

PRODUCT MONOGRAPH

Pr MYLAN-FINASTERIDE HG

Finasteride Tablets, USP

Film-coated Tablets 1 mg

Type II 5 α -reductase inhibitor

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Pr MYLAN-FINASTERIDE HG

finasteride tablets USP

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
oral	Tablet/ 1 mg	Anhydrous Lactose, Pregelatinized Starch <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

INDICATIONS AND CLINICAL USE

MYLAN-FINASTERIDE HG (finasteride tablets, USP) is a Type II 5 α -reductase inhibitor, indicated for the treatment of male pattern hair loss (androgenetic alopecia) in MEN who have mild to moderate scalp hair loss of the vertex and anterior mid-scalp. Clinical studies were conducted in men between 18 to 41 years of age.

MYLAN-FINASTERIDE HG is **not** indicated for use in women (see WARNINGS AND PRECAUTIONS and CLINICAL TRIALS) or children.

CONTRAINDICATIONS

MYLAN-FINASTERIDE HG (finasteride) is contraindicated in the following:

- Pregnancy - Use in women when they are or may potentially be pregnant (see WARNINGS AND PRECAUTIONS, Special Populations, Exposure to Finasteride - Risk to Male Fetus);
- Hypersensitivity to any component of this product.

MYLAN-FINASTERIDE HG (finasteride) is not indicated for use in women or children.

WARNINGS AND PRECAUTIONS

General

Caution should be used in the administration of MYLAN-FINASTERIDE HG in patients with liver function abnormalities, as finasteride is metabolized in the liver.

Other causes of alopecia should be ruled out prior to prescribing MYLAN-FINASTERIDE HG. Efficacy and duration of treatment should be assessed periodically by the treating physician.

Physicians should instruct their patients to promptly report any changes in their breasts such as lumps, pain or nipple discharge. Breast changes including breast enlargement, tenderness and neoplasm have been reported (see ADVERSE REACTIONS).

Increased Risk of High-Grade Prostate Cancer with 5 α -Reductase Inhibitors:

Men aged 55 and over with a normal digital rectal examination and PSA \leq 3.0 ng/mL at baseline taking finasteride 5 mg/day (5 times the dose of MYLAN-FINASTERIDE HG) in the 7-year Prostate Cancer Prevention Trial (PCPT) had an increased risk of Gleason score 8-10 prostate cancer (finasteride 1.8% vs placebo 1.1%). (See ADVERSE REACTIONS). Similar results were observed in a 4-year placebo-controlled clinical trial with another 5 α -reductase inhibitor (dutasteride, AVODART[®]) (1% dutasteride vs 0.5% placebo). 5 α -reductase inhibitors may increase the risk of development of high-grade prostate cancer. Whether the effect of 5 α -reductase inhibitors to reduce prostate volume, or study-related factors, impacted the results of these studies has not been established.

Special Populations

Pregnant Women and Nursing Mothers:

MYLAN-FINASTERIDE HG is not indicated for use in women. Women should not handle crushed or broken MYLAN-FINASTERIDE HG tablets when they are or may potentially be pregnant (see CONTRAINDICATIONS). Because of the ability of Type II 5 α -reductase inhibitors such as finasteride to inhibit conversion of testosterone to dihydrotestosterone, finasteride may cause abnormalities of the external genitalia of a male fetus when administered to a pregnant woman. It is not known whether finasteride is excreted in human milk.

Exposure to Finasteride - Risk to Male Fetus:

Women should not handle crushed or broken tablets of MYLAN-FINASTERIDE HG when they are or may potentially be pregnant because of the possibility of absorption of finasteride and the subsequent potential risk to a male fetus (see Pregnant Women and Nursing Mothers). MYLAN-FINASTERIDE HG tablets are coated and will prevent contact with the active ingredient during normal handling, provided that the tablets have not been broken or crushed.

Pediatrics: MYLAN-FINASTERIDE HG is not indicated for use in children.

Geriatrics (> 65 years of age): Clinical studies with finasteride have not been conducted in elderly men with male pattern hair loss.

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Use in Postmenopausal Women:

Results of a one year placebo-controlled study, enrolling 137 healthy postmenopausal women with androgenetic alopecia (age range: 41-60 years), showed no benefit of treatment with finasteride 1 mg daily on scalp hair growth.

Monitoring and Laboratory Tests

In clinical studies with finasteride, 1 mg in men 18-41 years of age, the mean value of serum prostate specific antigen (PSA) decreased from 0.7 ng/mL at baseline to 0.5 ng/mL at Month 12. Further, in clinical studies with finasteride, 5 mg when used in older men who have benign prostatic hyperplasia (BPH), PSA levels are decreased by approximately 50%. Other studies with finasteride, 5 mg showed it may also cause decreases in serum PSA in the presence of prostate cancer. These findings should be taken into account for proper interpretation of serum PSA when evaluating men treated with finasteride. Any confirmed increase from the lowest PSA value while on finasteride, 1 mg 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 α -reductase inhibitor. Non-compliance to therapy with finasteride, 1 mg may also affect PSA test results.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Finasteride for male pattern hair loss has been evaluated for safety in clinical studies involving more than 3,200 men and is generally well tolerated. In three 12-month, placebo-controlled, double-blind, multicenter studies of comparable design, the overall safety profiles of finasteride and placebo were similar. Discontinuation of therapy due to any clinical adverse experience occurred in 1.7% of 945 men treated with finasteride and 2.1% of 934 men treated with placebo.

In these studies, the following drug-related adverse experiences were reported in $\geq 1\%$ of men treated with finasteride or placebo, respectively: decreased libido (1.8%, 1.3%), erectile dysfunction (1.3%, 0.7%) and ejaculation disorder (1.2%, 0.7%; primarily decreased volume of ejaculate: [0.8%, 0.4%]). Integrated analysis of clinical adverse experiences showed that during treatment with finasteride, 36 (3.8%) of 945 men had reported one or more of these adverse experiences as compared to 20 (2.1%) of 934 men treated with placebo (p=0.04). Resolution of these adverse reactions occurred in men who discontinued therapy with finasteride and in most who continued therapy. In a separate study, the effect of finasteride on ejaculate volume was measured and was not different from that seen with placebo (see DETAILED PHARMACOLOGY, Pharmacodynamics).

The incidence of each of the above side effects decreased to $\leq 0.3\%$ by the fifth year of treatment with finasteride.

A sexual function questionnaire was self-administered by patients participating in the two vertex baldness trials to detect more subtle changes in sexual function. At month 12, statistically significant differences were found in 3 of 4 domains (sexual interest, erections, and perception of sexual problems) when compared to placebo. However, no significant difference was seen in the question on overall satisfaction with sex life.

Laboratory Tests

No difference in standard laboratory parameters was observed between patients treated with placebo or finasteride.

Post-Market Adverse Drug Reactions

The following additional adverse experiences have been reported in postmarketing use. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

Immune system disorders: hypersensitivity reactions such as rash, pruritus, urticaria, and angioedema including swelling of the lips, tongue, throat and face.

Psychiatric disorders: depression, decreased libido that continued after discontinuation of treatment.

Reproductive system and breast disorders: Sexual dysfunction (erectile dysfunction and ejaculation disorders) that continued after discontinuation of treatment, breast tenderness and enlargement, male breast cancer, testicular pain, male infertility and/or poor seminal quality. Normalization or improvement of seminal quality has been reported after discontinuation of finasteride.

Long-Term Studies for finasteride 5 mg in the Treatment of Benign Prostatic Hyperplasia:

The PCPT trial was a 7-year randomized, double-blind, placebo-controlled trial that enrolled 18,882 healthy men ≥ 55 years of age with a normal digital rectal examination and a PSA ≤ 3.0 ng/mL. Men received either finasteride 5 mg or placebo daily. Patients were evaluated annually with PSA and digital rectal exams. Biopsies were performed for elevated PSA, an abnormal digital rectal exam, or the end of study. The incidence of Gleason score 8-10 prostate cancer was higher in men treated with finasteride (1.8%) than in those treated with placebo (1.1%). In a 4-year placebo-controlled clinical trial with another 5α -reductase inhibitor (dutasteride, AVODART^{*}), similar results for Gleason score 8-10 prostate cancer were observed (1% dutasteride vs 0.5% placebo). The clinical significance of these findings with respect to use of finasteride 1 mg by men is unknown.

No clinical benefit has been demonstrated in patients with prostate cancer treated with finasteride 5 mg. Finasteride 5 mg is not approved for the prevention of prostate cancer.

DRUG INTERACTIONS

Overview

No drug interactions of clinical importance have been identified. Finasteride does not appear to affect significantly the cytochrome P450-linked drug metabolizing enzyme system. Compounds which have been tested in man have included antipyrine, digoxin, glyburide, propranolol, theophylline, and warfarin and no interactions were found. However, patients on medication with narrow therapeutic indices, such as phenytoin, should be carefully monitored when treatment with MYLAN-FINASTERIDE HG is initiated.

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Other Concomitant Therapy

Although specific interaction studies were not performed, in clinical studies finasteride doses of 1 mg or more were used concomitantly with ACE inhibitors, acetaminophen, alpha blockers, benzodiazepines, beta blockers, calcium-channel blockers, cardiac nitrates, diuretics, H₂ antagonists, HMG-CoA reductase inhibitors, prostaglandin synthetase inhibitors (NSAIDs), and quinolones, without evidence of clinically significant adverse interactions.

Drug-Laboratory Interactions

In clinical studies with finasteride in men 18-41 years of age, the mean value of serum prostate-specific antigen (PSA) decreased from 0.7 ng/mL at baseline to 0.5 ng/mL at month 12. When finasteride is used in older men who have benign prostatic hyperplasia (BPH), PSA levels are decreased by approximately 50%. Until further information is gathered in men >41 years of age without BPH, consideration should be given to doubling the PSA level in men undergoing this test while taking finasteride.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

The recommended dosage is one 1 mg tablet daily. MYLAN-FINASTERIDE HG (finasteride) may be taken with or without food.

In general, daily use for three months or more is necessary before hair growth is increased and/or further hair loss is prevented. Continued use is recommended to obtain maximum benefit. Withdrawal of treatment leads to reversibility of effect within 12 months

Dosage in Renal Insufficiency

Adjustments in dosage are not necessary in patients with varying degrees of renal insufficiency (creatinine clearances as low as 0.15 mL/s [9 mL/min]) as pharmacokinetic studies did not indicate any change in the disposition of finasteride.

Missed Dose

If a tablet is missed at its usual time, an extra dose should not be taken. The next dose should be taken as usual.

OVERDOSAGE

Patients have received single doses of finasteride up to 400 mg and multiple doses of finasteride up to 80 mg/day for three months without adverse reactions.

For management of a suspected drug overdose, contact your regional Poison Control Centre Immediately.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

MYLAN-FINASTERIDE HG (finasteride) is a competitive and specific inhibitor of Type II 5 α -reductase, an intracellular enzyme that converts the androgen testosterone into dihydrotestosterone (DHT). Two distinct isozymes of 5 α -reductase are found in mice, rats, monkeys, and humans: Type I and II. Each of these isozymes is differentially expressed in tissues and developmental stages. In humans, Type I 5 α -reductase is predominant in the sebaceous glands of most regions of skin, including scalp, and liver. Type I 5 α -reductase is responsible for approximately one-third of circulating DHT. The Type II 5 α -reductase isozyme is primarily found in prostate, seminal vesicles, epididymides, and hair follicles as well as liver, and is responsible for two-thirds of circulating DHT.

In humans, the mechanism of action of finasteride is based on its preferential inhibition of the Type II isozyme. Using native tissues (scalp and prostate), *in vitro* binding studies examining the potential of finasteride to inhibit either isozyme revealed a 100-fold selectivity for the human Type II 5 α -reductase over Type I isozyme (IC₅₀=500 and 4.2 nM for Type I and II, respectively). For both isozymes, the inhibition by finasteride is accompanied by reduction of the inhibitor to dihydrofinasteride and adduct formation with NADP⁺. The turnover for the enzyme complex is slow (t_{1/2} approximately 30 days for the Type II enzyme complex and 14 days for the Type I complex).

Finasteride has no affinity for the androgen receptor and has no androgenic, antiandrogenic, estrogenic, antiestrogenic, or progestational effects. Inhibition of Type II 5 α -reductase blocks the peripheral conversion of testosterone to DHT, resulting in significant decreases in serum and tissue DHT concentrations. Finasteride produces a rapid reduction in serum DHT concentration, reaching 65% suppression within 24 hours of oral dosing with a 1 mg tablet.

In men with male pattern hair loss (androgenetic alopecia), the balding scalp contains miniaturized hair follicles and increased amounts of DHT compared with hairy scalp. Administration of finasteride decreases scalp and serum DHT concentrations in these men. By this mechanism, finasteride interrupts a key factor in the development of androgenetic alopecia in those patients genetically predisposed.

Pharmacokinetics

In a study in 15 healthy male subjects, the mean bioavailability of finasteride 1 mg tablets was 65% (range, 26-170%), based on the ratio of AUC relative to a 5 mg intravenous dose infused over 60 minutes. Following the intravenous infusion, mean plasma clearance was 165 mL/min (range, 70-279 mL/min) and mean steady-state volume of distribution was 76 liters (range, 44- 96 liters). In a separate study, the bioavailability of finasteride was not affected by food.

Approximately 90% of circulating finasteride is bound to plasma proteins. Finasteride has been found to cross the blood-brain barrier.

Additional Pharmacokinetic/Pharmacodynamic data are provided under DETAILED PHARMACOLOGY.

STORAGE AND STABILITY

Store at room temperature 15°C - 30°C and protect from light to prevent discoloration.

SPECIAL HANDLING INSTRUCTIONS

Crushed or broken Tablets MYLAN-FINASTERIDE HG should not be handled by women when they are or may potentially be pregnant (see WARNINGS AND PRECAUTIONS, Special Populations, Exposure to Finasteride - Risk to Male Fetus).

DOSAGE FORMS, COMPOSITION AND PACKAGING

Each film-coated tablet of MYLAN-FINASTERIDE HG for oral administration contains 1 mg of finasteride and the following non-medicinal ingredients: anhydrous lactose, colloidal silicon dioxide, croscarmellose sodium, docusate sodium, magnesium stearate, microcrystalline cellulose, povidone and pregelatinized starch.

MYLAN-FINASTERIDE HG (finasteride) 1 mg tablets are pink-orange, film-coated, octagonal, biconvex tablets debossed with F9 on one side of the tablet and M on the other side. Available in blisters of 4 x 7 tablets, bottles of 30 tablets and bottles of 100 tablets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

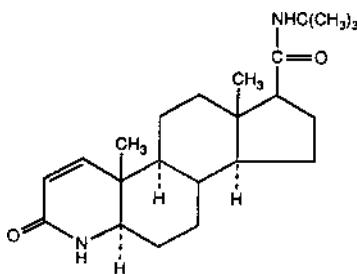
Proper name: finasteride

Chemical name: N-(1, 1-dimethylethyl)-3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide.

Molecular formula: C₂₃H₃₆N₂O₂

Molecular mass: 372.55 g/mol

Structural formula:



Physicochemical properties: Finasteride is a white, crystalline solid with a melting point at approximately 257°C. It is freely soluble in chloroform and in lower alcohol solvents but is practically insoluble in water (0.05 mg/mL at 25°C).

CLINICAL TRIALS

Comparative Bioavailability Studies

One comparative blinded, single-dose, randomized, two-period, two-treatment, crossover study investigating the bioequivalence of MYLAN-FINASTERIDE HG (finasteride) 1 mg tablets (Mylan Pharmaceuticals ULC) and ^{Pr}PROPECIA[®] (finasteride) 1 mg tablets (Merck Frosst Canada Inc.) following administration of a single, oral dose of 1 mg (1 x 1 mg) tablet in twenty-two (22) healthy adult male subjects under fasting conditions was conducted and summarized as follows:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Finasteride (1 x 1 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference [†]	% Ratio of Geometric Means	90% Confidence Interval
AUC _T (ng*hr/mL)	85.95 91.13 (33.0%)	84.57 88.13 (31.5%)	101.6%	97.22%-106.23%
AUC _I (ng*hr/mL)	93.71 101.3 (40.0%)	91.38 96.34 (37.4%)	102.6%	97.43%-107.94%
C _{max} (ng/mL)	9.44 9.703 (23.1%)	9.22 9.358 (19.7%)	102.4%	96.02%-109.28%
T _{max} [§] (h)	2.00 (1.00-4.00)	2.00 (1.00-5.00)		
T _{1/2} [€] (h)	9.411 (40.2%)	8.868 (37.5%)		

* MYLAN-FINASTERIDE HG, 1 mg tablets (Mylan Pharmaceuticals ULC).

[†] ^{Pr}PROPECIA[®] (finasteride) 1 mg tablets (Merck Frosst Canada Ltd., Canada) were purchased in Canada.

[§] Expressed as the arithmetic mean (range).

[€] Expressed as the arithmetic mean (CV%).

Studies in Men

The efficacy of finasteride was demonstrated in three studies in 1879 men 18 to 41 years of age with mild to moderate, but not complete, vertex and frontal/mid-area hair loss. In these studies, hair growth was assessed using four separate measures including hair count, rating of photographs of the head by an expert panel of dermatologists, investigator assessment, and patient self-assessment.

In the two studies in men with vertex hair loss, treatment with finasteride was continued for 5 years, during which time patients improved compared to both baseline and placebo beginning as early as 3 months. Treatment with finasteride for 5 years resulted in stabilization of hair loss in 90% of men based on photographic assessment and in 93% based on investigator assessment. In addition, increased hair growth was reported in 65% of men treated with finasteride based on hair counts (vs 0% of the placebo group), in 48% based on photographic assessment (vs 6% of the placebo group), and in 77% based on investigator assessment (vs 15% of the placebo group). In

contrast, in the placebo group, gradual hair loss over time was observed in 100% of men based on hair counts (vs 35% of men treated with finasteride), in 75% based on photographic assessment (vs 10% of men treated with finasteride), and in 38% based on investigator assessment (vs 7% of men treated with finasteride). In addition, patient self-assessment demonstrated significant increases in hair density, decreases in hair loss, and improvement in appearance of hair over 5 years of treatment with finasteride. While hair improvement measures compared to baseline were greatest in men treated with finasteride at 2 years and gradually declined thereafter (e.g., increase of 88 hairs in a representative 5.1 cm² area at 2 years and increase of 38 hairs at 5 years), hair loss in the placebo group progressively worsened compared to baseline (decrease of 50 hairs at 2 years and 239 hairs at 5 years). Thus, based on all four measures, the difference between treatment groups continued to increase throughout the 5 years of the studies.

The 12-month study in men with frontal/mid-area hair loss also demonstrated significant improvements in scalp hair growth and appearance as evaluated by the same measures as those described above.

A 48-week, placebo-controlled study designed to assess the effect of finasteride on the phases of the hair-growth cycle (growing phase [anagen] and resting phase [telogen]) in vertex baldness enrolled 212 men with androgenetic alopecia. At baseline and 48 weeks, total, telogen, and anagen hair counts were obtained in a 1-cm² target area of the scalp. Treatment with finasteride led to improvements in anagen hair counts, while men in the placebo group lost anagen hair. At 48 weeks, men treated with finasteride showed net increases in total and anagen hair counts of 17 hairs and 27 hairs, respectively, compared to placebo. This increase in anagen hair count, compared to total hair count, led to a net improvement in the anagen-totelogen ratio of 47% at 48 weeks for men treated with finasteride, compared to placebo. These data provide direct evidence that treatment with finasteride promotes the conversion of hair follicles into the actively growing phase.

In summary, these studies demonstrated that treatment with finasteride increases hair growth and prevents further hair loss in men with androgenetic alopecia.

Studies in Women

Lack of efficacy was demonstrated in postmenopausal women with androgenetic alopecia who were treated with finasteride in a 12-month, placebo-controlled study (n=137). These women showed no improvement in hair count, patient self-assessment, investigator assessment, or ratings based on standardized photographs, compared with the placebo group (see INDICATIONS AND CLINICAL USE).

DETAILED PHARMACOLOGY

HUMAN PHARMACOLOGY

Pharmacokinetics

Absorption

Relative to an intravenous reference dose, the oral bioavailability of finasteride is approximately 65%. The bioavailability is not affected by food. Maximum finasteride plasma concentrations are reached approximately 1 to 2 hours after dosing and the absorption is complete after 6-8 hours.

Distribution

There is a slow accumulation phase for finasteride after multiple dosing. At steady state following dosing with 1 mg/day, maximum finasteride plasma concentration averaged 9.2 ng/mL (range, 4.9-13.7 ng/mL) and was reached 1 to 2 hours postdose; AUC_(0-24 hr) was 53 ng•hr/mL (range, 20-154 ng•hr/mL) and mean terminal half-life of elimination was 4.8 hours (range, 3.3- 13.4 hours).

Finasteride has been recovered in the cerebrospinal fluid (CSF) of patients treated with a 7-10 day course of finasteride, but the drug does not appear to concentrate preferentially to the CSF.

Metabolism

Finasteride is metabolized primarily via the cytochrome P450 3A4 enzyme subfamily. Following an oral dose of ¹⁴C-finasteride in man, two metabolites of finasteride were identified that possess only a small fraction of the 5 α -reductase inhibitory activity of finasteride.

Elimination

Following an oral dose of ¹⁴C-finasteride in man, a mean of 39% (range, 32-46%) of the dose was excreted in the urine in the form of metabolites (virtually no unchanged drug was excreted in the urine) and 57% (range, 51-64%) of total dose was excreted in the feces. The major compound isolated from urine was the monocarboxylic acid metabolite; virtually no unchanged drug was recovered. The t-butyl side chain monohydroxylated metabolite has been isolated from plasma. These metabolites possess no more than 20% of the 5 α -reductase inhibitory activity of finasteride.

The elimination rate of finasteride decreases somewhat with age. Mean terminal half-life is approximately 5-6 hours in men 18-60 years of age and 8 hours in men more than 70 years of age. These findings are of no clinical significance and hence, a reduction in dosage in the elderly is not warranted.

Patients with Renal Impairment

No dosage adjustment is necessary in patients with renal insufficiency. In patients with chronic renal impairment, with creatinine clearances ranging from 0.15 to 0.92 mL/s (9.0 to 55 mL/min), AUC, maximum plasma concentration, half-life, and protein binding after a single dose of ¹⁴C-finasteride were similar to values obtained in healthy volunteers. Urinary excretion of metabolites was decreased in patients with renal impairment. This decrease was associated with an increase in fecal excretion of metabolites. Plasma concentrations of metabolites were significantly higher in patients with renal impairment (based on a 60% increase in total radioactivity AUC).

However, finasteride has been well tolerated in men with normal renal function receiving up to 80 mg/day for 12 weeks where exposure of these patients to metabolites would presumably be much greater.

Pharmacodynamics

Finasteride had no effect compared to placebo on circulating levels of cortisol, thyroid-stimulating hormone, or thyroxine, nor did it affect the plasma lipid profile (e.g., total cholesterol, low density lipoproteins, high density lipoproteins, and triglycerides) or bone mineral density. In studies with finasteride, no clinically meaningful changes in luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol or prolactin were detected. Gonadotropin-releasing hormone (GnRH) stimulated levels of LH or FSH were not altered, indicating that regulatory control of the hypothalamic-pituitary-testicular axis was not affected. Circulating levels of testosterone were increased by approximately 10-15%, compared to placebo, yet remained within the physiologic range.

In a study of finasteride 1 mg daily in healthy men, a median decrease in ejaculate volume of 0.3 mL (-11%) compared with 0.2 mL (-8%) for placebo was observed after 48 weeks of treatment. Two other studies showed that finasteride at 5 times the dosage of finasteride (5 mg daily) produced significant median decreases of approximately 0.5 mL (-25%) compared to placebo in ejaculate volume but this was reversible after discontinuation of treatment.

Finasteride appeared to inhibit both C₁₉ and C₂₁ steroid metabolism and hence appeared to have an inhibitory effect on both hepatic and peripheral Type II 5 α -reductase activity. The serum DHT metabolites androstenediol glucuronide and androsterone glucuronide were also significantly reduced. This metabolic pattern is similar to that observed in individuals with a genetic deficiency of Type II 5 α -reductase who have markedly decreased levels of DHT and who do not suffer from male pattern hair loss.

ANIMAL PHARMACOLOGY

The ability of finasteride to inhibit Type II 5 α -reductase and block the formation of DHT *in vivo* was demonstrated using intact male rats and dogs. Studies were designed to demonstrate a decrease in prostatic levels of DHT or shrinkage in prostate size. Four hours after receiving a subcutaneous injection of 0.1 mg finasteride, rats showed a decrease in the concentration of DHT in the prostate. In dogs, treatment with finasteride 1 mg/kg given orally in four divided doses over an 18-hour period showed a reduction in the prostatic DHT concentration 6 hours after the final dose. These studies demonstrated that finasteride is active *in vivo* in blocking the formation of DHT.

The decreased levels of DHT also resulted in a decrease in prostate size. Prostate shrinkage was seen in intact mature dogs, which received 1 mg/kg/day of finasteride by mouth for 6 weeks. A comparison of pre- and post-treatment prostate volumes showed that finasteride induced over 40% reduction in prostate size. A similar effect was noted in immature castrated male rats treated with testosterone. Finasteride, at oral doses of 0.1 mg/day, significantly inhibited the growth effect of exogenous testosterone on the accessory sex glands. This response is due to the specific inhibition of Type II 5 α -reductase, as 2.5 mg/day of finasteride failed to block the ability of exogenous DHT to stimulate growth of the seminal vesicles and ventral prostate in treated animals.

Finasteride has no direct anti-androgen activity as shown by its lack of affinity for the androgen receptor in rat prostate cytosol. Concentrations of finasteride as high as 10^{-4} M did not prevent the binding of 3 H-DHT whereas unlabelled DHT inhibited the binding with an IC_{50} of 2.9 nM.

Standard assays conducted in rats, mice and rabbits demonstrated that finasteride does not inhibit gonadotropin secretion or exhibit any antiestrogenic, uterotrophic, antiprogestational, androgenic, or progestational activity. These data are consistent with finasteride acting as a specific Type II 5α -reductase inhibitor with no other hormonal effects.

In a hepatotoxicity test, 40 mg/kg/day of finasteride was given orally to dogs for 28 days. Venous blood was analyzed for ALT (SGPT) and AST (SGOT). Neither transaminase was increased, illustrating that finasteride did not cause liver damage.

Ancillary pharmacology studies to assess effects on organ systems and biological parameters were conducted with finasteride. No important changes were seen in renal, gastric, and respiratory function in dogs nor in the cardiovascular system of dogs and rats.

TOXICOLOGY

TABLE 1
Acute Toxicity

Species	Sex	Finasteride Route	LD ₅₀ mg/kg
Mouse	Male	Oral	596
	Female	Oral	486
	Male	Intraperitoneal	391
	Female	Intraperitoneal	372
Rat	Male	Oral	967
	Female	Oral	418
	Male	Intraperitoneal	1027
	Female	Intraperitoneal	885
	Male	Subcutaneous	>2000
	Female	Subcutaneous	>2000
Dog	Male	Oral	>1000

Subacute and Chronic Toxicity Studies

The nature of the treatment-related changes in laboratory animals treated with finasteride are shown in Table 2.

TABLE 2
Finasteride
Target Organs Observed in Animal Studies

Treatment-Related Changes	Species	No Effect Dose (mg/kg/day)
Epididymal vacuolation (head)	Rat	0.1
Testes - Leydig cell hyperplasia	Rat	20
- Leydig cell adenoma	Mouse	2.5
	Mouse	25
Liver - increased weight	Mouse	2.5
	Rat	5
	Dog	15
Thyroid - increased weight	Rat	5
Increased serum alkaline phosphatase	Dog	5

For most of the treatment-related changes seen in laboratory animals, a clear no-effect dose has been defined. Furthermore, most of the observed treatment-related effects can be categorized under three broad headings based on the current understanding of the drug-induced changes (Table 3).

TABLE 3
Treatment-Related Changes Seen in Laboratory Animals

Treatment-Related Changes	Species
<ul style="list-style-type: none"> • Resulting from inhibition of 5α-reductase - Decreased accessory sex glands weight - Epididymis (head), vacuolation - Developmental effects in male fetuses - Decreased fertility in males 	Rats, mice, dogs Rats Rats Rats
<ul style="list-style-type: none"> • Resulting from altered endocrine balance - Leydig cell hyperplasia - Leydig cell adenoma 	Rats, mice Mice
<ul style="list-style-type: none"> • Resulting from induction of drug metabolizing enzymes - Increased liver weight - Increased thyroid weight 	Mice, rats, dogs Rats

Carcinogenicity

No evidence of a tumorigenic effect was observed in a 24-month study in rats receiving doses of finasteride up to 320 mg/kg/day (16,000 times the recommended human dose of 1 mg/day).

In a 19-month carcinogenicity study in mice, a statistically significant ($p \leq 0.05$) increase in the incidence of testicular Leydig cell adenoma was observed at a dose of 250 mg/kg/day (12,500 times

the recommended human dose of 1 mg/day); no adenomas were seen in mice given 2.5 or 25 mg/kg/day (125 and 1,250 times the recommended human dose of 1 mg/day, respectively [Table 2]).

In mice at a dose of 25 mg/kg/day and in rats at a dose of ≥ 40 mg/kg/day (1,250 and $\geq 2,000$ times the recommended human dose of 1 mg/day, respectively), an increase in the incidence of Leydig cell hyperplasia was observed.

A positive correlation between the proliferative changes of the Leydig cells and the increase in serum luteinizing hormone (LH) levels (2-3 fold above control) has been demonstrated in both rodent species treated with high doses of finasteride (Table 2).

No drug-related Leydig cell changes were seen in either rats or dogs treated with finasteride for one year, at doses of 20 mg/kg/day and 45 mg/kg/day (1,000 and 2,250 times the recommended human dose of 1 mg/day, respectively) or in mice treated for 19 months, at a dose of 2.5 mg/kg/day (125 times the recommended human dose of 1 mg/day [Table 2]).

Mutagenesis Studies

No evidence of mutagenicity was observed in an *in vitro* bacterial mutagenesis assay, a mammalian cell mutagenesis assay, or in an *in vitro* alkaline elution assay. In an *in vitro* chromosome aberration assay, when Chinese hamster ovary cells were treated with high concentrations (450-550 μmol) of finasteride, there was a slight increase in chromosome aberrations. These concentrations correspond to 18,000-22,000 times the peak plasma levels in man given a total dose of 1 mg. Furthermore, the concentrations (450-550 μmol) used in the *in vitro* studies are not achievable in a biological system. In an *in vivo* chromosome aberration assay in mice, no treatment-related increases in chromosome aberration were observed with finasteride at the maximum tolerated dose (250 mg/kg/day; 12,500 times the recommended human dose of 1 mg/day).

Reproductive Studies

In sexually mature male rabbits treated with finasteride at 80 mg/kg/day (4,000 times the recommended human dose of 1 mg/day) for up to 12 weeks, no effect on fertility, sperm count, or ejaculate volume was seen.

In sexually mature rats treated with the same dose of finasteride, there were no significant effects on fertility after 6 or 12 weeks of treatment; however, when treatment was continued for up to 24 or 30 weeks, there was an apparent decrease in fertility and fecundity, and an associated significant decrease in the weights of the seminal vesicles and prostate. All these effects were reversible within 6 weeks of discontinuation of treatment.

The decrease in fertility in finasteride-treated rats is secondary to its effect on accessory sex organs (prostate and seminal vesicles) resulting in failure to form a seminal plug. The seminal plug is essential for normal fertility in rats and is not relevant in man who do not form copulatory plugs. No drug-related effect on testes or on mating performance has been seen in rats or rabbits.

Developmental Studies

Dose-dependent development of hypospadias, at an incidence of 3.6 to 100%, were observed in the male offspring of pregnant rats given finasteride at doses ranging from 100 $\mu\text{g}/\text{kg}/\text{day}$ to 100 mg/kg/day

(5 to 5,000 times the recommended human dose of 1 mg/day). Additionally, pregnant rats produced male offspring with decreased prostatic and seminal vesicular weights, delayed preputial separation, and transient nipple development when given finasteride at doses $\geq 30 \mu\text{g}/\text{kg}/\text{day}$ (≥ 1.5 times the recommended human dose of 1 mg/day), and decreased anogenital distance when given finasteride in doses $\geq 3 \mu\text{g}/\text{kg}/\text{day}$ (approximately one-fifth the recommended human dose of 1 mg/day). The critical period during which these effects can be induced has been defined in male rats as Days 16-17 of gestation.

The changes described above are expected pharmacological effects of Type II 5α -reductase inhibitors. Many of the changes, such as hypospadias, observed in male rats exposed *in utero* to finasteride are similar to those reported in male infants with a genetic deficiency of Type II 5α -reductase. No effects were seen in female offspring exposed *in utero* to any dose of finasteride.

Administration of finasteride to rats during the late gestation and lactation period resulted in slightly decreased fertility in first generation male offspring (3 mg/kg/day; 150 times the recommended human dose of 1 mg/day). No developmental abnormalities have been observed in first generation male or female offspring resulting from mating finasteride-treated male rats (80 mg/kg/day; 4,000 times the recommended human dose of 1 mg/day) with untreated females.

No evidence of malformations has been observed in rabbit fetuses exposed to finasteride *in utero* from Days 6-18 of gestation at doses up to 100 mg/kg/day (5,000 times the recommended human dose of 1 mg/day).

The *in utero* effects of finasteride exposure during the period of embryonic and fetal development were evaluated in the rhesus monkey (gestation days 20-100), a species more predictive of human development than rats or rabbits. Intravenous administration of finasteride to pregnant monkeys at doses as high as 800 ng/day (at least 750 times the highest estimated exposure of pregnant women to finasteride from semen of men taking 1 mg/day) resulted in no abnormalities in male fetuses. In confirmation of the relevance of the rhesus model for human fetal development, oral administration of a very high dose of finasteride (2 mg/kg/day; 100 times the recommended human dose of 1 mg/day or approximately 12 million times the highest estimated exposure to finasteride from semen of men taking 1 mg/day) to pregnant monkeys resulted in external genital abnormalities in male fetuses. No other abnormalities were observed in male fetuses and no finasteride-related abnormalities were observed in female fetuses at any dose.

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9. ^{Pr}PROPECIA[®] Product Monograph, Merck Canada Ltd., Control No. 171286, March 19, 2014

IMPORTANT: PLEASE READ

PART III: CONSUMER INFORMATION

^{Pr}MYLAN-FINASTERIDE HG Finasteride Tablets, USP

This leaflet is part III of a three-part "Product Monograph" published when MYLAN-FINASTERIDE HG was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about MYLAN-FINASTERIDE HG. Contact your physician or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

MYLAN-FINASTERIDE HG IS FOR USE BY MEN ONLY.

What the medication is used for:

MYLAN-FINASTERIDE HG is used for the treatment of male pattern hair loss (also known as androgenetic alopecia).

What it does:

MYLAN-FINASTERIDE HG blocks an important enzyme (Type II 5- alpha reductase) involved in the regulation of the hair follicle and lowers the levels of dihydrotestosterone (DHT) in the scalp, a major cause of male pattern hair loss.

When it should not be used:

Do not take MYLAN-FINASTERIDE HG if you think you are allergic to any of its ingredients.

Women and children should not take MYLAN-FINASTERIDE HG. Do not take MYLAN-FINASTERIDE HG if you are or may potentially be pregnant (see WARNINGS AND PRECAUTIONS, Pregnancy).

What the medicinal ingredient is:

Finasteride

What the important nonmedicinal ingredients are:

Anhydrous lactose, colloidal silicon dioxide, croscarmellose sodium, docusate sodium, magnesium stearate, microcrystalline cellulose, povidone and pregelatinized starch.

What dosage form it comes in:

Each film-coated tablet of MYLAN-FINASTERIDE HG contains 1 mg of finasteride.

WARNINGS AND PRECAUTIONS

BEFORE you use MYLAN-FINASTERIDE HG talk to your physician or pharmacist about any medical

problems you have or have had, especially liver disease, and about any allergies.

Finasteride 5 mg (finasteride at 5 times the dose of MYLAN-FINASTERIDE HG) may increase the chance of a more serious form of prostate cancer.

Pregnancy

Women who are or may potentially be pregnant must not use MYLAN-FINASTERIDE HG. They should also not handle crushed or broken tablets of MYLAN-FINASTERIDE HG. If the active ingredient in MYLAN-FINASTERIDE HG is absorbed after oral use or through the skin by a woman who is pregnant with a male baby, it may cause the male baby to be born with abnormalities of the sex organs. MYLAN-FINASTERIDE HG tablets are coated and will prevent contact with the active ingredient during normal handling, provided that the tablets are not broken or crushed. If a woman who is pregnant comes into contact with the active ingredient in MYLAN-FINASTERIDE HG, a physician should be consulted.

INTERACTIONS WITH THIS MEDICATION

Finasteride usually does not interfere with other medicines. However, you should always tell your physician about all medicines you are taking or plan to take, including those obtained without prescription.

Finasteride can affect a blood test called PSA (prostate-specific antigen) used for the screening of prostate cancer. If you have a PSA test done, you should tell your physician that you are taking finasteride.

PROPER USE OF THIS MEDICATION

Take MYLAN-FINASTERIDE HG as your physician has prescribed.

Usual dose: Take one tablet of MYLAN-FINASTERIDE HG every day, with or without food.

Missed Dose: If you miss a dose, do not take an extra one. Just take the next tablet as usual.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

When can I expect to see results from using MYLAN-FINASTERIDE HG?

IMPORTANT: PLEASE READ

Male pattern hair loss is a condition that develops over a long period of time. On average, healthy hair grows only about 1 cm each month. Therefore, it will take time to see any effect. In general, daily use for three months or more may be necessary before you notice that hair growth is increased or further hair loss is prevented.

How long do I need to use MYLAN-FINASTERIDE HG?

MYLAN-FINASTERIDE HG can only work over the long term if you continue taking it.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like any medicine, finasteride may cause side effects.

Common side effects

- less desire to have sex
- difficulty in achieving an erection
- problems with ejaculation, such as a decrease in the amount of semen released during sex (this does not appear to interfere with normal sexual function).

In clinical studies, these side effects disappeared in men who stopped taking finasteride and in most men who continued treatment.

In general use, the following have been reported infrequently:

- breast enlargement (swelling) and/or tenderness;
- depression;
- decrease in sex drive that continued after stopping the medication;
- allergic reactions including rash, itching, hives, and swelling of the lips, tongue, throat and face;
- problems with ejaculation that continued after stopping the medication;
- testicular pain;
- difficulty in achieving an erection that continued after stopping the medication;
- male infertility and/or poor quality of semen. Improvement in the quality of semen has been reported after stopping the medication;
- male breast cancer.

Talk to your doctor about any changes in your breast such as lumps, pain or nipple discharge. Tell your physician or pharmacist promptly about these or any other unusual symptoms.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your physician or pharmacist		Stop taking drug and seek immediate medical attention
		Only if severe	In all cases	
Rare	Allergic reactions including rash, hives, and swelling of the lips, tongue, throat and face			√

This is not a complete list of side effects. For any unexpected effects while taking MYLAN-FINASTERIDE HG contact your physician or pharmacist.

HOW TO STORE IT

Store MYLAN-FINASTERIDE HG at room temperature (15°C - 30°C) and protect from light to prevent discoloration. Keep blister in the outer carton until all tablets are used.

KEEP MYLAN-FINASTERIDE HG AND ALL MEDICINES OUT OF THE REACH OF CHILDREN.

REPORTING SIDE EFFECTS

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report

Online at MedEffect (<http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php>);

- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
 - Fax to 1-866-678-6789 (toll-free), or
 - Mail to: Canada Vigilance Program
Health Canada, Postal Locator
0701E
Ottawa, ON
K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (<http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php>).

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document can be found at: www.mylan.ca.

The full Product Monograph prepared for health professionals can be obtained by contacting the sponsor, Mylan Pharmaceuticals ULC at: 1-800-575-1379

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