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MAXFLOW-D™ 0.5/0.4 Capsule

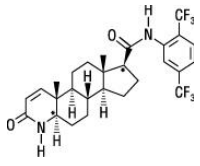
(Dutasteride + Tamsulosin HCl)

میکس فلو-ڈی

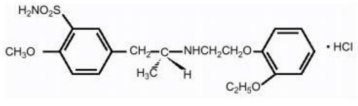
COMPOSITION:
Each capsule contains:
Dutasteride (softgel capsule) ..... 0.5 mg.
Extended release pellets of Tamsulosin HCl eq. to
Tamsulosin HCl USP ..... 0.4 mg.

Product Specs.: Innovator

DESCRIPTION:
MAXFLOW-D capsules contains dutasteride and tamsulosin Hcl.
Dutasteride: Dutasteride is a synthetic 4-azasteroid compound chemically designated as (5, 17)-N-{2, 5 bis (trifluoromethyl) phenyl}-3-oxo-4-azaandrost-1-ene-17-carboxamide. The empirical formula of dutasteride is $C_{27}H_{30}F_6N_2O_2$,representing a molecular weight of 528.5 with the following structural formula:



Tamsulosin HCl:
Tamsulosin hydrochloride is a synthetic compound chemically designated as (-)-(R)-5-[2-[[2-(o-Ethoxyphenoxy) ethyl] amino] propyl]-2-methoxybenzenesulfonamide, monohydrochloride. The empirical formula of tamsulosin hydrochloride is $C_{20}H_{28}N_2O_5S$•HCl. The molecular weight of tamsulosin hydrochloride is 444.97. Its structural formula is.



PHARMACOLOGY:
Mechanism of Action:
MAXFLOW-D is a combination of 2 drugs with different mechanisms of action to improve symptoms in patients with BPH
Dutasteride:
Dutasteride inhibits the conversion of testosterone to DHT. DHT is the androgen primarily responsible for the initial development and subsequent enlargement of the prostate gland. Testosterone is converted to DHT by the enzyme 5 alpha-reductase, which exists as 2 isoforms, type 1 and type 2. The type 2 isoenzyme is primarily active in the reproductive tissues, while the type 1 isoenzyme is also responsible for testosterone conversion in the skin and liver. Dutasteride is a competitive and specific inhibitor of both type 1 and type 25-alpha-reductase isoenzymes, with which it forms a stable enzyme complex. Dissociation from this complex has been evaluated under in vitro and in vivo conditions and is extremely slow. Dutasteride does not bind to the human androgen receptor.
Tamsulosin Hcl:
Smooth muscle tone is mediated by the sympathetic nervous stimulation of alpha1-adrenoceptors, which are abundant in the prostate, prostatic capsule, prostatic urethra, and bladder neck. Blockade of these adrenoceptors can cause smooth muscles in the bladder neck and prostate to relax, resulting in an improvement in urine flow rate and a reduction in symptoms of BPH. Tamsulosin HCl, an alpha1-adrenoceptor blocking agent, exhibits selectivity for alpha1-receptors in the human prostate. At least 3 discrete alpha1-adrenoceptor subtypes have been identified: alpha1A, alpha1B, and alpha1D; their distribution differs between human organs and tissue. Approximately 70% of the alpha1-receptors in human prostate are of the alpha1A subtype. Tamsulosin HCl is not intended for use as an antihypertensive.
Pharmacokinetics:
The pharmacokinetics of dutasteride and tamsulosin HCl from MAXFLOW-D are comparable to the pharmacokinetics of dutasteride and tamsulosin when administered separately.
Absorption:
The pharmacokinetic parameters of dutasteride and tamsulosin observed after administration of a single-dose are summarized.
Single-dose Pharmacokinetic Parameters under Fed Conditions:

Component	N	AUC(0-t) (ng h/mL)	Cmax (ng/mL)	Tmax (h)[a]	t½ (h)
Dutasteride	92	39.6 (23.1)	2.14 (0.77)	3.00 (1.00-10.00)	
Tamsulosin	92	187.2 (95.7)	11.3 (4.44)	6.00 (2.00-24.00)	13.5 (3.92)[b]

Following administration of a single 0.5-mg dose dutasteride, time to peak absolute bioavailability is approximately 60% (range: 40% to 94%). Absorption of tamsulosin is essentially complete (>90%) following oral administration of 0.4 mg tamsulosin hydrochloride capsules under fasting conditions. Tamsulosin exhibits linear kinetics following single and multiple dosing.
Distribution:
Dutasteride has a large volume of distribution (300 to 500 L). Dutasteride is highly bound to plasma albumin (99.0%) and alpha-1 acid glycoprotein (AAG, 96.6%). Apparent volume of distribution of tamsulosin after intravenous administration is 16 L, which is suggestive of Distribution into extracellular fluids in the body. Tamsulosin HCl is extensively bound to human plasma proteins (94% to 99%),
Metabolism:
Dutasteride is extensively metabolized in humans by the CYP3A4 and CYP3A5 isoenzymes. Both of these isoenzymes produced the 4'-hydroxydutasteride, 6-hydroxydutasteride, and the 6, 4'-dihydroxydutasteride metabolites. Tamsulosin HCl is extensively metabolized by cytochrome P450 enzymes in the liver and less than 10% of the dose is excreted in urine unchanged. In vitro studies indicate that CYP3A4 and CYP2D6 are involved in metabolism of tamsulosin Hcl.
Excretion:
Dutasteride and its metabolites were excreted mainly in feces approximately 5% unchanged dutasteride (approximately 1% to approximately 15%) and 40% as dutasteride-related metabolites (approximately 2% to approximately 90%). The terminal elimination half-life of dutasteride is approximately 5 weeks at steady state. For Tamsulosin urine (76%) represents the primary route of excretion compared with feces (21%) over 168 hours. the elimination half-life of tamsulosin HCl in plasma ranges from 5 to 7 hours.
Specific Populations:
Pediatric: The pharmacokinetics of dutasteride and tamsulosin HCl administered together have not been investigated in subjects younger than 18 years.
Geriatric:
For Dutasteride No dosage adjustment is necessary in the elderly. While for tamsulosin, over all exposure (AUC) and half-life may be slightly prolonged in geriatric males compared with young, healthy male volunteers
Gender. Dutasteride is contraindicated in pregnancy and women of childbearing potential and is not indicated for use in other women. Tamsulosin is not indicated for use in women.
Race: The effect of race on pharmacokinetics of dutasteride and tamsulosin administered together or separately has not been studied.
Renal Impairment:
For dutasteride no adjustment in dosage is anticipated for patients with renal impairment. The pharmacokinetics of tamsulosin have been compared in subjects with mild-moderate (30CLcr <70 mL/min/1.73 m^2) or moderate-severe (10≤ CLcr<30 mL/min/1.73 m^2) renal impairment and 6 normal subjects (CLcr >90 mL/min/1.73 m^2). While a change in the overall plasma concentration of tamsulosin HCl was observed as the result of altered binding to AAG, the unbound (active) concentration of tamsulosin, as well as the intrinsic clearance, remained relatively constant. Therefore, patients with renal impairment do not require an adjustment in tamsulosin HCl dosing. However, patients with end-stage renal disease (Clcr <10 mL/min/1.73 m^2) have not been studied.
Hepatic Impairment:
Dutasteride is extensively metabolized, exposure could be higher in hepatically impaired patients. Patients with moderate hepatic impairment do not require an adjustment in tamsulosin HCl dosage.

INDICATIONS AND USAGE:
Benign Prostatic Hyperplasia (BPH) Treatment:
MAXFLOW-D (dutasteride and tamsulosin hydrochloride) capsules are indicated for the treatment of symptomatic BPH in men with an enlarged prostate.
Limitations of Use: Dutasteride-containing products, including MAXFLOW-D, are not approved for the prevention of prostate cancer.

DOSAGE AND ADMINISTRATION:
The recommended dosage of MAXFLOW-D is 1 capsule (0.5 mg dutasteride and 0.4 mg tamsulosin hydrochloride) taken once daily approximately 30 minutes after the same meal each day.

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Administration:
The capsules should be swallowed whole and not chewed or opened. Contact with the contents of the MAXFLOW-D capsule may result in irritation of the oropharyngeal mucosa.

CONTRAINDICATIONS:
MAXFLOW-D is contraindicated for use in:
- Women of childbearing potential.
- Pediatric patients
- Patients with previously demonstrated, clinically significant hypersensitivity (e.g.,serious skin reactions, angioedema, urticaria, pruritus, respiratory symptoms) to dutasteride, other 5-alpha-reductase inhibitors, tamsulosin HCl, or any other component of MAXFLOW-D.

WARNINGS AND PRECAUTIONS:
- Orthostatic hypotension and/or syncope can occur. Advice patients of symptoms related to postural hypotension and to avoid situations where injury could result if syncope occurs.
- Do not use MAXFLOW-D with other alpha-adrenergic antagonists, as this may increase the risk of hypotension.
- MAXFLOW-D reduces serum prostate-specific antigen (PSA) concentration by approximately 50%. However, any confirmed increase in PSA while on MAXFLOW-D may signal the presence of prostate cancer and should be evaluated, even if those values are still within the normal range for Untreated men
- Do not use MAXFLOW-D with strong inhibitors of cytochrome P450 (CYP) 3A4 (e.g., ketoconazole). Use caution in combination with moderate CYP3A4 inhibitors (e.g., erythromycin) or strong (e.g., paroxetine) or moderate CYP2D6 inhibitors, a combination of both CYP3A4 and CYP2D6 inhibitors, or known poor metabolizers of CYP2D6. Concomitant use with known inhibitors can cause a marked increase in drug exposure.
- Exercise caution with concomitant use of phosphodiesterase-5 (PDE-5) inhibitors, as this may increase the risk of hypotension.
- Drugs that contain dutasteride, including MAXFLOW-D, may increase the risk of high-grade prostate cancer.
- Prior to initiating treatment with MAXFLOW-D, consideration should be given to other urological conditions that may cause similar symptoms.
- Women who are pregnant or could become pregnant should not handle MAXFLOW-D capsules due to potential risk to a male fetus.
- Advise patients about the possibility and seriousness of priapism.
- Patients should not donate blood until 6 months after their last dose of MAXFLOW-D.
- Intraoperative Floppy Iris Syndrome has been observed during cataract and glaucoma surgery after alpha-adrenergic antagonist exposure. Advise patients considering cataract or glaucoma surgery to tell their ophthalmologist that they take or have taken MAXFLOW-D capsules.
- Exercise caution with concomitant use of warfarin.

DRUG INTERACTIONS:
Cytochrome P450 Inhibition:
Dutasteride: Extensively metabolized in humans by the CYP3A4 and CYP3A5 isoenzymes. Because of the potential for drug-drug interactions, use caution when prescribing a dutasteride-containing product, including MAXFLOW-D, to patients taking potent, chronic CYP3A4 enzyme inhibitors. Concomitant administration of dutasteride 0.5 mg/day for 3 weeks with warfarin does not alter the steady-state pharmacokinetics of the S- or R-warfarin isomers or alter the effect of warfarin on prothrombin time. Dutasteride does not alter the steady-state pharmacokinetics of digoxin when administered concomitantly at a dose of 0.5 mg/day for 3 weeks. Coadministration of verapamil or diltiazem decreases dutasteride clearance and leads to increased exposure to dutasteride. The change in dutasteride exposure is not considered to be clinically significant. No dosage adjustment of dutasteride is recommended. Administration of a single 5-mg dose of dutasteride followed 1 hour later by a 12-g dose of cholestyramine does not affect the relative bioavailability of dutasteride.
Tamsulosin Hcl:
Tamsulosin HCl is extensively metabolized, mainly by CYP3A4 or CYP2D6. Concomitant treatment with ketoconazole (a strong inhibitor of CYP3A4) resulted in increases in the Cmax and area under the concentration-time curve (AUC) of tamsulosin HCl Concomitant treatment with paroxetine (a strong inhibitor of CYP2D6) resulted in increases in the Cmax and AUC of tamsulosin HCl. Tamsulosin HCl 0.4 mg capsules should not be used in combination with strong inhibitors of CYP3A4 (e.g., ketoconazole). There is a potential for significant increase in tamsulosin HCl exposure when tamsulosin HCl 0.4 mg is coadministered with a combination of both CYP3A4 and CYP2D6 inhibitors. Treatment with cimetidine resulted in a moderate increase in tamsulosin hydrochloride AUC (44%). Caution should be exercised with concomitant administration of warfarin and tamsulosin-containing products, including MAXFLOW-D. Dosage adjustments are not necessary when tamsulosin HCl is administered concomitantly with nifedipine, atenolol, or enalapril. Dosage adjustments are not necessary when tamsulosin HCl is administered concomitantly with digoxin or theophylline. Tamsulosin HCl had no effect on the pharmacodynamics (excretion of electrolytes) of furosemide.

USE IN SPECIFIC POPULATIONS:
Pregnancy:
Pregnancy Category X.
There are no adequate and well-controlled studies in pregnant women with MAXFLOW-D or its individual components.
Nursing Mothers:
MAXFLOW-D is contraindicated for use in women of childbearing potential, including nursing women.
Pediatric Use: MAXFLOW-D is contraindicated for use in pediatric patients.
Geriatric Use: No overall differences in safety or efficacy were observed between these subjects and younger subjects but greater sensitivity of some older individuals cannot be ruled out
Renal Impairment: Because no dosage adjustment is necessary for dutasteride or tamsulosin HCl in patients with moderate-to-severe renal impairment (10≤ CLcr <30 mL/min/1.73 m^2), no dosage adjustment is necessary for MAXFLOW-D in patients with moderate-to-severe renal impairment.
Hepatic Impairment:
Because dutasteride is extensively metabolized, exposure could be higher in hepatically impaired patients. Patients with moderate hepatic impairment do not require an adjustment in tamsulosin HCl dosage.

ADVERSE REACTIONS:
The most common adverse reactions, reported in 1% of subjects treated with coadministered dutasteride and tamsulosin HCl are ejaculation disorders, impotence, decreased libido, dizziness, and breast disorders.

OVERDOSAGE:
Dutasteride:
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.
Tamsulosin HCl:
Should overdosage of tamsulosin HCl lead to 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. Tamsulosin HCl is 94% to 99% protein bound; therefore, dialysis is unlikely to be of benefit.

INSTRUCTIONS:
Store below 30°C. Protect from heat, sunlight and moisture. Keep out of the reach of children. For use by men only. Leaking capsule should not be handled by women or children. Do not chew. Swallow the capsule whole. To be sold on the prescription of a registered medical practitioner only.

PRESENTATION:
MaxFlow-D 0.5/0.4 Capsule : Pack of 4 x 5 capsules.

ہدایات: ۳۰ درجہ سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔ گرمی، دھوپ
اور نمی سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔ صرف مرد استعمال کریں۔
کیپسول ایک ہونے کی صورت میں خواتین یا بچے اسے ہاتھ نہ لگائیں۔
کیپسول کو چبائیں نہیں۔ کیپسول کو سالم حالت میں نگلیں۔
صرف ڈاکٹر کے نسخہ پر فروخت کریں۔
خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

FOR FURTHER INFORMATION PLEASE CONTACT:

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