MAXPEE-D Tablets (Tamsulosin hydrochloride + Dutasteride)

Prescribing Information

Composition

Each film-coated tablet contains:

Tamsulosin Hydrochloride ..... 0.4 mg

(as modified-release tablets)

Dutasteride ..... 0.5 mg

Dosage Form

Oral tablet

Description

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 the prostate size, caused, in part, by a proliferation of smooth muscle cells in the prostatic stroma. 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.

MAXPEE-D Tablets contain the active ingredients, tamsulosin hydrochloride M.R and dutasteride.

Tamsulosin hydrochloride, a selective alpha$_{1A}$-adrenoceptor blocking agent, exhibits selectivity for alpha$_{1A}$-receptors in the human prostate. Tamsulosin hydrochloride acts by relaxing smooth muscles of the bladder neck, prostatic capsule and prostatic urethra.

Dutasteride is a synthetic 4-azasteroid compound that is a selective inhibitor of both the type I and type II isoforms of steroid 5 alpha-reductase, 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.

Pharmacology

Pharmacodynamics

Tamsulosin Hydrochloride

Mechanism of action

Tamsulosin hydrochloride, an alpha1-adrenoceptor blocking agent, exhibits selectivity for alpha1-receptors in the human prostate. At least three 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 the human prostate are of the alpha1A subtype. Blockade of these adrenoreceptors can cause smooth muscles in the bladder neck and prostate to relax, resulting in an improvement in the urine flow rate and a reduction in the symptoms of BPH.

Dutasteride

Mechanism of action

Dutasteride inhibits the conversion of testosterone to 5 alpha-dihydrotestosterone (DHT) by a competitive and specific inhibition 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. 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 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) and dehydroepiandrosterone. Statistically significant, baseline-adjusted mean increases compared with placebo were observed for total testosterone at 8 weeks (97.1 ng/dL, $p<0.003$) and thyroid-stimulating hormone at 52 weeks (0.4 mcIU/mL, $p<0.05$). The median percentage changes from baseline within the dutasteride group were 17.9% for testosterone at 8 weeks and 12.4% for thyroid stimulating hormone at 52 weeks. After stopping dutasteride for 24 weeks, the mean levels of testosterone and thyroid-stimulating hormone had returned to baseline in the group of subjects with available data at the visit. In patients with BPH treated with dutasteride in a large randomized, double-blind, placebo-controlled study, there was a median percent increase in the luteinizing hormone of 12% at 6 months and 19% at both 12 and 24 months.

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

Tamsulosin Hydrochloride

Absorption: Absorption of tamsulosin hydrochloride 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 4-5 hours under fasting conditions and by 6-7 hours when tamsulosin hydrochloride capsules are administered with food.

Distribution: The mean steady-state apparent volume of distribution of tamsulosin hydrochloride after intravenous administration to 10 healthy male adults was 16 L, which is suggestive of distribution into the extracellular fluids in the body. Tamsulosin hydrochloride is extensively bound to human plasma proteins (94-99%), 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 to the S(+) isomer in humans. Tamsulosin hydrochloride is extensively metabolized by cytochrome (CY) P450 enzymes in the liver and less than 10% of the dose is excreted in the urine unchanged. However, the pharmacokinetic profile of the metabolites in humans has not been established. Tamsulosin is extensively metabolized, mainly by CYP3A4 and CYP2D6 as well as via some minor participation of other CYP isoenzymes. Inhibition of hepatic drug-metabolizing enzymes may lead to increased exposure to tamsulosin hydrochloride. Inhibition of hepatic drug-metabolizing enzymes may lead to increased exposure to tamsulosin hydrochloride. The metabolites of tamsulosin hydrochloride undergo extensive conjugation to glucuronide or sulphate 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 (5 alpha-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 radiolabelled dose of tamsulosin hydrochloride to 4 healthy volunteers, 97% of the administered radioactivity was recovered, with urine (76%) representing the primary route of excretion compared to faeces (21%) over 168 hours. Because of absorption rate-controlled pharmacokinetics with tamsulosin hydrochloride modified-release capsules, the apparent half-life of tamsulosin hydrochloride is approximately 9-13 hours in healthy volunteers and 14-15 hours in the target population. Tamsulosin hydrochloride undergoes restrictive clearance in humans, with a relatively low systemic clearance (2.88 L/h).

Pharmacokinetics in special populations:
Pediatric Use: Tamsulosin hydrochloride tablets are not indicated for use in paediatric populations.

Geriatric Use: Cross-study comparison of Tamsulosin hydrochloride capsules overall exposure (AUC) and half-life indicates 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 Impairment: The pharmacokinetics of tamsulosin hydrochloride have been compared in 6 subjects with mild-moderate (30≤ CLcr 2) or moderate-severe (10≤ CLcr 2) renal impairment and 6 normal subjects (CLcr >90 mL/min/1.73 m2). 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 tamsulosin hydrochloride capsules dosing. However, patients with end-stage renal disease (CLcr <10 mL/min/1.73 m^2) have not been studied.

Hepatic Impairment: The pharmacokinetics of tamsulosin hydrochloride have been compared in 8 subjects with moderate hepatic impairment (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 impairment do not require an adjustment in tamsulosin hydrochloride capsules dosage. Tamsulosin hydrochloride has not been studied in patients with 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 is 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 alpha$_1$-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 6β-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

MAXPEE-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 dose of MAXPEE-D tablets is one tablet once daily with or without food. The tablet should be swallowed whole and should not be crushed or chewed. No dosage adjustment is required for subjects with renal impairment or for the elderly.

Contraindications

- MAXPEE-D Tablets are contraindicated for use in women of child bearing potential and during pregnancy.
- MAXPEE-D Tablets are contraindicated for use in pediatric patients.
- MAXPEE-D Tablets are contraindicated for patients with previously demonstrated, clinically significant hypersensitivity (e.g., serious skin reactions, angioedema) to dutasteride or other 5 alpha-reductase inhibitors, tamsulosin hydrochloride or to any component of the tablets.
- # Warnings and Precautions

General

Evaluation of Other Urological Diseases
Prior to initiating treatment with MAXPEE-D tablets, consideration should be given to other

urological conditions that may cause similar symptoms. In addition, BPH and prostate cancer may coexist.

Orthostasis

The signs and symptoms of orthostasis (postural hypotension, dizziness and vertigo) were detected more frequently in tamsulosin hydrochloride treated patients than in placebo recipients. As with other alpha-adrenergic blocking agents, there is a potential risk of syncope. Patients beginning treatment with MAXPEE-D Tablets should be cautioned to avoid situations in which injury could result should syncope occur.

Priapism

Rarely (probably less than 1 in 50,000 patients), tamsulosin hydrochloride, like other alpha$_1$-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.

Intraoperative Floppy Iris Syndrome

Intraoperative floppy iris syndrome (IFIS) has been observed during cataract surgery in some patients treated with alpha adrenergic antagonists, including tamsulosin hydrochloride.

Most reports were in patients taking the alpha1-blocker when IFIS occurred, but in some cases, the alpha adrenergic antagonist had been stopped prior to surgery. In most of these cases, the alpha adrenergic antagonist had been stopped recently prior to surgery (2-14 days), but in a few cases, IFIS was reported after the patient had been off the alpha1-blocker for a longer period (5 weeks - 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.

IFIS may increase the risk of eye complications during and after the operation. The benefit of stopping alpha adrenergic antagonist therapy prior to cataract surgery has not been

established. The initiation of therapy with tamsulosin hydrochloride in patients for whom cataract surgery is scheduled is not recommended.

Sulpha Allergy

In patients with sulpha allergy, allergic reaction to tamsulosin hydrochloride has been rarely reported. If a patient reports a serious or life-threatening sulpha allergy, caution is warranted when administering MAXPEE-D tablets.

Exposure of Women - Risk to Male Foetus

Women who are pregnant or may be pregnant should not handle MAXPEE-D Tablets because of the possibility of the absorption of dutasteride through the skin, which could result in unintended foetal exposure. If a woman who is pregnant or who could become pregnant comes in contact with MAXPEE-D tablets, the contact area should be washed immediately with soap and water.

Blood Donation

Men being treated with MAXPEE-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. Co-administration of dutasteride and tamsulosin hydrochloride resulted in similar changes to serum PSA as with dutasteride monotherapy.

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.

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. The effects of tamsulosin hydrochloride on sperm counts or sperm function have not been evaluated.

Drug Interactions

Cytochrome P450 Inhibitors

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.

Dutasteride does not inhibit the *in vitro* metabolism of model substrates for the major human cytochrome P450 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.

Strong and Moderate Inhibitors of CYP3A4 or CYP2D6

The effects of ketoconazole (a strong inhibitor of CYP3A4) at 400 mg once daily for 5 days on the pharmacokinetics of a single tamsulosin hydrochloride capsule 0.4 mg dose was investigated in 24 healthy volunteers (age range: 23 to 47 years). Concomitant treatment with ketoconazole resulted in increases in the C_{max} and AUC of tamsulosin by factors of 2.2 and 2.8, respectively. The effects of concomitant administration of a moderate CYP3A4 inhibitor (e.g., erythromycin) on the pharmacokinetics of tamsulosin have not been evaluated.

The effects of paroxetine (a strong inhibitor of CYP2D6) at 20 mg once daily for 9 days on the pharmacokinetics of a single tamsulosin capsule 0.4 mg dose was investigated in 24 healthy volunteers (age range: 23 to 47 years). Concomitant treatment with paroxetine resulted in increases in the C_{max} and AUC of tamsulosin by factors of 1.3 and 1.6, respectively. A similar increase in exposure is expected in poor metabolizers (PM) of CYP2D6 as compared to extensive metabolizers (EM). A fraction of the population (about 7% of Caucasians and 2% of African-Americans) are CYP2D6 PMs. Since CYP2D6 PMs cannot be readily identified and the potential for significant increase in tamsulosin exposure exists when tamsulosin 0.4 mg is co administered with strong CYP3A4 inhibitors in CYP2D6 PMs, tamsulosin 0.4 mg capsules should not be used in combination with strong inhibitors of CYP3A4 (e.g., ketoconazole).The effects of concomitant administration of a moderate

CYP2D6 inhibitor (e.g., terbinafine) on the pharmacokinetics of tamsulosin have not been evaluated.

The effects of co-administration of both a CYP3A4 and a CYP2D6 inhibitor with tamsulosin capsules have not been evaluated. However, there is a potential for significant increase in tamsulosin exposure when tamsulosin 0.4 mg is co administered with a combination of both CYP3A4 and CYP2D6 inhibitors.

Other Alpha-Adrenergic Antagonists

The pharmacokinetic and pharmacodynamic interactions between tamsulosin hydrochloride and other alpha-adrenergic blocking agents have not been determined. However, interactions may be expected and MAXPEE-D Tablets should not be used in combination with other alpha-adrenergic blocking agents.

In a single-sequence, crossover trial in healthy volunteers, the administration of tamsulosin or terazosin in combination with dutasteride had no effect on the steady-state pharmacokinetics of either alpha-adrenergic antagonist. Although 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 or in combination with tamsulosin or terazosin.

Cimetidine

The effects of cimetidine at the highest recommended dose (400 mg every 6 hours for 6 days) on the pharmacokinetics of tamsulosin hydrochloride 0.4 mg dose was investigated in 10 healthy volunteers (age range: 21 to 38 years). Treatment with cimetidine resulted in a significant decrease (26%) in the clearance of tamsulosin hydrochloride, which resulted in a moderate increase in the tamsulosin hydrochloride AUC (44%). Therefore, MAXPEE-D Tablets should be used with caution in combination with cimetidine.

Phosphodiesterase-5 Inhibitors (PDE5 Inhibitors)

Caution is advised when alpha-adrenergic blocking agent including tamsulosin hydrochloride is co-administered with PDE5 inhibitors. Alpha-adrenergic blockers and PDE5 inhibitors are both vasodilators that can lower blood pressure. Concomitant use of these two drug classes can potentially cause symptomatic hypotension.

Warfarin

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

Nifedipine, Atenolol, Enalapril

In 3 trials in hypertensive subjects (age range: 47 to 79 years) whose blood pressure was controlled with stable doses of nifedipine extended-release, atenolol, or enalapril for at least 3 months, tamsulosin hydrochloride capsules 0.4 mg for 7 days followed by tamsulosin hydrochloride capsules 0.8 mg for another 7 days (n = 8 per trial) resulted in no clinically significant effects on blood pressure and pulse rate compared with placebo (n = 4 per trial). Therefore, dosage adjustments are not necessary when tamsulosin is administered concomitantly with nifedipine extended-release, atenolol, or enalapril.

Digoxin and Theophylline

Dosage adjustments are not necessary when tamsulosin hydrochloride is administered concomitantly with digoxin or theophylline. Dutasteride does not alter the steady-state pharmacokinetics of digoxin when administered concomitantly at a dose of 0.5 mg/day for 3 weeks.

Furosemide

The pharmacokinetic and pharmacodynamic interaction between tamsulosin hydrochloride 0.8 mg/day (steady-state) and furosemide 20 mg intravenously (single dose) was evaluated in 10 healthy volunteers (age range: 21 to 40 years). Tamsulosin hydrochloride had no effect on the pharmacodynamics (excretion of electrolytes) of furosemide. While furosemide produced an 11-12% reduction in tamsulosin hydrochloride C_{max} and AUC, these changes are expected to be clinically insignificant and do not require adjustment of the tamsulosin hydrochloride dosage.

Calcium Channel Antagonists

In a population pharmacokinetics analysis, a decrease in clearance of dutasteride was

noted when coadministered 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 coadministered 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. The change in dutasteride exposure is not considered to be clinically significant. No dosage adjustment of dutasteride is recommended.

Cholestyramine: 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.

Information for Patients

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

Patients should be advised about the possibility of priapism as a result of treatment with MAXPEE-D tablets. 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).

Prostate cancer and BPH frequently co-exist; therefore, patients should be screened for the presence of prostate cancer prior to treatment with MAXPEE-D Tablets and at regular intervals afterwards.

Patients considering cataract surgery should be advised to tell their ophthalmologist that they have taken MAXPEE-D tablets.

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 MAXPEE-D Tablets 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 MAXPEE-D tablets, the contact area should be washed immediately with soap and water.

Physicians should inform men treated with MAXPEE-D Tablets that they 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.

Patients should be advised not to crush or chew the MAXPEE-D tablets.

Renal Impairment

Patients with renal impairment do not require any dosage adjustment in tamsulosin hydrochloride dosage. However, patients with end-stage renal disease (CL_{cr} <10 mL/min/1.73 m^2) have not been studied.

No dose adjustment is necessary for dutasteride in patients with renal impairment

Hepatic Impairment

Patients with moderate hepatic impairment do not require any dosage adjustment in tamsulosin hydrochloride dosage. Tamsulosin hydrochloride has not been studied in patients with severe 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. 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
MAXPEE-D Tablets are not indicated for use in women.

Dutasteride is contraindicated for use in women of childbearing potential and during pregnancy. Dutasteride is a 5 alpha-reductase inhibitor that prevents conversion of testosterone to dihydrotestosterone (DHT), a hormone necessary for normal development of male genitalia. In animal reproduction and developmental toxicity studies, dutasteride inhibited normal development of external genitalia in male fetuses. Therefore, dutasteride may cause fetal 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 fetus.

Abnormalities in the genitalia of male fetuses 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 fetal exposure, women who are pregnant or could become pregnant should not handle dutasteride-containing MAXPEE-D tablets. If contact is made with open tablets, the contact area should be washed immediately with soap and water. Dutasteride is secreted into 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 0.0175 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 (greater than 96%), which may reduce the amount of dutasteride available for vaginal absorption.

Lactation

MAXPEE-D Tablets are not indicated for use in nursing mothers. It is not known whether dutasteride or tamsulosin is excreted in human milk.

Paediatric Use

MAXPEE-D Tablets are not indicated for use in the paediatric population.

Geriatric Use

Of 1,610 male subjects treated with coadministered dutasteride and tamsulosin in the Combat trial, 58% of enrolled subjects were aged 65 years and older and 13% of enrolled subjects were aged 75 years and older. No overall difference in the safety or effectiveness were observed between these subjects and younger subjects, and the reported clinical experience has not been identified differences in responses between the elderly and younger patients, but the greater sensitivity of some older patients cannot be ruled out. No dose adjustment is necessary in the elderly.

Undesirable Effects

Clinical Trial Experience

The clinical efficacy and safety of coadministered dutasteride and tamsulosin, have been evaluated in a multicenter, randomized, double-blind, parallel group trial (the Combination with Alpha-Blocker Therapy, or Combat, trial). 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 co administered dutasteride and tamsulosin were impotence, decreased libido, breast disorders (including breast enlargement and tenderness), ejaculation disorders, and dizziness. Ejaculation disorders occurred significantly more in subjects receiving co administration 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 co administered dutasteride and tamsulosin and in 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%).

The clinical efficacy and safety of co-administered dutasteride and tamsulosin hydrochloride have been evaluated in 4,800 male subjects with BPH who were randomly assigned to receive 0.5 mg dutasteride, 0.4 mg tamsulosin hydrochloride or co-administration therapy (0.5 mg dutasteride and 0.4 mg tamsulosin hydrochloride) administered once daily in a 4-year, double-blind study. Table 1 summarizes adverse reactions reported in at least 1% of subjects receiving co-administration therapy and at a higher incidence than subjects receiving either dutasteride or tamsulosin hydrochloride as monotherapy.

Table 1: Adverse Reactions Reported Over a 48-Month Period in ≥ 1% of Subjects and More Frequently in the Co-administration Therapy Group than the Dutasteride or Tamsulosin Monotherapy Group (Combat) by Time of Onset

Adverse Reaction	Adverse Reaction Time of Onset				
	Year 1		Year 2	Year 3	Year 4
	Months 0-6	Months 7-12			
Co-administration[a] Dutasteride Tamsulosin	(n=1,610) (n=1,623) (n=1,611)	(n=1,527) (n=1,548) (n=1,545)	(n=1,428) (n=1,464) (n=1,468)	(n=1,283) (n=1,325) (n=1,281)	(n=1,200) (n=1,200) (n=1,112)
Ejaculation disorders [b,c] Co-administration Dutasteride Tamsulosin	7.8% 1.0% 2.2%	1.6% 0.5% 0.5%	1.0% 0.5% 0.5%	0.5% 0.2% 0.2%	<0.1% 0.3% 0.3%
Impotence [c, d] Co-administration Dutasteride Tamsulosin	5.4% 4.0% 2.6%	1.1% 1.1% 0.8%	1.8% 1.6% 1.0%	0.9% 0.6% 0.6%	0.4% 0.3% 0.1%
Decreased libido [c, e] Co-	4.5% 3.1% 2.0%	0.9% 0.7% 0.6%	0.8% 1.0% 0.7%	0.2% 0.2% 0.2%	0.0% 0.0% <0.1%

administration Dutasteride Tamsulosin					
Breast disorders [f] Co-administration Dutasteride Tamsulosin	1.1% 0.9% 0.4%	1.1% 0.9% 0.4%	0.8% 1.2% 0.4%	0.9% 0.5% 0.2%	0.6% 0.7% 0.0%
Dizziness Co-administration Dutasteride Tamsulosin	1.1% 0.5% 0.9%	0.4% 0.3% 0.5%	0.1% 0.1% 0.4%	<0.1% <0.1% <0.1%	0.2% <0.1% 0.0%

[a] Co-administration = Dutasteride 0.5 mg once daily plus tamsulosin hydrochloride 0.4 mg once daily.

[b] Includes anorgasmia, retrograde ejaculation, semen volume decreased, orgasmic sensation decreased, orgasm abnormal, ejaculation delayed, ejaculation disorder, ejaculation failure and premature ejaculation.

[c] 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.

[d] Includes erectile dysfunction and disturbance in sexual arousal.

[e] Includes libido decreased, libido disorder, loss of libido, sexual dysfunction and male sexual dysfunction.

[f] Includes breast enlargement, gynaecomastia, breast swelling, breast pain, breast tenderness, nipple pain and nipple swelling.

Cardiac Failure: In Combat, after 4 years of treatment, the incidence of the composite term, cardiac, failure in the co-administration group (12/1,610; 0.7%) was higher than in either monotherapy group: dutasteride, 2/1,623 (0.1%) and tamsulosin hydrochloride, 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 studies had co-morbidities 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 co-administered with tamsulosin hydrochloride, and cardiac failure has been established. No imbalance was observed in the incidence of overall cardiovascular adverse events in either study.

Additional information regarding adverse reactions in placebo-controlled trials with dutasteride or tamsulosin hydrochloride monotherapy was as follows:

Tamsulosin Hydrochloride

In two 13-week treatment trials with tamsulosin hydrochloride monotherapy, adverse reactions occurring in at least 2% of subjects receiving 0.4 mg tamsulosin hydrochloride and at an incidence higher than in subjects receiving placebo were as follows: infection, asthenia, back pain, chest pain, somnolence, insomnia, rhinitis, pharyngitis, cough increased, sinusitis, and diarrhoea.

Signs and Symptoms of Orthostasis: According to the tamsulosin hydrochloride prescribing information, in clinical studies with tamsulosin hydrochloride monotherapy, a positive orthostatic test result was observed in 16% (81/502) of subjects receiving 0.4 mg tamsulosin vs. 11% (54/493) of subjects receiving placebo. Because orthostasis was detected more frequently in the tamsulosin hydrochloride treated subjects than in placebo recipients, there is a potential risk of syncope.

Dutasteride

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 men 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.

Post marketing Experience

The following adverse reactions have been identified during post-approval use of the tamsulosin hydrochloride and 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 drug exposure.

Tamsulosin Hydrochloride

Immune system disorders: Hypersensitivity reactions, including rash, urticaria, pruritus, angioedema, and respiratory problems.

Cardiac disorders: Palpitations, dyspnoea, atrial fibrillation, arrhythmia, and tachycardia.

Skin disorders: Skin desquamation, including Stevens-Johnson syndrome. Gastrointestinal disorders: Constipation, vomiting.

Reproductive system and breast disorders: Priapism.

Vascular disorders: Hypotension.
Ophthalmologic disorders: During cataract surgery, a variant of small-pupil syndrome known as intraoperative floppy iris syndrome (IFIS), which is associated with alpha-adrenergic antagonist therapy.

Dutasteride
Immune system disorders: Hypersensitivity reactions, including rash, urticaria, pruritus, angioedema, and respiratory problems.
Cardiac disorders: Palpitations, dyspnoea, atrial fibrillation, arrhythmia, and tachycardia.
Skin disorders: Skin desquamation, including Stevens-Johnson syndrome. Gastrointestinal disorders: Constipation, vomiting.
Reproductive system and breast disorders: Priapism.
Vascular disorders: Hypotension.
Ophthalmologic disorders: During cataract surgery, a variant of small-pupil syndrome known as intra operative floppy iris syndrome (IFIS), which is >associated with alpha-adrenergic antagonist therapy.

Overdosage

Over dosage with MAXPEE-D Tablets could potentially lead to hypotension due to the tamsulosin 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 be used and renal function should be monitored and supported as needed. Laboratory data indicate that tamsulosin hydrochloride is 94-99% protein bound; therefore, dialysis is unlikely to 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, dry place.

Packaging Information

MAXPEE- D Tablets: Pack of 10 tablets

Last updated: March 2020
Last reviewed: April 2020