

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-788/S-020/S-021/S-023

Trade Name: Propecia

Generic Name: finasteride

Sponsor: Merck Sharp & Dohme Corp.

Approval Date: March 11, 2011

Labeling Changes: The addition of the adverse reaction “erectile dysfunction that continued after discontinuation of treatment”, to the Postmarketing Experience section.

The addition of the adverse reactions “male infertility and/or poor seminal quality (normalization or improvement of seminal quality has been reported after discontinuation of finasteride)”, to the Postmarketing Experience section.

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APPLICATION NUMBER:

NDA 20-788/S-020/S-021/S-023

APPROVAL LETTER



NDA 020788/S-020, S-021, S-023

SUPPLEMENT APPROVAL

Merck Sharp & Dohme Corp.
Attention: Frank J. Mellina, Pharm.D.
Manager, Regulatory Affairs
126 East Lincoln Avenue
P.O. Box 2000, RY33-208
Rahway, NJ 07065-0900

Dear Dr. Mellina:

Please refer to your Supplemental New Drug Applications (sNDA) dated April 8, 19, and May 6, 2011, received April 8, 19, and May 6, 2011, respectively, and submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Propecia™ (finasteride) Tablet, 1 mg.

We acknowledge receipt of your amendments dated as follows:

S-020

June 1, 23, 30, August 31, September 6, 8, 2011; February 6, March 7, 8, and April 3, 2012

S-021

June 23, 2011; February 6, March 7, 8, and April 3, 2012

S-023

June 23, 2011; February 6, March 7, 8, and April 3, 2012

S-020 is a “Prior Approval” sNDA that proposes the revision of the Propecia™ (finasteride) Tablet, 1 mg full prescribing information to comply with the new labeling content and format requirements for human prescription drug and biological products, according to 21 CFR 201.56(d) and 201.57.

S-021 is a “Changes Being Effected” sNDA that provides for the addition of the adverse reaction “erectile dysfunction that continued after discontinuation of treatment”, to the Postmarketing Experience section of the package insert and to the patient labeling.

S-023 is a “Prior Approval” sNDA that proposes the addition of the adverse reactions “male infertility and/or poor seminal quality (normalization or improvement of seminal quality has been reported after discontinuation of finasteride)”, to the Postmarketing Experience section of the package insert and to the patient labeling.

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert), with the addition of any labeling changes in pending “Changes Being Effected” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Paul Phillips, Regulatory Project Manager, at (301) 796-3935.

Sincerely,

{See appended electronic signature page}

Tatiana Oussova, MD, MPH
Deputy Director for Safety
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TATIANA OUSSOVA
04/11/2012

**CENTER FOR DRUG EVALUATION AND
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APPLICATION NUMBER:
NDA 20-788/S-020/S-021/S-023

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PROPECIA safely and effectively. See full prescribing information for PROPECIA.

PROPECIA® (finasteride) tablets for oral use

Initial U.S. Approval: 1992

RECENT MAJOR CHANGES

Warnings and Precautions, Increased Risk of High-Grade Prostate Cancer with 5 α -Reductase Inhibitors (5.3) 06/2011

INDICATIONS AND USAGE

- PROPECIA is a 5 α -reductase inhibitor indicated for the treatment of male pattern hair loss (androgenetic alopecia) in **MEN ONLY** (1).
- PROPECIA is not indicated for use in women (1, 4, 5.1).

DOSAGE AND ADMINISTRATION

- PROPECIA may be administered with or without meals (2).
- One tablet (1 mg) taken once daily (2.1).
- In general, daily use for three months or more is necessary before benefit is observed (2.2).

DOSAGE FORMS AND STRENGTHS

1 mg tablets (3).

CONTRAINDICATIONS

- Pregnancy (4, 5.1, 8.1, 16).
- Hypersensitivity to any components of this product (4).

WARNINGS AND PRECAUTIONS

- PROPECIA is not indicated for use in women or pediatric patients (5.1, 5.4).
- Women should not handle crushed or broken PROPECIA tablets when they are pregnant or may potentially be pregnant due to potential risk to a male fetus (5.1, 8.1, 16).
- PROPECIA causes a decrease in serum PSA levels. Any confirmed increase in PSA while on PROPECIA may signal the presence of prostate cancer and should be evaluated, even if those values are still within the normal range for men not taking a 5 α -reductase inhibitor (5.2).
- 5 α -reductase inhibitors may increase the risk of high-grade prostate cancer (5.3, 6.1).

ADVERSE REACTIONS

The most common adverse reactions, reported in $\geq 1\%$ of patients treated with PROPECIA and greater than in patients treated with placebo are: decreased libido, erectile dysfunction and ejaculation disorder (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 04/2012

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

PROPECIA® is indicated for the treatment of male pattern hair loss (androgenetic alopecia) in **MEN ONLY**.

Efficacy in bitemporal recession has not been established.

PROPECIA is not indicated for use in women.

2 DOSAGE AND ADMINISTRATION

PROPECIA may be administered with or without meals.

The recommended dose of PROPECIA is one tablet (1 mg) taken once daily.

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.

3 DOSAGE FORMS AND STRENGTHS

PROPECIA tablets (1 mg) are tan, octagonal, film-coated convex tablets with “stylized P” logo on one side and PROPECIA on the other.

4 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 5 α -reductase inhibitors to inhibit the conversion of testosterone to 5 α -dihydrotestosterone (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 *Warnings and Precautions* (5.1), *Use in Specific Populations* (8.1), *How Supplied/Storage and Handling* (16) and *Patient Counseling Information* (17.1).] 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.

5 WARNINGS AND PRECAUTIONS

5.1 Exposure of Women — Risk to Male Fetus

PROPECIA is not indicated for use in women. 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 *Indications and Usage* (1), *Contraindications* (4), *Use in Specific Populations* (8.1), *How Supplied/Storage and Handling* (16) and *Patient Counseling Information* (17.1).]

5.2 Effects on Prostate Specific Antigen (PSA)

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

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

Men aged 55 and over with a normal digital rectal examination and PSA \leq 3.0 ng/mL at baseline taking finasteride 5 mg/day (5 times the dose of 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* (6.1).] Similar results were observed in a 4-year placebo-controlled clinical trial with another 5 α -reductase inhibitor (dutasteride, AVODART) (1% dutasteride vs 0.5% placebo). 5 α -reductase inhibitors may increase the risk of development of high-grade prostate cancer. Whether the effect of 5 α -reductase inhibitors to reduce prostate volume, or study-related factors, impacted the results of these studies has not been established.

5.4 Pediatric Patients

PROPECIA is not indicated for use in pediatric patients [see *Use in Specific Populations* (8.4)].

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

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 \geq 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)
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 \leq 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.

Controlled Clinical Trials and Long-Term Open Extension Studies for PROSCAR® (finasteride 5 mg) and AVODART (dutasteride) 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 $\geq 1\%$ 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
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 sexual 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 were reported 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

PROPECIA® (finasteride) Tablets

(1.1%). In a 4-year placebo-controlled clinical trial with another 5 α -reductase inhibitor [AVODART (dutasteride)], 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.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of PROPECIA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure:

Hypersensitivity Reaction: hypersensitivity reactions including rash, pruritus, urticaria, and swelling of the lips and face;

Reproductive System: sexual dysfunction that continued after discontinuation of treatment, including erectile dysfunction, libido disorders, ejaculation disorders, and orgasm disorders; male infertility and/or poor seminal quality (normalization or improvement of seminal quality has been reported after discontinuation of finasteride); testicular pain. [See Adverse Reactions (6.1).]

Neoplasms: male breast cancer;

Breast disorders: breast tenderness and enlargement;

Nervous System/Psychiatric: depression

7 DRUG INTERACTIONS

7.1 Cytochrome P450-Linked Drug Metabolizing Enzyme System

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.

7.2 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, H₂ antagonists, HMG-CoA reductase inhibitors, prostaglandin synthetase inhibitors (also referred to as NSAIDs), and quinolone anti-infectives without evidence of clinically significant adverse interactions.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X [see Contraindications (4)].

PROPECIA is contraindicated for use in women who are or may become pregnant. PROPECIA is a Type II 5 α -reductase inhibitor that prevents conversion of testosterone to 5 α -dihydrotestosterone (DHT), a hormone necessary for normal development of male genitalia. In animal studies, finasteride caused abnormal development of external genitalia in male fetuses. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the male fetus.

Abnormal male genital development is an expected consequence when conversion of testosterone to 5 α -dihydrotestosterone (DHT) is inhibited by 5 α -reductase inhibitors. These outcomes are similar to those reported in male infants with genetic 5 α -reductase deficiency. Women could be exposed to finasteride through contact with crushed or broken PROPECIA tablets or semen from a male partner taking PROPECIA. With regard to finasteride exposure through the skin, PROPECIA tablets are coated and will prevent skin contact with finasteride during normal handling if the tablets have not been crushed or broken. Women who are pregnant or may become pregnant

PROPECIA® (finasteride) Tablets

should not handle crushed or broken PROPECIA tablets because of possible exposure of a male fetus. If a pregnant woman comes in contact with crushed or broken PROPECIA tablets, the contact area should be washed immediately with soap and water. With regard to potential finasteride exposure through semen, a study has been conducted in men receiving PROPECIA 1 mg/day that measured finasteride concentrations in semen [see *Clinical Pharmacology* (12.3)].

In an embryo-fetal development study, pregnant rats received finasteride during the period of major organogenesis (gestation days 6 to 17). At maternal doses of oral finasteride approximately 1 to 684 times the recommended human dose (RHD) of 1 mg/day (based on AUC at animal doses of 0.1 to 100 mg/kg/day) there was a dose-dependent increase in hypospadias that occurred in 3.6 to 100% of male offspring. Exposure multiples were estimated using data from nonpregnant rats. Days 16 to 17 of gestation is a critical period in male fetal rats for differentiation of the external genitalia. At oral maternal doses approximately 0.2 times the RHD (based on AUC at animal dose of 0.03 mg/kg/day), male offspring had decreased prostatic and seminal vesicular weights, delayed preputial separation and transient nipple development. Decreased anogenital distance occurred in male offspring of pregnant rats that received approximately 0.02 times the RHD (based on AUC at animal dose of 0.003 mg/kg/day). No abnormalities were observed in female offspring exposed to any dose of finasteride *in utero*.

No developmental abnormalities were observed in the offspring of untreated females mated with finasteride-treated male rats that received approximately 488 times the RHD (based on AUC at animal dose of 80 mg/kg/day). Slightly decreased fertility was observed in male offspring after administration of about 20 times the RHD (based on AUC at animal dose of 3 mg/kg/day) to female rats during late gestation and lactation. No effects on fertility were seen in female offspring under these conditions.

No evidence of male external genital malformations or other abnormalities were observed in rabbit fetuses exposed to finasteride during the period of major organogenesis (gestation days 6-18) at maternal doses up to 100 mg/kg/day (finasteride exposure levels were not measured in rabbits). However, this study may not have included the critical period for finasteride effects on development of male external genitalia in the rabbit.

The fetal effects of maternal finasteride exposure during the period of embryonic and fetal development were evaluated in the rhesus monkey (gestation days 20-100), in a species and development period more predictive of specific effects in humans than the studies in rats and rabbits. Intravenous administration of finasteride to pregnant monkeys at doses as high as 800 ng/day (estimated maximal blood concentration of 1.86 ng/mL or about 930 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 dose of finasteride (2 mg/kg/day or approximately 120,000 times the highest estimated blood levels of 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.

8.3 Nursing Mothers

PROPECIA is not indicated for use in women.

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

8.4 Pediatric Use

PROPECIA is not indicated for use in pediatric patients.

Safety and effectiveness in pediatric patients have not been established.

8.5 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* (12.3)]. However the efficacy of PROPECIA in the elderly has not been established.

PROPECIA® (finasteride) Tablets

8.6 Hepatic Impairment

Caution should be exercised in the administration of PROPECIA in those patients with liver function abnormalities, as finasteride is metabolized extensively in the liver [see *Clinical Pharmacology* (12.3)].

8.7 Renal Impairment

No dosage adjustment is necessary in patients with renal impairment [see *Clinical Pharmacology* (12.3)].

10 OVERDOSAGE

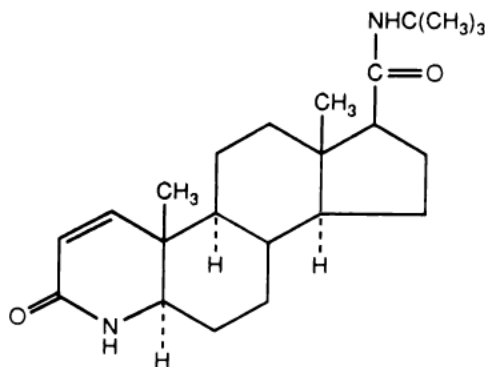
In clinical studies, single doses of finasteride up to 400 mg and multiple doses of finasteride up to 80 mg/day for three months did not result in adverse reactions. Until further experience is obtained, no specific treatment for an overdose with finasteride can be recommended.

Significant lethality was observed in male and female mice at single oral doses of 1500 mg/m² (500 mg/kg) and in female and male rats at single oral doses of 2360 mg/m² (400 mg/kg) and 5900 mg/m² (1000 mg/kg), respectively.

11 DESCRIPTION

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

The chemical name of finasteride is *N*-*tert*-Butyl-3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide. The empirical formula of finasteride is C₂₃H₃₆N₂O₂ 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 (finasteride) tablets are film-coated tablets for oral administration. Each tablet contains 1 mg of finasteride and the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, pregelatinized starch, sodium starch glycolate, hydroxypropyl methylcellulose, hydroxypropyl cellulose, titanium dioxide, magnesium stearate, talc, docusate sodium, yellow ferric oxide, and red ferric oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Finasteride is a competitive and specific inhibitor of Type II 5 α -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 5 α -reductase is predominant in the sebaceous glands of most regions of skin, including scalp, and liver. Type I 5 α -reductase is responsible for approximately one-third of circulating DHT. The Type II 5 α -reductase isozyme is primarily found in prostate, seminal vesicles, epididymides, and hair follicles as well as liver, and is responsible for two-thirds of circulating DHT.

PROPECIA® (finasteride) Tablets

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

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.

12.2 Pharmacodynamics

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

Finasteride has no affinity for the androgen receptor and has no androgenic, antiandrogenic, estrogenic, antiestrogenic, or progestational effects. 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. 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.

12.3 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_(0-24 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 650-fold less than the dose of finasteride (5 μ g) that had no effect on circulating DHT levels in men. [See *Use in Specific Populations* (8.1).]

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 5 α -reductase inhibitory activity of finasteride.

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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 ¹⁴C-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.

TABLE 3 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

TABLE 4 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

Renal Impairment

No dosage adjustment is necessary in patients with renal impairment. 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 ¹⁴C-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 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 Impairment

The effect of hepatic impairment 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.

13 NONCLINICAL TOXICOLOGY

13.1 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_(0-24 hr) for animals and mean AUC_(0-24 hr) for man (0.05 µg•hr/mL).

In a 19-month carcinogenicity study in CD-1 mice, a statistically significant (p≤0.05) increase in the incidence of testicular Leydig cell adenomas was observed at 1824 times the human exposure (250 mg/kg/day). In mice at 184

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times the human exposure, estimated (25 mg/kg/day) and in rats at 312 times the human exposure (≥ 40 mg/kg/day) 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 240 and 2800 times (20 mg/kg/day and 45 mg/kg/day, respectively), or in mice treated for 19 months at 18.4 times the human exposure, estimated (2.5 mg/kg/day).

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 4344 times the human exposure (80 mg/kg/day) for up to 12 weeks, no effect on fertility, sperm count, or ejaculate volume was seen. In sexually mature male rats treated with 488 times the human exposure (80 mg/kg/day), 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.

14 CLINICAL STUDIES

14.1 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).

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 1 below).

*Registered trademark of Johnson & Johnson

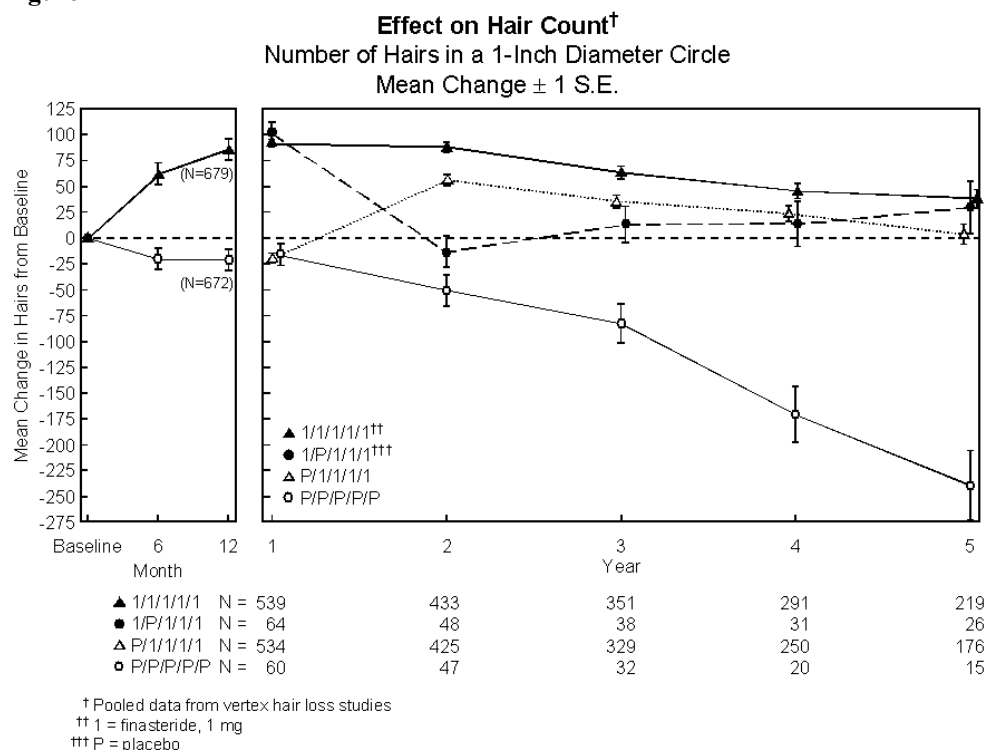
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Hair counts were assessed by photographic enlargements of a representative area of active hair loss. In these two studies in men with vertex baldness, significant increases in hair count were demonstrated at 6 and 12 months in men treated with PROPECIA, 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 1 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 1 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.

Figure 1



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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.

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-cm² 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.

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.

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.

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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.

14.2 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 (1.1)*].

16 HOW SUPPLIED/STORAGE AND HANDLING

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 bottles of 30 (with desiccant)

NDC 0006-0071-54 PROPAK® 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 and Precautions (5.1), Use in Specific Populations (8.1) and Patient Counseling Information (17.1)*].

17 PATIENT COUNSELING INFORMATION

“See FDA-approved patient labeling (Patient Information)”

17.1 Exposure of Women — Risk to Male Fetus

Physicians should inform patients that women who are pregnant or may potentially be pregnant should not handle crushed or broken PROPECIA tablets 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. If a woman who is pregnant or may potentially be pregnant comes in contact with crushed or broken PROPECIA tablets, the contact area should be washed immediately with soap and water [*see Contraindications (4), Warnings and Precautions (5.1), Use in Specific Populations (8.1) and How Supplied/Storage and Handling (16)*].

17.2 Increased Risk of High-Grade Prostate Cancer


Patients should be informed that there was an increase in high-grade prostate cancer in men treated with 5 α -reductase inhibitors indicated for BPH treatment, compared to those treated with placebo in studies looking at the use of these drugs to prevent prostate cancer [*see Warnings and Precautions (5.3) and Adverse Reactions (6.1)*].

17.3 Additional Instructions

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 (6.1)*].

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.

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Dist. by: Merck Sharp & Dohme Corp., a subsidiary of
 **MERCK & CO., INC.**, Whitehouse Station, NJ 08889, USA

US Patent Nos.: 5,547,957; 5,571,817

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Revised: 04/2012

Patient Information
PROPECIA (Pro-pee-sha)
(finasteride)
Tablets

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

Read this Patient Information before you start taking PROPECIA and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or treatment.

What is PROPECIA?

PROPECIA is a prescription medicine used for the treatment of male pattern hair loss (androgenetic alopecia).

It is not known if PROPECIA works for a receding hairline on either side of and above your forehead (temporal area).

PROPECIA is not for use by women and children.

Who should not take PROPECIA?

Do not take PROPECIA if you:

- are pregnant or may become pregnant. PROPECIA may harm your unborn baby.
 - PROPECIA tablets are coated and will prevent contact with the medicine during handling, as long as the tablets are not broken or crushed. Females who are pregnant or who may become pregnant should not come in contact with broken or crushed PROPECIA tablets. If a pregnant woman comes in contact with crushed or broken PROPECIA tablets, wash the contact area right away with soap and water. If a woman who is pregnant comes into contact with the active ingredient in PROPECIA, a healthcare provider should be consulted.
 - If a woman who is pregnant with a male baby swallows or comes in contact with the medicine in PROPECIA, the male baby may be born with sex organs that are not normal.
- are allergic to any of the ingredients in PROPECIA. See the end of this leaflet for a complete list of ingredients in PROPECIA.

What should I tell my healthcare provider before taking PROPECIA?

Before taking PROPECIA, tell your healthcare provider if you:

- have any other medical conditions, including problems with your prostate or liver

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I take PROPECIA?

- Take PROPECIA exactly as your healthcare provider tells you to take it.
- 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.

What are the possible side effects of PROPECIA?

- **decrease in your blood Prostate Specific Antigen (PSA) levels.** 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 healthcare provider that you are taking PROPECIA because PROPECIA decreases PSA levels. Changes in PSA levels will need to be evaluated by your healthcare provider. 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 healthcare provider if you have not been taking PROPECIA as prescribed because this may affect the PSA test results. For more information, talk to your healthcare provider.
- There may be an increased risk of a more serious form of prostate cancer in men taking finasteride at 5 times the dose of PROPECIA.

The most common side effects of PROPECIA include:

- decrease in sex drive

- trouble getting or keeping an erection
- a decrease in the amount of semen

The following have been reported in general use with PROPECIA:

- breast tenderness and enlargement. Tell your healthcare provider about any changes in your breasts such as lumps, pain or nipple discharge.
- depression;
- decrease in sex drive that continued after stopping the medication;
- allergic reactions including rash, itching, hives and swelling of the lips and face;
- problems with ejaculation that continued after stopping medication;
- testicular pain;
- difficulty in achieving an erection that continued after stopping the medication;
- male infertility and/or poor quality of semen.
- in rare cases, male breast cancer.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of PROPECIA. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store PROPECIA?

- Store PROPECIA at room temperature between 59°F to 86°F (15°C to 30°C).
- Keep PROPECIA in a closed container and keep PROPECIA tablets dry (protect from moisture).

Keep PROPECIA and all medicines out of the reach of children.

General information about the safe and effective use of PROPECIA.

Medicines are sometimes prescribed for purposes other than those listed in this Patient Information leaflet. Do not use PROPECIA for a condition for which it was not prescribed. Do not give PROPECIA to other people, even if they have the same symptoms you have. It may harm them.

This Patient Information leaflet summarizes the most important information about PROPECIA. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about PROPECIA


that is written for health professionals. For more information, **call 1-888-637-2522.**

What are the ingredients in PROPECIA?

Active ingredient: finasteride.

Inactive ingredients: lactose monohydrate, microcrystalline cellulose, pregelatinized starch, sodium starch glycolate, hydroxypropyl methylcellulose, hydroxypropyl cellulose, titanium dioxide, magnesium stearate, talc, docusate sodium, yellow ferric oxide, and red ferric oxide.

This Patient Information has been approved by the U.S. Food and Drug Administration.

 Dist. by: Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

US Patent Nos.: 5,547,957; 5,571,817

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Revised: 04/2012

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

NDA 20-788/S-020/S-021/S-023

MEDICAL REVIEW(S)

Clinical Review of NDA 20-788
Supplemental Label Request (SLR)

Submission date:	4/8/11; 4/14/11; 4/19/11; 5/6/11; 6/23/11; 6/23/11; 6/30/11; 2/6/12; 3/8/12
Supplement number:	SLR 20, 21, 23
SDN/ eCTD #:	203/30; 204/31; 205/32; 208/31; 215/42; 216/41; 217/43; 931/48; 940/52
Drug:	Propecia (finasteride) 1 mg
Pharmacologic Category:	5-alpha reductase inhibitor
Indication:	androgenetic alopecia
Dosage Form:	1 mg tablet
Route of Administration:	oral
Sponsor:	Merck Research Laboratories
RPM:	Phillips/ Gould
Clinical:	Woitach/Kettl
Review date:	June 27, 2011
Review revised:	11/16/11; 11/23/11; 2/27/12; 3/28/12
In DARRTS:	3/30/12

Regulatory Background:

Finasteride, a 5 α -reductase inhibitor (5ARI), reduces the conversion of testosterone to 5 α -dihydrotestosterone, and is used for treatment of benign prostatic hypertrophy and androgenetic alopecia. Two finasteride products are currently available in the United States. The FDA's Division of Reproductive and Urologic Products (DRUP) approved finasteride 5 mg (Proscar, NDA 20180) on June 19, 1992 for the treatment of symptomatic benign prostatic hyperplasia (BPH) and the Division of Dermatology and Dental Products (DDDP) approved finasteride 1 mg (Propecia, NDA 20788) on December 19, 1997 for the treatment of androgenetic alopecia in men.

On March 22, 2011, the Agency held a teleconference with Merck to discuss reported post-marketing cases of persistent sexual dysfunction and the differences in the global labeling of finasteride. The sponsor stated that their position, based on clinical trial data, is that the reported sexual dysfunction is reversible, but intends (b) (4) finasteride and would submit a labeling supplement addressing sexual dysfunction that continued after stopping Propecia. The sponsor submitted two labeling supplements proposing labeling changes.

In the 4/19/11 submission (CBE supplement 21) the sponsor is proposing the inclusion of *erectile dysfunction that continued after discontinuation of treatment* in the *ADVERSE REACTIONS Postmarketing Experience for PROPECIA (finasteride 1 mg)* section of the Package Insert, and *difficulty in achieving an erection that continued after stopping the medication* to the corresponding possible side effects section of the Patient Package Insert. The Division determined that this supplement should remain as a Changes Being Effective supplement.

On 5/6/11, the sponsor submitted a second labeling change related to sexual dysfunction. In this submission (PAS supplement 23), the sponsor is proposing the inclusion of information regarding male infertility and/or poor seminal quality in the *ADVERSE REACTIONS Postmarketing Experience for PROPECIA (finasteride 1 mg)* section of the Package Insert and corresponding possible side effects section of the Patient Package Insert.

These 2 submissions were received shortly after receiving the 4/8/11 submission for a conversion of the Propecia labeling to a format that would comply with the physician labeling rule (PLR). The Division determined that these supplements would be reviewed together and labeling changes from supplements 21 and 23 would be incorporated into the PLR version of the label (supplement 20).

Review:

Sexual Dysfunction

The Division consulted the Office of Surveillance and Epidemiology, Division of Pharmacovigilance I (OSE/ DPV I) to evaluate post-marketing cases of persistent sexual dysfunction reported in the Adverse Event Reporting System (AERS). Based on input from DRUP and DPV I, representative cases were considered to be cases that report ejaculation disorders, erectile disorders, libido disorders, orgasmic disorders, or sexual disorders that persist for at least three months after discontinuing finasteride.

OSE/ DPV I conducted a search of post-marketing adverse events involving sexual dysfunction that were reported from market approval (December 19, 1997) to April 14, 2011. The AERS search retrieved 421 reports out of 2527 total adverse event reports for Propecia. Cases were reviewed to determine if it was documented that Propecia was discontinued (220 cases). Cases were reviewed to determine if sexual dysfunction was unresolved and ongoing for at least 3 months at the time of reporting (63 cases) or had resolved, but took at least 3 months to resolve (2 cases). When the 65 cases were assessed for duplicates, the total number of cases identified was 59.

Dr. Namita Kothary's review (6/2/11) describes the 59 cases (51 U.S. and 8 Foreign) of sexual dysfunction that persisted at least three months after discontinuing finasteride 1 mg. Of the 59 cases, 30% reported events persisting for three to six months, 20% reported events persisting for seven to eleven months, 34% reported events persisting for one to two years, and 12% reported events persisting for three years or more. Additionally, two cases reported that the events persisted for "years." It is important to note that cases were categorized based on information available at the time of report; therefore, the reported duration of sexual dysfunction may not represent the true duration of adverse event persistence.

Review of the case series identified the following:

- Most commonly reported adverse events were erectile disorders and libido disorders (86% and 71% of the cases, respectively)

Sexual dysfunction related adverse events (more than one is possible per case)	<u>Erectile:</u>	Erectile dysfunction (49), Organic erectile dysfunction* (11)
	<u>Libido:</u>	Libido decreased (21), Loss of libido (19), Libido disorder (3)
	<u>Ejaculation:</u>	Ejaculation disorder (10), Ejaculation failure (4), Premature ejaculation (1)
	<u>Sexual:</u>	Sexual dysfunction (10), Male sexual dysfunction (1)
	<u>Orgasmic:</u>	Orgasm abnormal (4), Orgasmic sensation decreased (2), Anorgasmia (1)

- No apparent trends based on the duration of therapy (5 days-12.3 years)
- No apparent trends based on time from start of finasteride treatment to onset of the events (same day- 9.3 years)
- Majority of the cases (51/59) did not report potential confounding factors
- Three cases reported that they used Propecia in the past and experienced sexual dysfunction that resolved after discontinuing the drug. However, when they initiated Propecia for the second time, they experienced persistent sexual dysfunction
- 10 of the 20 cases that provided laboratory information for testosterone reported low testosterone values
- Population is consistent with the FDA approved indication in that all the cases occurred in males and 97% of the cases (57/59) reported the indication as alopecia and 32 cases in males < 30 years; 21 cases in males 30-49 years; 5 cases in males over 50 years of age

Dr. Namita Kothary's review (6/2/11) recommends the following changes to the finasteride 1 mg label:

Updating the Adverse Events, Postmarketing Experience section to reflect the potential risk for persistent sexual dysfunction, including erectile dysfunction, libido disorders, ejaculation disorders, and orgasm disorders.

Reviewer comment: Most of the adverse event reports lacked information relevant to the patients' baseline sexual functioning and confounding factors. Because of the limitations intrinsic to AERS reports and clinical trial data suggesting reversibility, this reviewer is unable to definitively determine causality of persistent sexual dysfunction as it relates to Propecia. However, given the known sexual side effects of finasteride in randomized, controlled trials and the temporal association of the onset of sexual dysfunction with the use of finasteride in apparently otherwise healthy men, it is reasonable to conclude that individual patients may vary in time to resolution of symptoms. This reviewer concurs with the sponsor and Dr. Kothary that persistent sexual dysfunction should be included in post-market labeling. This reviewer also agrees with Dr. Kothary that the various domains of sexual dysfunction should be stated (erectile dysfunction, libido disorders, ejaculation disorders and orgasm disorders) in labeling so that health care professionals and patients can consider this information when making decisions about medical treatment, yet be aware of uncertainties in the data.

Cases of sexual dysfunction have been provided to the Agency by the sponsor. From its Worldwide Adverse Experience System (WAES) database, the sponsor submitted 465 reports of sexual dysfunction which persisted after discontinuation of the medication. The sponsor's search parameters were similar to the Agency's parameters, but also included reports for the 0.2 mg dose that is marketed outside of the United States. In the majority of the reports, the information was provided shortly after the onset of the adverse experience and the sponsor states that despite attempts to obtain follow up information, no further information was provided.

Reviewer Comment: Like the AERS reports, the outcome information from these WAES reports is limited to what was provided at the time of the report and in most instances long term outcome data is not available. The cases retrieved in the Agency's AERS search appear to be representative of and overlapping with the 465 cases submitted by the sponsor. Evaluation of cases is ongoing to determine which of these cases have not been reported to the AERS database.

The clinical studies section of current Propecia labeling describes clinical trial data on sexual dysfunction that was obtained during the registration studies. Included is the result of a self-administered questionnaire from two vertex baldness trials which found statistically significant differences in favor of placebo 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. Also, current labeling describes reported adverse events related to sexual dysfunction. The label states:

“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”.

Seminal quality

Seminal quality was assessed during the development of finasteride (Proscar and Propecia). The sponsor provided summaries of the non-clinical and clinical outcomes:

1. The effect of finasteride on the reproductive system has been studied in rats, mice, rabbits and dogs and no relevant effects on fertility, testicular histology, spermatogenesis, semen production, or fertilizing capacity of sperm was demonstrated.

Reviewer comment: The non-clinical data is included in Propecia labeling as follows:

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.

2. Data from two placebo-controlled clinical studies with finasteride 5 mg demonstrated median reductions in ejaculate volume of approximately 0.5 mL (25%). The decrease in ejaculate volume was accompanied by a concomitant reduction in total sperm per ejaculate. These parameters remained within the normal range and reversed after discontinuation of treatment.

Reviewer comment: These studies were referenced in the Propecia label as “ 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”.

The Proscar label (section 5.5) discusses the outcome of these studies in more detail:

Effect on Semen Characteristics

Treatment with PROSCAR for 24 weeks to evaluate semen parameters in healthy male volunteers revealed no clinically meaningful effects on sperm concentration, mobility, morphology, or pH. A 0.6 mL (22.1%) median decrease in ejaculate volume with a concomitant reduction in total sperm per ejaculate was observed. These parameters remained within the normal range and were reversible upon discontinuation of therapy with an average time to return to baseline of 84 weeks.

3. A third study with finasteride 1 mg over 4 spermatogenic cycles (48 weeks) demonstrated no significant effect in men on spermatogenesis or semen production in healthy male volunteers.

Reviewer comment: This study is included in the Adverse reactions section of Propecia labeling and described as “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”.

Labeling also describes the decrease in ejaculate volume was seen in clinical studies for Propecia in the treatment of male pattern hair loss (0.8% vs. 0.4% in placebo).

The sponsor also provided a summary of postmarketing reports of male infertility for patients treated with finasteride 0.2-mg and 1-mg tablet (PROPECIA) retrieved from a search of the Worldwide Adverse Experience System (WAES) database from market introduction (11-Sept-1997) through 31-Dec-2010. The search was conducted with MedDRA preferred terms *aspermia, asthenospermia, azoospermia, infertility, infertility male, sperm analysis abnormal, sperm count decreased, sperm count abnormal, sperm count zero, spermatogenesis abnormal, spermatozoa abnormal, spermatozoa morphology abnormal, spermatozoa progressive motility abnormal, spermatozoa progressive motility decreased, and teratospermia*.

A total of 251 reports were identified and the sponsor provided the following information:

- Age ranged from 19 years to 68 years
- Majority of the infertility cases contained minimal information
- Evidence of fertility pre-finasteride treatment was not provided in most reports
- Baseline semen analyses prior to initiation of therapy with finasteride were provided in a minimal number of reports

The sponsor submitted 13 reports that represent the most complete clinical data. They are summarized below:

WAES cases of male infertility and/or poor seminal quality with finasteride 1 mg (n=13)	
Origin	US (2) Foreign (11)
Gender	Male
Age	Mean: 33 years range: 29 – 42 years
Indications	Alopecia
Daily dose	1 mg
Duration of therapy	Range: 4 mo- 8 years
adverse events (reported terms)	Oligospermia (9) Oligo-astheno-teratospermia (1) Asthenospermia (2) Azoospermia (2) Infertility (8)
Concomitant disease	Varicocele (2) History of infertility (2)
Reported Outcomes (<i>after discontinuation of finasteride</i>)	Recovered (7) Improved (6)

Reviewer comment: The sponsor submitted reports in which seminal analysis was available both on-drug and post discontinuation. The reports describe infertile patients with azoospermia or severe oligospermia who showed significant improvements in sperm concentrations months after the discontinuation of finasteride.

It is the sponsor's position that a causal relationship does not exist between finasteride use and male infertility, but intends to acknowledge the post-marketing reports in the

context of the other existing clinical data. Merck proposes to add the following text to the Side Effects, Post-marketing Experience section of the PI for PROPECIA:

"male infertility and/or poor seminal quality. Normalization or improvement of seminal quality has been reported after discontinuation of finasteride."

Reviewer comment: The number of positive dechallenge cases in these reports is suggestive of causality. However, clinical trial data suggests no effect on spermatogenesis in healthy males and although androgens are crucial for spermatogenesis, the relative importance of T and DHT in spermatogenesis remains unknown. DHT does not seem to be crucial for spermatogenesis as men with type 2, 5 α -reductase gene deficiency show markedly diminished ejaculate volumes due to rudimentary prostates and small seminal vesicles, but their spermatogenesis is often normal. Therefore, this reviewer is unable to definitively determine causality of effects on seminal quality as it relates to Propecia.

In the literature it is hypothesized that finasteride may not dramatically change the spermatogenesis process in healthy men, but in patients with conditions related to infertility, an amplification of the negative influence of finasteride could occur. It is this reviewer's recommendation that the post-marketing section of the label inform of this observed adverse reaction as there may be a population that is susceptible to the effects of Propecia on seminal quality.

Some reports describe recovery resulting in normal semen parameters and others report improvement after stopping Propecia. It is this reviewer's opinion to not comment on the reversibility seen in these cases. There is not sufficient evidence to determine causality nor reversibility and commenting on reversibility could falsely reassure patients that infertility will resolve or seminal quality will improve after stopping Propecia.

Labeling:

Current PI Labeling pertaining to sexual dysfunction:

The current finasteride 1 mg label includes the following information related to sexual dysfunction under the Clinical Studies and Adverse Reactions sections:

Clinical Studies section

Other Results in Vertex Baldness Studies (b) (4) 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. Adverse Reactions section Clinical adverse experiences that were reported as possibly, probably or definitely drug-related in $\geq 1\%$ of patients treated with Propecia or placebo are presented in Table 1.

Table B1. Drug-Related Adverse Experiences for Propecia (finasteride 1 mg) in Year 1 (%), Male Pattern Hair Loss (events related to sexual dysfunction)

	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)
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 $\leq 0.3\%$ 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.

(b) (4)

Adverse Reactions section

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 $\geq 1\%$ 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 B2. Drug-Related Adverse Experiences for Proscar (finasteride 5 mg), Benign Prostatic Hyperplasia (events related to sexual dysfunction)*

	Year 1 (%)		Combined years 2- 4 (%)	
	Finasteride 5 mg	Placebo	Finasteride 5 mg	Placebo
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

*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.

Proposed PI Labeling Pertaining to Sexual Dysfunction:

(b) (4)

Current PPI labeling pertaining to sexual dysfunction:

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.

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.

Proposed PPI Labeling pertaining to sexual dysfunction:

With S-023, the sponsor has proposed a different format for the PPI that supersedes the proposed labeling from S-021. The proposed PPI incorporates the proposed additional language “*difficulty in achieving an erection that continued after stopping the medication*” from S-021 and “*male infertility and/or poor seminal quality*.” (b) (4)

(b) (4)

PLR conversion:

With supplement 20, the applicant is converting the labeling to Physician’s Labeling Rule (PLR) format. Recommended changes to label are provided in the context of the sponsor-proposed label below. A brief overview of these changes to the PI includes:

Highlights:

Recent major changes

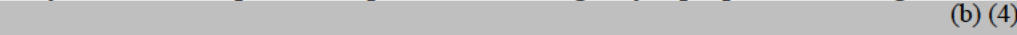
Warnings and Precautions, Increased Risk of High-Grade Prostate Cancer with 5a-Reductase Inhibitors (b) (4)


(b) (4)



Labeling Negotiation:

The team has provided recommendations to the PLR format labeling and as proposed the label is representative of the currently approved label. Text underlined in section of the PI and PPI above encompasses recommended revisions to the label based on supplements 21 and 23.

On February 6, 2012 the sponsor responded to the Agency's proposed labeling revision to include  (b) (4)



Regarding seminal quality, a decision has been made to include in the Propecia label the sponsor's proposal of "(Normalization or improvement of seminal quality has been reported after discontinuation of finasteride)."

Conclusion: The attached labeling has been agreed upon with the sponsor. It incorporates conversion to PLR format and includes post-marketing information to the post-marketing section of product labeling to reflect reports of sexual adverse events associated with the use of Propecia (finasteride) that may continue after patients stop using the drugs.

Recommended Regulatory Action:

Approval of supplements 20, 21, and 23 with the attached agreed upon labeling.

Amy S. Voitach, DO, MS
Medical Officer
CDER/ OND/ ODEIII/
Division of Dermatology and Dental Products

References:

Chiba K. et al. Finasteride-associated male infertility. Fertility and Sterility 2011 April: 95(5).

Liu K.E. et al. Propecia-induced spermatogenic failure. Fertility and Sterility 2008 Sept:90(3).

Irwig and Kolukula. Persistent Sexual Side Effects of Finasteride for Male Pattern Hair Loss. J Sex Med. 2011 Jun;8(6):1747-53.

Glina S et al. Finasteride- associated male infertility. Rev Hosp Clin Fac Med Sao Paulo 2004;59:203–5.

Overstreet JW et al. Chronic treatment with finasteride daily does not affect spermatogenesis or semen production in young men. J Urol 1999;162:1295–300.

Appendix:



18 Pages Immediately Following Withheld - b(4) Draft Labeling

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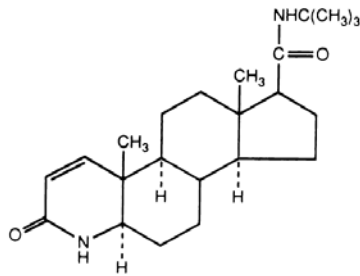
AMY S WOITACH
03/30/2012

DAVID L KETTL
03/30/2012

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 20-788/S-020/S-021/S-023

CHEMISTRY REVIEW(S)

Chemistry Review: #1	a. Division: HFD-540	b. NDA Number: 20-788
c. Name and Address of Applicant: Merck Sharp & Dohme Corp 126 East Lincoln Avenue P.O. Box 2000, RY33-208 Rahway, NJ 07065-0900		4. Supplement(s): CBE 30 Number: 020 Date(s): 08 Apr 2011 (Letter Date) 08 Apr 2011 (CDER Received) 05 May 2011 (Reviewer Received) 08 Oct 2011 (Goal Date)
5. Name of Drug: PROPECIA™		6. Nonproprietary name: Finasteride
7. Supplement Provides for Changes in the labeling section of the approved NDA in SPL format.		8. Amendment(s): NA
9. Pharmacological Category: Male pattern hair loss (androgenetic alopecia) in men only	10. How Dispensed: R _x	11. Related Documents:
12. Dosage Form: Film Coated Tablets	13. Potency: 1 mg	
14. Chemical Name and Structure: Chemical Name: N-(b) (4)-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide Molecular Formula: C ₂₃ H ₃₆ N ₂ O ₂ Molecular Weight: 372.55 		
15. Comments This CBE 30 labeling supplement provides changes in the labeling section of the approved NDA. The proposed package insert and patient information in SPL format were provided. The relevant sections containing CMC information were reviewed and found to be consistent with the relevant information provided in the previous approved labeling. However, some changes were recommended and have been forwarded to the clinical PM. <u>The applicant's response to our labeling comments will be evaluated in review #2.</u>		
16. Conclusion: <u>This Supplement is recommended for approval from CMC perspective pending acceptable resolution of the requested labeling changes (see review notes for details).</u>		
17. Name: Xuhong Li, Ph.D., Chemist	Signature:	Date:
18. Concurrence: Thomas F. Oliver, Ph.D., Branch Chief, Branch VI, ONDQA	Signature:	Date:

1 Pages Immediately Following Withheld - b(4)

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/s/

XUHONG LI
10/05/2011

THOMAS F OLIVER
10/05/2011

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

NDA 20-788/S-020/S-021/S-023

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology Review

NDA #:	020788
Submission Date:	June 1, 2011
Brand Name:	Propecia
Generic Name:	Finasteride
Dosage Form:	Tablets
Dosage Strength:	1 mg
Reviewer:	Chinmay Shukla, Ph.D.
Team Leader:	Doanh Tran, Ph.D.
OCP Division:	DCP-3
OND Division:	Division of Dermatology and Dental Products
Sponsor:	Merck Research Laboratories
Submission Type:	Risk/benefit analysis
Indication:	Treatment of male pattern baldness (androgenic alopecia) in Men only

Analysis of comparative pharmacodynamic effects of 1 and 5 mg dose of finasteride

Background: Finasteride is a synthetic structural analog of testosterone (T). It is a competitive and specific inhibitor of human Type II 5 α -reductase (5-AR), an intracellular enzyme that converts the androgen T to dihydrotestosterone (DHT). DHT is reported to be the predominant androgen involved in the pathophysiological changes that occur in the scalp (androgenic alopecia) and prostate with age.

The following brands of finasteride have been approved (same Sponsor for both):

NDA #	Brand Name	Dosing Frequency	Indication
020788	Propecia [®] (Tablet, 1 mg)	Orally, once a day	Treatment of male pattern hair loss (androgenic alopecia) in men only aged 18 years and older
020180	Proscar [®] (Tablet, 5 mg)	Orally, once a day	Treatment of symptomatic benign prostatic hyperplasia (BPH) in men with an enlarged prostate

The dose response of finasteride was evaluated (see Clinical Pharmacology review in DARRTS dated April 28, 2011) and on May 13, 2011 an information request (IR) was sent to the Sponsor requesting additional discussion regarding the pharmacodynamic effects of finasteride 1 mg vs. 5 mg dose pertaining to the risk/benefit discussion for finasteride 1 mg dose (see communication in DARRTS).

List of Acronyms:

5-AR: 5 α -reductase

BPH: Benign prostatic hyperplasia

DHT: Dihydrotestosterone

IR: Information request
PD: Pharmacodynamic
PK: Pharmacokinetics
PSA: Prostate-specific antigen
T: Testosterone

Purpose of this Review: The Sponsor responded to the above IR on June 01, 2011 and the purpose of this review is to evaluate the Sponsor's response.

Sponsor's Position and Reviewer's Comments:

1] Sponsor's Position: In the clinical development program for finasteride (1 mg) for the treatment of men with male pattern hair loss, only one study (Protocol number 065¹) included an assessment of the effects of finasteride on scalp skin DHT, scalp skin T, and serum DHT following administration of both 1 mg and 5 mg doses in the same study. The Sponsor further states that this study was not powered to detect any statistical significance on the effect of finasteride 1 and 5 mg doses on the aforementioned pharmacodynamic (PD) markers. The scalp DHT concentration showed numerically greater reductions with finasteride 5 mg than with finasteride 1 mg. The values of median % reductions were - 69.4 vs. - 64.1% and the mean % reductions were - 65.2% vs. - 57.6% for the 5 mg and 1 mg dose respectively. (From Figure 1, the 95% confidence interval about the median was approximately - 53 to -76 for the 1 mg dose and - 61 to - 79 for the 5 mg dose).

Reviewer's Comments: Study 065 was reviewed as a part of dose-response review (see Clinical Pharmacology review in DARRTS dated April 28, 2011) and the results are summarized below.

There was no significant difference in the scalp skin DHT and T levels between 1 mg and 5 mg dose (see Figure 1 and 2 below). A similar effect was observed in the serum DHT levels where there was no significant difference observed between 1 and 5 mg dose of finasteride as shown in Figure 3.

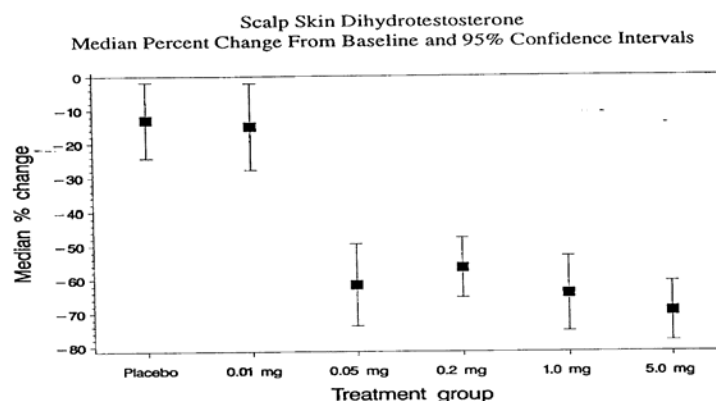


Figure 1: Median % change of scalp skin dihydrotestosterone from baseline and 95% confidence interval (CI) for different treatment groups (placebo and different doses of finasteride)

From Figure 1, there was no significant difference in the values of the median % change from baseline of scalp skin DHT from 0.05 mg to 5 mg dose. Hence, with respect to the scalp skin DHT, the 1 and 5 mg dose appear to be at the top of the dose – response curve.

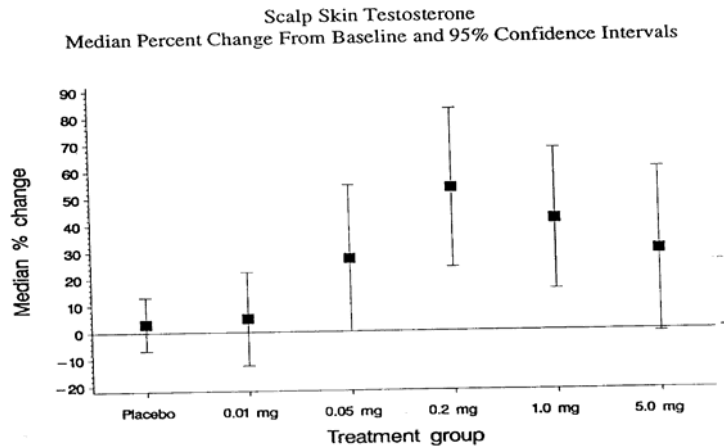


Figure 2: Median % Change of scalp skin testosterone from baseline and 95% CI for different treatment groups (placebo and different doses of finasteride)

From Figure 2, there was no significant difference in values of the median % change from baseline of scalp skin T from 0.05 mg to 5 mg dose. Hence this indicates that both 1 and 5 mg were at the top of the dose-response curve with regards to scalp skin T.

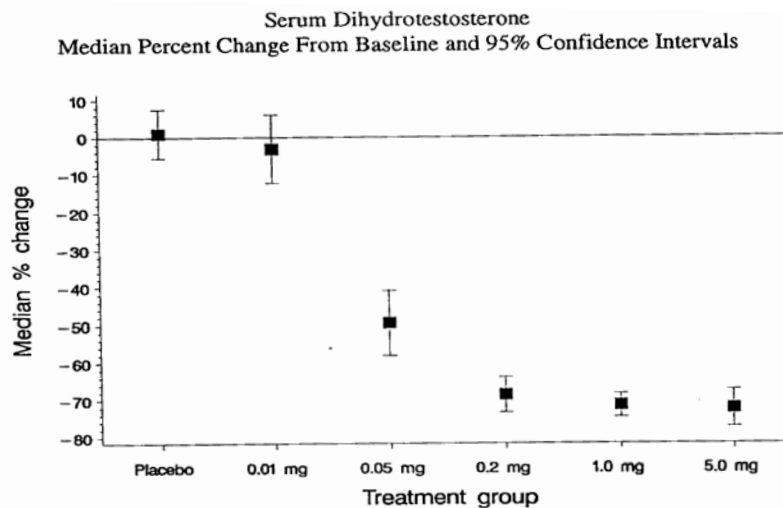


Figure 3: Median % Change of serum dihydrotestosterone from baseline and 95% CI for different treatment groups (placebo and different doses of finasteride)

From Figure 3, at the 0.2 mg dose, there appeared to be approximately 70% reduction in serum DHT. Further, there appears to be no further significant reduction in serum DHT between doses 0.2 mg to 5 mg compared to the magnitude of % reduction between placebo and 0.2 mg dose.

McConnell, JD et. al. also evaluated the serum DHT and T levels² (see Reference 4 in Clinical Pharmacology review in DARRTS dated April 28, 2011). The result is shown in Figure 4 below.

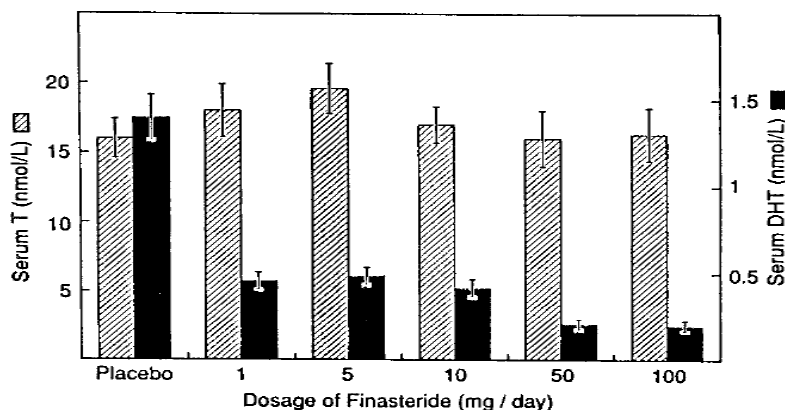


Figure 4: Serum androgen levels (mean \pm standard error of the mean) in men treated with daily finasteride doses of 1 mg, 5 mg, 10 mg, 50 mg and 100 mg

From Figure 4, there appears to be no significant difference in the levels of serum DHT at 1 and 5 mg dose. Further the magnitude of change in the serum DHT levels from between placebo and 1 mg dose is large compared to further reduction between 1 mg and 100 mg dose.

This reviewer acknowledges the Sponsor's position that Study 065 was neither designed nor powered to detect a dose dependent difference in the aforementioned pharmacodynamic (PD) markers. However, the results indicate that there is no significant difference between the 1 and 5 mg dose with regards to scalp skin DHT, scalp skin T and serum DHT.

2] Sponsor's Position: The Sponsor provided findings from their pivotal Phase III studies (Protocol numbers 008 and 508 – North American studies and Protocol number 507 – International study) where both 1 mg and 5 mg dose of finasteride were evaluated in men with benign prostatic hyperplasia (BPH). These studies permitted direct comparison of the effects of these doses of finasteride on the prostate. The results are shown in the Table 1 below.

Study	5 mg		1 mg		Placebo		5 vs 1 mg p-Value
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	
North American	286	-65.6** (20.8)	290	-61.7** (21.6)	295	7.2 (34.2)	<0.001
International	210	-50.6** (32.5)	217	-45.2** (37.7)	215	0.3 (33.9)	0.02

** p<0.001 vs placebo

Table 1: Mean percentage change in serum dihydrotestosterone levels at Month 12

The Sponsor has further demonstrated a greater shift to lower levels of DHT in the population treated with finasteride 5 mg than the population treated with finasteride 1 mg as shown in Figure 5.

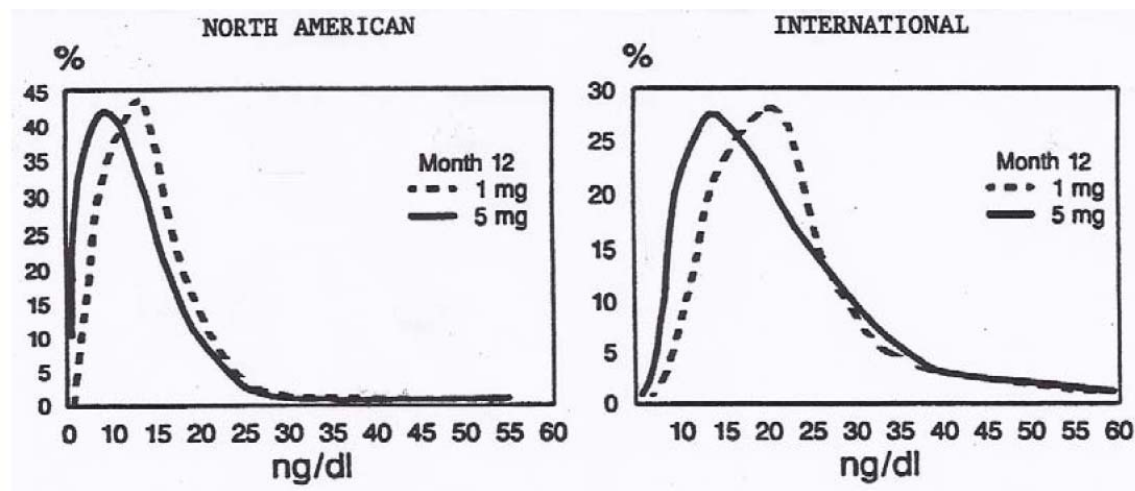


Figure 5: Distribution of patients for a given level of DHT (ng/dL)

In addition to this, the Sponsor also measured prostate volume (measured using MRI in North American Studies and using ultrasound in the International Study) and serum Prostate-specific antigen (PSA). In the Phase III North American study, the Sponsor has demonstrated that the median percent decrease in the prostate volume was **numerically greater** (emphasis added by the reviewer) with the 5 mg dose compared to 1 mg dose (-19.2% vs. -18% respectively). Likewise, the median percent decrease in the serum PSA in the Phase III North American study was also demonstrated to be **numerically greater** (emphasis added by the reviewer) with finasteride 5 mg dose than with the 1 mg dose (-48% vs. -46% respectively).

The results of prostate volume and PSA from the international study were not submitted for review.

Reviewer's Comments: Data from the North American study was the same as the one under Reference 3 (Gormley, GJ et. al. 1992) in the Clinical Pharmacology review in DARRTS dated April 28, 2011.

This study reported a significant difference in the mean % change in the serum DHT levels at month 12 between doses of 1 and 5 mg. However, from Figures 3 and 4 and Table 1, comparing the magnitude of change in the % serum DHT levels following finasteride administration with that observed for placebo, the difference between % serum DHT levels following 1 and 5 mg dose was small (-61.7% vs. -65.6% for the North American study and -45.2% and -50.6% for the International study).

This reviewer concurs with the Sponsor regarding the decrease in serum PSA levels being numerically higher with the 5 mg dose compared to 1 mg dose (-48% vs. -46% respectively) at 12 months post dose. However, according to Gormley, GJ et. al.,

opposite effect was observed at 6 and 9 months with median serum PSA levels lower with 1 mg dose compared to the 5 mg dose as shown in Figure 6 below⁴. Hence, there appears to be no dose response between 1 mg and 5 mg dose of finasteride with respect to serum PSA.

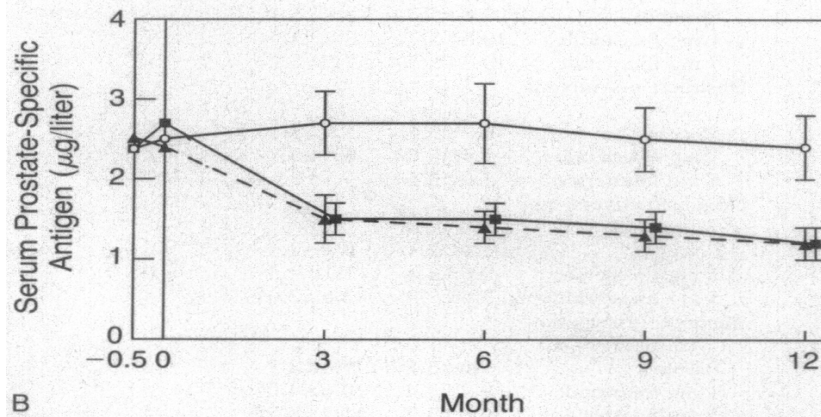


Figure 6: Effect of treatment with placebo (Circles), 1 mg of finasteride (Triangles) or 5 mg finasteride (Squares) on the median (\pm 95% CI) serum prostate-specific antigen concentrations

Figure 7 below shows the median % change in prostate volume in men with BPH⁴.

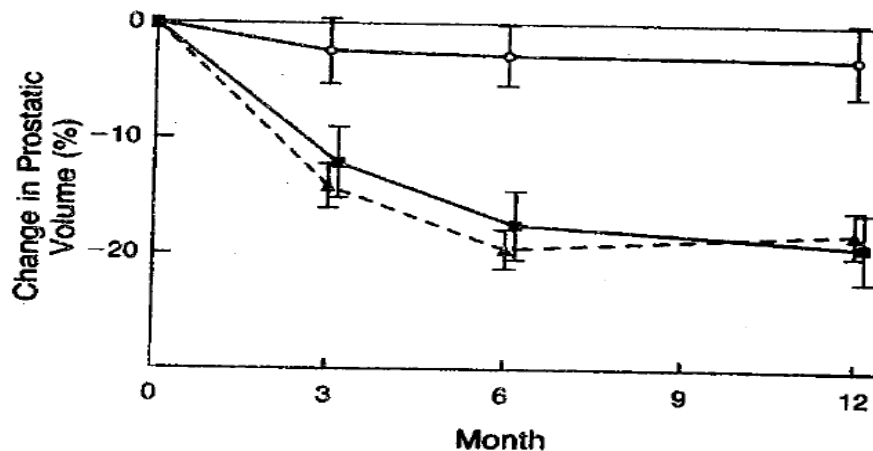


Figure 7: Median % change (\pm 95% CI) in prostatic volume in men with benign prostatic hyperplasia during treatment with placebo (Circles), 1 mg of finasteride (Triangles) or 5 mg finasteride (Squares)

This reviewer concurs with the Sponsor regarding the median % decrease in prostate volume with being numerically greater with the 5 mg dose compared to 1 mg dose (-19.2% vs. -18% respectively) at 12 months post dose. However, according to Gormley, GJ et. al., opposite effect was observed at 3 and 6 months with median % decrease in prostate volume being greater with the 1 mg dose compared to the 5 mg dose as shown in Figure 7 above⁴. Hence, there appears to be no dose response between 1 mg and 5 mg dose of finasteride with respect to prostate volume.

The results of prostate volume and PSA from the international Phase III study was not submitted for review.

3] Sponsor's Position: The Sponsor has cited findings from a published manuscript by McConnell J. D. et. al.², and the Sponsor claims that dose related suppression of intraprostatic DHT was observed across dose range from 1 mg/day to 100 mg/day with a ~ 7 fold decrease in the intraprostatic DHT concentration relative to placebo observed in the 1 mg group (1.4 vs. 10.3 nmol/kg) and a ~ 20 fold decrease relative to placebo in the 100 mg group (0.5 vs. 10.3 nmol/kg). The Sponsor further claims that both 1 mg and 5 mg doses are on the responsive portion of the dose-response curve for the effects of finasteride on intraprostatic DHT. In addition the Sponsor also states that the sample size of this study precluded detection of statistically significant differences between active doses.

Reviewer's Comments: *This study was reviewed in detail as a part of dose-response review (see Reference 4 (McConnell J. D. et. al. 1992) in Clinical Pharmacology review in DARRTS dated April 28, 2011) and the results are shown below (Figure 8).*

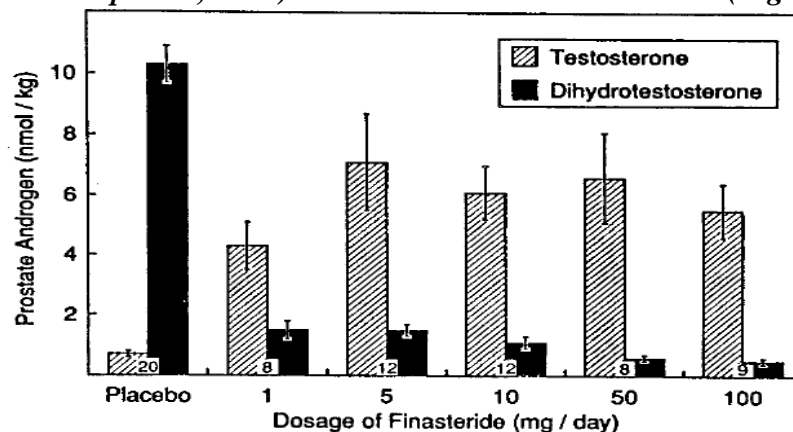


Figure 8: Prostatic androgen levels (mean \pm standard error of the mean) in men with BPH treated with daily finasteride doses of 1 mg, 5 mg, 10 mg, 50 mg and 100 mg

This reviewer acknowledges that the sample size studied might preclude detection of any statistical significance in the effect however; the available data showed that the magnitude of effect was similar between 1 and 5 mg doses. Further, the magnitude of reduction in the levels of prostatic DHT between placebo and 1 mg dose is large compared to the further reduction between 1 and 100 mg. In addition to this, the DHT levels were not statistically significant between each treatment arm suggesting that both 1 and 5 mg dose are at or near the top of the dose response curve with regard to the effect of finasteride on the intraprostatic DHT levels.

4] Sponsor's Position: In the Phase II dose ranging studies in men with BPH (Protocol numbers 003 and 006), dose-dependent effects on prostate volume were observed across a dose range from 0.2 to 5 mg/day, with statistically significant greater reduction in prostate volume observed with finasteride 1 and 5 mg than with finasteride 0.2 and 0.5 mg, while no dose response was observed at higher dose range from 5 mg to 80 mg/day,

consistent with the dose interval between 1 and 5 mg being at the top of the dose-response curve with regard to effects of finasteride on prostate volume³.

Reviewer's Comments: *This reviewer concurs with the Sponsor's assessment that finasteride 1 and 5 mg are at the top of the dose-response curve with regard to the effect of finasteride on prostate volume. The results from this study are described below in detail.*

The Sponsor conducted 2 studies. One of them studied doses ranging from 5 mg to 80 mg while the other studied doses from 0.2 mg to 40 mg/day. From the first study, the Sponsor concludes that no dose-response was observed at higher dose range from 5 mg to 80 mg/day. Hence results from only the second study (dose 0.2 mg to 40 mg/day) will be discussed in detail.

Table 2 below shows the mean prostate volume at baseline and mean percentage change from baseline measured by MRI for 0.2, 0.5, 1, 5 and 40 mg dose of finasteride at weeks 12 and 24. The same data is also shown in Figure 9.

	Placebo	Finasteride (mg.)				
		0.2	0.5	1.0	5.0	40
Baseline No. pts.	25	18	16	17	15	13
Mean \pm standard deviation	63.5 \pm 30.6	73.4 \pm 51.6	62.8 \pm 19.7	80.3 \pm 64.5	66.6 \pm 40.4	61.2 \pm 31.7
Mean % change \pm standard deviation:						
At wk. 12	-5.6 \pm 20.8	-11.5 \pm 11.3*	-13.9 \pm 13.3*	-14.6 \pm 16.8†	-17.3 \pm 11.8*	-15.9 \pm 30.3†
At wk. 24	-5.2 \pm 21.1	-18.8 \pm 18.6†	-17.9 \pm 14.4†	-24.4 \pm 17.5†	-27.7 \pm 10.8†	-25.5 \pm 17.8†

* Significant change ($p < 0.05$).

† Significant change ($p < 0.01$).

Table 2: Mean prostate volume at baseline and mean percentage change from baseline measured by MRI at week 12 and 24.

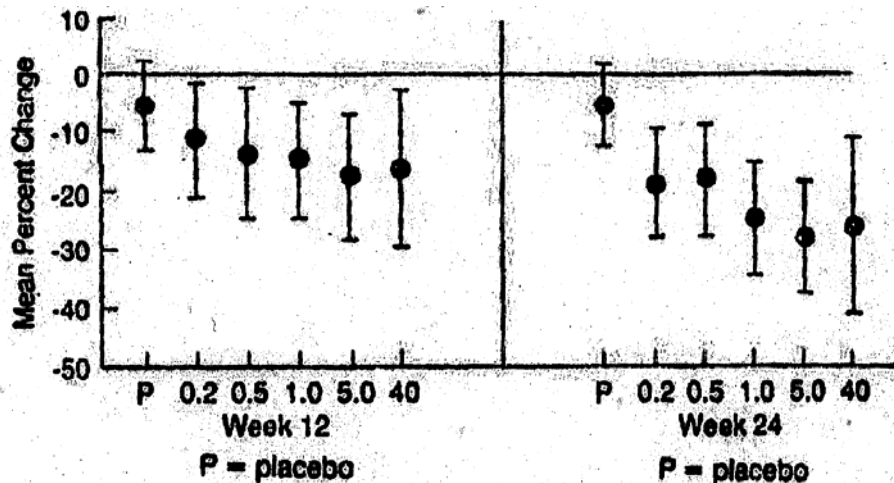


Figure 9: Mean percentage change from baseline in prostate volume measured by MRI at weeks 12 and 24 of finasteride and 95% confidence interval.

From Figure 9, the mean % decrease in prostate volume observed at week 24 in each finasteride treatment groups were significantly different from baseline ($p < 0.05$), while the mean decrease in placebo group was not. The authors also reported that the mean prostate volume observed in the 1, 5 and 40 mg groups were significantly greater than the placebo group.

From data shown in Table 2, there appears to be no significant difference in the mean percentage change in prostate volume between 1, 5 and 40 mg dose at week 12 and 24 (also no dose response was observed from 5 mg to 80 mg dose). From this data, the Sponsor has noted that 1 and 5 mg dose are at the top of the dose response curve and this reviewer concurs with this Sponsor's observation.

5] Sponsor's Position: The Sponsor has also provided results of the effects of urinary symptoms of BPH and the effects on semen parameters.

Reviewer's Comments: *These results were not reviewed by Clinical Pharmacology and will require Clinical inputs.*

Overall Summary:

With the objective of showing difference in the pharmacodynamic effects of finasteride 5 mg dose compared to 1 mg dose, the Sponsor has provided discussion for the following PD parameters: scalp skin DHT, scalp skin T, prostate volume, intra-prostatic DHT, serum DHT and serum PSA. The sponsor also provided data on the effects of urinary symptoms of BPH and the effects on semen parameters. These data are being reviewed by the Clinical team and were not considered in this review.

The sponsor's general argument is that finasteride exhibits a dose response relationship and that the 1 mg and 5 mg doses are within the dose-responsive portion of the pharmacodynamic dose-response curve.

On reviewing the supporting data submitted by the Sponsor, it appears that both 1 and 5 mg doses are at the top of the dose response curve with respect to scalp skin DHT (Figure 1), scalp skin T (Figure 2), and mean prostate volume (Figure 7 and 9 and Table 2). For serum PSA only 1 mg and 5 mg doses were evaluated and a dose response relationship can not be elucidated with data available only from 2 doses. However, the results indicated that there was no difference in the serum PSA levels produced with 1 and 5 mg dose of finasteride (Figure 6). Furthermore, depending on the model used (scalp skin DHT and scalp skin T) doses as low as 0.2 mg show significant activity that is indistinguishable from that of the 1.0 and 5.0 mg doses (Figure 1 and 2). With respect to intra-prostatic DHT, the 1 and 5 mg doses appear to be at or near the top of the dose response curve as observed in Figure 8.

The results of Phase III studies showed statistically significant difference in the serum DHT levels (Table 1), however the difference in the value of serum DHT produced following 1 and 5 mg dose was small. Further the results of the Phase II studies suggest

that both 1, 5 mg, and lower doses are at or near the top of the dose response curve (Figures 3 and 4).

The decrease in the serum PSA levels at 12 months was slightly higher with the 5 mg dose compared to the 1 mg dose. However, opposite effect was observed at 6 and 9 months indicating no dose response between 1 mg and 5 mg dose of finasteride (Figure 6).

The % decrease in prostate volume at 12 months was slightly higher with the 5 mg dose compared to the 1 mg dose. However, opposite effect was observed at 3 and 6 months indicating no dose response between 1 mg and 5 mg dose of finasteride (Figure 7).

Conclusions: The pharmacodynamic effects of both 1 and 5 mg dose of finasteride appear to be similar with respect to scalp skin DHT, scalp skin T, serum DHT, intra-prostatic DHT, serum PSA and mean prostate volume. It is not known if the similar effects observed on these PD markers would translate into a similar effect on the increased risk of high grade prostate cancer observed with the 5 mg dose because it is not known if the risk of high grade prostate cancer associated with finasteride is related to or mediated via these markers.

References:

1. Protocol 065: A double blind, placebo-controlled study to investigate the effects of finasteride on DHT and T in scalp skin and sebum
2. Finasteride, an inhibitor of 5 α -reductase, suppress prostatic dihydrotestosterone in men with benign prostatic hyperplasia; McConnell J.D. et. al.; Journal of Clinical Endocrinology and Metabolism; 1992; 74(3); 505-8
3. The clinical effects of a 5 α -reductase inhibitor, finasteride, on benign prostatic hyperplasia; Stoner E. et. al.; The Journal of Urology; May 1992; 147; 1298-1302
4. The effect of finasteride in men with benign prostatic hyperplasia; Gormley, GJ et. al., The New England Journal of Medicine; Oct 1992; 327(17); 1185-91

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/s/

CHINMAY SHUKLA
11/17/2011

DOANH C TRAN
11/18/2011

CLINICAL PHARMACOLOGY REVIEW

NDA	020788 (S-020)	Submission Letter Date(s)	April 08, 2011
Product Name	Propecia (finasteride) Tablets, 1 mg		
Primary Reviewer	Chinmay Shukla, Ph.D.		
Team Leader	Doanh Tran, Ph.D.		
OCP Division	Division of Clinical Pharmacology 3		
OND Division	Division of Dermatology and Dental Products		
Sponsor	Merck Research Laboratories		
Submission Type	Physician Labeling Rule (PLR) Conversion		
Approved Indication	Treatment of men with male pattern hair loss (androgenic alopecia) in men only		

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1. Executive Summary:

Propecia (finasteride) Tablets, 1 mg were approved on December 19, 1997 for the treatment of men with male pattern hair loss (androgenic alopecia) in men only. The Sponsor is submitting this supplement to convert the label into the PLR format.

1.1 Recommendations:

On review of the Sponsor's proposed changes to the format and the text of Section 12: Clinical Pharmacology of the PLR formatted label, the Office of Clinical Pharmacology has made recommended changes as specified in Section 3 of this review.

1.2 Phase IV Commitments:

None

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings:

None

Chinmay Shukla, Ph.D.
Clinical Pharmacology Reviewer
Division of Clinical Pharmacology 3
Office of Clinical Pharmacology

Date: _____

Doanh Tran, Ph.D.
Team Leader
Division of Clinical Pharmacology 3
Office of Clinical Pharmacology

Date: _____

2. **Question Based Review:**

Not Applicable

3. **Detailed Labeling Recommendations:**

The labeling recommendations for Section 12 (CLINICAL PHARMACOLOGY) of the label (deletions are “~~strike throughs~~” and additions are “**bold underlined**”) are shown below:

(b) (4)



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/s/

CHINMAY SHUKLA
11/23/2011

DOANH C TRAN
11/23/2011

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

NDA 20-788/S-020/S-021/S-023

OTHER REVIEW(S)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****PRE-DECISIONAL AGENCY MEMO****

Date: July 7, 2011

To: J. Paul Phillips, DDDP

From: Lynn Panholzer, PharmD, DDMAC
Sheetal Patel, PharmD, DDMAC

Re: NDA# 020788/S-020
Propecia (finasteride) Tablets

As requested in your consult dated May 17, 2011, DDMAC has reviewed the draft labeling (package insert [PI], patient package insert [PPI]) for Propecia (finasteride) Tablets. DDMAC reviewed the proposed, substantially complete, marked-up version of the labeling e-mailed by DDDP on June 17, 2011.

DDMAC's comments on the PI and PPI are provided directly in the attached copy of the labeling.

If you have any questions regarding the PI, please contact Lynn Panholzer at 6-0616 or at Lynn.Panholzer@fda.hhs.gov. If you have any questions regarding the Medication Guide please contact Sheetal Patel at (b) (6) or at Sheetal.Patel@fda.hhs.gov.

20 Pages Immediately Following Withheld - b(4) Draft Labeling

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/s/

LYNN M PANHOLZER
07/07/2011

SHEETAL PATEL
07/07/2011

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

PATIENT LABELING REVIEW

Date: July 5, 2011

To: Susan Walker, MD, Division Director
Division of Dermatology and Dental Products (DDDP)

Through: LaShawn Griffiths, RN, MSHS-PH, BSN
Acting Team Leader, Patient Labeling Reviewer
Division of Risk Management (DRISK)

Barbara Fuller, RN, MSN, CWOCN
Acting Team Leader, Patient Labeling Reviewer
Division of Risk Management (DRISK)

From: Steve L. Morin, RN, BSN, OCN
Patient Labeling Reviewer
Division of Risk Management

Subject: DRISK Review of Patient Labeling (Patient Package Insert)

Drug Name (established name): PROPECIA (finasteride) Tablets

Application Type/Number: NDA 20-788

Supplement number: S-020

Applicant: Merck Research Laboratories

OSE RCM #: 2011-2185

1 INTRODUCTION

This review is written in response to a request by the Division of Dermatology and Dental Products (DDDP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Patient Package Insert (PPI) for PROPECIA (finasteride) Tablets. This supplement provides for revision of prescribing information (PI) to comply with the Physicians Labeling Rule.

2 MATERIAL REVIEWED

- Draft PROPECIA (finasteride) Tablets Patient Package Insert (PPI) received on April 8, 2011, and revised by the review division throughout the review cycle and provided to DRISK on June 20, 2011.
- Draft PROPECIA (finasteride) Tablets prescribing information (PI) received April 8, 2011, and revised by the review division throughout the review cycle and provided to DRISK on June 20, 2011.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APhont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 11.

In our review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the prescribing information (PI)
- rearranged information due to conversion of the PI to PLR format
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DRISK on the correspondence.

- Our annotated versions of the PPI are appended to this memo. Consult DRISK regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

13 Pages Immediately Following Withheld - b(4) Draft Labeling

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/s/

STEVE L MORIN
07/05/2011

LASHAWN M GRIFFITHS
07/05/2011

SEALD Director Sign-Off Memo and Labeling Review

Product Trade Name (Non-Propriety Name)	PROPECIA (finasteride) tablets, for oral use
Application/Supplement Number	NDA 20788, Supplement 020
Type of Application	PLR Conversion
Indication	Treatment of male pattern hair loss (androgenetic alopecia) in MEN ONLY
Applicant	Merck Research Laboratories Division Merck Company, Inc.
Office/Division	ODE III/DDDP
Division Project Manager	Paul Phillips
Received Date	April 8, 2011
PDUFA Goal Date	October 8, 2011
SEALD Review Date	March 12, 2012
SEALD Labeling Reviewer	Jeanne M. Delasko
SEALD Director	Laurie B. Burke

This memo confirms that a Study Endpoints and Labeling Development (SEALD) review of final agreed-upon prescribing information (USPI) determined that there are **NO** outstanding labeling issues in the USPI. This determination follows active engagement throughout the review process between the Division and the SEALD Labeling Team concerning labeling regulations (21 CFR 201.56 and 201.57), labeling guidances, and best labeling practices. The 46-item Selected Requirements for Prescribing Information (SRPI) checklist contains a subset of these policies that apply to all approved USPIs. At this time, no SRPI deficiencies were found (see below for the SRPI checklist).

This memo also confirms that because there are no outstanding SRPI issues in the USPI, the SEALD Director has **NO OBJECTION** to the approval of the USPI at this time.

SEALD Labeling Review: Selected Requirements for Prescribing Information (SRPI)

Only identified deficiencies are checked (no checks means no deficiencies).

Highlights (HL)

- **General comments**

- ☐ HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
- ☐ HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.
- ☐ There is no redundancy of information.
- ☐ If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
- ☐ A horizontal line must separate the HL and Table of Contents (TOC).
- ☐ All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
- ☐ Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- ☐ Section headings are presented in the following order:

• Highlights Limitation Statement (required statement)
• Drug names, dosage form, route of administration, and controlled substance symbol, if applicable (required information)
• Initial U.S. Approval (required information)
• Boxed Warning (if applicable)
• Recent Major Changes (for a supplement)
• Indications and Usage (required information)
• Dosage and Administration (required information)
• Dosage Forms and Strengths (required information)
• Contraindications (required heading – if no contraindications are known, it must state “None”)
• Warnings and Precautions (required information)
• Adverse Reactions (required AR contact reporting statement)
• Drug Interactions (optional heading)
• Use in Specific Populations (optional heading)
• Patient Counseling Information Statement (required statement)
• Revision Date (required information)

SEALD Labeling Review: Selected Requirements for Prescribing Information (SRPI)

- **Highlights Limitation Statement**

- ☐ Must be placed at the beginning of HL, **bolded**, and read as follows: “**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**”

- **Product Title**

- ☐ Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.

- **Initial U.S. Approval**

- ☐ The verbatim statement “Initial U.S. Approval” followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.

- **Boxed Warning**

- ☐ All text in the boxed warning is **bolded**.
- ☐ Summary of the warning must not exceed a length of 20 lines.
- ☐ Requires a heading in UPPER-CASE, **bolded** letters containing the word “**WARNING**” and other words to identify the subject of the warning (e.g., “**WARNING: LIFE-THREATENING ADVERSE REACTIONS**”).
- ☐ Must have the verbatim statement “*See full prescribing information for complete boxed warning.*” If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.

- **Recent Major Changes (RMC)**

- ☐ Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
- ☐ The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, “Dosage and Administration, Coronary Stenting (2.2) --- 2/2010.”
- ☐ For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line (“margin mark”) on the left edge.
- ☐ A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.
- ☐ Removal of a section or subsection should be noted. For example, “Dosage and Administration, Coronary Stenting (2.2) --- removal 2/2010.”

SEALD Labeling Review: Selected Requirements for Prescribing Information (SRPI)

- **Indications and Usage**

- ☐ If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product] is a (name of class) indicated for (indication(s)).” Identify the established pharmacologic class for the drug at:

<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>.

- **Contraindications**

- ☐ This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”
- ☐ All contraindications listed in the FPI must also be listed in HL.
- ☐ List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.
- ☐ For drugs with a pregnancy Category X, state “Pregnancy” and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**

- ☐ Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).
- ☐ For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**” must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**

- ☐ Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”)**”.

- **Revision Date**

- ☐ A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval.

SEALD Labeling Review: Selected Requirements for Prescribing Information (SRPI)

Contents: Table of Contents (TOC)

- ☐ The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- ☐ The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- ☐ All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- ☐ When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:
 - 8.1 Pregnancy
 - 8.3 Nursing Mothers (not 8.2)
 - 8.4 Pediatric Use (not 8.3)
 - 8.5 Geriatric Use (not 8.4)
- ☐ If a section or subsection is omitted from the FPI and TOC, the heading “**Full Prescribing Information: Contents**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Full Prescribing Information (FPI)

• General Format

- ☐ A horizontal line must separate the TOC and FPI.
- ☐ The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
- ☐ The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

• Boxed Warning

- ☐ Must have a heading, in UPPER CASE, **bold** type, containing the word “**WARNING**” and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.
- ☐ Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

SEALD Labeling Review: Selected Requirements for Prescribing Information (SRPI)

- **Contraindications**

- ☐ For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**

- ☐ Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided.
- ☐ For the “Clinical Trials Experience” subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”
- ☐ For the “Postmarketing Experience” subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

- **Use in Specific Populations**

- ☐ Subsections 8.4 Pediatric Use and 8.5 Geriatric Use (not needed for “peds only” indications) are required and cannot be omitted.

- **Patient Counseling Information**

- ☐ This section is required and cannot be omitted.
- ☐ Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling ... (insert type of patient labeling).” should appear at the beginning of Section 17 for prominence. For example:
 - “See FDA-approved patient labeling (Medication Guide)”
 - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information)”
 - “See FDA-approved patient labeling (Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

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/s/

JEANNE M DELASKO
03/12/2012

LAURIE B BURKE
03/12/2012

Memorandum

To: NDA 20-788
From: Renqin Duan, Ph.D., Pharmacology/Toxicology Reviewer
Through: Barbara Hill, Ph.D., Pharmacology/Toxicology Supervisor

Re:

Submission date: 4-08-2011, 6-23-11
SDN: 203 (S-020), 213
Submission type: Labeling supplement
Drug: Propecia (finasteride) Tablets, 1 mg
Indication: Androgenetic alopecia
Route: Oral
Sponsor: Merck Research Laboratories

Review date: February 23, 2011

Introduction:

Finasteride is a type II 5 α -reductase inhibitor that reduces the conversion of testosterone to 5 α -dihydrotestosterone. Propecia (finasteride, 1 mg) was approved for the treatment of androgenetic alopecia in men on December 19, 1997. The last approved label was in non-PLR format. Proscar (finasteride, 5 mg) was approved for the treatment of symptomatic benign prostatic hyperplasia (BPH) on June 19, 1992. The PLR-format label for Proscar was approved on June 9, 2011.

With this submission, the sponsor proposes modification of the Propecia label under NDA 20-788 S-020 to conform to the PLR format and to harmonize both finasteride (Proscar and Propecia) labels. (b) (4)

The nonclinical sections of the Propecia PLR label (Sections 8.1, 12.1 and 13.1) are evaluated in the following section of this review.

The sponsor's submitted labeling:

Reviewer comment: The pharmacologic class designation of "5 α -reductase inhibitor" in the "INDICATIONS AND USAGE" highlights section of the Propecia PLR label is correct.

(b) (4)

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions:

This labeling supplement is approvable from a Pharmacology/Toxicology perspective.

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/s/

Renqin DUAN
02/23/2012

BARBARA A HILL
02/23/2012

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
NDA 20-788/S-020/S-021/S-023

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

From: Phillips, J. Paul
Sent: Friday, March 30, 2012 2:12 PM
To: Mellina, Frank J.
Cc: Gould, Barbara
Subject: NDA 020788 (Propecia)

Dr. Mellina,

I have attached a copy of the PI for Propecia with an additional edit to put back in a piece of information that Merck originally proposed. Please see section 6.2.

We ask that you respond **by C.O.B. on Monday, April 2, 2012.**

Thank you.

J. Paul Phillips, MS
Regulatory Health Project Manager

Division of Dermatology and Dental Products
Center for Drug Evaluation and Research
Food & Drug Administration
W.O. Bldg. 22, Room 5189
10903 New Hampshire Ave.
Silver Spring, MD 20993

Telephone: (301) 796-3935
Fax: (301) 796-9895
e-mail: Paul.Phillips@fda.hhs.gov

14 Pages Immediately Following Withheld - b(4) Draft Labeling

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/s/

J P PHILLIPS
03/30/2012

From: Phillips, J. Paul
Sent: Tuesday, March 06, 2012 5:50 PM
To: (b) (6)@merck.com'
Cc: Gould, Barbara; 'Mellina, Frank J.'
Subject: NDA 020788 (Propecia)

Mr. (b) (6)

Please see the attached document with FDA edits to the patient labeling for NDA 020788 (Propecia).



Propecia PPI_FDA
edits 3-6-12....

You should respond by **C.O.B. tomorrow (3/7/12)**.

Thank you.

J. Paul Phillips, MS
Regulatory Health Project Manager

Division of Dermatology and Dental Products
Center for Drug Evaluation and Research
Food & Drug Administration
W.O. Bldg. 22, Room 5189
10903 New Hampshire Ave.
Silver Spring, MD 20993

Telephone: (301) 796-3935
Fax: (301) 796-9895
e-mail: Paul.Phillips@fda.hhs.gov

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/s/

J P PHILLIPS
03/06/2012

From: Phillips, J. Paul
Sent: Monday, March 05, 2012 4:11 PM
To: (b) (6)@merck.com'
Cc: Gould, Barbara; 'Mellina, Frank J.'
Subject: NDA 020788 (Propecia)

Mr. (b) (6)

Please see the attached document with FDA edits to the PLR label for NDA 020788 (Propecia).



Propecia PI_FDA
edits 3-5-12.d...

You should respond by **C.O.B. tomorrow (3/6/12)**.

Thank you.

J. Paul Phillips, MS
Regulatory Health Project Manager

Division of Dermatology and Dental Products
Center for Drug Evaluation and Research
Food & Drug Administration
W.O. Bldg. 22, Room 5189
10903 New Hampshire Ave.
Silver Spring, MD 20993

Telephone: (301) 796-3935
Fax: (301) 796-9895
e-mail: Paul.Phillips@fda.hhs.gov

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/s/

J P PHILLIPS
03/06/2012

From: Phillips, J. Paul
Sent: Wednesday, December 21, 2011 5:01 PM
To: 'Mellina, Frank J.'
Cc: Gould, Barbara; (b) (6)@merck.com'
Subject: NDA 020788 Propecia

Dr. Mellina,

Regarding NDA 020788 (Propecia) and the pending supplements S-020, S-021 and S-023, please see the attached draft labeling which includes FDA edits.

We ask that you respond by C.O.B. on January 6, 2012.



Propecia_PLR
proposed label_FD..



Propecia_PPI
proposed label_FD..

Thank you.

J. Paul Phillips, MS
Regulatory Health Project Manager

Division of Dermatology and Dental Products
Center for Drug Evaluation and Research
Food & Drug Administration
W.O. Bldg. 22, Room 5189
10903 New Hampshire Ave.
Silver Spring, MD 20993

Telephone: (301) 796-3935
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e-mail: Paul.Phillips@fda.hhs.gov

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/s/

J P PHILLIPS
02/02/2012



NDA 020788

INFORMATION REQUEST

Merck Sharp & Dohme Corp.
Attention: Frank J. Mellina, Pharm.D.
Manager, Regulatory Affairs
126 East Lincoln Ave.
P.O. Box 2000, RY33-208
Rahway, NJ 07065-0900

Dear Dr. Mellina:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for PropeciaTM (finasteride) Tablet, 1 mg.

We also refer to your June 1, 2011, submission, containing supporting information related to your risk/benefit analysis.

We have reviewed the referenced material and have the following requests for information.

Provide final study reports for the following studies:

Protocol 008 and Protocol 508

A Double-Blind, Placebo-Controlled, Multicenter study to Investigate the Safety, Tolerability and Efficacy of MK-906 in Patients with benign Prostatic Hyperplasia. (North American)

Protocol 507

A Double-Blind, Placebo-Controlled, Multicenter study to Investigate the Safety, Tolerability and Efficacy of MK-906 in Patients with benign Prostatic Hyperplasia. (International)

Protocol 012

A Double-Blind, Placebo-Controlled, Multicenter Study to Determine the Effect of Finasteride on Semen Production in Male Volunteers.

Protocol 056

A Double-Blind, Placebo-Controlled, Multicenter Study to Determine the Effect of Finasteride on Semen Production in Male Volunteers.

Protocol 094

A Double-Blind, Randomized, Placebo-Controlled, Multicenter Study to Evaluate the Safety of Low-Dose Finasteride in Male Volunteers.

Please provide the above requested information by close of business on August 31, 2011.

If you have any questions, call Paul Phillips, Regulatory Project Manager, at (301) 796-3935.

Sincerely,

{See appended electronic signature page}

David Kettl, M.D.
Clinical Team Leader
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

DAVID L KETTL
08/24/2011



MEMORANDUM OF TCON

Date of Teleconference: 07/27/2011
Time: 3:00 p.m. (ET)
Application: NDA 020788
Product: Propecia[®] (finasteride) 1 mg
Sponsor/Applicant: Merck

FDA Participants:

Tatiana Oussova, M.D., M.P.H., Deputy Director for Safety, DDDP
David Kettl, M.D., Clinical Team Leader, DDDP
Amy Weitach, D.O., M.S., Clinical Reviewer, DDDP
Hon Sum Ko, M.D., Medical Officer, DDDP
Doanh Tran, Ph.D., Clinical Pharmacology Team Leader, DCP3
Chinmay Shukla, Ph.D., Clinical Pharmacology Reviewer, DCP 3
Barbara Gould, M.B.A.H.C.M., Chief, Project Management Staff, DDDP
J. Paul Phillips, M.S., Regulatory Health Project Manager, DDDP

Sponsor/Applicant Participants:

Frank Mellina, Worldwide Regulatory Affairs
Charlotte Merritt, Worldwide Regulatory Affairs
Keith Kaufman, Clinical Research
Elizabeth Round, Clinical Research
Tom Armstrong, Worldwide Product Labeling
Suzanne Amo, Worldwide Product Labeling
Celina Edmonds, Worldwide Product Labeling
Mary Frances Schubert, Clinical Risk Management and Safety Surveillance

Purpose:

To clarify and discuss points related the applicant's risk/benefit analysis.

Discussion Summary:

The following two questions and related references were discussed.

1. To discuss conclusions regarding the pharmacodynamic effects of 1 vs. 5 mg (clinpharm team)
2. Discussion re: [REDACTED] (b) (4)

References:

- i. Protocol 065: A double blind, placebo-controlled study to investigate the effects of finasteride on dihydrotestosterone and testosterone in scalp skin and sebum
- ii. Finasteride, an inhibitor of 5 α -reductase, suppress prostatic dihydrotestosterone in men with benign prostatic hyperplasia; McConnell, J.D. et. al.; Journal of Clinical Endocrinology and Metabolism; 1992; 74(3); 505-8
- iii. The clinical effects of a 5 α -reductase inhibitor, finasteride, on benign prostatic hyperplasia; Stoner, E. et. al.; The Journal of Urology; May 1992; 147; 1298-1302
- iv. The effect of finasteride in men with benign prostatic hyperplasia; Gormley, GJ et. al., The New England Journal of Medicine; Oct 1992; 327(17); 1185-91

The discussion was led mainly by Dr. Doanh Tran from DCP3. His questions to the sponsor related to PK comparisons between the 1 mg (Propecia) and 5 mg (Proscar) dose of finasteride. The focus was on six different biomarkers: 1. scalp skin DHT, 2. scalp skin T, 3. serum DHT, 4. intra-prostatic DHT, 5. serum PSA, and 6. prostate volume.

The Agency requested that the sponsor re-submit a courtesy copy of the final clinical study report (CSR) for protocol 065 "A double blind, placebo-controlled study to investigate the effects of finasteride on dihydrotestosterone and testosterone in scalp skin and sebum." The sponsor agreed.

The conversation ended amicably.

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/s/

J P PHILLIPS
08/04/2011



NDA 020788/S-020

INFORMATION REQUEST

Merck Sharp & Dohme Corp.
Attention: Frank J. Mellina, PharmD
Manager, Regulatory Affairs
126 East Lincoln Ave.
P.O. Box 2000, RY33-208
Rahway, NJ 07065-0900

Dear Dr. Mellina:

Please refer to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Propecia™ (finasteride) Tablet, 1 mg.

We also refer to your submission dated April 8, 2011.

We have the following information request:

Provide the data and calculation method you used to derive the exposure multiples found in the last paragraph of section 8.1 of the proposed PLR label for Propecia.

We ask that you submit this information by close of business on June 21, 2011.

If you have questions, call Paul Phillips, Regulatory Project Manager, at (301) 796-3935.

Sincerely,

{See appended electronic signature page}

David Kettl, M.D.
Clinical Team Leader
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

DAVID L KETTL
06/16/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR DDMAC LABELING REVIEW CONSULTATION **Please send immediately following the Filing/Planning meeting**				
TO: CDER-DDMAC-RPM		FROM: (Name/Title, Office/Division/Phone number of requestor) BJ Gould, CPMS 6-4224/Amy Weitach, MO 6-4078 ODE III/DDDP/6-2110				
REQUEST DATE 16 May 2011	IND NO.	NDA/BLA NO. 020788/S-020	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)			
NAME OF DRUG Propecia (finasteride) Tablet, 1 mg	PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG 4027510	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting) 14 July 2011			
NAME OF FIRM: Merck Sharp & Dohme		PDUFA Date: 08 October 2011 DDDP Target Date: 07 September 2011				
TYPE OF LABEL TO REVIEW						
<table border="0"> <tr> <td> TYPE OF LABELING: (Check all that apply) <input checked="" type="checkbox"/> PACKAGE INSERT (PI) <input checked="" type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input type="checkbox"/> CARTON/CONTAINER LABELING <input type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE (IFU) </td> <td> TYPE OF APPLICATION/SUBMISSION <input type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> IND <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input checked="" type="checkbox"/> LABELING SUPPLEMENT <input checked="" type="checkbox"/> PLR CONVERSION </td> <td> REASON FOR LABELING CONSULT <input type="checkbox"/> INITIAL PROPOSED LABELING <input checked="" type="checkbox"/> LABELING REVISION </td> </tr> </table>				TYPE OF LABELING: (Check all that apply) <input checked="" type="checkbox"/> PACKAGE INSERT (PI) <input checked="" type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input type="checkbox"/> CARTON/CONTAINER LABELING <input type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE (IFU)	TYPE OF APPLICATION/SUBMISSION <input type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> IND <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input checked="" type="checkbox"/> LABELING SUPPLEMENT <input checked="" type="checkbox"/> PLR CONVERSION	REASON FOR LABELING CONSULT <input type="checkbox"/> INITIAL PROPOSED LABELING <input checked="" type="checkbox"/> LABELING REVISION
TYPE OF LABELING: (Check all that apply) <input checked="" type="checkbox"/> PACKAGE INSERT (PI) <input checked="" type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input type="checkbox"/> CARTON/CONTAINER LABELING <input type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE (IFU)	TYPE OF APPLICATION/SUBMISSION <input type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> IND <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input checked="" type="checkbox"/> LABELING SUPPLEMENT <input checked="" type="checkbox"/> PLR CONVERSION	REASON FOR LABELING CONSULT <input type="checkbox"/> INITIAL PROPOSED LABELING <input checked="" type="checkbox"/> LABELING REVISION				
EDR link to submission: Application Type/Number: NDA 020788/S-020 Incoming Document Category/Sub Category: Electronic_Gateway Supporting Document Number: 203 eCTD Sequence Number: 0030 Letter Date: 04/08/2011 Stamp Date: 4/8/2011 EDR Location: \\CDSESUB1\EVSPROD\NDA020788\0030						
Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to DDMAC. Once the substantially complete labeling is received, DDMAC will complete its review within 14 calendar days.						
COMMENTS/SPECIAL INSTRUCTIONS: Labeling Meetings: #1 05 July 2011 @ 14:00, #2 12 July 2011 @ 10:00-12:00 if necessary #3 19 July 2011 @ 10:00, if necessary						
SIGNATURE OF REQUESTER Amy Weitach/BJ Gould						
SIGNATURE OF RECEIVER		METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DARRTS <input type="checkbox"/> HAND				

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/s/

BARBARA J GOULD
05/17/2011



NDA 020788/S-020

INFORMATION REQUEST

Merck Sharp & Dohme Corporation
Attention: Frank J. Mellina, PharmD
Manager, Regulatory Affairs
126 East Lincoln Avenue
P.O. Box 2000, RY33-208
Rahway, NJ 07065-0900

Dear Dr. Mellina:

Please refer to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Propecia (finasteride) Tablets, 1 mg.

We also refer to your submission dated April 8, 2011.

We are reviewing the risk/benefit assessment of your submission and have the following comments and information requests. We request a prompt written response by May 31, 2011 in order to continue our evaluation of your supplemental application.

While the Agency acknowledges that there are no data related to finasteride 1 mg therapy in prostate cancer studies, we request additional discussion regarding the pharmacodynamic effects of finasteride 1 mg vs. finasteride 5 mg. Agency review of at least certain parameters (e.g., serum DHT, prostatic DHT, and prostatic volume) suggests similar effects between finasteride 1 mg and finasteride 5 mg dose. The risk/benefit discussion for finasteride 1 mg for androgenetic hair loss will need to address the comparative pharmacodynamic effects of the two approved doses as it relates to the approved indication for Propecia.

If you have questions, call Barbara Gould, Chief, Project Management Staff, at (301) 796-4224.

Sincerely,

{See appended electronic signature page}

David Kettl, M.D.
Clinical Team Leader
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

DAVID L KETTL
05/13/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			REQUEST FOR CONSULTATION	
TO (Division/Office): Mail: OSE			FROM: ODE III/Division of Dermatology and Dental Products BJ Gould, CPMS 6-4224 Amy Weitach, MD 6-4078	
DATE 11 May 2011	IND NO.	NDA NO. 020788/S-020	TYPE OF DOCUMENT Label Supplement SDN 203	DATE OF DOCUMENT 08 April 2011
NAME OF DRUG Propecia (finasteride) Tablets, 1 mg		PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG 4027510	DESIRED COMPLETION DATE 26 June 2011
NAME OF FIRM: Merck Research Laboratories				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH			STATISTICAL APPLICATION BRANCH	
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):			<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):	
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES			<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST	
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP			<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS	
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL			<input type="checkbox"/> PRECLINICAL	
COMMENTS/SPECIAL INSTRUCTIONS: Please review the proposed labeling submitted for conversion of current approved label format to PLR format. Attached is the sponsor's currently approved label and the sponsor's proposed PLR formatted label. The submission for review is located @ EDR Location: \\CDSESUB1\EVSPROD\NDA020788\0030 EDR Location: \\CDSESUB1\EVSPROD\NDA020788\020788.enx --Gateway				
SIGNATURE OF REQUESTER Amy Weitach/BJ Gould			METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> EMAIL <input type="checkbox"/> HAND <input checked="" type="checkbox"/> DARRTS	
SIGNATURE OF RECEIVER			SIGNATURE OF DELIVERER	

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/s/

BARBARA J GOULD
05/17/2011