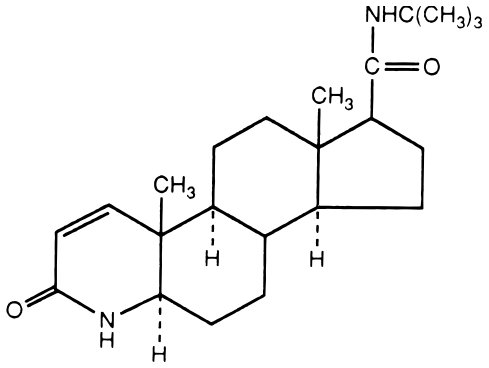
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PROPECIA®
(finasteride)
Tablets, 1 mg

DESCRIPTION

PROPECIA® (finasteride), a synthetic 4-azasteroid compound, is a specific inhibitor of steroid Type II 5α-reductase, an intracellular enzyme that converts the androgen testosterone into 5α-dihydrotestosterone (DHT).

Finasteride is 4-azaandrost-1-ene-17-carboxamide,*N*-(1,1-dimethylethyl)-3-oxo-,(5α,17β)-. The empirical formula of finasteride is $C_{23}H_{36}N_2O_2$ and its molecular weight is 372.55. Its structural formula is:



Finasteride is a white crystalline powder with a melting point near 250°C. It is freely soluble in chloroform and in lower alcohol solvents but is practically insoluble in water.

PROPECIA tablets for oral administration are film-coated tablets that contain 1 mg of finasteride and the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, pregelatinized starch, sodium starch glycolate, hydroxypropyl methylcellulose, hydroxypropyl cellulose LF, titanium dioxide, magnesium stearate, talc, docusate sodium, yellow ferric oxide, and red ferric oxide.

CLINICAL PHARMACOLOGY

Finasteride is a competitive and specific inhibitor of Type II 5α-reductase, an intracellular enzyme that converts the androgen testosterone into DHT. Two distinct isozymes 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 5α-reductase is predominant in the sebaceous glands of most regions of skin, including scalp, and liver. Type I 5α-reductase is responsible for approximately one-third of circulating DHT. The Type II 5α-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 5α-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 5α-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. Mean circulating levels of testosterone and

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estradiol were increased by approximately 15% as compared to baseline, but these remained within the physiologic range.

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. The relative contributions of these reductions to the treatment effect of finasteride have not been defined. By this mechanism, finasteride appears to interrupt a key factor in the development of androgenetic alopecia in those patients genetically predisposed.

A 48-week, placebo-controlled study designed to assess by phototrichogram the effect of PROPECIA on total and actively growing (anagen) scalp hairs in vertex baldness enrolled 212 men with androgenetic alopecia. At baseline and 48 weeks, total and anagen hair counts were obtained in a 1-cm^2 target area of the scalp. Men treated with PROPECIA showed increases from baseline in total and anagen hair counts of 7 hairs and 18 hairs, respectively, whereas men treated with placebo had decreases of 10 hairs and 9 hairs, respectively. These changes in hair counts resulted in a between-group difference of 17 hairs in total hair count ($p<0.001$) and 27 hairs in anagen hair count ($p<0.001$), and an improvement in the proportion of anagen hairs from 62% at baseline to 68% for men treated with PROPECIA.

Pharmacokinetics

Absorption

In a study in 15 healthy young male subjects, the mean bioavailability of finasteride 1-mg tablets was 65% (range 26-170%), based on the ratio of area under the curve (AUC) relative to an intravenous (IV) reference dose. At steady state following dosing with 1 mg/day (n=12), maximum finasteride plasma concentration averaged 9.2 ng/mL (range, 4.9-13.7 ng/mL) and was reached 1 to 2 hours postdose; $AUC_{(0\text{-}24\ hr)}$ was 53 ng•hr/mL (range, 20-154 ng•hr/mL). Bioavailability of finasteride was not affected by food.

Distribution

Mean steady-state volume of distribution was 76 liters (range, 44-96 liters; n=15). Approximately 90% of circulating finasteride is bound to plasma proteins. There is a slow accumulation phase for finasteride after multiple dosing.

Finasteride has been found to cross the blood-brain barrier.

Semen levels have been measured in 35 men taking finasteride 1 mg/day for 6 weeks. In 60% (21 of 35) of the samples, finasteride levels were undetectable (<0.2 ng/mL). The mean finasteride level was 0.26 ng/mL and the highest level measured was 1.52 ng/mL. Using the highest semen level measured and assuming 100% absorption from a 5-mL ejaculate per day, human exposure through vaginal absorption would be up to 7.6 ng per day, which is 750 times lower than the exposure from the no-effect dose for developmental abnormalities in Rhesus monkeys and 650-fold less than the dose of finasteride (5 μg) that had no effect on circulating DHT levels in men (see PRECAUTIONS, *Pregnancy*).

Metabolism

Finasteride is extensively metabolized in the liver, primarily via the cytochrome P450 3A4 enzyme subfamily. Two metabolites, the t-butyl side chain monohydroxylated and monocarboxylic acid metabolites, have been identified that possess no more than 20% of the 5α-reductase inhibitory activity of finasteride.

Excretion

Following intravenous infusion in healthy young subjects (n=15), mean plasma clearance of finasteride was 165 mL/min (range, 70-279 mL/min). Mean terminal half-life in plasma was 4.5 hours (range, 3.3-13.4 hours; n=12). Following an oral dose of ^{14}C-finasteride in man (n=6), a mean of 39% (range, 32-46%) of the dose was excreted in the urine in the form of metabolites; 57% (range, 51-64%) was excreted in the feces.

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.

Special Populations

Pediatric: Finasteride pharmacokinetics have not been investigated in patients <18 years of age.

Gender: PROPECIA is not indicated for use in women.

Geriatric: No dosage adjustment is necessary in the elderly. Although the elimination rate of finasteride is decreased in the elderly, these findings are of no clinical significance. See also *Pharmacokinetics, Excretion*, and PRECAUTIONS, *Geriatric Use* sections.

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Race: The effect of race on finasteride pharmacokinetics has not been studied.
Renal Insufficiency: *No dosage adjustment is necessary in patients with renal insufficiency. In patients with chronic renal impairment, with creatinine clearances ranging from 9.0 to 55 mL/min, AUC, maximum plasma concentration, half-life, and protein binding after a single dose of ^{14}C-finasteride were similar to those 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.*
Hepatic Insufficiency: The effect of hepatic insufficiency on finasteride pharmacokinetics has not been studied. Caution should be used in the administration of PROPECIA in patients with liver function abnormalities, as finasteride is metabolized extensively in the liver.
Drug Interactions (also see PRECAUTIONS, *Drug Interactions*)

No drug interactions of clinical importance have been identified. Finasteride does not appear to affect the cytochrome P450-linked drug-metabolizing enzyme system. Compounds that have been tested in man include antipyrine, digoxin, propranolol, theophylline, and warfarin and no clinically meaningful interactions were found.

Mean (SD) Pharmacokinetic Parameters in Healthy Men (ages 18-26)	
	Mean (± SD) n=15
Bioavailability	65% (26-170%)*
Clearance (mL/min)	165 (55)
Volume of Distribution (L)	76 (14)

*Range

Mean (SD) Noncompartmental Pharmacokinetic Parameters After Multiple Doses of 1 mg/day in Healthy Men (ages 19-42)	
	Mean (± SD) (n=12)
AUC (ng•hr/mL)	53 (33.8)
Peak Concentration (ng/mL)	9.2 (2.6)
Time to Peak (hours)	1.3 (0.5)
Half-Life (hours)*	4.5 (1.6)

*First-dose values; all other parameters are last-dose values

Clinical Studies
Studies in Men

The efficacy of PROPECIA was demonstrated in men (88% Caucasian) with mild to moderate androgenetic alopecia (male pattern hair loss) between 18 and 41 years of age. In order to prevent seborrheic dermatitis which might confound the assessment of hair growth in these studies, all men, whether treated with finasteride or placebo, were instructed to use a specified, medicated, tar-based shampoo (Neutrogena T/Gel®* Shampoo) during the first 2 years of the studies.

There were three double-blind, randomized, placebo-controlled studies of 12-month duration. The two primary endpoints were hair count and patient self-assessment; the two secondary endpoints were investigator assessment and ratings of photographs. In addition, information was collected regarding sexual function (based on a self-administered questionnaire) and non-scalp body hair growth. The three studies were conducted in 1879 men with mild to moderate, but not complete, hair loss. Two of the studies enrolled men with predominantly mild to moderate vertex hair loss (n=1553). The third enrolled men having mild to moderate hair loss in the anterior mid-scalp area with or without vertex balding (n=326).

*Registered trademark of Johnson & Johnson

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Studies in Men with Vertex Baldness

Of the men who completed the first 12 months of the two vertex baldness trials, 1215 elected to continue in double-blind, placebo-controlled, 12-month extension studies. There were 547 men receiving PROPECIA for both the initial study and first extension periods (up to 2 years of treatment) and 60 men receiving placebo for the same periods. The extension studies were continued for 3 additional years, with 323 men on PROPECIA and 23 on placebo entering the fifth year of the study.

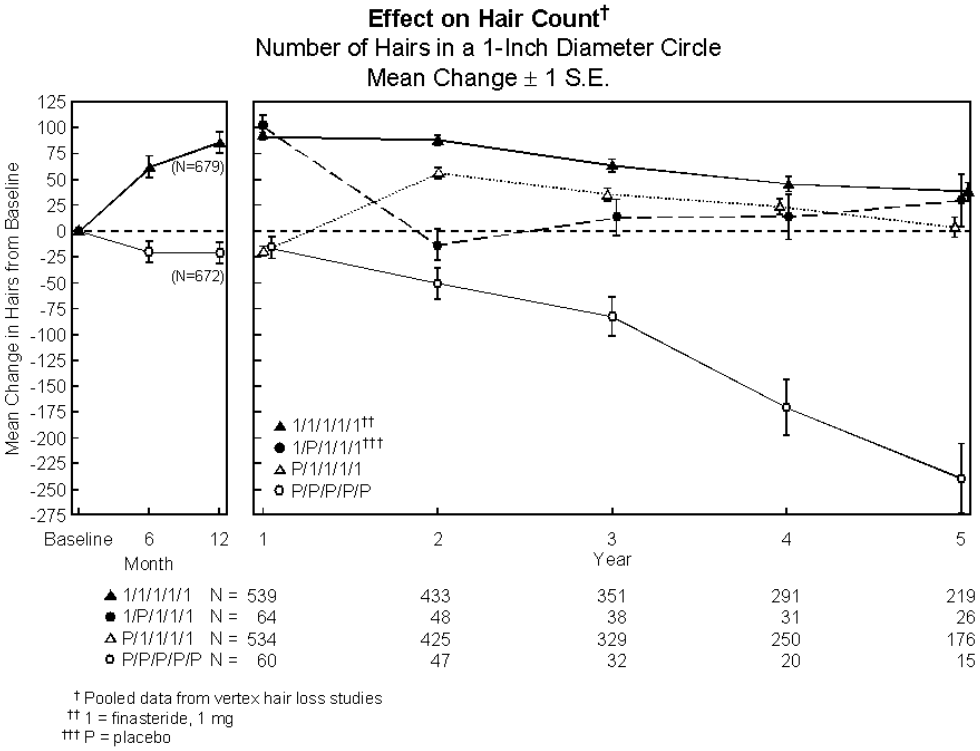
In order to evaluate the effect of discontinuation of therapy, there were 65 men who received PROPECIA for the initial 12 months followed by placebo in the first 12-month extension period. Some of these men continued in additional extension studies and were switched back to treatment with PROPECIA, with 32 men entering the fifth year of the study. Lastly, there were 543 men who received placebo for the initial 12 months followed by PROPECIA in the first 12-month extension period. Some of these men continued in additional extension studies receiving PROPECIA, with 290 men entering the fifth year of the study (see Figure below).

Hair counts were assessed by photographic enlargements of a representative area of active hair loss. In these two studies in men with vertex baldness, significant increases in hair count were demonstrated at 6 and 12 months in men treated with PROPECIA, while significant hair loss from baseline was demonstrated in those treated with placebo. At 12 months there was a 107-hair difference from placebo ($p<0.001$, PROPECIA [n=679] vs placebo [n=672]) within a 1-inch diameter circle (5.1 cm^2). Hair count was maintained in those men taking PROPECIA for up to 2 years, resulting in a 138-hair difference between treatment groups ($p<0.001$, PROPECIA [n=433] vs placebo [n=47]) within the same area. In men treated with PROPECIA, the maximum improvement in hair count compared to baseline was achieved during the first 2 years. Although the initial improvement was followed by a slow decline, hair count was maintained above baseline throughout the 5 years of the studies. Furthermore, because the decline in the placebo group was more rapid, the difference between treatment groups also continued to increase throughout the studies, resulting in a 277-hair difference ($p<0.001$, PROPECIA [n=219] vs placebo [n=15]) at 5 years (see Figure below).

Patients who switched from placebo to PROPECIA (n=425) had a decrease in hair count at the end of the initial 12-month placebo period, followed by an increase in hair count after 1 year of treatment with PROPECIA. This increase in hair count was less (56 hairs above original baseline) than the increase (91 hairs above original baseline) observed after 1 year of treatment in men initially randomized to PROPECIA. Although the increase in hair count, relative to when therapy was initiated, was comparable between these two groups, a higher absolute hair count was achieved in patients who were started on treatment with PROPECIA in the initial study. This advantage was maintained through the remaining 3 years of the studies. A change of treatment from PROPECIA to placebo (n=48) at the end of the initial 12 months resulted in reversal of the increase in hair count 12 months later, at 24 months (see Figure below).

At 12 months, 58% of men in the placebo group had further hair loss (defined as any decrease in hair count from baseline), compared with 14% of men treated with PROPECIA. In men treated for up to 2 years, 72% of men in the placebo group demonstrated hair loss, compared with 17% of men treated with PROPECIA. At 5 years, 100% of men in the placebo group demonstrated hair loss, compared with 35% of men treated with PROPECIA.

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Patient self-assessment was obtained at each clinic visit from a self-administered questionnaire, which included questions on their perception of hair growth, hair loss, and appearance. This self-assessment demonstrated an increase in amount of hair, a decrease in hair loss, and improvement in appearance in men treated with PROPECIA. Overall improvement compared with placebo was seen as early as 3 months ($p<0.05$), with improvement maintained over 5 years.

Investigator assessment was based on a 7-point scale evaluating increases or decreases in scalp hair at each patient visit. This assessment showed significantly greater increases in hair growth in men treated with PROPECIA compared with placebo as early as 3 months ($p<0.001$). At 12 months, the investigators rated 65% of men treated with PROPECIA as having increased hair growth compared with 37% in the placebo group. At 2 years, the investigators rated 80% of men treated with PROPECIA as having increased hair growth compared with 47% of men treated with placebo. At 5 years, the investigators rated 77% of men treated with PROPECIA as having increased hair growth, compared with 15% of men treated with placebo.

An independent panel rated standardized photographs of the head in a blinded fashion based on increases or decreases in scalp hair using the same 7-point scale as the investigator assessment. At 12 months, 48% of men treated with PROPECIA had an increase as compared with 7% of men treated with placebo. At 2 years, an increase in hair growth was demonstrated in 66% of men treated with PROPECIA, compared with 7% of men treated with placebo. At 5 years, 48% of men treated with PROPECIA demonstrated an increase in hair growth, 42% were rated as having no change (no further visible progression of hair loss from baseline) and 10% were rated as having lost hair when compared to baseline. In comparison, 6% of men treated with placebo demonstrated an increase in hair growth, 19% were rated as having no change and 75% were rated as having lost hair when compared to baseline.

Other Results in Vertex Baldness Studies

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 in favor of placebo were found in 3 of 4 domains (sexual interest, erections, and perception of sexual problems). However, no significant difference was seen in the question on overall satisfaction with sex life.

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In one of the two vertex baldness studies, patients were questioned on non-scalp body hair growth. PROPECIA did not appear to affect non-scalp body hair.

Study in Men with Hair Loss in the Anterior Mid-Scalp Area

A study of 12-month duration, designed to assess the efficacy of PROPECIA in men with hair loss in the anterior mid-scalp area, also demonstrated significant increases in hair count compared with placebo. Increases in hair count were accompanied by improvements in patient self-assessment, investigator assessment, and ratings based on standardized photographs. Hair counts were obtained in the anterior mid-scalp area, and did not include the area of bitemporal recession or the anterior hairline.

Summary of Clinical Studies in Men

Clinical studies were conducted in men aged 18 to 41 with mild to moderate degrees of androgenetic alopecia. All men treated with PROPECIA or placebo received a tar-based shampoo (Neutrogena T/Gel®* Shampoo) during the first 2 years of the studies. Clinical improvement was seen as early as 3 months in the patients treated with PROPECIA and led to a net increase in scalp hair count and hair regrowth. In clinical studies for up to 5 years, treatment with PROPECIA slowed the further progression of hair loss observed in the placebo group. In general, the difference between treatment groups continued to increase throughout the 5 years of the studies.

Ethnic Analysis of Clinical Data from Men

In a combined analysis of the two studies on vertex baldness, mean hair count changes from baseline were 91 vs -19 hairs (PROPECIA vs placebo) among Caucasians (n=1185), 49 vs -27 hairs among Blacks (n=84), 53 vs -38 hairs among Asians (n=17), 67 vs 5 hairs among Hispanics (n=45) and 67 vs -15 hairs among other ethnic groups (n=20). Patient self-assessment showed improvement across racial groups with PROPECIA treatment, except for satisfaction of the frontal hairline and vertex in Black men, who were satisfied overall.

Study in Women

In a study involving 137 postmenopausal women with androgenetic alopecia who were treated with PROPECIA (n=67) or placebo (n=70) for 12 months, effectiveness could not be demonstrated. There was no improvement in hair counts, patient self-assessment, investigator assessment, or ratings of standardized photographs in the women treated with PROPECIA when compared with the placebo group (see INDICATIONS AND USAGE).

INDICATIONS AND USAGE

PROPECIA is indicated for the treatment of male pattern hair loss (androgenetic alopecia) in **MEN ONLY**. Safety and efficacy were demonstrated in men between 18 to 41 years of age with mild to moderate hair loss of the vertex and anterior mid-scalp area (see CLINICAL PHARMACOLOGY, *Clinical Studies*).

Efficacy in bitemporal recession has not been established.

PROPECIA is not indicated in women (see CLINICAL PHARMACOLOGY*, Clinical Studies* and CONTRAINDICATIONS).

PROPECIA is not indicated in children (see PRECAUTIONS, *Pediatric Use*).

CONTRAINDICATIONS

PROPECIA is contraindicated in the following:

Pregnancy. Finasteride use is contraindicated in women when they are or may potentially be pregnant. Because of the ability of Type II 5α-reductase inhibitors to inhibit the conversion of testosterone to DHT, finasteride may cause abnormalities of the external genitalia of a male fetus of a pregnant woman who receives finasteride. If this drug is used during pregnancy, or if pregnancy occurs while taking this drug, the pregnant woman should be apprised of the potential hazard to the male fetus. (See also WARNINGS, EXPOSURE OF WOMEN - RISK TO MALE FETUS; and PRECAUTIONS, *Information for Patients* and *Pregnancy*.) In female rats, low doses of finasteride administered during pregnancy have produced abnormalities of the external genitalia in male offspring.

Hypersensitivity to any component of this medication.

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WARNINGS

PROPECIA is not indicated for use in pediatric patients (see INDICATIONS AND USAGE; and PRECAUTIONS, *Pediatric Use*) or women (see also WARNINGS, EXPOSURE OF WOMEN - RISK TO MALE FETUS; PRECAUTIONS, *Information for Patients* and *Pregnancy;* and HOW SUPPLIED, *Storage and Handling*).

EXPOSURE OF WOMEN - RISK TO MALE FETUS

Women should not handle crushed or broken PROPECIA tablets when they are pregnant or may potentially be pregnant because of the possibility of absorption of finasteride and the subsequent potential risk to a male fetus. 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. (See also CONTRAINDICATIONS; PRECAUTIONS, *Information for Patients* and *Pregnancy;* and HOW SUPPLIED, *Storage and Handling*.)

PRECAUTIONS

General

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

Information for Patients

Women should not handle crushed or broken PROPECIA tablets when they are pregnant or may potentially be pregnant because of the possibility of absorption of finasteride and the subsequent potential risk to a male fetus. 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. (See also CONTRAINDICATIONS; WARNINGS, EXPOSURE OF WOMEN - RISK TO MALE FETUS; PRECAUTIONS, *Pregnancy;* and HOW SUPPLIED, *Storage and Handling.*)

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).

See also Patient Package Insert.

Physicians should instruct their patients to read the patient package insert before starting therapy with PROPECIA and to read it again each time the prescription is renewed so that they are aware of current information for patients regarding PROPECIA.

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

Men aged 55 and over with a normal digital rectal examination and PSA ≤3.0 ng/mL at baseline taking finasteride 5 mg/day (5 times the dose of PROPECIA) 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 5α-reductase inhibitor (dutasteride, AVODART) (1% dutasteride vs 0.5% placebo). 5α-reductase inhibitors may increase the risk of development of high-grade prostate cancer. Whether the effect of 5α-reductase inhibitors to reduce to reduce prostate volume, or study-related factors, impacted the results of these studies has not been established.

Drug/Laboratory Test Interactions

Finasteride had no effect 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) or prolactin were detected. In healthy volunteers, treatment with finasteride did not alter the response of LH and FSH to gonadotropin-releasing hormone indicating that the hypothalamic-pituitary-testicular axis was not affected.

In clinical studies with PROPECIA (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 PROSCAR (finasteride, 5 mg) when used in older men who have benign prostatic hyperplasia (BPH), PSA levels are decreased by approximately 50%. Other studies with PROSCAR 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 PROPECIA may signal the

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presence of prostate cancer and should be evaluated, even if PSA levels are still within the normal range for men not taking a 5α-reductase inhibitor. Non-compliance to therapy with PROPECIA may also affect PSA test results.

Drug Interactions

No drug interactions of clinical importance have been identified. Finasteride does not appear to affect the cytochrome P450-linked drug-metabolizing enzyme system. Compounds that have been tested in man include antipyrine, digoxin, propranolol, theophylline, and warfarin and no clinically meaningful interactions were found.

Other concomitant therapy: Although specific interaction studies were not performed, finasteride doses of 1 mg or more were concomitantly used in clinical studies with acetaminophen, acetylsalicylic acid, α-blockers, analgesics, angiotensin-converting enzyme (ACE) inhibitors, anticonvulsants, benzodiazepines, beta blockers, calcium-channel blockers, cardiac nitrates, diuretics, H_2 antagonists, HMG-CoA reductase inhibitors, prostaglandin synthetase inhibitors (also referred to as NSAIDs), and quinolone anti-infectives without evidence of clinically significant adverse interactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of a tumorigenic effect was observed in a 24-month study in Sprague-Dawley rats receiving doses of finasteride up to 160 mg/kg/day in males and 320 mg/kg/day in females. These doses produced respective systemic exposure in rats of 888 and 2192 times those observed in man receiving the recommended human dose of 1 mg/day. All exposure calculations were based on calculated $AUC_{(0\text{-}24\ hr)}$ for animals and mean $AUC_{(0\text{-}24\ hr)}$ for man (0.05 µg•hr/mL).

In a 19-month carcinogenicity study in CD-1 mice, a statistically significant ($p \leq 0.05$) increase in the incidence of testicular Leydig cell adenomas was observed at a dose of 250 mg/kg/day (1824 times the human exposure). In mice at a dose of 25 mg/kg/day (184 times the human exposure, estimated) and in rats at a dose of ≥40 mg/kg/day (312 times the human exposure) an increase in the incidence of Leydig cell hyperplasia was observed. A positive correlation between the proliferative changes in the Leydig cells and an increase in serum LH levels (2- to 3-fold above control) has been demonstrated in both rodent species treated with high doses of finasteride. No drug-related Leydig cell changes were seen in either rats or dogs treated with finasteride for 1 year at doses of 20 mg/kg/day and 45 mg/kg/day (240 and 2800 times, respectively, the human exposure) or in mice treated for 19 months at a dose of 2.5 mg/kg/day (18.4 times the human exposure, estimated).

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, using Chinese hamster ovary cells, there was a slight increase in chromosome aberrations. In an *in vivo* chromosome aberration assay in mice, no treatment-related increase in chromosome aberration was observed with finasteride at the maximum tolerated dose of 250 mg/kg/day (1824 times the human exposure) as determined in the carcinogenicity studies.

In sexually mature male rabbits treated with finasteride at 80 mg/kg/day (4344 times the human exposure) for up to 12 weeks, no effect on fertility, sperm count, or ejaculate volume was seen. In sexually mature male rats treated with 80 mg/kg/day of finasteride (488 times the human exposure), 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, 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. No drug-related effect on testes or on mating performance has been seen in rats or rabbits. This 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 but is not relevant in man.

Pregnancy

Teratogenic Effects: Pregnancy Category X

See CONTRAINDICATIONS.

PROPECIA is not indicated for use in women.

Administration of finasteride to pregnant rats on gestational days 6-20 at doses ranging from 100 µg/kg/day to 100 mg/kg/day (1-684 times the human exposure, estimated) resulted in dose-dependent development of hypospadias in 3.6 to 100% of male offspring. Pregnant rats produced male offspring with decreased prostatic and seminal vesicular weights, delayed preputial separation, and transient nipple

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development when given finasteride at ≥30 µg/kg/day (0.2 times the human exposure, estimated) and decreased anogenital distance when given finasteride at ≥3 µg/kg/day (0.02 times the human exposure, estimated). The critical period during which these effects can be induced in male rats has been defined to be days 16-17 of gestation. The changes described above are expected pharmacological effects of drugs belonging to the class of Type II 5α-reductase inhibitors and are similar to those reported in male infants with a genetic deficiency of Type II 5α-reductase. No abnormalities were observed in female offspring exposed to any dose of finasteride *in utero*.

No developmental abnormalities have been observed in first filial generation (F_1) male or female offspring resulting from mating finasteride-treated male rats (80 mg/kg/day; 488 times the human exposure) with untreated females. Administration of finasteride at 3 mg/kg/day (20 times the human exposure, estimated) during the late gestation and lactation period resulted in slightly decreased fertility in F_1 male offspring. No effects were seen in female offspring.

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 (1908 times the recommended human dose of 1 mg/day, based on body surface area comparison). However, effects on male genitalia would not be expected since the rabbits were not exposed during the critical period of genital system development.

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 up to 800 ng/day (at least 250 times the highest estimated exposure of pregnant women to finasteride from semen of men taking 1 mg/day, based on body surface area comparison) resulted in no abnormalities in male fetuses. In confirmation of the relevance of the rhesus model for human fetal development, oral administration of a 2 mg/kg/day dose of finasteride 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.

Nursing Mothers

PROPECIA is not indicated for use in women.

It is not known whether finasteride is excreted in human milk.

Pediatric Use

PROPECIA is not indicated for use in pediatric patients.

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical efficacy studies with PROPECIA did not include subjects aged 65 and over. Based on the pharmacokinetics of finasteride 5 mg, no dosage adjustment is necessary in the elderly for PROPECIA (see CLINICAL PHARMACOLOGY, *Pharmacokinetics*). However the efficacy of PROPECIA in the elderly has not been established.

ADVERSE REACTIONS

Clinical Studies for PROPECIA (finasteride 1 mg) in the Treatment of Male Pattern Hair Loss

In three controlled clinical trials for PROPECIA of 12-month duration, 1.4% of patients taking PROPECIA (n=945) were discontinued due to adverse experiences that were considered to be possibly, probably or definitely drug-related (1.6% for placebo; n=934).

Clinical adverse experiences that were reported as possibly, probably or definitely drug-related in ≥1% of patients treated with PROPECIA or placebo are presented in Table 1.

TABLE 1
Drug-Related Adverse Experiences for PROPECIA (finasteride 1 mg) in Year 1 (%)
MALE PATTERN HAIR LOSS

	PROPECIA N=945	Placebo N=934
Decreased Libido	1.8	1.3
Erectile Dysfunction	1.3	0.7
Ejaculation Disorder *(Decreased Volume of Ejaculate)*	1.2 *(0.8)*	0.7 *(0.4)*

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Discontinuation due to drug-related sexual adverse experiences	1.2	0.9

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 occurred in men who discontinued therapy with PROPECIA due to these side effects and in most of those who continued therapy. The incidence of each of the above adverse experiences decreased to ≤0.3% by the fifth year of treatment with PROPECIA.

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.

In the clinical studies with PROPECIA, the incidences for breast tenderness and enlargement, hypersensitivity reactions, and testicular pain in finasteride-treated patients were not different from those in patients treated with placebo.

Postmarketing Experience for PROPECIA (finasteride 1 mg)

Breast tenderness and enlargement; depression; hypersensitivity reactions including rash, pruritus, urticaria, and swelling of the lips and face; testicular pain; and male breast cancer. 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. See *Controlled Clinical Trials and Long-Term Open Extension Studies for PROSCAR® (finasteride 5 mg) in the Treatment of Benign Prostatic Hyperplasia*.

Controlled Clinical Trials and Long-Term Open Extension Studies for PROSCAR® (finasteride 5 mg) in the Treatment of Benign Prostatic Hyperplasia

In the PROSCAR Long-Term Efficacy and Safety Study (PLESS), a 4-year controlled clinical study, 3040 patients between the ages of 45 and 78 with symptomatic BPH and an enlarged prostate were evaluated for safety over a period of 4 years (1524 on PROSCAR 5 mg/day and 1516 on placebo). 3.7% (57 patients) treated with PROSCAR 5 mg and 2.1% (32 patients) treated with placebo discontinued therapy as a result of adverse reactions related to sexual function, which are the most frequently reported adverse reactions.

Table 2 presents the only clinical adverse reactions considered possibly, probably or definitely drug related by the investigator, for which the incidence on PROSCAR was ≥1% and greater than placebo over the 4 years of the study. In years 2-4 of the study, there was no significant difference between treatment groups in the incidences of impotence, decreased libido and ejaculation disorder.

TABLE 2
Drug-Related Adverse Experiences for PROSCAR (finasteride 5 mg)
BENIGN PROSTATIC HYPERPLASIA

	Year 1 (%)		Years 2, 3 and 4* (%)	
	Finasteride, 5 mg	Placebo	Finasteride, 5 mg	Placebo

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Impotence	8.1	3.7	5.1	5.1
Decreased Libido	6.4	3.4	2.6	2.6
Decreased Volume of Ejaculate	3.7	0.8	1.5	0.5
Ejaculation Disorder	0.8	0.1	0.2	0.1
Breast Enlargement	0.5	0.1	1.8	1.1
Breast Tenderness	0.4	0.1	0.7	0.3
Rash	0.5	0.2	0.5	0.1

*Combined Years 2-4
N = 1524 and 1516, finasteride vs placebo, respectively

The adverse experience profiles in the 1-year, placebo-controlled, Phase III BPH studies and the 5-year open extensions with PROSCAR 5 mg and PLESS were similar.

There is no evidence of increased adverse experiences with increased duration of treatment with PROSCAR 5 mg. New reports of drug-related sexual adverse experiences decreased with duration of therapy.

During the 4- to 6-year placebo- and comparator-controlled Medical Therapy of Prostatic Symptoms (MTOPS) study that enrolled 3047 men, there were 4 cases of breast cancer in men treated with PROSCAR but no cases in men not treated with PROSCAR. During the 4-year placebo-controlled PLESS study that enrolled 3040 men, there were 2 cases of breast cancer in placebo-treated men but no cases in men treated with PROSCAR. During the 7-year placebo-controlled Prostate Cancer Prevention Trial (PCPT) that enrolled 18,882 men, there was 1 case of breast cancer in men treated with PROSCAR, and 1 case of breast cancer in men treated with placebo. The relationship between long-term use of finasteride and male breast neoplasia is currently unknown.

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 PROSCAR (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 PROPECIA by men is unknown.

No clinical benefit has been demonstrated in patients with prostate cancer treated with PROSCAR. PROSCAR is not approved to reduce the risk of developing prostate cancer.

OVERDOSAGE

In clinical studies, single doses of finasteride up to 400 mg and multiple doses of finasteride up to 80 mg/day for three months did not result in adverse reactions. Until further experience is obtained, no specific treatment for an overdose with finasteride can be recommended.

Significant lethality was observed in male and female mice at single oral doses of 1500 mg/m^2 (500 mg/kg) and in female and male rats at single oral doses of 2360 mg/m^2 (400 mg/kg) and 5900 mg/m^2 (1000 mg/kg), respectively.

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DOSAGE AND ADMINISTRATION

The recommended dosage is 1 mg orally once a day.

PROPECIA may be administered with or without meals.

In general, daily use for three months or more is necessary before benefit is observed. Continued use is recommended to sustain benefit, which should be re-evaluated periodically. Withdrawal of treatment leads to reversal of effect within 12 months.

HOW SUPPLIED

No. 6642 — PROPECIA tablets, 1 mg, are tan, octagonal, film-coated convex tablets with “stylized P” logo on one side and PROPECIA on the other. They are supplied as follows:

NDC 0006-0071-31 unit of use bottles of 30 (with desiccant)

NDC 0006-0071-54 PROPAK® - unit of use bottles of 90 (with desiccant).

Storage and Handling

Store at room temperature, 15-30°C (59-86°F). Keep container closed and protect from moisture.

Women should not handle crushed or broken PROPECIA tablets when they are pregnant or may potentially be pregnant because of the possibility of absorption of finasteride and the subsequent potential risk to a male fetus. PROPECIA tablets are coated and will prevent contact with the active ingredient during normal handling, provided that the tablets are not broken or crushed. (See WARNINGS, EXPOSURE OF WOMEN - RISK TO MALE FETUS; and PRECAUTIONS, *Information for Patients* and *Pregnancy.*)

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PROPECIA®
(finasteride) Tablets, 1 mg
Patient Information about
PROPECIA® (Pro-pee-sha)

Generic name: finasteride
(fin-AS-tur-eyed)

PROPECIA® is for use by MEN ONLY.

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

What is PROPECIA used for?

PROPECIA is used for the treatment of male pattern hair loss on the vertex and the anterior mid-scalp area.

PROPECIA is for use by **MEN ONLY** and should **NOT** be used by women or children.

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. These changes typically begin gradually in men in their 20s.

Doctors believe male pattern hair loss is due to heredity and is dependent on hormonal effects. Doctors refer to this type of hair loss as androgenetic alopecia.

Results of clinical studies:

For 12 months, doctors studied over 1800 men aged 18 to 41 with mild to moderate amounts of ongoing hair loss. Of these men, approximately 1200 with hair loss at the top of the head participated in additional extension studies, resulting in a total study time of up to five years. In general, men who took PROPECIA maintained or increased the number of visible scalp hairs and noticed improvement in their hair in the first year. Improvement, compared to the start of the study, was maintained through the remaining years of treatment. Hair counts in men who did not take PROPECIA continued to decrease.

In one study, patients were questioned on the growth of body hair. PROPECIA did not appear to affect hair in places other than the scalp.

Will PROPECIA work for me?

For most men, PROPECIA increases the number of scalp hairs in the first year of treatment, helping to fill in thin or balding areas of the scalp. In addition, men taking PROPECIA may note a slowing of hair loss. Although results will vary, generally you will not be able to grow back all of the hair you have lost. There is not sufficient evidence that PROPECIA works in the treatment of receding hairline in the temporal area on both sides of the head.

Male pattern hair loss occurs gradually over time. On average, healthy hair grows only about half an inch each month. Therefore, it will take time to see any effect.

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You may need to take PROPECIA daily for three months or more before you see a benefit from taking PROPECIA. PROPECIA can only work over the long term if you continue taking it. If the drug has not worked for you in twelve months, further treatment is unlikely to be of benefit. If you stop taking PROPECIA, you will likely lose the hair you have gained within 12 months of stopping treatment. You should discuss this with your doctor.
PROPECIA is not effective in the treatment of hair loss due to androgenetic alopecia in postmenopausal women. PROPECIA should not be taken by women.

How should I take PROPECIA?

Follow your doctor's instructions.

- Take one tablet by mouth each day.
- You may take PROPECIA with or without food.
- If you forget to take PROPECIA, do not take an extra tablet. Just take the next tablet as usual.

PROPECIA will not work faster or better if you take it more than once a day.

Who should NOT take PROPECIA?

- PROPECIA is for the treatment of male pattern hair loss in **MEN ONLY** and should not be taken by women (see **A warning about PROPECIA and pregnancy**).
- PROPECIA should not be taken by children.
- Anyone allergic to any of the ingredients.

A warning about PROPECIA and pregnancy.

- **Women who are or may potentially be pregnant:**
  - **must not use PROPECIA**
  - **should not handle crushed or broken tablets of PROPECIA.**

If a woman who is pregnant with a male baby absorbs the active ingredient in PROPECIA, either by swallowing or through the skin, it may cause abnormalities of a male baby's sex organs. If a woman who is pregnant comes into contact with the active ingredient in PROPECIA, a doctor 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.

What are the possible side effects of PROPECIA?

Like all prescription products, PROPECIA may cause side effects. In clinical studies, side effects from PROPECIA were uncommon and did not affect most men. A small number of men experienced certain sexual side effects. These men reported one or more of the following: less desire for sex; difficulty in achieving an erection; and, a decrease in the amount of semen. Each of these side effects occurred in less than 2% of men. These side effects went away in men who stopped taking PROPECIA. They also disappeared in most men who continued taking PROPECIA.

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In general use, the following have been reported: breast tenderness and enlargement; depression; allergic reactions including rash, itching, hives and swelling of the lips and face; problems with ejaculation; testicular pain; and, in rare cases, male breast cancer. You should promptly report to your doctor any changes in your breasts such as lumps, pain or nipple discharge. Tell your doctor promptly about these or any other unusual side effects.

- **PROPECIA can affect a blood test called PSA (Prostate-Specific Antigen) for the screening of prostate cancer. If you have a PSA test done, you should tell your doctor(s) that you are taking PROPECIA. Because PROPECIA decreases PSA levels, changes in PSA levels will need to be evaluated by your doctor(s). Any increase in follow-up PSA levels from their lowest point may signal the presence of prostate cancer and should be evaluated even if the test results are still within the normal range for men not taking PROPECIA. You should also tell your doctor if you have not been taking PROPECIA as prescribed because this may affect the PSA test results. For more information, talk to your doctor.**

Storage and handling.

Keep PROPECIA in the original container and keep the container closed. Store it in a dry place at room temperature. **PROPECIA tablets are coated and will prevent contact with the active ingredient during normal handling, provided that the tablets are not broken or crushed.**

Do not give your PROPECIA tablets to anyone else. It has been prescribed only for you. Keep PROPECIA and all medications out of the reach of children.

THIS LEAFLET PROVIDES A SUMMARY OF INFORMATION ABOUT PROPECIA. IF AFTER READING THIS LEAFLET YOU HAVE ANY QUESTIONS OR ARE NOT SURE ABOUT ANYTHING, TALK TO YOUR DOCTOR, PHARMACIST, OR HEALTH CARE PROVIDER.

1-888-637-2522, Monday through Friday, 8:30 A.M. TO 7:00 P.M. (ET).

www.propecia.com

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