ALFUSIN D Tablets (Alfuzosin hydrochloride + Dutasteride)

Composition

ALFUSIN D Tablets
Each film-coated tablet contains:
Alfuzosin hydrochloride BP... 10 mg
(as extended-release)
Dutasteride..... 0.5 mg
Colour: Titanium Dioxide IP

Description

ALFUSIN D tablets contain the active ingredients, alfuzosin hydrochloride and dutasteride. Alfuzosin hydrochloride is a selective alpha1-adrenoreceptor blocking agent and exhibits selectivity for alpha1-adrenergic receptors in the lower urinary tract. Blockade of these adrenoreceptors can cause smooth muscles in the bladder neck and prostate to relax, resulting in an improvement in urine flow and a reduction in the symptoms of benign prostatic hyperplasia (BPH).

Dutasteride is a synthetic 4-azasteroid compound that is a selective inhibitor of both type I and type II isoforms of steroid 5 alpha-reductase (5AR), an intracellular enzyme that converts testosterone to 5 alpha-dihydrotestosterone (DHT). DHT is the androgen primarily responsible for the initial development and subsequent enlargement of the prostate gland. The type II isoenzyme is primarily active in the reproductive tissues while the type I isoenzyme is also responsible for testosterone conversion in the skin and liver. **ALFUSIN D** tablets act on both the dynamic and the static components of BPH.

Dosage Form

Film-coated oral tablet

Pharmacology

Pharmacodynamics

Alfuzosin Hydrochloride
Mechanism of action
Alfuzosin is a selective antagonist of post-synaptic alpha1-

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adrenoreceptors, which are located in the prostate, bladder base, bladder neck, prostatic capsule, and prostatic urethra.

Alfuzosin exhibits selectivity for alpha adrenergic receptors in the lower urinary tract. Blockade of these adrenoreceptors can cause smooth muscle in the bladder neck and prostate to relax, resulting in an improvement in urine flow and a reduction in symptoms of BPH.

Cardiac Electrophysiology

The effect of 10 mg and 40 mg alfuzosin on QT interval was evaluated in a double-blind, randomized, placebo and active-controlled (moxifloxacin 400 mg), 4-way crossover single dose study in 45 healthy white male subjects aged 19 to 45 years. The QT interval was measured at the time of peak alfuzosin plasma concentrations. The 40 mg dose of alfuzosin was chosen because this dose achieves higher blood levels than those achieved with the co-administration of alfuzosin and ketoconazole 400 mg. Table 1 summarizes the effect on uncorrected QT and mean corrected QT interval (QTc) with different methods of correction (Fridericia, population-specific and subject-specific correction methods) at the time of peak alfuzosin plasma concentrations. No single one of these correction methodologies is known to be more valid. The mean change of heart rate associated with a 10 mg dose of alfuzosin in this study was 5.2 beats/minute and 5.8 beats/minute with 40 mg alfuzosin. The change in heart rate with moxifloxacin was 2.8 beats/minute.

Table 1. Mean QT and QTc changes in msec (95% CI) from baseline at T_{max} (relative to placebo) with different methodologies to correct for effect of heart rate.

Drug/Dose	QT	Fridericia method	Population-specific method	Subject-specific method
Alfuzosin 10 mg	-5.8 (-10.2, -1.4)	4.9 (0.9, 8.8)	1.8 (-1.4, 5.0)	1.8 (-1.3, 5.0)
Alfuzosin 40 mg	-4.2 (-8.5, 0.2)	7.7 (1.9, 13.5)	4.2 (-0.6, 9.0)	4.3 (-0.5, 9.2)
Moxifloxacin* 400 mg	6.9 (2.3, 11.5)	12.7 (8.6, 16.8)	11.0 (7.0, 15.0)	11.1 (7.2, 15.0)

**Active control*

The QT effect appeared greater for 40 mg compared to 10 mg alfuzosin. The effect of the highest alfuzosin dose (four times the therapeutic dose) studied did not appear as large as that of the active control moxifloxacin at its therapeutic dose. This study, however, was not designed to make direct statistical comparisons between the drugs or the dose levels. There has been no signal of Torsade de Pointes in the extensive post-marketing experience with alfuzosin outside the United States. A separate post-marketing QT study evaluated the effect of the co-administration of 10 mg

(https://www.ciplamed.com/conte
5-mg-once-daily-12-
week-monotherapy-
effective-and-safe-in-
men-with-lutsbph)

alfuzosin with a drug of similar QT effect size. In this study, the mean placebo-subtracted QTcF increase of alfuzosin 10 mg alone was 1.9 msec (upperbound 95% CI, 5.5 msec). The concomitant administration of the two drugs showed an increased QT effect when compared with either drug alone. This QTcF increase was not more than additive. Although this study was not designed to make direct statistical comparisons between drugs, the QT increase with both drugs given together appeared to be lower than the QTcF increase seen with the positive control moxifloxacin 400 mg . The clinical impact of these QTc changes is unknown.

Dutasteride

Mechanism of action

Dutasteride is a synthetic 4-azasteroid compound that is a competitive and specific inhibitor of both the type I and type II isoforms of steroid 5 alpha-reductase (5AR). Testosterone is converted to DHT by the enzyme 5 alpha-reductase, which exists as 2 isoforms, type I and type II. The type II isoenzyme is primarily active in the reproductive tissues, while the type I isoenzyme is also responsible for testosterone conversion in the skin and liver. Dutasteride inhibits the conversion of testosterone to 5 alpha-dihydrotestosterone (DHT). DHT is the androgen primarily responsible for the initial development and subsequent enlargement of the prostate gland.

Effect on 5 Alpha-Dihydrotestosterone and Testosterone

The maximum effect of daily doses of dutasteride on the reduction of DHT is dose-dependent and is observed within 1-2 weeks. After 1 and 2 weeks of daily dosing with dutasteride 0.5 mg, median serum DHT concentrations were reduced by 85% and 90%, respectively. In patients with BPH treated with dutasteride 0.5 mg/day for 4 years, the median decrease in serum DHT was 94% at 1 year, 93% at 2 years and 95% at both 3 and 4 years. The median increase in serum testosterone was 19% at both 1 and 2 years, 26% at 3 years and 22% at 4 years, but the mean and median levels remained within the physiologic range.

In patients with BPH treated with 5 mg/day of dutasteride or placebo for up to 12 weeks prior to transurethral resection of the prostate, mean DHT concentrations in prostatic tissue were significantly lower in the dutasteride group compared with placebo (784 and 5,793 pg/g, respectively; ($p < 0.001$).

Adult males with genetically inherited type II 5 alpha-reductase deficiency also have decreased DHT levels. These 5 alpha-reductase deficient males have a small prostate gland throughout life and do not develop BPH. Except for the associated urogenital defects present at birth, no other clinical abnormalities related to 5 alpha-reductase deficiency have been observed in these individuals.

Effects on Other Hormones

In healthy volunteers, 52 weeks of treatment with dutasteride 0.5 mg/day (n=26) resulted in no clinically significant change, compared with placebo (n=23), in sex hormone-binding globulin, oestradiol, luteinizing hormone, follicle-stimulating hormone, thyroxine (free T4)

anddehydroepiandrosterone. Statistically significant, baseline-adjusted mean increases compared with placebo were observed for total testosterone at 8 weeks (97.1 ng/dL, (p <0.001).

Other Effects

Plasma lipid panel and bone mineral density were evaluated following 52 weeks of dutasteride 0.5 mg once daily in healthy volunteers. There was no change in bone mineral density as measured by dual energy X-ray absorptiometry (DEXA) compared with either placebo or baseline. In addition, the plasma lipid profile (i.e., total cholesterol, low-density lipoproteins, high-density lipoproteins and triglycerides) was unaffected by dutasteride. No clinically significant changes in adrenal hormone responses to ACTH stimulation were observed in a subset population (n=13) of the 1-year healthy volunteer study.

Pharmacokinetics

Alfuzosin Hydrochloride

Absorption: The absolute bioavailability of alfuzosin hydrochloride 10 mg tablets under fed conditions is 49%. Following multiple dosing of 10 mg alfuzosin hydrochloride under fed conditions, the time to maximum concentration was 8 hours. The C_{max} and AUC_{0-24} were 13.6 (SD = 5.6) ng/mL and 194 (SD = 75) ng.h/mL, respectively. Alfuzosin hydrochloride exhibits linear kinetics following single and multiple dosing up to 30 mg. Steady-state plasma levels are reached with the second dose of alfuzosin hydrochloride administration. Steady-state alfuzosin hydrochloride plasma concentrations are 1.2- to1.6-fold higher than those observed after a single administration.

Effect of Food: The extent of absorption is 50% lower under fasting conditions. Therefore, alfuzosin hydrochloride should be taken with food and with the same meal each day.

Distribution: The volume of distribution following intravenous administration in healthy male, middle-aged volunteers was 3.2 L/kg. Results of in vitro studies indicate that alfuzosin hydrochloride is moderately bound to human plasma proteins (82-90%), with linear binding over a wide concentration range (5 to 5,000 ng/mL).

Metabolism: Alfuzosin hydrochloride undergoes extensive metabolism by the liver, with only 11% of the administered dose excreted unchanged in the urine. Alfuzosin hydrochloride is metabolized by three metabolic pathways: oxidation, O-demethylation and N-dealkylation. The metabolites are not pharmacologically active. CYP3A4 is the principal hepatic enzyme isoform involved in its metabolism.

Excretion: Following oral administration of 14C-labelled alfuzosin hydrochloride solution, the recovery of radioactivity after 7 days (expressed as a percentage of the administered dose) was 69% in the faeces and 24% in the urine. Following oral administration of 10 mg alfuzosin hydrochloride, the apparent elimination half-life is 10 hours.

Pharmacokinetics in special populations

Pediatric Use: Alfuzosin tablets are not indicated for use in the pediatric population

Geriatric Use: In a pharmacokinetic assessment during phase 3 clinical studies in patients with BPH, there was no relationship between peak plasma concentrations of alfuzosin and age. However, trough levels were positively correlated with age. The concentrations in subjects ?75 years of age were approximately 35% greater than in those below 65 years of age.

Renal Impairment: The Pharmacokinetic profiles of alfuzosin 10 mg tablets in subjects with normal renal function (CLCR>80 mL/min), mild impairment (CLCR 60 to 80 mL/min), moderate impairment (CLCR 30 to 59 mL/min), and severe impairment (CLCR max and AUC values were increased by approximately 50% in patients with mild, moderate, or severe renal impairment.

Hepatic Impairment: The pharmacokinetics of alfuzosin have not been studied in patients with mild hepatic impairment. In patients with moderate or severe hepatic insufficiency (Child-Pugh categories B and C), the plasma apparent clearance (CL/F) was reduced to approximately one-third to one-fourth that observed in healthy subjects. This reduction in clearance results in three to four-fold higher plasma concentrations of alfuzosin in these patients compared to healthy subjects. Therefore, alfuzosin is contraindicated in patients with moderate to severe hepatic impairment.

Dutasteride

Absorption: Following administration of a single 0.5 mg dose of dutasteride, time to peak serum concentrations (T_{max}) occurs within 2-3 hours. Absolute bioavailability in 5 healthy subjects was approximately 60% (range: 40% to 94%). When the drug is administered with food, the maximum serum concentrations were reduced by 10-15%. This reduction is of no clinical significance.

Distribution: Pharmacokinetic data following single and repeat oral doses show that dutasteride has a large volume of distribution (300-500 L). Dutasteride is highly bound to plasma albumin (99.0%) and alpha1-acid glycoprotein (96.6%). In a study of healthy subjects (n = 26) receiving dutasteride 0.5 mg/day for 12 months, semen dutasteride concentrations averaged 3.4 ng/mL (range: 0.4 to 14 ng/mL) at 12 months and, similar to serum, achieved steady-state concentrations at 6 months. On average, at 12 months 11.5% of serum dutasteride concentrations partitioned into semen.

Metabolism: Dutasteride is extensively metabolized in humans. In vitro studies showed that dutasteride is metabolized by the CYP3A4 and CYP3A5 isoenzymes. Both of these isoenzymes produced the 4'-hydroxydutasteride, 6-hydroxydutasteride and the 6,4'-dihydroxydutasteride metabolites. In addition, the 15-hydroxydutasteride metabolite was formed by CYP3A4. In human serum following dosing to a steady state, unchanged dutasteride, three major metabolites (4'-hydroxydutasteride, 1,2-dihydrodutasteride and 6-hydroxydutasteride) and two minor metabolites (6,4-dihydroxydutasteride and 15-hydroxydutasteride), as assessed by mass spectrometric response, have been detected. In vitro, the 4-

hydroxydutasteride and 1,2-dihydrodutasteride metabolites are much less potent than dutasteride against both isoforms of human 5 alpha-reductase. The activity of 6 beta-hydroxydutasteride is comparable to that of dutasteride.

Excretion: Dutasteride and its metabolites were excreted mainly in the faeces. As a percent of dose, there was approximately 5% unchanged dutasteride (~1% to ~15%) and 40% as dutasteride-related metabolites (~2% to ~90%). Only trace amounts of unchanged dutasteride were found in urine (<1%). Therefore, on average, the dose unaccounted for approximated 55% (range: 5% to 97%).The terminal elimination half-life of dutasteride is approximately 5 weeks at the steady state. The average steady-state serum dutasteride concentration was 40 ng/mL following 0.5 mg/day for 1 year. Following daily dosing, dutasteride serum concentrations achieve 65% of steady-state concentration after 1 month and approximately 90% after 3 months. Due to the long half-life of dutasteride, serum concentrations remain detectable (greater than 0.1 ng/mL) for up to 4-6 months after discontinuation of treatment.

Pharmacokinetics in special populations

Paediatric: Dutasteride pharmacokinetics has not been investigated in subjects younger than 18 years of age.

Geriatric: No dose adjustment is necessary in the elderly. The pharmacokinetics and pharmacodynamics of dutasteride were evaluated in 36 healthy male subjects aged between 24 and 87 years following administration of a single 5 mg dose of dutasteride. In this single-dose trial, dutasteride half-life increased with age (approximately 170 hours in men aged 20 to 49 years, approximately 260 hours in men aged 50 to 69 years, and approximately 300 hours in men older than 70 years). Of 2,167 men treated with dutasteride in the three pivotal trials, 60% were aged 65 years and over, and 15% were aged 75 years and over. No overall differences in safety or efficacy were observed between these patients and younger patients.

Gender: Dutasteride is contraindicated in pregnancy and women of childbearing potential and is not indicated for use in other women. The pharmacokinetics of dutasteride in women has not been studied.

Race: The effect of race on dutasteride pharmacokinetics has not been studied.

Renal Impairment: The effect of renal impairment on dutasteride pharmacokinetics has not been studied. However, less than 0.1% of a steady-state 0.5 mg dose of dutasteride is recovered in human urine, so no adjustment in dosage is anticipated for patients with renal impairment.

Hepatic Impairment: The effect of hepatic impairment on dutasteride pharmacokinetics has not been studied. Because dutasteride is extensively metabolized, exposure could be higher in hepatically impaired patients.

Indications

ALFUSIN D tablets are indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH) in men with an enlarged prostate.

The tablets are not intended for use as an anti-hypertensive drug.

Dutasteride is not approved for the prevention of prostate cancer.

Dosage And Administration

The recommended dosage of **ALFUSIN D** is one tablet daily, to be taken immediately after the same meal each day. The tablet should be swallowed whole and should not be chewed or crushed.

Special Populations

Renal Impairment
Caution should be exercised when alfuzosin is administered in patients with severe renal impairment (creatinine clearance No dose adjustment is necessary for dutasteride in patients with renal impairment

Hepatic Impairment
Alfuzosin is contraindicated for use in patients with moderate or severe hepatic impairment. Although the pharmacokinetics of alfuzosin have not been studied in patients with mild hepatic impairment, caution should be exercised when alfuzosin is administered to such patients.

The effect of hepatic impairment on dutasteride pharmacokinetics has not been studied. Because dutasteride is extensively metabolized, exposure could be higher in hepatically impaired patients.

Contraindications

ALFUSIN D tablets are contraindicated for use in women of childbearing potential and during pregnancy.

ALFUSIN D tablets are contraindicated for use in paediatric patients.

ALFUSIN D tablets should not be used in patients with moderate or severe hepatic impairment (Childs-Pugh categories B and C) since alfuzosin hydrochloride blood levels are increased in these patients.

ALFUSIN D tablets should not be co-administered with potent CYP3A4 inhibitors such as ketoconazole, itraconazole and ritonavir, since alfuzosin hydrochloride blood levels are increased.

ALFUSIN D tablets are contraindicated in patients with known hypersensitivity to alfuzosin hydrochloride (e.g., urticaria and angioedema) or to dutasteride (e.g., serious skin reactions, angioedema) or any component of **ALFUSIN D** tablets.

Warnings And Precautions

Evaluation for Other Urological Diseases

Prior to initiating treatment with ALFUSIN D, consideration should be given to other urological conditions that may cause similar symptoms. In addition, BPH and prostate cancer may coexist.

Postural Hypotension

Postural hypotension with or without symptoms (e.g., dizziness) may develop within a few hours following administration of **ALFUSIN D** tablets. There is a potential for syncope. Patients should be warned of the possible occurrence of such events and should avoid situations where injury could result, should syncope occur. There may be an increased risk of hypotension/postural hypotension and syncope when taking **ALFUSIN D** tablets concomitantly with antihypertensive medication and nitrates. Care should be taken when **ALFUSIN D** tablets are administered to patients with symptomatic hypotension or patients who have had a hypotensive response to other medications.

Priapism

Rarely (probably less than 1 in 50,000), alfuzosin hydrochloride, like other alpha-adrenergic antagonists, has been associated with priapism (persistent painful penile erection unrelated to sexual activity). Because this condition can lead to permanent impotence if not properly treated, patients should be advised about the seriousness of the condition.

Intraoperative Floppy Iris Syndrome (IFIS)

IFIS has been observed during cataract surgery in some patients on or previously treated with alpha-adrenergic antagonists. This variant of small-pupil syndrome is characterized by the combination of a flaccid iris that billows in response to intraoperative irrigation currents, progressive intraoperative miosis despite preoperative dilation with standard mydriatic drugs and potential prolapse of the iris toward the phacoemulsification incisions. The patient's ophthalmologist should be prepared for possible modifications to their surgical technique, such as the utilization of iris hooks, iris dilator rings or viscoelastic substances. There does not appear to be a benefit of stopping alpha-adrenergic antagonist therapy prior to cataract surgery.

Increased Risk of High-grade Prostate Cancer

In men aged 50 to 75 years, with a prior negative biopsy for prostate cancer and a baseline PSA between 2.5 ng/mL and 10.0 ng/mL, who were taking dutasteride in the 4-year Reduction by Dutasteride of prostate Cancer Events (REDUCE) trial, there was an increased incidence of Gleason score 8-10 prostate cancer compared with men taking placebo (dutasteride 1.0% versus placebo 0.5%). In a 7-year, placebo-controlled clinical trial with another 5 alpha-reductase inhibitor (finasteride 5 mg), similar results for Gleason score 8-10 prostate cancer were observed (finasteride 1.8% versus placebo 1.1%). The 5 alpha-reductase inhibitors may increase the risk of development of high-grade prostate cancer. It has not been established as to whether the effect of 5 alpha-reductase inhibitors to reduce prostate volume, or study-related factors, impacted the results of these studies.

Exposure of Women - Risk to Male Foetus

ALFUSIN D tablets should not be handled by a woman who is pregnant or who could become pregnant. Dutasteride is absorbed through the skin and could result in unintended foetal exposure. If a woman who is pregnant or who could become pregnant comes in contact with leaking ALFUSIN D tablets, the contact area should be washed immediately with soap and water.

Blood Donation

Men being treated with **ALFUSIN D** tablets should not donate blood until at least 6 months have passed following their last dose, so as to prevent pregnant women from receiving dutasteride through blood transfusion.

Effects on Prostate-specific Antigen (PSA) and the use of PSA in Prostate Cancer Detection

In clinical studies, dutasteride reduced serum prostate-specific antigen (PSA) concentration by approximately 50% within 3-6 months of treatment. This decrease was predictable over the entire range of PSA values in patients with symptomatic BPH, although it may vary in individuals. Dutasteride may also cause decreases in serum PSA in the presence of prostate cancer. To interpret serial PSAs in men taking dutasteride, a new PSA baseline should be established at least 3 months after starting treatment and the PSA monitored periodically thereafter. Any confirmed increase from the lowest PSA value while on dutasteride may signal the presence of prostate cancer and should be evaluated, even if PSA levels are still within the normal range for men not taking a 5 alpha-reductase inhibitor. Non-compliance with dutasteride may also affect PSA test results.

To interpret an isolated PSA value in a man treated with dutasteride for 3 months or more, the PSA value should be doubled for comparison with normal values in untreated men.

The free-to-total PSA ratio (percent-free PSA) remains constant, even under the influence of dutasteride. If clinicians elect to use percent-free PSA as an aid in the detection of prostate cancer in men receiving dutasteride, no adjustment to its value appears necessary.

Effect on Semen Characteristics

The effects of dutasteride 0.5 mg/day on semen characteristics were evaluated in normal volunteers aged 18 to 52 years (n=27 dutasteride, n=23 placebo) throughout 52 weeks of treatment and 24 weeks of post-treatment follow-up. At 52 weeks, the mean percent reduction from baseline in total sperm count, semen volume and sperm motility were 23%, 26% and 18%, respectively, in the dutasteride group when adjusted for changes from baseline in the placebo group. Sperm concentration and sperm morphology were unaffected. After 24 weeks of follow-up, the mean percent change in total sperm count in the dutasteride group remained 23% lower than baseline. While mean values for all semen parameters at all-time points remained within the normal ranges and did not meet predefined criteria for a clinically significant change (30%), 2 subjects in the

dutasteride group had decreases in sperm count of greater than 90% from baseline at 52 weeks, with partial recovery at the 24-week follow-up. The clinical significance of dutasteride's effect on semen characteristics for an individual patient's fertility is not known.

Coronary Insufficiency

If symptoms of angina pectoris should newly appear or worsen, **ALFUSIN D** tablets should be discontinued.

Patients with Congenital or Acquired QT Prolongation

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

Drug Interactions

Potent CYP3A4 Inhibitors: CYP3A4 is the principal hepatic enzyme isoform involved in the metabolism of alfuzosin hydrochloride. Repeated administration of 400 mg of ketoconazole, a potent inhibitor of CYP3A4, increased the alfuzosin hydrochloride C_{max} by 2.3-fold and the AUC_{last} by 3.2-fold, following a single 10 mg dose of alfuzosin hydrochloride. In another study, repeated oral administration of a lower (200 mg/day) dose of ketoconazole increased the alfuzosin hydrochloride C_{max} by 2.1-fold and the AUC_{last} by 2.5-fold, following a single 10 mg dose of alfusion hydrochloride. Alfuzosin hydrochloride should not be co-administered with potent inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole or ritonavir) because of increased alfuzosin hydrochloride exposure.

Dutasteride is extensively metabolized in humans by the CYP3A4 and CYP3A5 isoenzymes. No clinical drug interaction trials have been performed to evaluate the impact of CYP3A enzyme inhibitors on dutasteride pharmacokinetics. However, based on in vitro data, blood concentrations of dutasteride may increase in the presence of inhibitors of CYP3A4/5 such as ritonavir, ketoconazole, verapamil, diltiazem, cimetidine, troleandomycin, and ciprofloxacin. Because of the potential for drug-drug interactions, use caution when prescribing dutasteride to patients taking potent, chronic CYP3A4 enzyme inhibitors.

Dutasteride does not inhibit the in vitro metabolism of model substrates for the major human CYP450 isoenzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) at a concentration of 1,000 ng/mL, 25 times greater than steady-state serum concentrations in humans.

Moderate CYP3A4 Inhibitors: Repeated co-administration of 240 mg/day of diltiazem, a moderately potent inhibitor of CYP3A4, with 7.5 mg/day (2.5 mg three times daily) alfuzosin hydrochloride increased the C_{max} and AUC_{0-24} of alfuzosin hydrochloride 1.5- and 1.3-fold, respectively. Alfuzosin hydrochloride increased the C_{max} and AUC_{0-12} of diltiazem 1.4-fold. Although no changes in blood pressure were observed in this study, diltiazem is an antihypertensive medication and the combination of alfuzosin hydrochloride and antihypertensive medications has the potential to cause hypotension in some patients.

In human liver microsomes, at concentrations that are achieved at the therapeutic dose, alfuzosin did not inhibit CYP1A2, 2A6, 2C9, 2C19, 2D6 or 3A4 isoenzymes. In primary culture of human hepatocytes, alfuzosin did not induce CYP1A, 2A6 or 3A4 isoenzymes.

Alpha-Adrenergic Antagonists: The pharmacokinetic and pharmacodynamic interactions between alfuzosin hydrochloride and other alpha-blockers have not been determined. However, interactions may be expected and **ALFUSIN D** tablets should not be used in combination with other alpha-blockers.

The administration of dutasteride in combination with tamsulosin or terazosin has no effect on the steady-state pharmacokinetics of either alpha-adrenergic antagonist. The effect of administration of tamsulosin or terazosin on dutasteride pharmacokinetic parameters was not evaluated; the percent change in DHT concentrations was similar for dutasteride alone compared with the combination treatment.

Phosphodiesterase-5 (PDE5) Inhibitors: Caution is advised when alpha-adrenergic antagonists, including alfuzosin hydrochloride, are co-administered with PDE5 inhibitors. Alpha-adrenergic antagonists and PDE5 inhibitors are both vasodilators that can lower blood pressure. Concomitant use of these two drug classes can potentially cause symptomatic hypotension.

Antihypertensive Medication and Nitrates: There may be an increased risk of hypotension/postural hypotension and syncope when taking **ALFUSIN D** tablets concomitantly with antihypertensive medication and nitrates.

Cimetidine: Repeated administration of 1 g/day cimetidine increased both the alfuzosin hydrochloride C_{max} and AUC values by 20%.

Digoxin: Repeated co-administration of alfuzosin hydrochloride 10 mg and digoxin 0.25 mg/day for 7 days did not influence the steady-state pharmacokinetics of either drug. Dutasteride did not alter the steady-state pharmacokinetics of digoxin when administered concomitantly at a dose of 0.5 mg/day for 3 weeks.

Warfarin: Multiple dose administration of an immediate-release tablet formulation of alfuzosin hydrochloride 5 mg twice daily for 6 days to 6 healthy male volunteers did not affect the pharmacological response to a single 25 mg oral dose of warfarin. Dutasteride 0.5 mg/day for 3 weeks did not alter the steady-state pharmacokinetics of the S- or R-warfarin isomers or alter the effect of warfarin on the prothrombin time when administered with warfarin.

Atenolol: Single administration of 100 mg atenolol with a single dose of 2.5 mg of an immediate-release alfuzosin hydrochloride tablet in 8 healthy young male volunteers increased alfuzosin hydrochloride Cmax and AUC values by 28% and 21%, respectively. Alfuzosin hydrochloride increased atenolol C_{max} and AUC values by 26% and 14%, respectively. In this study, the combination of alfuzosin hydrochloride with atenolol caused significant reductions in the mean blood pressure and in mean heart rate.

Hydrochlorothiazide: Single administration of 25 mg hydrochlorothiazide did not modify the pharmacokinetic parameters of alfuzosin hydrochloride. There was no evidence of pharmacodynamic interaction between alfuzosin hydrochloride and hydrochlorothiazide in the 8 patients in the study.

Calcium Channel Antagonists: In a population pharmacokinetics analysis, a decrease in clearance of dutasteride was noted when co-administered with the CYP3A4 inhibitors verapamil (37%, n=6) and diltiazem (44%, n=5). In contrast, no decrease in clearance was seen when amlodipine, another calcium channel antagonist that is not a CYP3A4 inhibitor, was co-administered with dutasteride (+7%, n=4).

The decrease in clearance and subsequent increase in exposure to dutasteride in the presence of verapamil and diltiazem is not considered to be clinically significant. No dose adjustment is recommended.

Cholestyramine: Administration of a single 5 mg dose of dutasteride followed 1 hour later by 12 g cholestyramine did not affect the relative bioavailability of dutasteride.

Other Concomitant Therapy: No clinically significant adverse interactions could be attributed to the combination of dutasteride and concurrent therapy when dutasteride was co-administered with anti-hyperlipidaemics, angiotensin-converting enzyme (ACE) inhibitors, beta-adrenergic blocking agents, calcium channel blockers, corticosteroids, diuretics, non-steroidal anti-inflammatory drugs (NSAIDs), PDE-5 inhibitors and quinolone antibiotics.

Information for Patients

Patients should be told about the possible occurrence of symptoms related to postural hypotension, such as dizziness, when beginning alfuzosin which is one of the component of **ALFUSIN D** tablets, and they should be cautioned about driving, operating machinery, or performing hazardous tasks during this period. This is important for those with low blood pressure or who are taking antihypertensive medications or nitrates.

Patients should be instructed to tell their ophthalmologist about their use of **ALFUSIN D** tablets before cataract surgery or other procedures involving the eyes, even if the patient is no longer taking alfuzosin hydrochloride.

Patients should be advised about the possibility of priapism resulting from treatment with alfuzosin which is one of the component of **ALFUSIN D** tablets and medications in the same class. Although this reaction is extremely rare, if it is not brought to immediate medical attention, it can lead to permanent erectile dysfunction (impotence).

Physicians should inform patients that dutasteride reduces serum PSA levels by approximately 50% within 3-6 months of therapy, although it may vary for each individual. For patients undergoing PSA screening, increases in PSA levels while on treatment with dutasteride may signal the presence of prostate cancer and should be evaluated.

Physicians should inform patients that there was an increase in high-grade prostate cancer in men treated with 5 alpha-reductase inhibitors (which are indicated for BPH treatment), including dutasteride, compared with those treated with placebo in studies looking at the use of these drugs to reduce the risk of prostate cancer.

Physicians should inform patients that **ALFUSIN D** tablets containing dutasteride as it's one of the component should not be handled by a woman who is pregnant or who could become pregnant because of the potential for absorption of dutasteride and the subsequent potential risk to a developing male foetus. Dutasteride is absorbed through the skin and could result in unintended foetal exposure. If a pregnant woman or woman of childbearing potential comes in contact with broken **ALFUSIN D** tablet, the contact area should be washed immediately with soap and water.

Physicians should inform men treated with **ALFUSIN D** tablets containing dutasteride as it's one of the component, should not donate blood until at least 6 months following their last dose, so as to prevent pregnant women from receiving dutasteride through blood transfusion. Serum levels of dutasteride are detectable for 4-6 months after treatment ends.

Renal Impairment

Caution should be exercised when alfuzosin hydrochloride is administered in patients with severe renal impairment (creatinine clearance <30 mL/min). Systemic exposure was increased by approximately 50% in pharmacokinetic studies of patients with mild, moderate, and severe renal impairment. In phase 3 studies, the safety profile of patients with mild (n=172) or moderate (n=56) renal impairment was similar to the patients with normal renal function in those studies. Safety data are available in only a limited number of patients (n=6) with creatinine clearance below 30 mL/min.

The effect of renal impairment on dutasteride pharmacokinetics has not been studied. However, less than 0.1% of a steady-state 0.5-mg dose of dutasteride is recovered in human urine, so no adjustment in dosage is anticipated for patients with renal impairment.

Hepatic Impairment

Alfuzosin hydrochloride is contraindicated for use in patients with moderate or severe hepatic impairment. Although the pharmacokinetics of alfuzosin hydrochloride has not been studied in patients with mild hepatic impairment, caution should be exercised when alfuzosin hydrochloride is administered to such patients.

The effect of hepatic impairment on dutasteride pharmacokinetics has not been studied. Because dutasteride is extensively metabolized, exposure could be higher in hepatically impaired patients. However, in a clinical study where 60 subjects received 5 mg (10 times the therapeutic dose) daily for 24 weeks, no additional adverse events were observed compared with those observed at the therapeutic dose of 0.5 mg.

Pregnancy

Pregnancy Category X

ALFUSIN D tablets are contraindicated for use in women of childbearing potential and during pregnancy. Dutasteride is a 5 alpha-reductase inhibitor that prevents conversion of testosterone to DHT, a hormone necessary for the normal development of male genitalia. In animal reproduction and developmental toxicity studies, dutasteride inhibited normal development of external genitalia in male foetuses. Therefore, dutasteride may cause foetal harm when administered to a pregnant woman. If dutasteride is used during pregnancy or if the patient becomes pregnant while taking dutasteride, the patient should be apprised of the potential hazard to the foetus.

Abnormalities in the genitalia of male foetuses is an expected physiological consequence of inhibition of the conversion of testosterone to DHT by 5 alpha-reductase inhibitors. These results are similar to observations in male infants with genetic 5 alpha-reductase deficiency. Dutasteride is absorbed through the skin. To avoid potential foetal exposure, women who are pregnant or may become pregnant should not handle dutasteride. If contact is made with broken **ALFUSIN D** tablet, the contact area should be washed immediately with soap and water. Dutasteride is secreted into male semen. The highest measured semen concentration of dutasteride in treated men was 14 ng/mL. Assuming exposure of a 50 kg woman to 5 mL of semen and 100% absorption, the woman's dutasteride concentration would be about 0.175 ng/mL. This concentration is more than 100 times less than concentrations producing abnormalities of male genitalia in animal studies. Dutasteride is highly protein-bound in human semen (>96%), which may reduce the amount of dutasteride available for vaginal absorption.

Lactation

ALFUSIN D tablets are not indicated for use in nursing mothers. It is not known whether dutasteride is excreted in human milk.

Paediatric Use

ALFUSIN D tablets are not indicated for use in the paediatric population.

Efficacy of alfuzosin hydrochloride was not demonstrated in a randomized, double-blind, placebo-controlled, efficacy and safety trial conducted in 172 patients ages 2 to 16 years with elevated detrusor leak point pressure (LPP ≥40 cm H2O) of neurologic origin treated with alfuzosin hydrochloride using pediatric formulations. The trial included a 12-week efficacy phase followed by a 40-week safety extension period. No statistically significant difference in the proportion of patients achieving a detrusor leak point pressure of <40 cm H20 was observed between the alfuzosin and placebo groups.

During the placebo-controlled trial, the adverse reactions reported in #8805;2% of patients treated with alfuzosin and at a higher incidence than in the placebo group were: pyrexia, headache, respiratory tract infection, cough, epistaxis and diarrhea. The adverse reactions reported for the whole

12-month trial period, which included the open-label extension, were similar in type and frequency to the reactions observed during the 12-week period. Alfuzosin hydrochloride was not studied in patients below the age of 2. Safety and effectiveness of dutasteride in the paediatric population have not been established.

Geriatric Use

Of the total number of subjects in clinical studies of alfuzosin hydrochloride, 48% were 65 years of age and over, whereas 11% were 75 years and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, but the greater sensitivity of some older individuals cannot be ruled out.

Of 2,167 male subjects treated with dutasteride in three clinical trials, 60% were aged 65 years and older and 15% were aged 75 years and older. No overall differences in safety or efficacy were observed between these subjects and younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Undesirable Effects

Alfuzosin Hydrochloride

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The incidence of treatment-emergent adverse events has been ascertained from three placebo-controlled clinical trials involving 1,608 men where daily doses of 10 and 15 mg alfuzosin hydrochloride were evaluated. In these 3 trials, 473 men received alfuzosin Hydrochloride 10 mg extended-release tablets. In these trials, 4% of patients taking alfuzosin Hydrochloride 10 mg extended-release tablets withdrew from the trial due to adverse reactions, compared with 3% in the placebo group.

Table 2 summarizes adverse reactions that occurred in ≥2% of patients receiving alfuzosin, and at a higher incidence than that of the placebo group. In general, the adverse reactions seen in long-term use were similar in type and frequency to the events described below for the 3-month trials.

Table 2: Adverse Reactions Occurring in ≥2% of Alfuzosin Hydrochloride Treated Patients and More Frequently than with Placebo in 3-Month, Placebo-Controlled Clinical Trials

Adverse Reaction	Placebo (n=678)	Alfuzosin Hydrochloride (n=473)
Dizziness	19 (2.8%)	27 (5.7%)
Upper respiratory tract infection	4 (0.6%)	14 (3.0%)
Headache	12 (1.8%)	14 (3.0%)
Fatigue	12 (1.8%)	13 (2.7%)

The other adverse reactions, reported by between 1% and 2% of patients receiving alfuzosin hydrochloride and occurring more frequently than with placebo are listed alphabetically by body system and by decreasing frequency within body system:
Body as a whole: pain
Gastrointestinal system: abdominal pain, dyspepsia, constipation, nausea
Reproductive system: impotence
Respiratory system: bronchitis, sinusitis, pharyngitis

Signs and Symptoms of Orthostasis in Clinical Studies: The adverse events related to orthostasis that occurred in the double-blind Phase 3 trials with alfuzosin hydrochloride 10 mg are summarized in table 3. Approximately 20-30% of patients in these studies were taking antihypertensive medication.

Table 3: Number (%) of Patients with Symptoms Possibly Associated with Orthostasis in 3-Month, Placebo-Controlled Clinical Trials

Symptoms	Placebo (n=678)	Alfuzosin Hydrochloride (n=473)
Dizziness	19 (2.8%)	27 (5.7%)
Hypotension or postural hypotension	0	2 (0.4%)
Syncope	0	1 (0.2%)

Testing for blood pressure changes or orthostatic hypotension was conducted in three controlled studies. Decreased systolic blood pressure (≤90 mmHg, with a decrease ≥20 mmHg from baseline) was observed in none of the 674 placebo patients and in 1 (0.2%) of the 469 alfuzosin hydrochloride patients. Decreased diastolic blood pressure (≤50 mmHg,

with a decrease ≥15 mmHg from baseline) was observed in 3 (0.4%) of the placebo patients and in 4 (0.9%) of the alfuzosin hydrochloride patients. A positive orthostatic test (decrease in systolic blood pressure of ≥20 mmHg upon standing from the supine position) was seen in 52 (7.7%) of placebo patients and in 31 (6.6%) of the alfuzosin hydrochloride patients.

Dutasteride

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trial of another drug and may not reflect the rates observed in practice.

The most common adverse reactions reported in subjects receiving dutasteride were impotence, decreased libido, breast disorders (including breast enlargement and tenderness), and ejaculation disorders.

Study withdrawal due to adverse reactions occurred in 4% of subjects receiving dutasteride, and 3% of subjects receiving placebo in placebo-controlled trials with dutasteride. The most common adverse reaction leading to study withdrawal was impotence (1%).

Monotherapy

Over 4,300 male subjects with BPH were randomly assigned to receive placebo or 0.5 mg daily doses of dutasteride in three identical 2-year, placebo-controlled, double-blind, Phase 3 treatment trials, each followed by a 2-year, open-label extension. During the double-blind treatment period, 2,167 male subjects were exposed to dutasteride, including 1,772 exposed for 1 year and 1,510 exposed for 2 years. When including the open-label extensions, 1,009 male subjects were exposed to dutasteride for 3 years and 812 were exposed for 4 years. The population was aged 47 to 94 years (mean age: 66 years) and greater than 90% were Caucasian. Table 4 summarizes clinical adverse reactions reported in at least 1% of subjects receiving dutasteride and at a higher incidence than subjects receiving placebo.

Table 4: Adverse Reactions Reported in #8805;1% of Subjects Over a 24-Month Period and More Frequently in the Group Receiving Dutasteride than the Placebo Group (Randomized, Double-Blind, Placebo-Controlled Studies Pooled) by Time of Onset

Adverse Reaction	Adverse Reaction Time of Onset			
	Months 0-6	Months 7-12	Months 13-18	Months 19-24
Dutasteride (n)	**(n=2,167)**	**(n=1,901)**	**(n=1,725)**	**(n=1,605)**
Placebo (n)	(n=2,158)	(n=1,922)	(n=1,714)	(n=1,555)

Impotence Dutasteride Placebo	4.7% 1.7%	1.4% 1.5%	1.0% 0.5%	0.8% 0.9%
Decreased libido Dutasteride Placebo	3.0% 1.4%	0.7% 0.6%	0.3% 0.2%	0.3% 0.1%
Ejaculation disorders[a] Dutasteride Placebo	1.4% 0.5%	0.5% 0.3%	0.5% 0.1%	0.1% 0.0%
Breast disorders[b] Dutasteride Placebo	0.5% 0.2%	0.8% 0.3%	1.1% 0.3%	0.6% 0.1%

[a] These sexual adverse reactions are associated with dutasteride treatment (including monotherapy and combination with tamsulosin). These adverse reactions may persist after treatment discontinuation. The role of dutasteride in this persistence is unknown.
[b] Includes breast tenderness and breast enlargement.

Long-Term Treatment (Up to 4 Years)
High-grade Prostate Cancer: The REDUCE trial was a randomized, double-blind, placebo-controlled trial that enrolled 8,231 men aged 50 to 75 years with a serum PSA of 2.5 ng/mL to 10 ng/mL and a negative prostate biopsy within the previous 6 months. Subjects were randomized to receive placebo (N=4,126) or 0.5 mg daily doses of dutasteride (N=4,105) for up to 4 years. The mean age was 63 years and 91% were Caucasian. Subjects underwent protocol-mandated scheduled prostate biopsies at 2 and 4 years of treatment or had ' for-cause biopsies' at non-scheduled times if clinically indicated. There was a higher incidence of Gleason score 8-10 prostate cancer in receiving dutasteride (1.0%) compared with men on placebo (0.5%). In a 7-year placebo-controlled clinical trial with another 5 alpha-reductase inhibitor (finasteride 5 mg), similar results for Gleason score 8-10 prostate cancer were observed (finasteride 1.8% versus placebo 1.1%). No clinical benefit has been demonstrated in patients with prostate cancer treated with dutasteride.

Reproductive and Breast Disorders
In the three pivotal placebo-controlled BPH trials with dutasteride, each of 4 years in duration, there was no evidence of increased sexual adverse reactions (impotence, decreased libido, and ejaculation disorder) or breast disorders with increased duration of treatment. Among these three trials, there was one case of breast cancer in the dutasteride group and one case in the placebo group. No cases of breast cancer were reported in any treatment group in the 4-year CombAT trial or the 4-year REDUCE trial. The relationship between the long-term use of dutasteride and male breast neoplasia is currently unknown.

Combination with Alpha-Blocker Therapy

Over 4,800 male subjects with BPH were randomly assigned to receive 0.5-mg dutasteride, 0.4-mg tamsulosin, or combination therapy (0.5-mg dutasteride plus 0.4-mg tamsulosin) administered once daily in a 4-year double-blind trial. Overall, 1,623 subjects received monotherapy with dutasteride; 1,611 subjects received monotherapy with tamsulosin; and 1,610 subjects received combination therapy. The population was aged 49 to 88 years (mean age: 66 years) and 88% were Caucasian.

The most common adverse reactions reported in subjects receiving combination therapy (dutasteride plus tamsulosin) were impotence, decreased libido, breast disorders (including breast enlargement and tenderness), ejaculation disorders, and dizziness. Ejaculation disorders occurred significantly more in subjects receiving combination therapy (11%) compared with those receiving dutasteride (2%) or tamsulosin (4%) as monotherapy.

Trial withdrawal due to adverse reactions occurred in 6% of subjects receiving combination therapy (dutasteride plus tamsulosin) and 4% of subjects receiving dutasteride or tamsulosin as monotherapy. The most common adverse reaction in all treatment arms leading to trial withdrawal was erectile dysfunction (1% to 1.5%).

Cardiac Failure: In a trial with combination therapy with dutasteride and alpha-blocker, after 4 years of treatment, the incidence of the composite term cardiac failure in the combination therapy group (12/1,610; 0.7%) was higher than in either monotherapy group: dutasteride, 2/1,623 (0.1%) and tamsulosin, 9/1,611 (0.6%). Composite cardiac failure was also examined in a separate 4-year placebo-controlled trial evaluating dutasteride in men at risk for development of prostate cancer. The incidence of cardiac failure in subjects taking dutasteride was 0.6% (26/4,105) compared with 0.4% (15/4,126) in subjects on placebo. A majority of subjects with cardiac failure in both trials had comorbidities associated with an increased risk of cardiac failure. Therefore, the clinical significance of the numerical imbalances in cardiac failure is unknown. No causal relationship between dutasteride alone or in combination with tamsulosin and cardiac failure has been established. No imbalance was observed in the incidence of overall cardiovascular adverse events in either trial.

Postmarketing Experience

Alfuzosin Hydrochloride

The following adverse reactions have been identified during post-approval use of alfuzosin hydrochloride. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

General disorders: Oedema.

Cardiac disorders: Tachycardia, chest pain, angina pectoris in patients with pre-existing coronary artery disease, atrial fibrillation.

Gastrointestinal disorders: Diarrhoea.

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, pruritus, urticaria, angioedema.
Vascular disorders: Flushing.
Blood and lymphatic system disorders: thrombocytopenia

Dutasteride
The following adverse reactions have been identified during post-approval use of dutasteride. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These reactions have been chosen for inclusion due to a combination of their seriousness, frequency of reporting or potential causal connection to dutasteride.

Immune system disorders: Hypersensitivity reactions, including rash, pruritus, urticaria, localized oedema, serious skin reactions, and angioedema.

Neoplasms: Male breast cancer.

Psychiatric Disorders: Depressed mood.

Reproductive System and Breast Disorders: Testicular pain and testicular swelling.

Overdosage

Overdosage with **ALFUSIN D** tablets could potentially lead to hypotension due to the alfuzosin hydrochloride component. In case of hypotension, support of the cardiovascular system is of first importance. Restoration of blood pressure and normalization of heart rate may be accomplished by keeping the patient in the supine position. If this measure is inadequate, then administration of intravenous fluids should be considered. If necessary, vasopressors should then be used and renal function should be monitored and supported as needed. Alfuzosin hydrochloride is 82-90% protein-bound; therefore, dialysis may not be of benefit.

In volunteer studies, single doses of dutasteride up to 40 mg (80 times the therapeutic dose) for 7 days have been administered without significant safety concerns. In a clinical study, daily doses of 5 mg (10 times the therapeutic dose) were administered to 60 subjects for 6 months with no additional adverse effects to those seen at therapeutic doses of 0.5 mg.

There is no specific antidote for dutasteride. Therefore, in cases of suspected overdosage, symptomatic and supportive treatment should be given as appropriate, taking the long half-life of dutasteride into consideration.

Storage And Handling Instructions

Store in a cool and dry place, protected from light.

Packaging Information

ALFUSIN D

Strip of 10 tablets

Last updated: December 2013
Last reviewed: December 2013

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