Draft USPC for Task Force Meeting on 10/23/00

MERCK & CO., INC.
Whitehouse Station, NJ 08889, USA

9328500

PROPECIA®

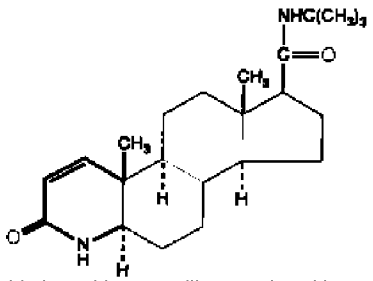
(Finasteride)

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

* Registered trademark of MERCK & CO., INC.

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.

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.

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.

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) or follicle-stimulating hormone (FSH) 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. Mean circulating levels of testosterone and estradiol were increased by approximately 15% as compared to baseline, but these remained within the physiologic range.

Pharmacokinetics

Following an oral dose of ^{14}C-finasteride in man, 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. 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 possessed no more than 20% of the 5α-reductase inhibitory activity of finasteride.

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 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.

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; $AUC_{(0\text{-}24\ hr)}$ was 53 ng•hr/mL (range, 20-154 ng•hr/mL) and mean terminal half-life of elimination was 4.8 hours (range, 3.3-13.4 hours).

Semen levels have been measured in 35 men taking finasteride 1 mg daily for 6 weeks. In 60% (21 of 35) of the samples, finasteride levels were undetectable. The mean finasteride level was 0.26 ng/mL and the highest level measured was 1.52 ng/mL. Using this 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 (see PRECAUTIONS, *Pregnancy*).

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 a reduction in dosage in the elderly is not warranted.

No dosage adjustment is necessary in patients with renal insufficiency. In patients with chronic renal impairment (creatinine clearance ranging from 9.0 to 55 mL/min), the values for 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). Furthermore, 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.

Clinical Studies

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 (controlled phase and extensions), all men, whether treated with finasteride or placebo, were instructed to use a specified, medicated, tar-based shampoo (Neutrogena T/Gel®** Shampoo).~~

Remove or revise information on shampoo, because use of Neutrogena was not continued throughout all of the extension 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. The three studies were conducted in 1,879 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=1,553). The third enrolled men having mild to moderate hair loss in the anterior mid-scalp area with or without vertex balding (n=326).

Two studies on Vertex Baldness

Of the men who completed the first 12 months of the two vertex baldness trials, 1,215 elected to continue in double-blind, placebo-controlled, 12-month extension studies. There were 547 men receiving PROPECIA for both the initial and extension periods (up to ~~24 months~~2 years) and 60 men receiving placebo for the same periods. In additional extension

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.

** Registered trademark of Johnson & Johnson

studies, 323 of these men continued on PROPECIA and 23 on placebo resulting in a total study time of up to 5 years.

In addition, there were 65 men who received PROPECIA for the initial 12 months followed by placebo in the 12-month extension period;, 46 of these men, having switched back to PROPECIA, continued in additional extension studies (total study time, up to 5 years). There were and 543 men who received placebo for the initial 12 months followed by PROPECIA in the 12-month extension period; 429 of these men continued to receive PROPECIA in additional extension studies (total study time, up to 5 years). (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 evaluable men] vs placebo [n=672 evaluable men]) within a 1-inch diameter circle (5.1 cm^2). Hair count was maintained in those men taking PROPECIA (n=433 evaluable men) for up to 24 months2 years, while the placebo group (n=47 evaluable men) continued to show progressive hair loss. At 24 months2 years, this resulted in a 138-hair difference between treatment groups ($p<0.001$) within the same area. At 5 years, there was a 277-hair difference between treatment groups ($p < 0.001$, PROPECIA [n=219 evaluable men] vs placebo [n=15 evaluable men]).

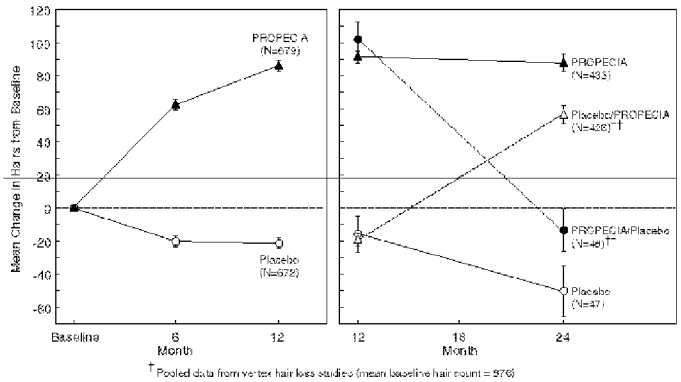
Patients who switched from placebo to PROPECIA (n=426 evaluable men) at the end of the initial 12 months had an increase in hair count at 24 months2 years. A change of treatment from PROPECIA to placebo (n=48 evaluable men) at the end of the initial 12 months resulted in reversal of the increase in hair count 12 months later, at 24 months. See figure below for combined study results.

At 12 months, 58% of men in the placebo group 14% of men treated with PROPECIA had hair loss (defined as any decrease in hair count from baseline) compared with 58% of men in the placebo grouponly 14% of men treated with PROPECIA. In men treated for up to 24 months2 years, 72% of those in the placebo group 17% of those treated with PROPECIA demonstrated hair loss compared with 72% of those in the placebo grouponly 17% of those treated with PROPECIA. At 5 years, 100% of those in the placebo group demonstrated hair loss compared with only 35% of those treated with PROPECIA.

Marketing would like the label to be able to say that those patients who took placebo for one year and were then switched to PROPECIA had a significant beneficial effect, but never caught up to those patients who started on PROPECIA at the beginning of the trial.

Effect on Hair Count†

Number of Hairs in a 1-Inch Diameter Circle
Mean Change ± 1 S.E.



† Pooled data from vertex hair loss studies (mean baseline hair count = 576)

†† At the end of initial 12-month period, treatment switched from PROPECIA to placebo (———— PROPECIA/Placebo or from placebo to PROPECIA (---------- Placebo/PROPECIA).

Insert new figure.

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 continued improvement over ~~24 months~~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 ~~24 months~~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 Sstandardized photographs of the head were assessed in a blinded fashion based on increases or decreases in scalp hair using , at the beginning of the study and at 6, 12, 18 and 24 months. An independent panel rated increases or decreases in scalp hair on the same 7-point scale used in 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 24 months2 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, an increase in hair growth was demonstrated in 48% of men treated with PROPECIA compared with 6% of men treated with placebo. Based on this assessment, continued treatment with PROPECIA resulted in further improvement. These results were observed in the context of no further increase in hair count between month 12 and month 24.

Based on all four endpoints, the difference between treatment groups continued to increase throughout the 5 years of the studies.

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 on Hair Loss in the Anterior Mid-Scalp Area

A third 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

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). 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 addition, clinical studies (for up to 5 years) demonstrated slowing of hair loss with in men treated with PROPECIA , whereas in the placebo group, hair loss progressively worsened. by patient self-assessment. These effectsImprovements were maintained through the second fifth year of treatment. Maintenance of or improvement in clinical efficacy has also been demonstrated in controlled and open-extension studies for up to 3 years.

Ethnic Analysis of Clinical Data

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=1,185), 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.

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.

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 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 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.

WARNINGS

PROPECIA is not indicated for use in pediatric patients (See INDICATIONS AND USAGE; and PRECAUTIONS, *Pediatric Use*) or women (See also 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*.)

See also Patient Package Insert.

Drug/Laboratory Test 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.

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 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, 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 (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 2,192 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 (1,824 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 (2-3 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 2,800 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).

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. Further, the concentrations (450-550 μmol) used in *in vitro* studies are not achievable in a biological system. 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 (1,824 times the human exposure, estimated) as determined in the carcinogenicity studies.

In sexually mature male rabbits treated with finasteride at 80 mg/kg/day (4,344 times the estimated 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 estimated 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 at doses ranging from 100 μg/kg/day to 100 mg/kg/day (5-5,000 times the recommended human dose of 1 mg/day) 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 development when given finasteride at ≥30 μg/kg/day (≥ 1.5 times the recommended human dose of 1 mg/day) and decreased anogenital distance when given finasteride at ≥3 μg/kg/day (one-fifth the recommended human dose of 1 mg/day). 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 (150 times the recommended human dose of 1 mg/day) 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 (5000 times the recommended human dose of 1 mg/day). 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 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.

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 pharmacokinetics, no dosage adjustment is necessary in the elderly (see CLINICAL PHARMACOLOGY, *Pharmacokinetics*).

ADVERSE REACTIONS

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

In controlled clinical trials for PROPECIA of 12-month duration, 1.4% of the patients were discontinued due to adverse experiences that were considered to be possibly, probably or definitely drug-related (1.6% for placebo); 1.2% of patients on PROPECIA and 0.9% of patients on placebo discontinued therapy because of a drug-related sexual adverse

experience. The following clinical adverse reactions were reported as possibly, probably or definitely drug-related in ≥1% of patients treated for 12 months 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 occurred in all men who discontinued therapy with PROPECIA due to these side effects and in 58% of those who continued therapy. The incidence of each of the above side effects 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; hypersensitivity reactions including rash, pruritus, urticaria, and swelling of the lips and face; and testicular pain.

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

In controlled clinical trials for PROSCAR of 12-month duration, 1.3% of the patients were discontinued due to adverse experiences that were considered to be possibly, probably or definitely drug-related (0.9% for placebo); only one patient on PROSCAR (0.2%) and one patient on placebo (0.2%) discontinued therapy because of a drug-related sexual adverse experience. The following clinical adverse reactions were reported as possibly, probably or definitely drug-related in ≥1% of patients treated for 12 months with PROSCAR or placebo, respectively: erectile dysfunction (3.7%, 1.1%), decreased libido (3.3%, 1.6%) and decreased volume of ejaculate (2.8%, 0.9%). The adverse experience profiles for patients treated with finasteride 1 mg/day for 12 months and those maintained on PROSCAR for 24 to 48 months were similar to that observed in the 12-month controlled studies with PROSCAR. Sexual adverse experiences resolved with continued treatment in over 60% of patients who reported them.

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 1,500 mg/m^2 (500 mg/kg) and in female and male rats at single oral doses of 2,360 mg/m^2 (400 mg/kg) and 5,900 mg/m^2 (1,000 mg/kg), respectively.

DOSAGE AND ADMINISTRATION

The recommended dosage is 1 mg 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. 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

NDC 0006-0071-61 ProPak®*** - carton of 3 unit of use bottles of 30.

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*.)

*** Registered trademark of MERCK & CO., INC.

Draft USPC for Task Force Meeting on 10/23/00
PROPECIA® (Finasteride) Tablets, 1 mg 9328500

Dist. by:
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

Issued May 2000
Printed in USA

