Alfuzosin Hydrochloride

(BANM, USAN, rINNM)

Alfutsosiinihydrokloridi; Alfuzosin Hidroklorür; Alfuzosine, chlorhydrate d'; Alfuzosin-hydrochlorid; Alfuzosinhydroklorid; Alfuzosini hydrochloridum; Alfuzozin-hidroklorid; Alfuzozino hidrochloridas; Hidrocloruro de alfuzosina; SL-77499-10; SL-77499 (alfuzosin). *N*-{3-[4-Amino-6,7-dimethoxyquinazolin-2-yl(methyl)amino]propyl}tetrahydro-2-furamide hydrochloride.

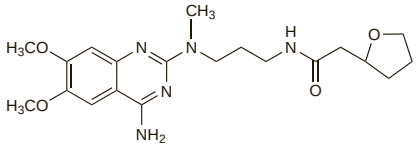
Альфузозина Гидрохлорид

$C_{19}H_{27}N_5O_4,HCl$ = 425.9.

CAS — 81403-80-7 (alfuzosin); 81403-68-1 (alfuzosin hydrochloride).

ATC — G04CA01.

ATC Vet — QG04CA01.



(alfuzosin)

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Alfuzosin Hydrochloride). A white or almost white, slightly hygroscopic, crystalline powder. Freely soluble in water; sparingly soluble in alcohol; practically insoluble in dichloromethane. A 2% solution in water has a pH of 4.0 to 5.5. Store in airtight containers. Protect from light.

Adverse Effects, Treatment, and Precautions

As for Prazosin Hydrochloride, p.1375. Alfuzosin may be more selective for the urinary tract and vasodilator effects may be less frequent. It should be avoided in severe hepatic impairment, and doses may need to be reduced in mild to moderate hepatic impairment and in renal impairment (see below).

Incidence of adverse effects. In postmarketing surveillance involving 13 389 patients given alfuzosin 2.5 mg three times daily by mouth for benign prostatic hyperplasia, about 3.7% of patients failed to complete treatment because of adverse effects. These were mostly vasodilatory in nature (vertigo or dizziness, syncope or malaise, hypotension, and headache), and were more common in patients over 75 years of age and during the first week of treatment.[1]

1. Lukacs B, *et al.* Safety profile of 3 months' therapy with alfuzosin in 13,389 patients suffering from benign prostatic hypertrophy. *Eur Urol* 1996; **29:** 29–35.

Surgical procedures. Alpha blockers, including alfuzosin, have been associated with intraoperative floppy iris syndrome in cataract surgery patients. For further details, see under Tamsulosin, p.2197.

Interactions

As for Prazosin Hydrochloride, p.1376. Potent inhibitors of the cytochrome P450 isoenzyme CYP3A4, such as ketoconazole, itraconazole, and ritonavir, may increase blood concentrations of alfuzosin.

Pharmacokinetics

Alfuzosin is readily absorbed after oral doses and peak plasma concentrations generally occur 0.5 to 3 hours after a dose; bioavailability is about 64%. Absorption from modified-release preparations is improved if given with food. It is extensively metabolised in the liver, mainly by the cytochrome P450 isoenzyme CYP3A4, to inactive metabolites that are excreted primarily in faeces via the bile. Only about 11% of a dose is excreted unchanged in the urine. Alfuzosin has a plasma elimination half-life of 3 to 5 hours. It is 90% bound to plasma proteins.

Uses and Administration

Alfuzosin is an alpha$_1$-adrenoceptor blocker (p.1153) with actions similar to those of prazosin (p.1376). It acts preferentially on receptors in the lower urinary tract and is therefore used in benign prostatic hyperplasia (p.2178) to relieve symptoms of urinary obstruction, including acute urinary retention.

Alfuzosin is given orally as the hydrochloride. Like other alpha$_1$-adrenoceptor blockers, it may cause collapse in some patients after the first dose, which should therefore be given just before bedtime to reduce the risk. Doses may need to be reduced in patients with hepatic or renal impairment (see below); the initial dose should also be reduced in the elderly.

In **benign prostatic hyperplasia,** the usual dose of alfuzosin hydrochloride is 2.5 mg three times daily, increased to 10 mg daily if necessary. In elderly patients, and those receiving treatment for hypertension, a lower initial dose of 2.5 mg twice daily should be considered. A modified-release preparation may also be used in a dose of 10 mg once daily after a meal.

In patients aged over 65 years catheterised for **acute urinary retention** associated with benign prostatic hyperplasia, a modified-release preparation may be given in a dose of 10 mg once daily after a meal for 3 to 4 days.

◊ Reviews.

1. Wilde MI, *et al.* Alfuzosin: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in benign prostatic hyperplasia. *Drugs* 1993; **45:** 410–29.
2. McKeage K, Plosker GL. Alfuzosin: a review of the therapeutic use of the prolonged-release formulation given once daily in the management of benign prostatic hyperplasia. *Drugs* 2002; **62:** 633–53.
3. Lee M. Alfuzosin hydrochloride for the treatment of benign prostatic hyperplasia. *Am J Health-Syst Pharm* 2003; **60:** 1426–39. Correction. *ibid.* 2004; **61:** 437.
4. Weiner DM, Lowe FC. Alfuzosin for the management of benign prostate hyperplasia. *Expert Opin Pharmacother* 2003; **4:** 2057–63.
5. Guay DR. Extended-release alfuzosin hydrochloride: a new alpha-adrenergic receptor antagonist for symptomatic benign prostatic hyperplasia. *Am J Geriatr Pharmacother* 2004; **2:** 14–23.
6. MacDonald R, Wilt TJ. Alfuzosin for treatment of lower urinary tract symptoms compatible with benign prostatic hyperplasia: a systematic review of efficacy and adverse effects. *Urology* 2005; **66:** 780–8.
7. McVary KT. Alfuzosin for symptomatic benign prostatic hyperplasia: long-term experience. *J Urol (Baltimore)* 2006; **175:** 35–42.

Administration in hepatic or renal impairment. In patients with mild to moderate hepatic impairment the initial dose of alfuzosin hydrochloride should be 2.5 mg daily, increased to 2.5 mg twice daily according to response; modified-release preparations are not recommended.

In patients with renal impairment, 2.5 mg twice daily should be given initially, adjusted according to response. Although UK and US licensed product information advises caution with the use of modified-release preparations in severe renal impairment (creatinine clearance below 30 mL/minute), a study[1] in patients with varying degrees of renal impairment (including severe) suggested that no dose reduction was necessary.

1. Marbury TC, *et al.* 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:** 1311–17.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Dalfaz; UroXatral; ***Austria:*** Urion†; Xatral; ***Belg.:*** Xatral; ***Braz.:*** Xatral; ***Canad.:*** Xatral; ***Chile:*** UroXatral; ***Cz.:*** Alfuzostad; Xatral; ***Denm.:*** Xatral; ***Fin.:*** Xatral; ***Fr.:*** Urion; Xatral; ***Ger.:*** Urion; UroXatral; ***Gr.:*** Alfuprost; Alfural; Alfuzin; Innosensitive; Spedamyl; Xatral; ***Hong Kong:*** Xatral; ***Hung.:*** Alfetim; Alfuzostad; ***India:*** Flotral; ***Indon.:*** Xatral; ***Irl.:*** Xatral; ***Israel:*** Xatral; ***Ital.:*** Mittoval; Xatral; ***Malaysia:*** Xatral; ***Mex.:*** Xatral; ***Neth.:*** Mittoval; Urion; UroXatral; Xatral; ***Norw.:*** Xatral; ***Philipp.:*** Xatral; ***Pol.:*** Alfuzostad; Dalfaz; ***Port.:*** Benestan; ***Rus.:*** Dalfaz (Дальфаз); ***S.Afr.:*** Xatral; ***Singapore:*** Xatral; ***Spain:*** Alfetim†; Benestan; Unibenestan; ***Swed.:*** Xatral; ***Switz.:*** Xatral; ***Thai.:*** Xatral; ***Turk.:*** Xatral; ***UK:*** Besavar; Xatral; ***USA:*** UroXatral; ***Venez.:*** Xatral.

Alprostadil *(BAN, USAN, rINN)*

Alprostadiili; Alprostadilis; Alprostadilum; Alprosztadil; PGE$_1$; Prostaglandin E$_1$; U-10136. (*E*)-(8*R*,11*R*,12*R*,15*S*)-11,15-Dihydroxy-9-oxoprost-13-enoic acid; 7-{(1*R*,2*R*,3*R*)-3-Hydroxy-2-[(*E*)-(3*S*)-3-hydroxyoct-1-enyl]-5-oxocyclopentyl}heptanoic acid.

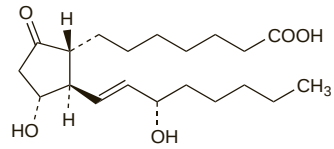
Алпростадил

$C_{20}H_{34}O_5$ = 354.5.

CAS — 745-65-3.

ATC — C01EA01; G04BE01.

ATC Vet — QC01EA01; QG04BE01.



NOTE. In *Martindale* the term alprostadil is used for the exogenous substance and prostaglandin E$_1$ for the endogenous substance.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US*.

Ph. Eur. 6.2 (Alprostadil). A white or slightly yellowish crystalline powder. Practically insoluble in water; freely soluble in alcohol; soluble in acetone; slightly soluble in ethyl acetate.

USP 31 (Alprostadil). A white to off-white crystalline powder. M.p. about 110°. Soluble in water; freely soluble in alcohol; soluble in acetone; very slightly soluble in chloroform and in ether; slightly soluble in ethyl acetate. Store between 2° and 8° in airtight containers.

Alprostadil Alfadex *(BAN, rINNM)*

Alprostadilum Alfadexum; α-Cyclodextrin Alprostadil; PGE$_1$ α-CD; Prostaglandin E$_1$ α-Cyclodextrin Clathrate Compound.

Алпростадил Альфадекс

$C_{20}H_{34}O_5,x[C_{36}H_{60}O_{30}]$.

ATC — C01EA01; G04BE01.

ATC Vet — QC01EA01; QG04BE01.

Pharmacopoeias. In *Jpn.*

Adverse Effects, Treatment, and Precautions

The adverse effects reported most commonly in **infants** with congenital heart disease treated with alprostadil are apnoea, fever, flushing, hypotension, bradycardia, tachycardia, diarrhoea, and convulsions. Other adverse effects reported include oedema, cardiac arrest, hypokalaemia, disseminated intravascular coagulation, and cortical proliferation of the long bones. Weakening of the wall of the ductus arteriosus and pulmonary artery may occur on prolonged infusion. Alprostadil should be avoided in neonates with respiratory distress syndrome and should be used with caution in those with bleeding tendencies; blood pressure and respiratory status should be monitored during infusion.

Adverse effects reported in **adults** given alprostadil have included headache, flushing, hypotension, diarrhoea, and pain and inflammation at the infusion site.

After intracavernosal or intra-urethral alprostadil for the treatment of erectile dysfunction, the most frequently reported adverse effect is pain during erection. Local reactions including penile fibrosis, fibrotic nodules, and Peyronie's disease have been reported. Priapism may occur (see below). Systemic effects are less common but hypotension and other adverse effects have been reported. Intracavernosal or intra-urethral use should be avoided in patients with complicating penile deformities or with sickle-cell disease, myeloma, leukaemias, or other conditions predisposing to prolonged erection.

In children. Reviews[1,2] of adverse effects associated with alprostadil in infants with congenital heart disease.

1. Lewis AB, *et al.* Side effects of therapy with prostaglandin E in infants with critical congenital heart disease. *Circulation* 1981; **64:** 893–8.
2. Lucron H, *et al.* Complications du traitement par prostaglandines E1 des cardiopathies congénitales en réanimation médicale pédiatrique. *Arch Mal Coeur Vaiss* 2005; **98:** 524–30.

Effects on the bones. Periosteal or cortical hyperostosis has been reported in infants given alprostadil for cyanotic congenital heart disease.[1-4] A retrospective review of 30 infants[2] treated with alprostadil revealed radiographic signs of periosteal reactions in 5. Changes could be detected after even short courses of therapy; 3 developed relatively mild periosteal changes in the ribs after infusions ranging from 9 to 205 hours and one had involvement of the left femur after infusion for 71 hours. Resolution of lesions had occurred in most bones 6 to 12 months later. In a further study,[5] radiological evidence of cortical hyperostosis was found in 53 of 86 infant heart transplant recipients who had received alprostadil infusion pre-operatively. Of 53 of the infants who had received alprostadil for less than 30 days, 21 were affected (2 severely). Correspondingly, of those treated for 30 to 60 days, 18 of 22 were affected (13 severely). All 14 infants treated