

PROPECIA®

TABLETS

Composition

Each tablet contains:

Active Ingredient

Finasteride 1 mg

Inactive Ingredients

Lactose monohydrate, microcrystalline cellulose, pregelatinized starch, sodium starch glycolate, docusate sodium, magnesium stearate, hydroxypropyl methylcellulose 2910, hydroxypropyl cellulose, titanium dioxide, talc, yellow ferric oxide, and red ferric oxide.

Mechanism of Action

Finasteride, MSD, is a synthetic 4-azasteroid compound that is a specific inhibitor of Type II 5 α -reductase, an intracellular enzyme that metabolizes the androgen testosterone into dihydrotestosterone (DHT).

Clinical Pharmacology

Pharmacodynamics

Finasteride is a competitive and specific inhibitor of Type II 5 α -reductase with which it slowly forms a stable enzyme complex. Turnover from this complex is extremely slow ($t_{1/2}$ ~ 30 days).

Finasteride has no affinity for the androgen receptor and has no androgenic, antiandrogenic, estrogenic, antiestrogenic, or progestational effects. Inhibition of this enzyme blocks the peripheral conversion of testosterone to the androgen dihydrotestosterone (DHT), resulting in significant decreases in serum and tissue DHT concentrations. Finasteride produces a rapid reduction in serum DHT concentration, reaching significant suppression within 24 hours of dosing.

Hair follicles contain Type II 5 α -reductase. In men with male pattern hair loss, the balding scalp contains miniaturized hair follicles and increased amount of DHT. Administration of finasteride decreases scalp and serum DHT concentrations in these men. In addition, men with a genetic deficiency of Type II 5 α -reductase do not suffer from male pattern hair loss. These data and the results of the clinical studies confirm that finasteride inhibits the process responsible for miniaturization of the scalp hair follicles, leading to reversal of the balding process.

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), 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 with placebo, yet remained within the physiologic range. There was no effect on semen parameters in men treated with finasteride 1 mg per day for 48 weeks.

Finasteride appeared to inhibit both C₁₉ and C₂₁ steroid metabolism and hence appeared to have an inhibitory effect on both hepatic and peripheral Type II 5 α -reductase activity. The serum DHT metabolites, androstenediol glucuronide and androsterone glucuronide, were also significantly reduced. This metabolic pattern is similar to that observed in individuals with a genetic deficiency of

Type II 5 α -reductase who have markedly decreased levels of DHT and who do not suffer from male pattern hair loss.

Pharmacokinetics

Absorption

Relative to an intravenous reference dose, the oral bioavailability of finasteride is approximately 80%. The bioavailability is not affected by food. Maximum finasteride plasma concentrations are reached approximately two hours after dosing and the absorption is complete after 6-8 hours.

Distribution

Protein binding is approximately 93%. The volume of distribution of finasteride is approximately 76 liters.

There is modest accumulation of finasteride in plasma after multiple dosing. At steady state following dosing with 1 mg/day, maximum finasteride plasma concentration averaged 9.2 ng/mL and was reached 1 to 2 hours post-dose; AUC_(0-24 hr) was 53 ng•hr/mL.

Finasteride has been recovered in the cerebrospinal fluid (CSF) but the drug does not appear to concentrate preferentially to the CSF. A very small amount of finasteride has also been detected in the seminal fluid of subjects receiving finasteride.

Metabolism

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

Elimination

Following an oral dose of ¹⁴C-finasteride in man, 39% of the dose was excreted in the urine in the form of metabolites (virtually no unchanged drug was excreted in the urine) and 57% of total dose was excreted in the feces. Plasma clearance is approximately 165 mL/min.

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.

Characteristics in Patients

In patients with chronic renal impairment whose creatinine clearance ranged from 9 to 55 mL/min, the disposition of a single dose of ¹⁴C-finasteride was not different from that in healthy volunteers. Protein binding also did not differ in patients with renal impairment. A portion of the metabolites, that normally is excreted renally, was excreted in the feces. It therefore appears that fecal excretion increases commensurate to the decrease in urinary excretion of metabolites. No adjustment in dosage is necessary in nondialyzed patients with renal impairment.

Clinical Studies

Studies in Men

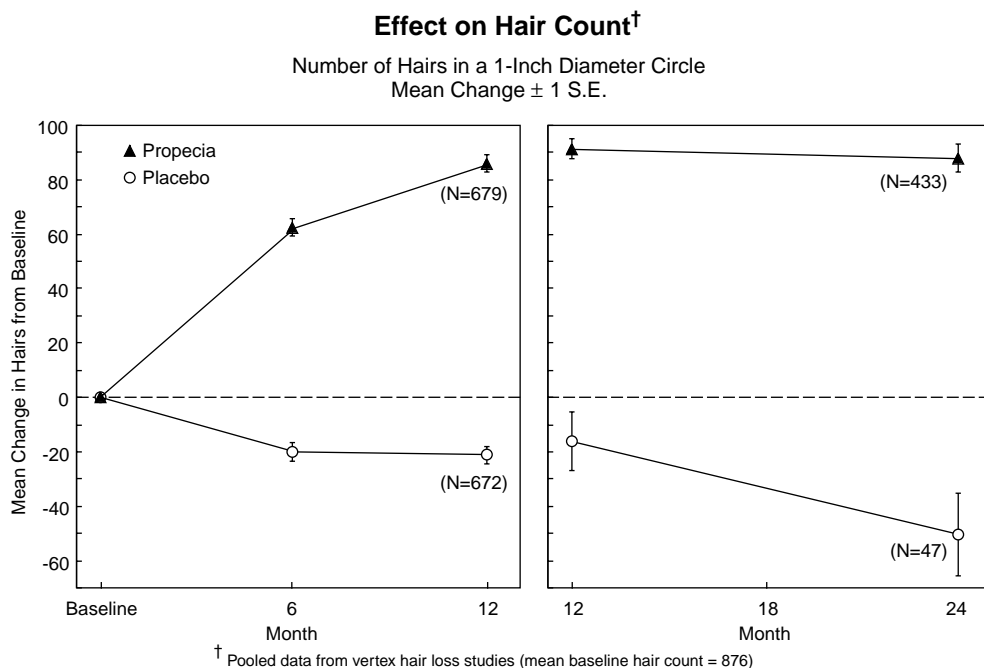
The efficacy of Propecia in men with male pattern hair loss was demonstrated in 3 double-blind, randomized, placebo-controlled studies of 12-month duration, using four endpoints: hair count, patient self-assessment, investigator assessment, and ratings by an expert panel of dermatologists. These three studies were conducted in 1,879 men between 18 and 41 years of age with mild to moderate, but not complete, hair loss. Two of the studies enrolled men with predominantly vertex hair loss (n=1,553), while the third enrolled men with predominantly frontal/mid-area hair loss (n=326). These studies demonstrated that treatment with Propecia increases hair growth and prevents further hair loss in men with androgenetic alopecia.

Of the men with vertex hair loss, 1,215 elected to continue in double-blind, placebo-controlled, 12-month extension studies. As randomized at the beginning of the study, patients were assigned to treatment in the extension phase, with 535 men receiving Propecia for both initial and extension periods (up to 24 months) and 60 remaining on placebo for the initial and extension periods (up to 24 months).

Hair counts were assessed by photographic enlargements of a small representative area of active hair loss. In the 2 studies in men with vertex hair loss, 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 growth was maintained in those men taking Propecia ($n = 433$) for up to 24 months, while the placebo group ($n = 47$) continued to show progressive hair loss. At 24 months, this resulted in a 138-hair difference between treatment groups ($p < 0.001$) within the same area (see figure below for combined study results).

At 12 months, only 14% of men treated with Propecia demonstrated hair loss (based on any decrease in hair count from baseline) compared with 58% of men in the placebo group. In men treated for up to 24 months, only 17% of those treated with Propecia demonstrated hair loss compared with 72% of those in the placebo group.

The hair count measurements show that Propecia prevented the progression of hair loss over time. The clinical significance of the effect on hair count was demonstrated by the three other endpoints: patient self-assessment, investigator assessment, and ratings by an expert panel of dermatologists.



Patient self-assessment was obtained at each clinic visit from a validated self-administered questionnaire, which included questions on hair growth, hair loss, and appearance.

This self-assessment demonstrated significant increases in hair growth, decreases 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 continued improvement over 24 months.

Investigator assessment was based on a 7-point scale evaluating increases or decreases in scalp hair at each patient visit in the clinic. 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 24 months, the investigators rated 80% of men treated with Propecia as having increased hair growth, compared with 47% of men in the placebo group.

An expert panel of dermatologists rated standardized photographs of the head, in a blinded fashion, at the beginning of the study and at 6, 12, 18 and 24 months. This panel rated increases or decreases in scalp hair on the same 7-point scale. At 12 months, increased hair growth was demonstrated in 48% of men treated with Propecia, compared with 7% of men treated with placebo. At 24 months, increased hair growth was demonstrated in 66% of men treated with Propecia, compared with 7% of men in the placebo group. Based on this assessment, continued treatment with Propecia resulted in further improvement.

The third 12-month study designed to assess the efficacy of Propecia in men with frontal/mid-area hair loss, also demonstrated significant increases in hair count, compared with placebo. The clinical significance of these increases in hair count was confirmed by significant improvement in patient self-assessment, investigator assessment, and ratings by an expert panel of dermatologists.

In each of these studies, clinical improvement was seen as early as 3 months and efficacy continued to improve thereafter. Efficacy was also observed in Black men with male pattern hair loss. Maintenance of, or improvement in, clinical efficacy has also been demonstrated in controlled and open-extension studies for up to 3 years.

In summary, these studies demonstrated that treatment with Propecia increases hair growth and prevents further hair loss associated 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).

Indications

Propecia is indicated for the treatment of men with male pattern hair loss (androgenetic alopecia) to increase hair growth and prevent further hair loss.

Propecia is **not** indicated for use in women (see *Use in PREGNANCY* and *Clinical Studies*) or children.

Contraindications

Propecia is contraindicated in the following :

Use in women when they are or may potentially be pregnant (see *Use in Pregnancy*).

Hypersensitivity to any component of this product.

Propecia is not indicated for use in women or children.

Warnings

Mutagenicity

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 μ mol) 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 finasteride. Further, the concentrations (450-550 μ mol) 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).

Carcinogenicity

No evidence of a tumorigenic effect was observed in a 24-month study in Sprague-Dawley 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 CD-1 mice, a statistically significant ($p < 0.05$) 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).

In mice at a dose of 25 mg/kg/day and in rats at a dose of 40 mg/kg/day (1,250 and 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 LH levels (2-3 fold above control) has been demonstrated in both rodent species treated with high doses of finasteride. This suggests that the Leydig cell changes are secondary to elevated serum LH levels and not due to a direct effect of finasteride.

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).

Reproduction

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.

Teratogenicity

Dose-dependent development of hypospadias was observed in the male offspring of pregnant rats given finasteride at doses ranging from 100 μ g/kg/day to 10 mg/kg/day (5 to 5,000 times the recommended human dose of 1 mg/day) at an incidence of 3.6 to 100%. 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 μ g/kg/day (1.5 times the recommended human dose of 1 mg/day), and decreased anogenital distance, when given finasteride in doses 3 μ g/kg/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 α -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 α -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 of 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 of 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.

Use in Pregnancy

Propecia is contraindicated for use in women when they are or may potentially be pregnant. Because of the ability of Type II 5 α -reductase inhibitors to inhibit the conversion of testosterone to DHT in some tissues, this class of drugs, including finasteride, may cause abnormalities of the external genitalia of a male fetus, when administered to a pregnant woman.

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.

Propecia tablets are coated and will prevent contact with the active ingredient during normal handling, provided that the tablets have not been crushed or broken.

Use in Breastfeeding

Propecia is not indicated for use in women.

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

Use in Pediatrics

Propecia is not indicated for use in children.

Use in the Elderly

Clinical studies with Propecia have not been conducted in elderly men with male pattern hair loss.

Use in Patients with Liver Function Abnormalities

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

Adverse Reactions

Propecia is generally well tolerated. Side effects, which usually have been mild, generally have not required discontinuation of therapy.

Finasteride for male pattern hair loss has been evaluated for safety in clinical studies involving more than 3,200 men. In three 12-month, placebo-controlled, double-blind, multicenter studies of comparable design, the overall safety profiles of Propecia 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 1% of men treated with Propecia: decreased libido (Propecia, 1.8% vs placebo, 1.3%) and erectile dysfunction (1.3%, 0.7%). In addition, decreased volume of ejaculate was reported in 0.8% of men treated with Propecia and 0.4% of men treated with placebo. Resolution of these side effects occurred in men who discontinued therapy with Propecia and in many 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.

The side effect profile for 547 patients who continued on Propecia for up to 24 months was similar to that observed in the 12-month controlled studies.

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.

Precautions

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, even at the presence of prostate cancer.

When Propecia is used for treatment of male pattern hair loss in older men who also have BPH, consideration should be given to the fact that in older men with BPH, PSA levels are decreased by approximately 50%, and does not rule out concomitant prostate cancer.

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 which have been tested in men, have included antipyrine, digoxin, glibenclamide, propranolol, theophylline, and warfarin; no interactions were found.

Although specific interaction studies were not performed, in clinical studies with finasteride doses of 1 mg or more were used concomitantly with angiotensin-converting enzyme (ACE) inhibitors, paracetamol, alpha-blockers, benzodiazepines, beta-blockers, calcium channel blockers, cardiac nitrates, diuretics, H₂-receptor antagonists, HMG-CoA reductase inhibitors, non-steroidal anti-inflammatory drugs (NSAIDs), and quinolone anti-infectives, without evidence of clinically significant adverse reactions.

Dosage and Administration

The recommended dosage is one 1-mg tablet of Propecia per day. Propecia may be taken with or without food.

In general, daily use for 3 months or more is necessary before increased hair growth and/or prevention of further hair loss is observed. Continued use is recommended to obtain maximum benefit. Withdrawal of treatment leads to reversibility of effect within 12 months.

Overdosage

In clinical studies, single doses of finasteride up to 400 mg and multiple doses of finasteride up to 80 mg/day for 3 months did not result in side effects.

No specific treatment for an overdose with Propecia is recommended.