PACKAGING PAONTA

Description:	Ranfuzosin 10 mg tablets (PIL)
Market:	Malaysia
Dimensions:	140x200 mm
New SAP Code:	5118914
Old SAP Code:	5088960
Pharma Code:	18914
Revision date:	14.07.2015/ 31.03.2016

Colours

Black