AUSTRALIAN PRODUCT INFORMATION – XATRAL® SR (ALFUZOSIN HYDROCHLORIDE)

1 NAME OF THE MEDICINE

Alfuzosin hydrochloride

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Xatral (alfuzosin hydrochloride) is an orally active quinazoline derivative.

Each tablet contains 10 mg of alfuzosin hydrochloride as the active ingredient.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Modified release tablet.

Three-layered, round biconvex, prolonged release tablet containing the active ingredient in a white matrix layer between two inactive yellow layers.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Treatment of the functional symptoms of benign prostatic hyperplasia.

4.2 DOSE AND METHOD OF ADMINISTRATION

The recommended dose is one 10 mg tablet daily to be taken immediately after the meal. The tablets should be swallowed whole.

4.3 CONTRAINDICATIONS

Xatral SR must not be administered to patients with known hypersensitivity to alfuzosin hydrochloride or any other ingredient in this product, to patients with a history of orthostatic hypotension or hepatic insufficiency.

Xatral SR is contraindicated in combination with other alpha-blockers.

Concomitant administration of Xatral SR with potent CYP3A4 inhibitors is contraindicated (see Section 4.5 Interactions with other medicines and other forms of interactions)

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Xatral SR should be administered carefully to patients with known hypersensitivity to α1 blockers.

In certain subjects, in particular elderly patients and 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 symptoms have completely disappeared. These effects are usually transient, occur at the beginning of treatment and do not usually prevent the continuation of treatment. Pronounced drop in blood pressure has been reported in post-marketing surveillance in patients with pre-existing risk factors (such as underlying cardiac diseases and/or concomitant treatment with antihypertensive medication). The risk of developing hypotension and related adverse reactions may be greater in elderly patients. The patients should be warned about the possible occurrence of such events.

Xatral SR should be administered carefully to patients being treated with antihypertensives. Blood pressure should be monitored regularly, especially at the beginning of treatment.

Xatral SR should be administered carefully to patients who have had a pronounced hypotensive response to another α1-blocker.

Care should be taken when alfuzosin is administered to patients with symptomatic orthostatic hypotension or in patients on antihypertensive medication or nitrates.

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

Alfuzosin, like other alpha adrenergic antagonists, has been associated with priapism (persistent painful penile erection unrelated to sexual activity). Patients should be advised about the seriousness of this condition as it can lead to permanent impotence if not properly treated.

Xatral SR should not be prescribed alone in coronary patients: specific treatment for coronary insufficiency should be continued. If the angina reappears or worsens, Xatral SR should be discontinued.

Patients with Parkinson’s disease, multiple sclerosis, unstable angina or severe heart failure were excluded from Phase II studies. As a result, the safety of Xatral SR in these patients has not been formally assessed.

Carcinoma of the prostate should be excluded in any patients for whom alfuzosin therapy is being considered for presumed BPH.

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

Cataract surgery

The 'Intra-operative Floppy Iris Syndrome' (IFIS) has been observed during cataract surgery in some patients on, or previously treated with, tamsulosin. Isolated reports have also been received with other α1-blockers and the possibility of a class effect cannot be excluded. This variant of small pupil syndrome is characterised by the combination of a flaccid iris that billows in response to intra-operative miosis, despite pre-operative dilation with standard mydriatic drugs, and potential prolapse of the iris toward the phacoemulsification incisions. As IFIS may lead to increased procedural complications during the cataract operation, current or past use of α1-blockers should be made known to the ophthalmic surgeon in advance of the surgery.

Use in hepatic impairment

See Section 4.3 Contraindications.

Use in renal impairment

See Section 5.2 Pharmacokinetic properties - Pharmacokinetics in special populations.

Use in the elderly

In elderly patients, 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 symptoms have completely disappeared. These effects are usually transient, occur at the beginning of treatment and do not usually prevent the continuation of treatment. Pronounced drop in blood pressure has been reported in post-marketing surveillance in patients with pre-existing risk factors (such as underlying cardiac diseases and/or concomitant treatment with antihypertensive medication). The risk of developing hypotension and related adverse reactions may be greater in elderly patients. Patients should be warned about the possible occurrence of such events.

Paediatric use

Efficacy of alfuzosin has not been demonstrated in children aged less than 16 years. Therefore alfuzosin is not indicated for use in the paediatric population.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

The following combinations are contraindicated:

- Use with other α1-blockers e.g. prazosin, terazosin, doxazosin, tamsulosin.

- Concomitant use with potent CYP3A4 inhibitors such as ketoconazole, itraconazole and ritonavir since alfuzosin blood levels are increased (see Section 5.2 Pharmacokinetic properties - Metabolic Interactions).

The following combinations are to be avoided:

- Non-selective α1-blockers: phentolamine, labetalol and phenoxybenzamine.

The following combinations are to be taken into account:

- Combination with general anaesthetics: the administration to patients treated with alfuzosin may lead to blood pressure instability. Alfuzosin treatment should be stopped 24 hours prior to surgery.
- Concomitant use with antihypertensives (see Section 4.4 Special warnings and precautions for use).
- Concomitant use with nitrates.

Grapefruit juice contains one or more components that inhibit cytochrome CYP3A4. It is not known how combined exposure of any medications metabolised by CYP3A4 (such as modern α1-blockers), herbal remedies (particularly St. John's Wort, Milk thistle) and grapefruit juice may influence the overall efficacy and unwanted side effects of these medications, therefore, caution should be exercised.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Although α1-adrenoreceptor blockers as a class impair reproductive function in rats, there was no evidence of reproductive organ toxicity when male rats were given alfuzosin at daily oral doses of up to 250mg/kg/day for 26 weeks, which corresponds to levels of exposure several hundred fold greater than in humans. No impairment of fertility was observed following oral administration to male rats at doses of up to 125mg/kg/day for 70 days. Oestrous cycling was inhibited in rats and dogs at doses >5mg/kg/day, corresponding to levels of systemic exposure (based on AUC of unbound drug) 12 and 18-fold higher than in humans respectively, although this did not result in impaired fertility in rats.

Use in pregnancy – Pregnancy Category B2

Drugs which have been taken by only a limited number of pregnant women and women of child-bearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of foetal damage.

Alfuzosin in not intended for use in women. There was no evidence of teratogenicity or embryotoxicity in rats at maternal doses corresponding to systemic exposure levels 1200 fold higher than in humans. Oral treatment with alfuzosin in the rabbit did not show any evidence of foetal toxicity or teratogenicity with maternal doses up to 100 mg/kg/day (250 times the expected human exposure based on BSA).

Gestation was slightly prolonged in rats with maternal dose >5mg/kg/day, which corresponds to systemic exposure levels (based on AUC of unbound drug) 12 times higher than human exposure levels, but there were no apparent difficulties with parturition.

Use in lactation

Alfuzosin in not intended for use in women. There are no animal or human data indicating whether alfuzosin is excreted in breast milk.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

There are no data available on the use of Xatral SR and its effect on driving vehicles, however, adverse effects such as vertigo, dizziness and asthenia may occur, essentially at the beginning of treatment, and this should be taken into account when driving vehicles and operating machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical trials data

Adverse effects for which an incidence >1% and greater than placebo was observed during the pivotal clinical study are presented in Table 1 below. Overall, the incidence of adverse effects in the placebo and alfuzosin 10 mg group was similar (29.2% [45/154] and 32.9% [47/143] respectively). The frequency of study discontinuations due to adverse effects was also comparable between groups (placebo: 3.9% [6/154] and alfuzosin 10 mg daily: 5.6% [8/143]).

Table 1 - Comparative incidence (%) of adverse events in the pivotal study conducted with alfuzosin daily (>1% and greater than placebo)

Event	Alfuzosin 10 mg daily N = 143	Placebo N = 154
Respiratory System Disorders		
Rhinitis	3 (2.1%)	2 (1.3%)
Pharyngitis	2 (1.4%)	-
Upper respiratory tract infection	2 (1.4%)	-
Vasodilatory Disorders		
Dizziness	3 (2.1%)	2 (1.3%)
Malaise	2 (1.4%)	-
Body as a whole – General Disorders		
Asthenia	3 (2.1%)	2 (1.3%)
Fatigue	2 (1.4%)	2 (1.3%)
Musculo-Skeletal System Disorders		
Arthralgia	2 (1.4%)	2 (1.3%)

Event	Alfuzosin 10 mg daily N = 143	Placebo N = 154
Skin and Appendages Disorders		
Pruritus	2 (1.4%)	-
Central and Peripheral Nervous System Disorders		
Headache	2 (1.4%)	1 (0.6%)
Urinary System Disorders		
Renal calculus	2 (1.4%)	-

The following other adverse events have also been observed with alfuzosin:

Body as a whole

Common: asthenia

Uncommon: oedema, flushes, chest pain

Blood and lymphatic system disorders

Thrombocytopenia has been reported.

CNS and psychiatric disorders

Common: faintness/dizziness, headache

Uncommon: drowsiness, vertigo

Cardiovascular disorders

Uncommon: hypotension, hypotension (postural), syncope, palpitations, tachycardia

Very rare: angina pectoris in patients with pre-existing coronary artery disease (see Section 4.4 Special warnings and precautions for use)

Atrial fibrillation has been reported.

Eye disorders

Intraoperative floppy iris syndrome (see Section 4.4 Special warnings and precautions for use) has been reported.

Gastro-intestinal disorders

Common: nausea, abdominal pain/gastralgia, vomiting

Uncommon: diarrhoea, dry mouth

Hepato-biliary disorders

Hepatocellular injury and cholestatic liver disease have been reported.

Respiratory system disorders

Uncommon: rhinitis

Skin and appendages disorders

Uncommon: rash, pruritis

Very rare: sweating, urticaria, angioedema

Reproductive system and breast disorders

Priapism has been reported.

Note *very common* ≥1/10 (≥10%)

common ≥1/100 and <1/10 (≥1% and <10%)

uncommon ≥1/1000 and <1/100 (≥0.1% and <1.0%)

rare ≥1/10,000 and <1/1000 (≥0.01% and <0.1%)

very rare <1/10,000 (<0.01%)

4.8.1 Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

In case of overdosage, the patient should be hospitalised, kept in the supine position, and conventional treatment of hypotension should take place.

Alfuzosin in not easily dialyzable because of its high degree of protein binding.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: alpha-adrenoreceptor antagonists, ATC code: G04CA01.

Mechanism of action

Alfuzosin is a selective antagonist of postsynaptic α1-adrenoreceptors. In vitro pharmacology studies have documented the antagonist properties of alfuzosin for the α1-receptors located in the trigone of the urinary bladder, urethra and prostate. In vivo animal studies have shown that alfuzosin decreases urethral pressures and therefore resistance to the urine flow during micturition.

In benign prostatic hyperplasia (BPH), the development and severity of urinary functional symptoms are related not only to the size of the prostate but also to the tone of the sympathetic nervous system. An α1-adrenergic influence has been shown in smooth muscle fibres of the prostatic stroma. Alfuzosin shows selective tissue distribution in the prostate. There is a hyperplasia of prostate stroma that involves smooth muscle fibres. The lower urinary tract muscle tone is increased by stimulation of the post-synaptic α1-adrenoreceptors. Blockade of these receptors by alfuzosin results in relaxation of smooth muscle fibres. In a study in anaesthetised cats, alfuzosin showed a degree of functional uroselectivity by preferentially decreasing urethral pressure over arterial blood pressure. Evidence of uroselectivity was also seen in a study of conscious male rats. However, in studies of anaesthetised rats and anaesthetised dogs, a selectivity for urethral over vascular smooth muscle was not observed. Pharmacodynamic studies of uroselectivity with alfuzosin have not been conducted in patients with prostate hypertrophy.

α1-Adrenergic blocking agents reduce standing blood pressure and increase heart rate and these effects are maximal after the first intake and at peak plasma concentrations. In clinical studies with alfuzosin, adverse effects related to these effects were infrequent (see Section 4.8 Adverse effects (undesirable effects)).

Clinical trials

Benign Prostatic Hyperplasia

The efficacy of alfuzosin 10 mg daily was assessed in a three-month double-blind placebo controlled study in patients suffering from benign prostatic hyperplasia: 143 patients received alfuzosin 10 mg daily and 154 patients received placebo.

As shown in Table 2 below, there was a statistically significant reduction in the overall International Prostate Symptom Score (IPSS) indicating a reduction in symptom severity. This was due to a statistically significant improvement in both the irritative and obstructive subscores. The reduction in Symptom Score was observed at the first post-baseline visit at day 28.

Peak flow rate was also significantly increased, indicating a lessening of obstruction to flow. The effect of Xatral SR was observed as early as day 14 (the first post-baseline assessment). In this study, the assessment of peak flow was made at the end of the dosing interval.

Table 2 - Mean Change (SD) from Baseline[a] in the Efficacy Variables at Week 12: International Prostate Symptom Scores (IPSS) and Peak Flow Rate

	Placebo	Xatral SR 10 mg
Symptom Score		
Baseline Score	17.7 (4.1)	17.3 (3.5)
Change in Scorea	-4.9 (5.9)	-6.9 (4.9)
p-value vs. Placebo		0.002
Irritative Subscore		
Baseline Score	7.0 (2.6)	6.8 (2.5)
Change in score	-1.6 (2.6)	-2.3 (2.3)
p-valueb vs. Placebo		0.02
Obstructive Subscore		
Baseline Score	10.7 (3.2)	10.4 (3.2)
Change in Score	-3.3 (4.0)	-4.6 (3.5)
p-valueb vs. Placebo		0.005
Peak Flow Rate		
Baseline Rate	9.2 (2.0)	9.4 (1.9)
Change in Rate	1.4 (3.2)	2.3 (3.6)
p-valueb vs. Placebo		0.03

[a] Change is difference between baseline value and value at the end of week 12, or for patients without a week 12 value, the last observation is used.
[b]One-way ANOVA followed by two non-adjusted t-tests if global F-test significant at a 5% level

Acute Urinary Retention

The use of alfuzosin in the adjuvant therapy of catheterisation after an acute episode of acute urinary retention (AUR) related to BPH and prevention of relapse of AUR have been evaluated in two placebo-controlled studies.

In one study (ALFAUR), alfuzosin has been shown to improve the chances of success of spontaneous voiding after a first episode of AUR related to BPH and, during the 6 months after this episode, to postpone the risk of need for surgery. In the first phase of this double-blind placebo controlled study, alfuzosin (sustained release formulation) 10 mg/day (N=241) or placebo (N=122) was administered for a duration of 3 to 4 days following urethral catheterisation for AUR (starting during the first day of catheterisation to one day after catheter removal). Patients were catheterised for a minimum of 39 hours to a maximum of 70 hours. In the alfuzosin group, 61.9% of patients returned to successful voiding after catheter removal following a first episode of AUR compared with 47.9% of patients in the placebo group (p=0.012). In men aged 65 years and over, alfuzosin increased the success rate of spontaneous voiding after catheter removal, with 88 successfully voiding (56.1%) in the alfuzosin group, vs 30 (35.7%) in the placebo group (p=0.003). No benefit was observed in patients in the 50 to 64 year age group, with success in 58 subjects (73.4%) in the alfuzosin group, vs 28 (75.7%) in the placebo group (p=0.80). Of 204 patients (alfuzosin or placebo)

who voided successfully during the first phase of the study, 165 were re-randomised to the second phase of the study, where the need for surgery during the 6 months following the initial AUR episode was assessed. Alfuzosin reduced the risk of need for surgery (emergency surgery due to recurrence of urinary retention or non emergency surgery) compared to placebo: RR (risk reduction) 61% (p=0.04), 52% (p=0.04), 29% (p=0.2), respectively, at 1, 3 and 6 months treatment with alfuzosin. Survival rates (Kaplan-Meier estimates) for alfuzosin compared to placebo were 93.9% vs 84.3% (p=0.04) at 1 month, 90.2% vs 78.8% (p=0.04) at 3 months and 82.5% vs 74.2% (p=0.2) at 6 months, indicating a statistically significant difference from placebo up to 3 months.

A second study (ALFAURUS) investigated the efficacy of alfuzosin (sustained release formulation) 10 mg/day in the management of AUR secondary to BPH. In this study including 806 patients with a first episode of AUR related to BPH, the success rate at 6 months (successful TWOC [trial without catheter] and no AUR relapse nor need for surgery) was 43.5% for the alfuzosin-treated patients and 39.7% for the placebo treated patients.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

The mean bioavailability relative to the immediate release formulation (2.5 mg three times a day) in middle aged healthy volunteers was 104.4%. The maximum plasma concentration is achieved 9 hours after administration (compared with 1 hour for the immediate release formulation).

Studies have shown that consistent pharmacokinetic profiles are obtained when alfuzosin prolonged release is administered after a meal.

Distribution

The binding to plasma proteins is about 90%, 68.2% to human serum albumin and 52.5% to human serum α1-glycoprotein.

Metabolism

The apparent elimination half-life of the prolonged release alfuzosin is 9.1 hours.

Alfuzosin is predominantly metabolised by CYP3A4, with other isoenzymes (e.g. CYP1A2) implicated to a minor extent. Alfuzosin has no significant inhibitory effect on CYP450 isoenzymes (CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4) and is devoid of induction potential on CYP1A, CYP2A6 and CYP3A4 isoenzymes.

Metabolic Interactions

CYP3A4 is the principal hepatic enzyme isoform involved in the metabolism of alfuzosin. Ketoconazole is a potent inhibitor of CYP3A4. Repeated 200mg once daily dosing of ketoconazole for seven days, resulted in an increase of the C_{max} (2.11-fold) and AUC_{last} (2.46 fold) of alfuzosin 10 mg (Xatral SR) daily under fed conditions. Other parameters such as t_{max} and $t_{1/2z}$ were not modified. The 8 day repeated administration of ketoconazole 400mg daily

increased C_{max} of alfuzosin by 2.3-fold, AUC_{last} and AUC by 3.2 and 3.0, respectively, and $t_{1/2Z}$ by 16% (see Section 4.4 Special warnings and precautions for use and Section 4.5 Interactions with other medicines and other forms of interactions).

Pharmacokinetics in Special Populations

Compared to middle aged healthy volunteers, the pharmacokinetic parameters (C_{max} and AUC) are not increased in elderly patients.

Compared to subjects with normal renal function, mean C_{max} and AUC values are moderately increased in patients with renal impairment, without modification of the apparent elimination half-life. This change in the pharmacokinetic profile is not considered clinically relevant. Therefore this does not necessitate a dosing adjustment.

The pharmacokinetic profile of alfuzosin is not affected by chronic cardiac insufficiency.

Excretion

Alfuzosin undergoes extensive metabolism by the liver, with only 11% of the parent compound being excreted unchanged in the urine. The majority of the metabolites (which are inactive) are excreted in the faeces (75 to 91%).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

The Ames assay (although inadequate because a single test was conducted) and the mouse lymphoma assay showed that alfuzosin is not mutagenic. Weak evidence of a non dose related clastogenic effect was observed in Chinese Hamster Ovary cells in the absence of S9 fraction. However, this effect was not observed in the same assay in the presence of S9 fraction or in the mouse micronucleus test. Alfuzosin treatment did not induce DNA repair in a human cell line in culture.

Carcinogenicity

There was no evidence of a drug-related increase in the incidence of tumours in mice and rats following dietary administration of alfuzosin (for 98 and 104 weeks respectively) at doses corresponding to respective levels of systemic exposure (based on AUC of unbound drug) 20-24 and 120-150 times the level of exposure to humans.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Ethylcellulose,

Hydrogenated castor oil,

Hypromellose,

Iron oxide yellow,

Magnesium stearate,

Microcrystalline cellulose,

Povidone,

Silicon dioxide,

Mannitol.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Available in a polyvinyl chloride (PVC) / Aluminum foil blister pack of 30 tablets.

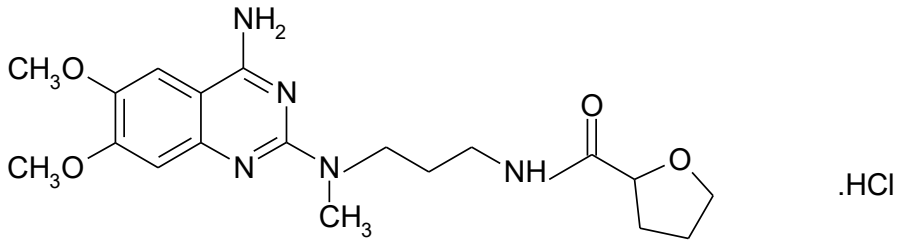
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Alfuzosin hydrochloride is a white to off white crystalline powder. It is freely soluble in water.

Chemical structure



Molecular Weight: 425.9

Chemical Name: (+,-) N-[3-[(4-amino-6,7-dimethoxy-2-quinazolinyl) methylamino] propyl] tetrahydro-2-furancarboxamide hydrochloride

CAS number

81403-68-1

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 (Prescription Only Medicine)

8 SPONSOR

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International Tower 3, Level 23
300 Barangaroo Avenue
Sydney NSW 2000
Freecall: 1800 818 806
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9 DATE OF FIRST APPROVAL

17 September 2002

10 DATE OF REVISION

12 May 2026

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
8	Sponsor details updated