

PRODUCT MONOGRAPH

 **PROPECIA[®]**

finasteride, USP

Film-coated Tablets 1 mg

Type II 5 alpha-reductase inhibitor

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Submission Control No: 105560

1041-b,9,06

Date of Preparation:
May 30, 2005

Date of Revision:
July 24, 2006

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PROPECIA®
finasteride, USP

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

| Route of Administration | Dosage Form/Strength | Clinically Relevant Nonmedicinal Ingredients |
|--------------------------------|-----------------------------|--|
| oral | tablet 1 mg | <i>Lactose monohydrate</i> <i>For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.</i> |

INDICATIONS AND CLINICAL USE

PROPECIA® (finasteride, USP) is 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.

PROPECIA® is **not** indicated for use in women (see WARNINGS AND PRECAUTIONS and DETAILED PHARMACOLOGY, Clinical Studies) or children.

CONTRAINDICATIONS

PROPECIA® (finasteride, USP) is contraindicated in the following:

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

PROPECIA® is not indicated for use in women or children.

WARNINGS AND PRECAUTIONS

General

Caution should be used in the administration of PROPECIA® (finasteride, USP) in patients with liver function abnormalities, as finasteride is metabolized in the liver.

Other causes of alopecia should be ruled out prior to prescribing PROPECIA®. Efficacy and duration of treatment should be assessed periodically by the treating physician.

Special Populations

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

Exposure to Finasteride - Risk to Male Fetus

Women should not handle crushed or broken tablets of PROPECIA® 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). PROPECIA® 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: PROPECIA® is not indicated for use in children.

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

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 PROPECIA® 1 mg daily on scalp hair growth.

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 PROPECIA® (finasteride, USP) and placebo were similar. Discontinuation of therapy due to any clinical adverse experience occurred in 1.7% of 945 men treated with PROPECIA® 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 PROPECIA® 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 PROPECIA®, 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 PROPECIA® and in most who continued therapy. In a separate study, the effect of PROPECIA® 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 PROPECIA®.

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.

The following adverse experiences have been reported in postmarketing use: ejaculation disorder; breast tenderness and enlargement; hypersensitivity reactions including rash, pruritus, urticaria, and swelling of the lips and face; and testicular pain.

Laboratory Tests

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

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 PROPECIA® is initiated.

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 PROPECIA® 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 PROPECIA®.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

The recommended dosage is one 1 mg tablet daily. PROPECIA® (finasteride, USP) 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.

No specific treatment for overdosage with PROPECIA® (finasteride, USP) is recommended.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

PROPECIA® (finasteride, USP) is a competitive and specific inhibitor of Type II 5 alpha-reductase, an intracellular enzyme that converts the androgen testosterone into dihydrotestosterone (DHT). Two distinct isozymes of 5 alpha-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 alpha-reductase is predominant in the sebaceous glands of most regions of skin, including scalp, and liver. Type I 5 alpha-reductase is responsible for approximately one-third of circulating DHT. The Type II 5a-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 alpha-reductase over Type I isozyme (IC_{50} =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 alpha-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 moisture.

SPECIAL HANDLING INSTRUCTIONS

Crushed or broken Tablets of PROPECIA® 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 PROPECIA® for oral administration contains 1 mg of finasteride and the following non-medicinal ingredients: docusate sodium, hydroxypropylcellulose, lactose monohydrate, magnesium stearate, methylhydroxypropylcellulose, microcrystalline cellulose, pregelatinized starch, sodium starch glycolate, talc, titanium dioxide, red ferric oxide and yellow ferric oxide.

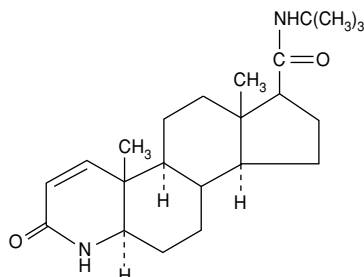
PROPECIA® (finasteride, USP) 1 mg tablets are tan-colored, 8-sided, film-coated convex tablets with the code "P" logo on one side and PROPECIA on the other. Available in blister packages of 28 tablets.

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: | C ₂₃ H ₃₆ N ₂ O ₂ |
| Molecular weight: | 372.55 |
| 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

Studies in Men

The efficacy of PROPECIA® 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 PROPECIA® was continued for 5 years, during which time patients improved compared to both baseline and placebo beginning as early as 3 months. Treatment with PROPECIA® 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 PROPECIA® 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 PROPECIA®), in 75% based on photographic assessment (vs 10% of men treated with PROPECIA®), and in 38% based on investigator assessment (vs 7% of men treated with PROPECIA®). 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 PROPECIA®. While hair improvement measures compared to baseline were greatest in men treated with PROPECIA® 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 PROPECIA® 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 PROPECIA® led to improvements in anagen hair counts, while men in the placebo group lost anagen hair. At 48 weeks, men treated with PROPECIA® 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-to-telogen ratio of 47% at 48 weeks for men treated with PROPECIA®, compared to placebo. These data provide direct evidence that treatment with PROPECIA® promotes the conversion of hair follicles into the actively growing phase.

In summary, these studies demonstrated that treatment with PROPECIA® 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 PROPECIA® 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; $AUC_{(0-24 \text{ hr})}$ 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 alpha-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 alpha-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 PROPECIA® (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 alpha-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 alpha-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 alpha-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 alpha-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 5 alpha-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 I
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 II.

TABLE II
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 |
| | | Mouse | 2.5 |
| | – Leydig cell adenoma | 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 III).

TABLE III
Treatment-Related Changes Seen
in Laboratory Animals

| Treatment-Related Changes | Species |
|--|------------------|
| • Resulting from inhibition of 5 alpha-reductase | |
| – Decreased accessory sex glands weight | Rats, mice, dogs |
| – Epididymis (head), vacuolation | Rats |
| – Developmental effects in male fetuses | Rats |
| – Decreased fertility in males | Rats |
| • Resulting from altered endocrine balance | |
| – Leydig cell hyperplasia | Rats, mice |
| – Leydig cell adenoma | Mice |
| • Resulting from induction of drug metabolizing enzymes | |
| – Increased liver weight | Mice, rats, dogs |
| – Increased thyroid weight | 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 II]).

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 II].

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 II]).

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 men 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 ≥ 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 ≥ 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 5 alpha-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 5 alpha-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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PART III: CONSUMER INFORMATION

PROPECIA®
finasteride, USP

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

ABOUT THIS MEDICATION

PROPECIA® IS FOR USE BY MEN ONLY.

What the medication is used for: Your physician has prescribed PROPECIA® because you have male pattern hair loss (also known as androgenetic alopecia).

Note: PROPECIA® is not for use by women or children.

In whom is PROPECIA® expected to work?

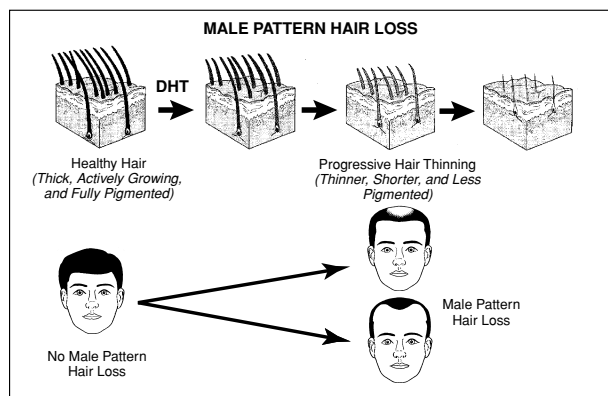
Men with mild to moderate, but not complete, hair loss can expect to benefit from the use of PROPECIA®. In post-menopausal women who were studied, PROPECIA® was not effective in the treatment of hair loss (androgenetic alopecia).

In most men, PROPECIA® prevented further hair loss during five years of use. Moreover, for the majority of men PROPECIA® increased the number of scalp hairs, helping to fill in thin or balding areas of the scalp. Although results will vary, in general you will not be able to grow back all of the hair you have lost.

What is Male Pattern Hair Loss?

Male pattern hair loss is a common condition in which men experience thinning of the hair on the scalp. Often, this results in a receding hairline and/or balding on the top of the head. This condition is thought to be caused by a combination of heredity and a particular hormone, DHT (dihydrotestosterone).

DHT contributes to shortening of the growth phase and thinning of the hair (see picture). This process leads to male pattern hair loss. These changes typically start to occur in some men in their 20’s and become more common with age. Once hair loss has occurred over a long period of time, the hair may be permanently lost.



How does scalp hair grow?

On average, your hair grows about 1 cm each month. Hairs grow from hair follicles, which are located beneath the skin.

A single scalp hair grows continuously for 2 to 4 years (growth phase) and then stops growing for 2 to 4 months (rest phase). After that time the hair falls out. In its place a new healthy hair begins to grow, and the cycle is repeated. The hairs on your scalp are always in different stages of this cycle so it is normal to lose scalp hair every day.

What it does:

PROPECIA® 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:

- PROPECIA® should not be taken by women or children.

Do not take PROPECIA® if you:

- are or may potentially be pregnant (see Pregnancy).
- think you are allergic to any ingredient in PROPECIA®.

What the medicinal ingredient is:

finasteride

What the important nonmedicinal ingredients are:

docusate sodium, hydroxypropylcellulose, lactose monohydrate, magnesium stearate, methylhydroxypropylcellulose, microcrystalline cellulose, pregelatinized starch, sodium starch glycolate, talc, titanium dioxide, red ferric oxide and yellow ferric oxide.

What dosage form it comes in:

PROPECIA® is a tan-colored, 8-sided, film-coated tablet. It contains 1 mg of finasteride as the active ingredient.

WARNINGS AND PRECAUTIONS

PROPECIA® is for use in male pattern hair loss only.

BEFORE you use PROPECIA® talk to your physician or pharmacist about any medical problems you have or have had, especially liver disease, and about any allergies.

Pregnancy

PROPECIA® is for the treatment of male pattern hair loss in men only. Women who are or may potentially be pregnant must not use PROPECIA®. They should also not handle crushed or broken tablets of PROPECIA®. If the active ingredient in PROPECIA® 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. If a woman who is pregnant comes into contact with the active ingredient in PROPECIA®, a physician should be consulted. PROPECIA® tablets are coated and will prevent contact with the active ingredient during normal handling, provided that the tablets are not broken or crushed.

Can I drive or operate machinery while using PROPECIA®?

PROPECIA® should not affect your ability to drive or operate machinery.

If you have questions, ask your physician.

INTERACTIONS WITH THIS MEDICATION

PROPECIA® 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.

Can I continue my current hair care routine?

There should be no need to change your current hair care routine (for example, shampooing or haircuts).

PROPECIA® 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 PROPECIA®.

PROPER USE OF THIS MEDICATION

THIS MEDICINE IS PRESCRIBED FOR YOUR SPECIFIC MEDICAL CONDITION AND FOR YOUR OWN USE. USE ONLY AS SPECIFICALLY DIRECTED AND DO NOT GIVE TO OTHER PEOPLE.

Usual dose: Take one tablet of PROPECIA® every day, with or without food. Follow your physician's advice.

Overdose: If you take too many tablets, contact your physician promptly.

Missed Dose: Try to take PROPECIA® as your physician has prescribed. However, if you miss a dose, do not take an extra one. Just take the next tablet as usual.

Can I use PROPECIA® more than once a day?

PROPECIA® will not work faster or better if you take it more than once a day. You should only take one tablet of PROPECIA® each day.

How long do I need to use PROPECIA®?

It is important to take PROPECIA® for as long as your physician prescribes it. PROPECIA® can only work over the long-term if you continue taking it.

When can I expect to see results from using PROPECIA®?

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.

What happens if I stop using PROPECIA®?

Continued use of PROPECIA® is recommended to obtain maximum benefit. If you stop taking PROPECIA®, you will likely lose the hair you have gained within 12 months of stopping treatment.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like any medicine, PROPECIA® may have unintended or undesirable effects, so-called side effects. These are uncommon and do not affect most men.

Only a small number of men may experience less desire to have sex and/or difficulty in achieving an erection. An even smaller number may have 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 PROPECIA® and in most men who continued treatment.

In general use, the following have been reported infrequently: allergic reactions including rash, itching, hives, and swelling of the lips and face; problems with ejaculation; breast tenderness and enlargement; and testicular pain.

Tell your physician or pharmacist promptly about these or any other unusual symptoms.

Does the use of PROPECIA® affect the hair on other parts of my body?

In clinical studies, PROPECIA® did not affect hair on other parts of the body.

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 call your physician or pharmacist |
|------------------|--|--------------|--|
| | Only if severe | In all cases | |
| Rare | swelling of the lips and face | | √ |

This is not a complete list of side effects. For any unexpected effects while taking PROPECIA®, contact your physician or pharmacist.

How can I learn more about PROPECIA® and male pattern hair loss?

If after reading this leaflet you still have any questions or are not sure about anything, ask your physician or pharmacist, who have more detailed information about PROPECIA® and male pattern hair loss.

HOW TO STORE IT

Store PROPECIA® in a dry place at room temperature (15°C - 30°C) and protect from moisture. Keep blister in the outer carton until all tablets are used.

KEEP ALL MEDICINES OUT OF THE REACH OF CHILDREN.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

Toll-free telephone: 1-866-234-2345

Toll-free fax: 1-866-678-6789

By email: cadmp@hc-sc.gc.ca

By regular mail:

National AR Centre
Marketed Health Products Safety
and Effectiveness Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa, ON K1A 0K9

or Merck Frosst Canada Ltd. by:

Toll-free telephone: 1-800-567-2594

Toll-free fax: 1-877-428-8675

By regular mail:

Merck Frosst Canada Ltd.

P.O. Box 1005

Pointe-Claire - Dorval, QC H9R 4P8

NOTE: Before contacting Health Canada or Merck Frosst, you should contact your physician or pharmacist.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:

<http://www.merckfrosst.com>

or by contacting the sponsor, Merck Frosst Canada Ltd., at: 1-800-567-2594.

This leaflet was prepared by Merck Frosst Canada Ltd.

Last revised: July 24, 2006.

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KIRKLAND, QUEBEC, CANADA