

ATTENTION PHARMACIST: Detach "Patient Information" from package insert and dispense with the product.



Flomax®

(tamsulosin hydrochloride)

Capsules, 0.4 mg

Rx only

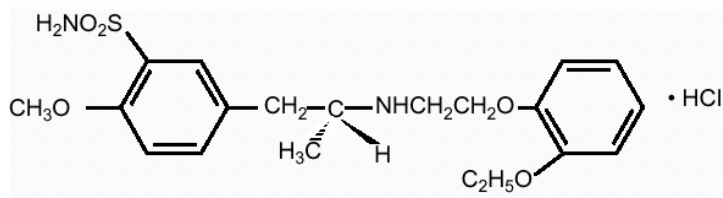
Prescribing Information

DESCRIPTION

Tamsulosin hydrochloride is an antagonist of α_{1A} adrenoceptors in the prostate.

Tamsulosin hydrochloride is (-)-(R)-5-[2-[[2-(*o*-Ethoxyphenoxy) ethyl]amino]propyl]-2-methoxybenzenesulfonamide, monohydrochloride. Tamsulosin hydrochloride is a white crystalline powder that melts with decomposition at approximately 230°C. It is sparingly soluble in water and methanol, slightly soluble in glacial acetic acid and ethanol, and practically insoluble in ether.

The empirical formula of tamsulosin hydrochloride is $C_{20}H_{28}N_2O_5S \cdot HCl$. The molecular weight of tamsulosin hydrochloride is 444.98. Its structural formula is:



Each FLOMAX capsule for oral administration contains tamsulosin hydrochloride 0.4 mg, and the following inactive ingredients: methacrylic acid copolymer dispersion NF, microcrystalline cellulose, triacetin, calcium stearate, talc, FD&C blue No. 2, titanium dioxide, ferric oxide, gelatin, and trace amounts black edible ink.

CLINICAL PHARMACOLOGY

The symptoms associated with benign prostatic hyperplasia (BPH) are related to bladder outlet obstruction, which is comprised of two underlying components: static and dynamic. The static component is related to an increase in prostate size caused, in part, by a proliferation of smooth muscle cells in the prostatic stroma. However, the severity of BPH symptoms and the degree of urethral obstruction do not correlate well with the size of the

prostate. The dynamic component is a function of an increase in smooth muscle tone in the prostate and bladder neck leading to constriction of the bladder outlet. Smooth muscle tone is mediated by the sympathetic nervous stimulation of α_1 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, an α_1 adrenoceptor blocking agent, exhibits selectivity for α_1 receptors in the human prostate. At least three discrete α_1 -adrenoceptor subtypes have been identified: α_{1A} , α_{1B} and α_{1D} ; their distribution differs between human organs and tissue. Approximately 70% of the α_1 -receptors in human prostate are of the α_{1A} subtype.

Flomax® (tamsulosin hydrochloride) capsules are not intended for use as an antihypertensive drug.

Pharmacokinetics

The pharmacokinetics of tamsulosin hydrochloride have been evaluated in adult healthy volunteers and patients with BPH after single and/or multiple administration with doses ranging from 0.1 mg to 1 mg.

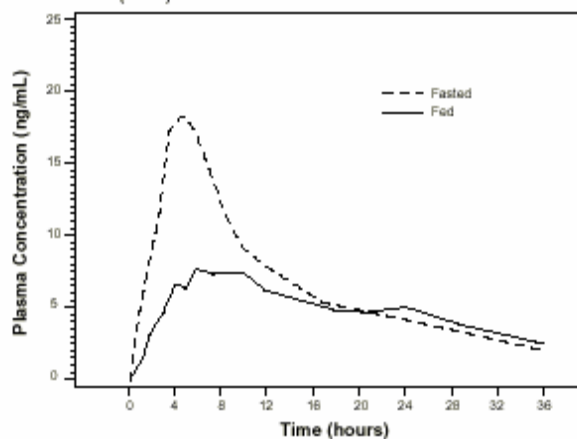
Absorption

Absorption of tamsulosin hydrochloride from FLOMAX capsules 0.4 mg is essentially complete (>90%) following oral administration under fasting conditions. Tamsulosin hydrochloride exhibits linear kinetics following single and multiple dosing, with achievement of steady-state concentrations by the fifth day of once-a-day dosing.

Effect of Food

The time to maximum concentration (T_{max}) is reached by four to five hours under fasting conditions and by six to seven hours when FLOMAX capsules are administered with food. Taking FLOMAX capsules under fasted conditions results in a 30% increase in bioavailability (AUC) and 40% to 70% increase in peak concentrations (C_{max}) compared to fed conditions (Figure 1).

Figure 1 Mean Plasma Tamsulosin Hydrochloride Concentrations Following Single-Dose Administration of FLOMAX capsules 0.4 mg Under Fasted and Fed Conditions (n=8)



The effects of food on the pharmacokinetics of tamsulosin hydrochloride are consistent regardless of whether a Flomax® (tamsulosin hydrochloride) capsule is taken with a light breakfast or a high-fat breakfast (Table 1).

Table 1 Mean (± S.D.) Pharmacokinetic Parameters Following FLOMAX capsules 0.4 mg Once Daily or 0.8 mg Once Daily with a Light Breakfast, High-Fat Breakfast or Fasted

Pharmacokinetic Parameter	0.4 mg QD to healthy volunteers; n=23 (age range 18-32 years)		0.8 mg QD to healthy volunteers; n=22 (age range 55-75 years)		
	Light Breakfast	Fasted	Light Breakfast	High-Fat Breakfast	Fasted
Cmin (ng/mL)	4.0 ± 2.6	3.8 ± 2.5	12.3 ± 6.7	13.5 ± 7.6	13.3 ± 13.3
Cmax (ng/mL)	10.1 ± 4.8	17.1 ± 17.1	29.8 ± 10.3	29.1 ± 11.0	41.6 ± 15.6
Cmax/Cmin Ratio	3.1 ± 1.0	5.3 ± 2.2	2.7 ± 0.7	2.5 ± 0.8	3.6 ± 1.1
Tmax (hours)	6.0	4.0	7.0	6.6	5.0
T1/2 (hours)	-	-	-	-	14.9 ± 3.9
AUCτ (ng•hr/mL)	151 ± 81.5	199 ± 94.1	440 ± 195	449 ± 217	557 ± 257

Cmin = observed minimum concentration

Cmax = observed maximum tamsulosin hydrochloride plasma concentration

Tmax = median time-to-maximum concentration

T1/2 = observed half-life

AUCτ = Area under the tamsulosin hydrochloride plasma time curve over the dosing interval

Distribution

The mean steady-state apparent volume of distribution of tamsulosin hydrochloride after intravenous administration to ten healthy male adults was 16L, which is suggestive of distribution into extracellular fluids in the body.

Tamsulosin hydrochloride is extensively bound to human plasma proteins (94% to 99%), primarily alpha-1 acid glycoprotein (AAG), with linear binding over a wide concentration range (20 to 600 ng/mL). The results of two-way *in vitro* studies indicate that the binding of

tamsulosin hydrochloride to human plasma proteins is not affected by amitriptyline, diclofenac, glyburide, simvastatin plus simvastatin-hydroxy acid metabolite, warfarin, diazepam, propranolol, trichlormethiazide, or chlormadinone. Likewise, tamsulosin hydrochloride had no effect on the extent of binding of these drugs.

Metabolism

There is no enantiomeric bioconversion from tamsulosin hydrochloride [R(-) isomer] to the S(+) isomer in humans. Tamsulosin hydrochloride is extensively metabolized by cytochrome P450 enzymes in the liver and less than 10% of the dose is excreted in urine unchanged. However, the pharmacokinetic profile of the metabolites in humans has not been established. In vitro results indicate that CYP3A4 and CYP2D6 are involved in metabolism of tamsulosin as well as some minor participation of other CYP isoenzymes. Inhibition of hepatic drug metabolizing enzymes may lead to increased exposure to tamsulosin (see ***Drug-Drug Interactions, Cytochrome P450 Inhibition***). The metabolites of tamsulosin hydrochloride undergo extensive conjugation to glucuronide or sulfate prior to renal excretion.

Incubations with human liver microsomes showed no evidence of clinically significant metabolic interactions between tamsulosin hydrochloride and amitriptyline, albuterol (beta agonist), glyburide (glibenclamide) and finasteride (5alpha-reductase inhibitor for treatment of BPH). However, results of the *in vitro* testing of the tamsulosin hydrochloride interaction with diclofenac and warfarin were equivocal.

Excretion

On administration of the radiolabeled dose of tamsulosin hydrochloride to four healthy volunteers, 97% of the administered radioactivity was recovered, with urine (76%) representing the primary route of excretion compared to feces (21%) over 168 hours.

Following intravenous or oral administration of an immediate-release formulation, the elimination half-life of tamsulosin hydrochloride in plasma range from five to seven hours. Because of absorption rate-controlled pharmacokinetics with Flomax® (tamsulosin hydrochloride) capsules, the apparent half-life of tamsulosin hydrochloride is approximately 9 to 13 hours in healthy volunteers and 14 to 15 hours in the target population.

Tamsulosin hydrochloride undergoes restrictive clearance in humans, with a relatively low systemic clearance (2.88 L/h).

Special Populations

Geriatrics (Age)

Cross-study comparison of FLOMAX capsules overall exposure (AUC) and half-life indicate that the pharmacokinetic disposition of tamsulosin hydrochloride may be slightly prolonged in geriatric males compared to young, healthy male volunteers. Intrinsic clearance is independent of tamsulosin hydrochloride binding to AAG, but diminishes with age, resulting in a 40% overall higher exposure (AUC) in subjects of age 55 to 75 years compared to subjects of age 20 to 32 years.

Renal Dysfunction

The pharmacokinetics of tamsulosin hydrochloride have been compared in 6 subjects with mild-moderate ($30 \leq \text{CL}_{\text{cr}} < 70$ mL/min/1.73m²) or moderate-severe ($10 \leq \text{CL}_{\text{cr}} < 30$ mL/min/1.73m²) renal impairment and 6 normal subjects ($\text{CL}_{\text{cr}} < 90$ mL/min/1.73m²). While a change in the overall plasma concentration of tamsulosin hydrochloride was observed as the result of altered binding to AAG, the unbound (active) concentration of tamsulosin hydrochloride, as well as the intrinsic clearance, remained relatively constant. Therefore, patients with renal impairment do not require an adjustment in Flomax® (tamsulosin hydrochloride) capsules dosing. However, patients with endstage renal disease ($\text{CL}_{\text{cr}} < 10$ mL/min/1.73m²) have not been studied.

Hepatic Dysfunction

The pharmacokinetics of tamsulosin hydrochloride have been compared in 8 subjects with moderate hepatic dysfunction (Child-Pugh's classification: Grades A and B) and 8 normal subjects. While a change in the overall plasma concentration of tamsulosin hydrochloride was observed as the result of altered binding to AAG, the unbound (active) concentration of tamsulosin hydrochloride does not change significantly with only a modest (32%) change in intrinsic clearance of unbound tamsulosin hydrochloride. Therefore, patients with moderate hepatic dysfunction do not require an adjustment in FLOMAX capsules dosage. FLOMAX has not been studied in patients with severe hepatic dysfunction.

Drug-Drug Interactions

Nifedipine, Atenolol, Enalapril

In three studies in hypertensive subjects (age range 47-79 years) whose blood pressure was controlled with stable doses of Procardia XL®, atenolol, or enalapril for at least three months, FLOMAX capsules 0.4 mg for seven days followed by FLOMAX capsules 0.8 mg for another seven days (n=8 per study) resulted in no clinically significant effects on blood pressure and pulse rate compared to placebo (n=4 per study). Therefore, dosage adjustments are not necessary when FLOMAX capsules are administered concomitantly with Procardia XL®, atenolol, or enalapril.

Warfarin

A definitive drug-drug interaction study between tamsulosin hydrochloride and warfarin was not conducted. Results from limited *in vitro* and *in vivo* studies are inconclusive. Therefore, caution should be exercised with concomitant administration of warfarin and FLOMAX capsules.

Digoxin and Theophylline

In two studies in healthy volunteers (n=10 per study; age range 19-39 years) receiving FLOMAX capsules 0.4 mg/day for two days, followed by FLOMAX capsules 0.8 mg/day for five to eight days, single intravenous doses of digoxin 0.5 mg or theophylline 5 mg/kg resulted in no change in the pharmacokinetics of digoxin or theophylline. Therefore, dosage adjustments are not necessary when a FLOMAX capsule is administered concomitantly with digoxin or theophylline.

Furosemide

The pharmacokinetic and pharmacodynamic interaction between Flomax® (tamsulosin hydrochloride) capsules 0.8 mg/day (steady-state) and furosemide 20 mg intravenously (single dose) was evaluated in ten healthy volunteers (age range 21-40 years). FLOMAX capsules had no effect on the pharmacodynamics (excretion of electrolytes) of furosemide. While furosemide produced an 11% to 12% reduction in tamsulosin hydrochloride C_{max} and AUC, these changes are expected to be clinically insignificant and do not require adjustment of the FLOMAX capsules dosage.

Cytochrome P450 Inhibition:

Cimetidine

The effects of cimetidine at the highest recommended dose (400 mg every six hours for six days) on the pharmacokinetics of a single FLOMAX capsule 0.4 mg dose was investigated in ten healthy volunteers (age range 21-38 years). Treatment with cimetidine resulted in a significant decrease (26%) in the clearance of tamsulosin hydrochloride which resulted in a moderate increase in tamsulosin hydrochloride AUC (44%). Therefore, FLOMAX capsules should be used with caution in combination with cimetidine, particularly at doses higher than 0.4 mg.

Strong and Moderate Inhibitors of CYP2D6 or CYP3A4

No studies have been conducted to examine the effect of concomitant administration of a strong or moderate inhibitor of CYP2D6 or CYP3A4 on the pharmacokinetics of tamsulosin.

CLINICAL STUDIES

Four placebo-controlled clinical studies and one active-controlled clinical study enrolled a total of 2296 patients (1003 received FLOMAX capsules 0.4 mg once daily, 491 received FLOMAX capsules 0.8 mg once daily, and 802 were control patients) in the U.S. and Europe.

In the two U.S. placebo-controlled, double-blind, 13-week, multicenter studies [Study 1 (US92-03A) and Study 2 (US93-01)], 1486 men with the signs and symptoms of BPH were enrolled. In both studies, patients were randomized to either placebo, FLOMAX capsules 0.4 mg once daily, or FLOMAX capsules 0.8 mg once daily. Patients in FLOMAX capsules 0.8 mg once daily treatment groups received a dose of 0.4 mg once daily for one week before increasing to the 0.8 mg once daily dose. The primary efficacy assessments included: 1) total American Urological Association (AUA) Symptom Score questionnaire, which evaluated irritative (frequency, urgency, and nocturia), and obstructive (hesitancy, incomplete emptying, intermittency, and weak stream) symptoms, where a decrease in score is consistent with improvement in symptoms; and 2) peak urine flow rate, where an increased peak urine flow rate value over baseline is consistent with decreased urinary obstruction.

Mean changes from baseline to week 13 in total AUA Symptom Score were significantly greater for groups treated with FLOMAX capsules 0.4 mg and 0.8 mg once daily compared to placebo in both U.S. studies (Table 2, Figures 2A and 2B). The changes from baseline to

week 13 in peak urine flow rate were also significantly greater for the FLOMAX capsules 0.4 mg and 0.8 mg once daily groups compared to placebo in Study 1, and for the FLOMAX capsules 0.8 mg once daily group in Study 2 (Table 2, Figures 3A and 3B). Overall there were no significant differences in improvement observed in total AUA Symptom Scores or peak urine flow rates between the 0.4 mg and the 0.8 mg dose groups with the exception that the 0.8 mg dose in Study 1 had a significantly greater improvement in total AUA Symptom Score compared to the 0.4 mg dose.

Table 2 Mean (\pm S.D.) Changes from Baseline to Week 13 in Total AUA Symptom Score ** and Peak Urine Flow Rate (mL/sec)

	Total AUA Symptom Score		Peak Urine Flow Rate	
	Mean Baseline Value	Mean Change	Mean Baseline Value	Mean Change
Study 1[†]				
FLOMAX capsules 0.8 mg once daily	19.9 \pm 4.9 n=247	-9.6* \pm 6.7 n=237	9.57 \pm 2.51 n=247	1.78* \pm 3.35 n=247
FLOMAX capsules 0.4 mg once daily	19.8 \pm 5.0 n=254	-8.3* \pm 6.5 n=246	9.46 \pm 2.49 n=254	1.75* \pm 3.57 n=254
Placebo	19.6 \pm 4.9 n=254	-5.5 \pm 6.6 n=246	9.75 \pm 2.54 n=254	0.52 \pm 3.39 n=253
Study 2[‡]				
FLOMAX capsules 0.8 mg once daily	18.2 \pm 5.6 n=244	-5.8* \pm 6.4 n=238	9.96 \pm 3.16 n=244	1.79* \pm 3.36 n=237
FLOMAX capsules 0.4 mg once daily	17.9 \pm 5.8 n=248	-5.1* \pm 6.4 n=244	9.94 \pm 3.14 n=248	1.52 \pm 3.64 n=244
Placebo	19.2 \pm 6.0 n=239	-3.6 \pm 5.7 n=235	9.95 \pm 3.12 n=239	0.93 \pm 3.28 n=235

* Statistically significant difference from placebo (p-value \leq 0.050;Bonferroni-Holm multiple test procedure);

** Total AUA Symptom Scores ranged from 0 to 35.

[†] Peak urine flow rate measured 4 to 8 hours post dose at Week 13.

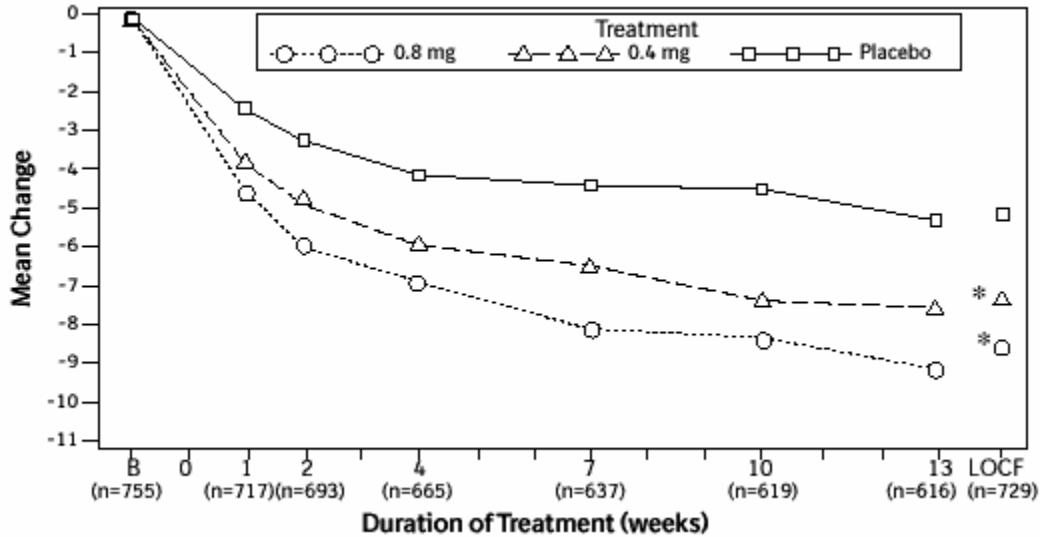
[‡] Peak urine flow rate measured 24 to 27 hours post dose at Week 13.

Week 13: For patients not completing the 13 week study the last observation was carried forward.

Mean total AUA Symptom Scores for both Flomax® (tamsulosin hydrochloride) capsules 0.4 mg and 0.8 mg once daily groups showed a rapid decrease starting at one week after dosing and remained decreased through 13 weeks in both studies (Figures 2A and 2B).

In Study 1, 400 patients (53% of the originally randomized group) elected to continue in their originally assigned treatment groups in a double-blind, placebo controlled, 40 week extension trial (138 patients on 0.4 mg, 135 patients on 0.8 mg and 127 patients on placebo). Three hundred and twenty-three patients (43% of the originally randomized group) completed one year. Of these, 81% (97 patients) on 0.4 mg, 74% (75 patients) on 0.8 mg and 56% (57 patients) on placebo had a response \geq 25% above baseline in total AUA Symptom Score at one year.

Figure 2A Mean Change from Baseline in Total AUA Symptom Score (0-35) Study 1



* indicates significant difference from placebo (p-value ≤ 0.050).

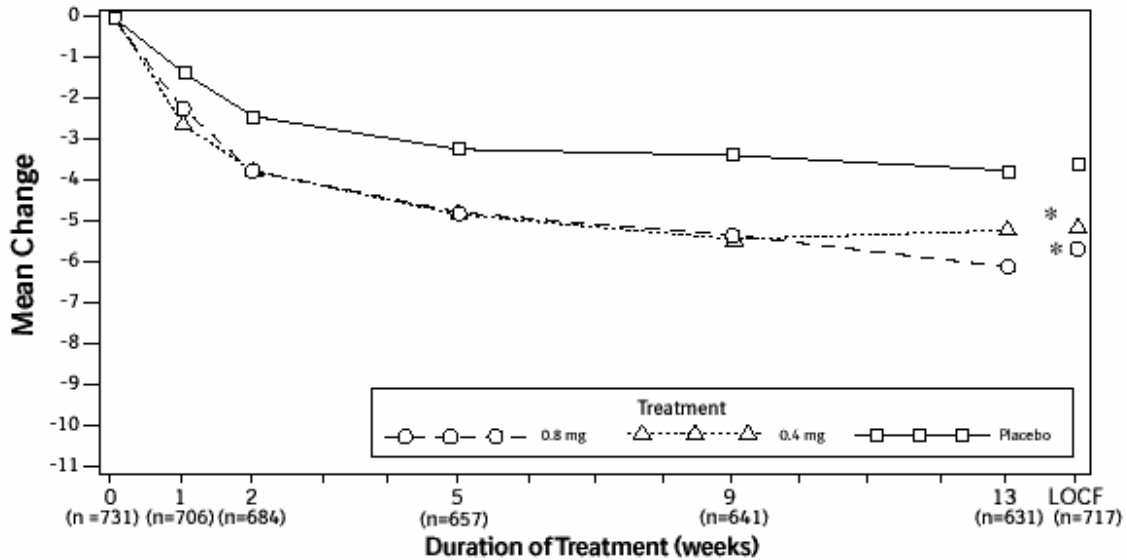
B = Baseline determined approximately one week prior to the initial dose of double-blind medication at Week 0. Subsequent values are observed cases.

LOCF= Last observation carried forward for patients not completing the 13-week study.

Note: Patients in the 0.8 mg treatment group received 0.4 mg for the first week.

Note: Total AUA Symptom Scores range from 0 to 35.

Figure 2B Mean Change from Baseline in Total AUA Symptom Score (0-35) Study 2



* indicates significant difference from placebo (p-value ≤ 0.050).

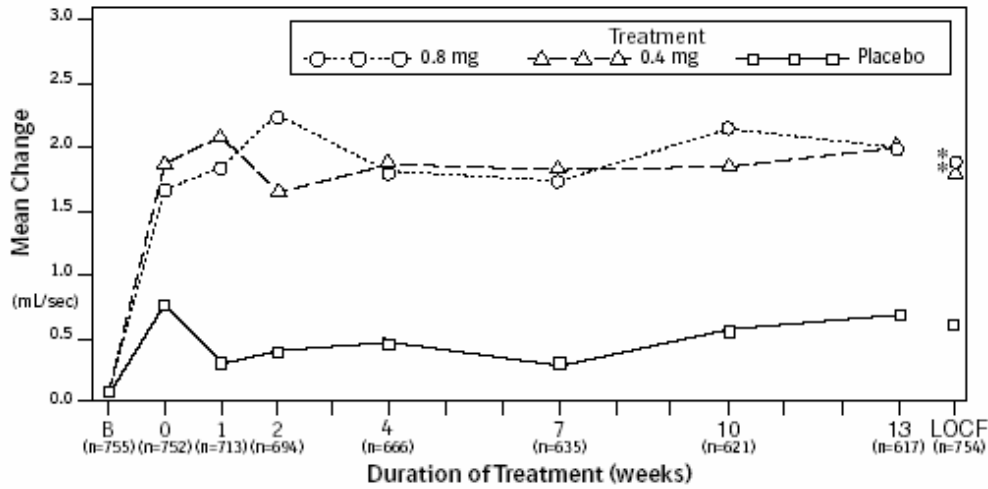
Baseline measurement was taken Week 0. Subsequent values are observed cases.

LOCF= Last observation carried forward for patients not completing the 13-week study.

Note: Patients in the 0.8 mg treatment group received 0.4 mg for the first week.

Note: Total AUA Symptom Scores range from 0 to 35.

Figure 3A Mean Increase in Peak Urine Flow Rate (mL/Sec) Study 1



* indicates significant difference from placebo (p-value ≤ 0.050).

B = Baseline determined approximately one week prior to the initial dose of double-blind medication at Week 0. Subsequent values are observed cases.

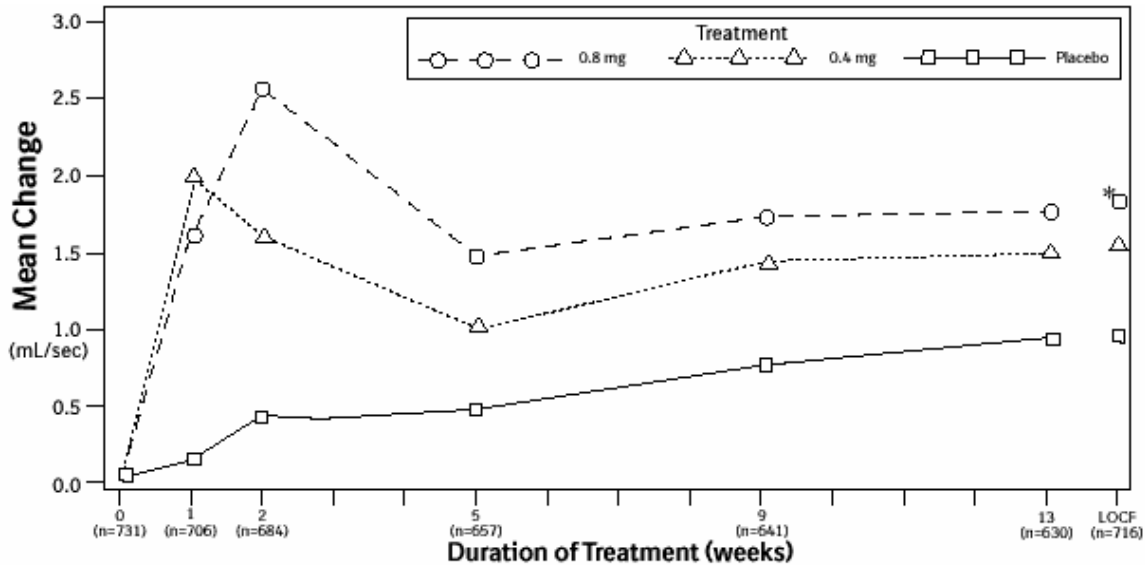
LOCF= Last observation carried forward for patients not completing the 13-week study.

Note: The uroflowmetry assessments at week 0 were recorded 4-8 hours after patients received the first dose of double-blind medication.

Measurements at each visit were scheduled 4-8 hours after dosing (approximately peak plasma tamsulosin concentration).

Note: Patients in the 0.8 mg treatment groups received 0.4 for the first week.

Figure 3B Mean Increase in Peak Urine Flow Rate (mL/Sec) Study 2



* indicates significant difference from placebo (p-value ≤ 0.050).

Baseline measurement was taken Week 0. Subsequent values are observed cases.

LOCF= Last observation carried forward for patients not completing the 13-week study.

Note: Patients in the 0.8 mg treatment group received 0.4 mg for the first week.

Note: Week 1 and Week 2 measurements were scheduled 4-8 hours after dosing (approximate peak plasma tamsulosin concentration).

All other visits were scheduled 24-27 hours after dosing (approximate trough tamsulosin concentration).

INDICATIONS AND USAGE

Flomax® (tamsulosin hydrochloride) capsules are indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH). FLOMAX capsules are not indicated for the treatment of hypertension.

CONTRAINDICATIONS

FLOMAX capsules are contraindicated in patients known to be hypersensitive to tamsulosin hydrochloride or any component of FLOMAX capsules.

WARNINGS

The signs and symptoms of orthostasis (postural hypotension, dizziness and vertigo) were detected more frequently in FLOMAX capsule treated patients than in placebo recipients. As with other alpha-adrenergic blocking agents there is a potential risk of syncope (see **ADVERSE REACTIONS**).

Patients beginning treatment with FLOMAX capsules should be cautioned to avoid situations where injury could result should syncope occur.

Rarely (probably less than one in fifty thousand patients), tamsulosin, like other alpha₁ 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 must be advised about the seriousness of the condition (see **PRECAUTIONS, Information for Patients**).

PRECAUTIONS

General

1. *Carcinoma of the prostate:* Carcinoma of the prostate and BPH cause many of the same symptoms. These two diseases frequently co-exist. Patients should be evaluated prior to the start of FLOMAX capsules therapy to rule out the presence of carcinoma of the prostate.
2. *Intraoperative Floppy Iris Syndrome:* Intraoperative Floppy Iris Syndrome (IFIS) has been observed during cataract surgery in some patients treated with alpha-1 blockers, including FLOMAX capsules. Most reports were in patients taking the alpha-1 blocker when IFIS occurred, but in some cases, the alpha-1 blocker had been stopped prior to surgery. In most of these cases, the alpha-1-blocker had been stopped recently prior to surgery (2 to 14 days), but in a few cases, IFIS was reported after the patient had been off the alpha-1 blocker for a longer period (5 weeks to 9 months). IFIS is a variant of small pupil syndrome and 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. The benefit of stopping alpha-1 blocker therapy prior to cataract surgery has not been established.

3. *Sulfa Allergy*: In patients with sulfa allergy, allergic reaction to Flomax® (tamsulosin hydrochloride) capsules has been rarely reported. If a patient reports a serious or life threatening sulfa allergy, caution is warranted when administering FLOMAX capsules.
4. *Drug-Drug Interactions*: The pharmacokinetic and pharmacodynamic interactions between FLOMAX capsules and other alpha-adrenergic blocking agents have not been determined. However, interactions may be expected and FLOMAX capsules should NOT be used in combination with other alpha-adrenergic blocking agents.

The pharmacokinetic interaction between cimetidine, a mild inhibitor of several CYP enzymes, and FLOMAX capsules was investigated in 10 subjects (see **CLINICAL PHARMACOLOGY, Drug-Drug Interactions**). The results indicate significant changes in both tamsulosin hydrochloride clearance (26% decrease) and exposure (44% increase in AUC). Therefore, FLOMAX capsules should be used with caution in combination with cimetidine, particularly at doses higher than 0.4 mg.

Additional pharmacokinetic interactions between strong or moderate CYP2D6 or CYP3A4 inhibitors with FLOMAX have not been examined. As FLOMAX is extensively metabolized (mainly by CYP2D6 and CYP3A4) and as concomitant administration with cimetidine caused 44% increase in FLOMAX exposure, concomitant administration of FLOMAX and an inhibitor of CYP2D6 or CYP3A4 may lead to increased FLOMAX plasma exposure. FLOMAX capsules should be used with caution in combination with moderate or strong inhibitors of CYP2D6 (e.g., fluoxetine) or CYP3A4 (e.g., ketoconazole), particularly at doses higher than 0.4 mg.

Results from limited *in vitro* and *in vivo* drug-drug interaction studies between tamsulosin hydrochloride and warfarin are inconclusive. Therefore, caution should be exercised with concomitant administration of warfarin and FLOMAX capsules.

See also *Drug-Drug Interactions* studies in **CLINICAL PHARMACOLOGY, Pharmacokinetics** subsection.

Information for Patients (see PATIENT INFORMATION ABOUT FLOMAX CAPSULES)

Patients should be told about the possible occurrence of symptoms related to postural hypotension such as dizziness when taking FLOMAX capsules, and they should be cautioned about driving, operating machinery or performing hazardous tasks.

Patients should be advised not to crush, chew or open the FLOMAX capsules.

Patients should be advised about the possibility of priapism as a result of treatment with FLOMAX capsules and other similar medications. Patients should be informed that this

reaction is extremely rare, but if not brought to immediate medical attention, can lead to permanent erectile dysfunction (impotence).

Patients should be advised that if they are considering cataract surgery, to tell their ophthalmologist that they have taken Flomax® (tamsulosin hydrochloride) capsules.

Laboratory Tests

No laboratory test interactions with FLOMAX capsules are known. Treatment with FLOMAX capsules for up to 12 months had no significant effect on prostate-specific antigen (PSA).

Pregnancy

Teratogenic Effects, Pregnancy Category B.

Administration of tamsulosin hydrochloride to pregnant female rats at dose levels up to 300 mg/kg/day (approximately 50 times the human therapeutic AUC exposure) revealed no evidence of harm to the fetus. Administration of tamsulosin hydrochloride to pregnant rabbits at dose levels up to 50 mg/kg/day produced no evidence of fetal harm. FLOMAX capsules are not indicated for use in women.

Geriatric Use

Of the total number of subjects (1,783) in clinical studies of tamsulosin, 36% were 65 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and the 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 (see **CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations, Geriatrics (Age)**).

Nursing Mothers

FLOMAX capsules are not indicated for use in women.

Pediatric Use

FLOMAX capsules are not indicated for use in pediatric populations.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Rats administered doses up to 43 mg/kg/day in males and 52 mg/kg/day in females had no increases in tumor incidence with the exception of a modest increase in the frequency of mammary gland fibroadenomas in female rats receiving doses ≥ 5.4 mg/kg ($P < 0.015$). The highest doses of tamsulosin hydrochloride evaluated in the rat carcinogenicity study produced systemic exposures (AUC) in rats 3 times the exposures in men receiving the maximum therapeutic dose of 0.8 mg/day.

Mice were administered doses up to 127 mg/kg/day in males and 158 mg/kg/day in females. There were no significant tumor findings in male mice. Female mice treated for 2 years with the two highest doses of 45 and 158 mg/kg/day had statistically significant increases in the incidence of mammary gland fibroadenomas ($P < 0.0001$) and adenocarcinomas ($P < 0.0075$). The highest dose levels of tamsulosin hydrochloride evaluated in the mice carcinogenicity study produced systemic exposures (AUC) in mice 8 times the exposures in men receiving the maximum therapeutic dose of 0.8 mg/day.

The increased incidences of mammary gland neoplasms in female rats and mice were considered secondary to tamsulosin hydrochloride-induced hyperprolactinemia. It is not known if Flomax® (tamsulosin hydrochloride) capsules elevate prolactin in humans. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is not known.

Tamsulosin hydrochloride produced no evidence of mutagenic potential *in vitro* in the Ames reverse mutation test, mouse lymphoma thymidine kinase assay, unscheduled DNA repair synthesis assay, and chromosomal aberration assays in Chinese hamster ovary cells or human lymphocytes. There were no mutagenic effects in the *in vivo* sister chromatid exchange and mouse micronucleus assay.

Studies in rats revealed significantly reduced fertility in males dosed with single or multiple daily doses of 300 mg/kg/day of tamsulosin hydrochloride (AUC exposure in rats about 50 times the human exposure with the maximum therapeutic dose). The mechanism of decreased fertility in male rats is considered to be an effect of the compound on the vaginal plug formation possibly due to changes of semen content or impairment of ejaculation. The effects on fertility were reversible showing improvement by 3 days after a single dose and 4 weeks after multiple dosing. Effects on fertility in males were completely reversed within nine weeks of discontinuation of multiple dosing. Multiple doses of 10 and 100 mg/kg/day tamsulosin hydrochloride (1/5 and 16 times the anticipated human AUC exposure) did not significantly alter fertility in male rats. Effects of tamsulosin hydrochloride on sperm counts or sperm function have not been evaluated.

Studies in female rats revealed significant reductions in fertility after single or multiple dosing with 300 mg/kg/day of the R-isomer or racemic mixture of tamsulosin hydrochloride, respectively. In female rats, the reductions in fertility after single doses were considered to be associated with impairments in fertilization. Multiple dosing with 10 or 100 mg/kg/day of the racemic mixture did not significantly alter fertility in female rats.

ADVERSE REACTIONS

The incidence of treatment-emergent adverse events has been ascertained from six short-term U.S. and European placebo-controlled clinical trials in which daily doses of 0.1 to 0.8 mg FLOMAX capsules were used. These studies evaluated safety in 1783 patients treated with FLOMAX capsules and 798 patients administered placebo. Table 3 summarizes the treatment-emergent adverse events that occurred in $\geq 2\%$ of patients receiving either FLOMAX capsules 0.4 mg, or 0.8 mg and at an incidence numerically higher than that in the

placebo group during two 13-week U.S. trials (US92-03A and US93-01) conducted in 1487 men.

Table 3 Treatment Emergent¹ Adverse Events Occurring in $\geq 2\%$ of Flomax® (tamsulosin hydrochloride) capsules or Placebo Patients in Two U.S. Short-Term Placebo-Controlled Clinical Studies

BODY SYSTEM/ ADVERSE EVENT	FLOMAX CAPSULES GROUPS		PLACEBO
	0.4 mg n=502	0.8 mg n=492	n=493
BODY AS WHOLE			
Headache	97 (19.3%)	104 (21.1%)	99 (20.1%)
Infection ²	45 (9.0%)	53 (10.8%)	37 (7.5%)
Asthenia	39 (7.8%)	42 (8.5%)	27 (5.5%)
Back pain	35 (7.0%)	41 (8.3%)	27 (5.5%)
Chest Pain	20 (4.0%)	20 (4.1%)	18 (3.7%)
NERVOUS SYSTEM			
Dizziness	75 (14.9%)	84 (17.1%)	50 (10.1%)
Somnolence	15 (3.0%)	21 (4.3%)	8 (1.6%)
Insomnia	12 (2.4%)	7 (1.4%)	3 (0.6%)
Libido Decreased	5 (1.0%)	10 (2.0%)	6 (1.2%)
RESPIRATORY SYSTEM			
Rhinitis ³	66 (13.1%)	88 (17.9%)	41 (8.3%)
Pharyngitis	29 (5.8%)	25 (5.1%)	23 (4.7%)
Cough Increased	17 (3.4%)	22 (4.5%)	12 (2.4%)
Sinusitis	11 (2.2%)	18 (3.7%)	8 (1.6%)
DIGESTIVE SYSTEM			
Diarrhea	31 (6.2%)	21 (4.3%)	22 (4.5%)
Nausea	13 (2.6%)	19 (3.9%)	16 (3.2%)
Tooth Disorder	6 (1.2%)	10 (2.0%)	7 (1.4%)
UROGENITAL SYSTEM			
Abnormal Ejaculation	42 (8.4%)	89 (18.1%)	1 (0.2%)
SPECIAL SENSES			
Blurred vision	1 (0.2%)	10 (2.0%)	2 (0.4%)

- ¹ A treatment-emergent adverse event was defined as any event satisfying one of the following criteria:
- The adverse event occurred for the first time after initial dosing with double-blind study medication.
 - The adverse event was present prior to or at the time of initial dosing with double-blind study medication and subsequently increased in severity during double-blind treatment; or
 - The adverse event was present prior to or at the time of initial dosing with double-blind study medication, disappeared completely, and then reappeared during double-blind treatment.
- ² Coding preferred terms also include cold, common cold, head cold, flu, and flu-like symptoms.
- ³ Coding preferred terms also include nasal congestion, stuffy nose, runny nose, sinus congestion, and hay fever.

Signs and Symptoms of Orthostasis: In the two U.S. studies, symptomatic postural hypotension was reported by 0.2% of patients (1 of 502) in the 0.4 mg group, 0.4% of patients (2 of 492) in the 0.8 mg group, and by no patients in the placebo group. Syncope was reported by 0.2% of patients (1 of 502) in the 0.4 mg group, 0.4% of patients (2 of 492) in the 0.8 mg group and 0.6% of patients (3 of 493) in the placebo group. Dizziness was reported by 15% of patients (75 of 502) in the 0.4 mg group, 17% of patients (84 of 492) in the 0.8 mg group, and 10% of patients (50 of 493) in the placebo group. Vertigo was reported

by 0.6% of patients (3 of 502) in the 0.4 mg group, 1% of patients (5 of 492) in the 0.8 mg group and by 0.6% of patients (3 of 493) in the placebo group.

Multiple testing for orthostatic hypotension was conducted in a number of studies. Such a test was considered positive if it met one or more of the following criteria: (1) a decrease in systolic blood pressure of ≥ 20 mmHg upon standing from the supine position during the orthostatic tests; (2) a decrease in diastolic blood pressure ≥ 10 mmHg upon standing, with the standing diastolic blood pressure < 65 mmHg during the orthostatic test; (3) an increase in pulse rate of ≥ 20 bpm upon standing with a standing pulse rate ≥ 100 bpm during the orthostatic test; and (4) the presence of clinical symptoms (faintness, lightheadedness/lightheaded, dizziness, spinning sensation, vertigo, or postural hypotension) upon standing during the orthostatic test.

Following the first dose of double-blind medication in Study 1, a positive orthostatic test result at 4 hours post-dose was observed in 7% of patients (37 of 498) who received Flomax® (tamsulosin hydrochloride) capsules 0.4 mg once daily and in 3% of the patients (8 of 253) who received placebo. At 8 hours post-dose, a positive orthostatic test result was observed for 6% of the patients (31 of 498) who received FLOMAX capsules 0.4 mg once daily and 4% (9 of 250) who received placebo (Note: patients in the 0.8 mg group received 0.4 mg once daily for the first week of Study 1).

In Studies 1 and 2, at least one positive orthostatic test result was observed during the course of these studies for 81 of the 502 patients (16%) in the FLOMAX capsules 0.4 mg once daily group, 92 of the 491 patients (19%) in the FLOMAX capsules 0.8 mg once daily group and 54 of the 493 patients (11%) in the placebo group.

Because orthostasis was detected more frequently in FLOMAX capsule-treated patients than in placebo recipients, there is a potential risk of syncope (see **WARNINGS**).

Abnormal Ejaculation: Abnormal ejaculation includes ejaculation failure, ejaculation disorder, retrograde ejaculation and ejaculation decrease. As shown in Table 3, abnormal ejaculation was associated with FLOMAX capsules administration and was dose-related in the U.S. studies. Withdrawal from these clinical studies of FLOMAX capsules because of abnormal ejaculation was also dose-dependent with 8 of 492 patients (1.6%) in the 0.8 mg group, and no patients in the 0.4 mg or placebo groups discontinuing treatment due to abnormal ejaculation.

Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of FLOMAX capsules. 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. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of reporting, or (3) strength of causal connection to FLOMAX capsules. Allergic-type reactions such as skin rash, urticaria, pruritus, angioedema and respiratory symptoms have been reported with positive rechallenge in some cases. Priapism has been reported rarely.

Infrequent reports of palpitations, hypotension, skin desquamation, constipation and vomiting have been received during the post-marketing period.

During cataract surgery, a variant of small pupil syndrome known as Intraoperative Floppy Iris Syndrome (IFIS) has been reported in association with alpha-1 blocker therapy (see **PRECAUTIONS, General**).

OVERDOSAGE

Should overdosage of Flomax® (tamsulosin hydrochloride) capsules lead to hypotension (see **WARNINGS** and **ADVERSE REACTIONS**), 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. Laboratory data indicate that tamsulosin hydrochloride is 94% to 99% protein bound; therefore, dialysis is unlikely to be of benefit.

One patient reported an overdose of thirty 0.4 mg FLOMAX capsules. Following the ingestion of the capsules, the patient reported a severe headache.

DOSAGE AND ADMINISTRATION

FLOMAX capsules 0.4 mg once daily is recommended as the dose for the treatment of the signs and symptoms of BPH. It should be administered approximately one-half hour following the same meal each day.

For those patients who fail to respond to the 0.4 mg dose after two to four weeks of dosing, the dose of FLOMAX capsules can be increased to 0.8 mg once daily. If FLOMAX capsules administration is discontinued or interrupted for several days at either the 0.4 mg or 0.8 mg dose, therapy should be started again with the 0.4 mg once daily dose.

HOW SUPPLIED

FLOMAX capsules 0.4 mg are supplied in high density polyethylene bottles containing 100 hard gelatin capsules with olive green opaque cap and orange opaque body. The capsules are imprinted on one side with “Flomax 0.4 mg” and on the other side with “BI 58.”

FLOMAX capsules 0.4 mg, 100 capsules (NDC 0597-0058-01)

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature].

Keep FLOMAX capsules and all medicines out of reach of children.

Patients should be reminded to read and follow the accompanying “PATIENT INFORMATION ABOUT FLOMAX CAPSULES ”, which should be dispensed with the product.



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Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, CT 06877 USA
and
Astellas Pharma US, Inc.
Deerfield, IL 60015 USA

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Flomax®

(tamsulosin hydrochloride)

Capsules, 0.4 mg

PATIENT INFORMATION ABOUT FLOMAX CAPSULES

FLOMAX capsules are for use by men only. **FLOMAX capsules are not indicated for use in women.**

Please read this leaflet before you start taking FLOMAX capsules. Also, read it each time you renew your prescription, just in case new information has been added. Remember, this leaflet does not take the place of careful discussions with your doctor. You and your doctor should discuss FLOMAX capsules when you start taking your medication and at regular checkups.

Why has your doctor prescribed FLOMAX capsules?

Your doctor has prescribed FLOMAX capsules because you have a medical condition called benign prostatic hyperplasia (BPH) also commonly referred to as enlarged prostate. This occurs only in men.

What is BPH?

Benign prostatic hyperplasia is an enlargement of the prostate gland. After age 50, most men develop enlarged prostates. The prostate is located below the bladder. As the prostate enlarges, it may slowly restrict the flow of urine. This can lead to symptoms such as:

- a weak or interrupted urinary stream
- a feeling that you cannot empty your bladder completely
- a feeling of delay or hesitation when you start to urinate
- a need to urinate often, especially at night
- a feeling that you must urinate right away

Since cancer of the prostate may cause similar symptoms, you should be evaluated by your doctor to rule out prostate cancer. Your doctor will likely examine your prostate gland manually to detect abnormalities and may measure prostate-specific antigen (PSA) in your blood to help in evaluating for the presence of prostate cancer. FLOMAX capsules do not affect PSA levels.

Treatment Options for BPH

There are three main treatment options for BPH:

- Program of monitoring or “Watchful Waiting”. Some men have an enlarged prostate gland, but no symptoms, or symptoms that are not bothersome. If this applies, you and your doctor may decide on a program of monitoring, including regular checkups, instead of medication or surgery.
- There are different kinds of medication used to treat BPH. Your doctor has prescribed Flomax® (tamsulosin hydrochloride) capsules for you (see **What a FLOMAX capsule does to treat BPH**) below.
- Surgery. Some patients may need surgery. Your doctor can describe several different surgical procedures to treat BPH. Which procedure is best depends on your symptoms and medical condition.

What a FLOMAX capsule does to treat BPH

FLOMAX capsules act by relaxing muscles in the prostate and bladder neck at the site of the obstruction, resulting in improved urine flow and reduced BPH symptoms.

What you need to know while taking FLOMAX capsules

- **You must see your doctor regularly.**

While taking FLOMAX capsules, you must have regular checkups. Follow your doctor's advice about when to have these checkups.

- **It is important for you to recognize that FLOMAX capsules can cause a sudden drop in blood pressure especially following the first dose or when changing doses of FLOMAX capsules.** Such a drop in blood pressure, although rare in occurrence, may be associated with fainting, dizziness, or lightheadedness. Therefore, get up slowly from a chair or bed at any time until you learn how you react to FLOMAX capsules. You should not drive or do any hazardous tasks until you are used to the side effects of FLOMAX capsules. If you begin to feel dizzy, sit down until you feel better. Although these symptoms are unlikely, you should avoid driving or hazardous tasks for 12 hours after the initial dose or after your doctor recommends an increase in dose. If you interrupt your treatment for several days or more, resume treatment at one capsule a day, after consulting with your physician. Other side effects may include sleeplessness, runny nose, or ejaculatory problems. In some cases, side effects may decrease or disappear when you continue to take FLOMAX capsules.
- Extremely rarely, FLOMAX capsules and similar medications have caused prolonged, painful erection of the penis, which is unrelieved by sexual intercourse or masturbation. This condition, if untreated, can lead to permanent inability to have an erection. If you

have a prolonged erection, call your doctor or go to an Emergency Room as soon as possible.

- If you are contemplating cataract surgery, make certain to advise your eye surgeon that you have taken Flomax® (tamsulosin hydrochloride) capsules.

You should discuss side effects with your doctor before taking FLOMAX capsules and anytime you think you are having a side effect.

How to take FLOMAX capsules

Follow your doctor's advice about how to take FLOMAX capsules. You should take it approximately 30 minutes following the same meal every day.

Do not share FLOMAX capsules with anyone else; it was prescribed only for you.

Do not crush, chew, or open FLOMAX capsules.

Keep FLOMAX capsules and all medicines out of reach of children.

FOR MORE INFORMATION ABOUT FLOMAX CAPSULES AND BPH, TALK WITH YOUR DOCTOR. IN ADDITION, TALK TO YOUR PHARMACIST OR OTHER HEALTHCARE PROVIDER.



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