**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***

# NDA 20-788/S-017

| | |
|---|---|
| ***Trade Name:*** | Propecia |
| ***Generic Name:*** | finasteride |
| ***Sponsor:*** | Merck Sharp & Dohme Corp. |
| ***Approval Date:*** | March 11, 2011 |
| ***Labeling Changes:*** | Addition of depression to the post-marketing experience section of the label |

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# NDA 20-788/S-017

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# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# NDA 20-788/S-017

# APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020788/S-017

**SUPPLEMENT APPROVAL**

Merck Sharp & Dohme Corp.
Attention: Siyoung Ahn
Manager, Regulatory Affairs
126 East Lincoln Avenue
P.O. Box 2000, RY33-208
Rahway, NJ 07065-0900

Dear Ms. Ahn:

Please refer to your Supplemental New Drug Application (sNDA) dated July 16, 2010, received July 16, 2010, 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 amendment dated September 15, 2010.

This "Changes Being Effected" supplemental new drug application provides for inclusion of the term "depression" to the ADVERSE REACTIONS Postmarketing Experience section of the labeling and Patient Package Insert.

We have completed our review of this supplemental application, as amended. It is 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 and 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).

## LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

## 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 Kim Shiley, Regulatory Project Manager, at (301) 301-796-2117.

Sincerely,

*{See appended electronic signature page}*

Tatiana Oussova, M.D., M.P.H.
Deputy Director for Safety
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

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

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/s/

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TATIANA OUSSOVA
03/11/2011

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# NDA 20-788/S-017

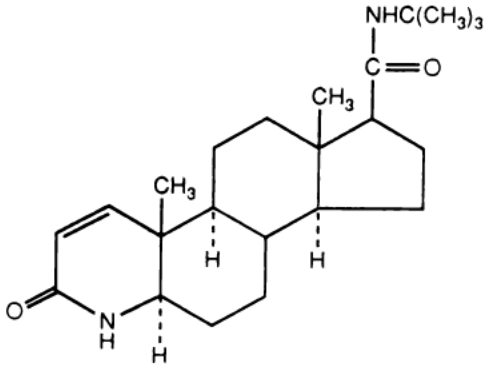
# LABELING

# PROPECIA®
**(finasteride)**
Tablets, 1 mg

## DESCRIPTION

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

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




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

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

## CLINICAL PHARMACOLOGY

Finasteride is a competitive and specific inhibitor of Type II 5α-reductase, an intracellular enzyme that converts the androgen testosterone into DHT. Two distinct isozymes are found in mice, rats, monkeys, and humans: Type I and II. Each of these isozymes is differentially expressed in tissues and developmental stages. In humans, Type I 5α-reductase is predominant in the sebaceous glands of most regions of skin, including scalp, and liver. Type I 5α-reductase is responsible for approximately one-third of circulating DHT. The Type II 5α-reductase isozyme is primarily found in prostate, seminal vesicles, epididymides, and hair follicles as well as liver, and is responsible for two-thirds of circulating DHT.

In humans, the mechanism of action of finasteride is based on its preferential inhibition of the Type II isozyme. Using native tissues (scalp and prostate), *in vitro* binding studies examining the potential of finasteride to inhibit either isozyme revealed a 100-fold selectivity for the human Type II 5α-reductase over Type I isozyme ($IC_{50}$=500 and 4.2 nM for Type I and II, respectively). For both isozymes, the inhibition by finasteride is accompanied by reduction of the inhibitor to dihydrofinasteride and adduct formation with NADP+. The turnover for the enzyme complex is slow ($t_{1/2}$ approximately 30 days for the Type II enzyme complex and 14 days for the Type I complex).

Finasteride has no affinity for the androgen receptor and has no androgenic, antiandrogenic, estrogenic, antiestrogenic, or progestational effects. Inhibition of Type II 5α-reductase blocks the peripheral conversion of testosterone to DHT, resulting in significant decreases in serum and tissue DHT concentrations. Finasteride produces a rapid reduction in serum DHT concentration, reaching 65% suppression within 24 hours of oral dosing with a 1-mg tablet. Mean circulating levels of testosterone and estradiol were increased by approximately 15% as compared to baseline, but these remained within the physiologic range.

In men with male pattern hair loss (androgenetic alopecia), the balding scalp contains miniaturized hair follicles and increased amounts of DHT compared with hairy scalp. Administration of finasteride decreases scalp and serum DHT concentrations in these men. The relative contributions of these

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Reference ID: 2917198

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

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

*Pharmacokinetics*

*Absorption*

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

*Distribution*

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

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

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

*Metabolism*

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

*Excretion*

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

Mean terminal half-life is approximately 5-6 hours in men 18-60 years of age and 8 hours in men more than 70 years of age.

*Special Populations*

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

*Gender:* PROPECIA is not indicated for use in women.

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

*Race:* The effect of race on finasteride pharmacokinetics has not been studied.

*Renal Insufficiency:* No dosage adjustment is necessary in patients with renal insufficiency. In patients with chronic renal impairment, with creatinine clearances ranging from 9.0 to 55 mL/min, AUC, maximum plasma concentration, half-life, and protein binding after a single dose of $^{14}$C-finasteride were similar to those obtained in healthy volunteers. Urinary excretion of metabolites was decreased in patients with renal impairment. This decrease was associated with an increase in fecal excretion of metabolites. Plasma concentrations of metabolites were significantly higher in patients with renal impairment (based on a 60% increase in total radioactivity AUC). However, finasteride has been well tolerated in men with normal renal function receiving up to 80 mg/day for 12 weeks where exposure of these patients to metabolites would presumably be much greater.

*Hepatic Insufficiency:* The effect of hepatic insufficiency on finasteride pharmacokinetics has not been studied. Caution should be used in the administration of PROPECIA in patients with liver function abnormalities, as finasteride is metabolized extensively in the liver.

*Drug Interactions* (also see PRECAUTIONS, *Drug Interactions*)

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

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

*Range

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

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

*Clinical Studies*

Studies in Men

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

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

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

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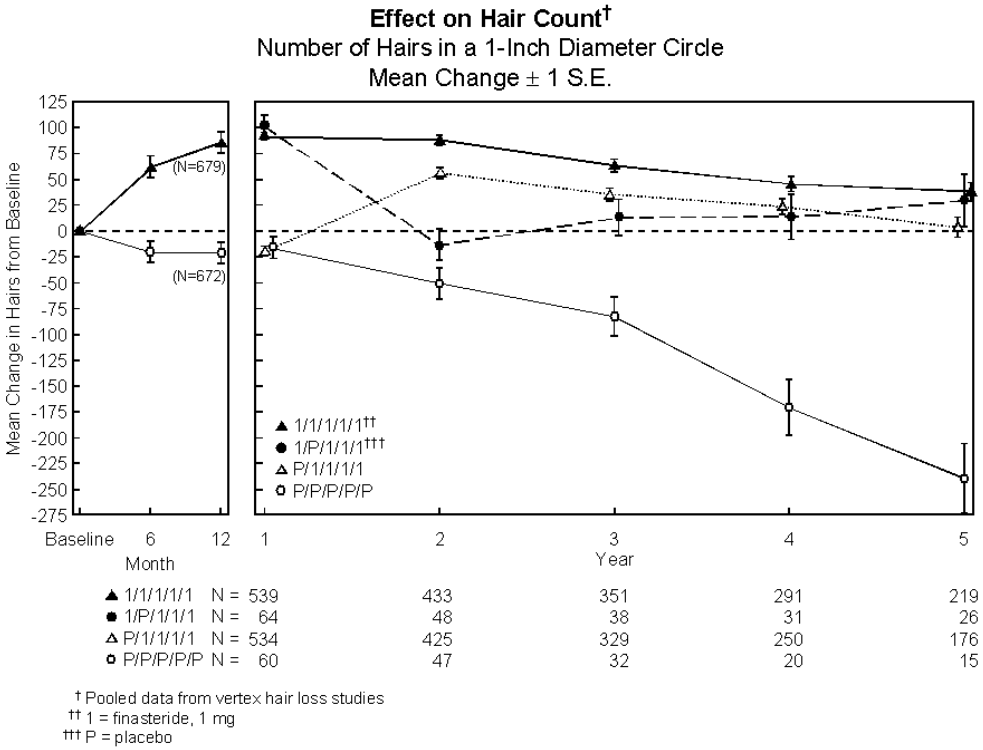
receiving placebo for the same periods. The extension studies were continued for 3 additional years, with 323 men on PROPECIA and 23 on placebo entering the fifth year of the study.

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

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

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

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




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

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

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

Other Results in Vertex Baldness Studies

A sexual function questionnaire was self-administered by patients participating in the two vertex baldness trials to detect more subtle changes in sexual function. At Month 12, statistically significant differences in favor of placebo were found in 3 of 4 domains (sexual interest, erections, and perception of sexual problems). However, no significant difference was seen in the question on overall satisfaction with sex life.

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

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

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

Summary of Clinical Studies in Men

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

Ethnic Analysis of Clinical Data from Men

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

Study in Women

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

## INDICATIONS AND USAGE

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

Efficacy in bitemporal recession has not been established.

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

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

## CONTRAINDICATIONS

PROPECIA is contraindicated in the following:

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

Hypersensitivity to any component of this medication.

## WARNINGS

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

EXPOSURE OF WOMEN - RISK TO MALE FETUS

Women should not handle crushed or broken PROPECIA tablets when they are pregnant or may potentially be pregnant because of the possibility of absorption of finasteride and the subsequent potential risk to a male fetus. PROPECIA tablets are coated and will prevent contact with the active ingredient during normal handling, provided that the tablets have not been broken or crushed. (See also CONTRAINDICATIONS; PRECAUTIONS, *Information for Patients* and *Pregnancy;* and HOW SUPPLIED, *Storage and Handling*.)

**PRECAUTIONS**

*General*

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

*Information for Patients*

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

Physicians should instruct their patients to promptly report any changes in their breasts such as lumps, pain or nipple discharge. Breast changes including breast enlargement, tenderness and neoplasm have been reported (see ADVERSE REACTIONS).

See also Patient Package Insert.

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

*Drug/Laboratory Test Interactions*

Finasteride had no effect on circulating levels of cortisol, thyroid-stimulating hormone, or thyroxine, nor did it affect the plasma lipid profile (e.g., total cholesterol, low-density lipoproteins, high-density lipoproteins and triglycerides) or bone mineral density. In studies with finasteride, no clinically meaningful changes in luteinizing hormone (LH), follicle-stimulating hormone (FSH) or prolactin were detected. In healthy volunteers, treatment with finasteride did not alter the response of LH and FSH to gonadotropin-releasing hormone indicating that the hypothalamic-pituitary-testicular axis was not affected.

In clinical studies with PROPECIA (finasteride, 1 mg) in men 18-41 years of age, the mean value of serum prostate-specific antigen (PSA) decreased from 0.7 ng/mL at baseline to 0.5 ng/mL at Month 12. Further, in clinical studies with PROSCAR (finasteride, 5 mg) when used in older men who have benign prostatic hyperplasia (BPH), PSA levels are decreased by approximately 50%. Other studies with PROSCAR showed it may also cause decreases in serum PSA in the presence of prostate cancer. These findings should be taken into account for proper interpretation of serum PSA when evaluating men treated with finasteride. Any confirmed increases in PSA levels from nadir while on PROPECIA may signal the presence of prostate cancer and should be carefully evaluated, even if those values are still within the normal range for men not taking a 5α-reductase inhibitor. Non-compliance to therapy with PROPECIA may also affect PSA test results.

*Drug Interactions*

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

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

*Carcinogenesis, Mutagenesis, Impairment of Fertility*

No evidence of a tumorigenic effect was observed in a 24-month study in Sprague-Dawley rats receiving doses of finasteride up to 160 mg/kg/day in males and 320 mg/kg/day in females. These doses

produced respective systemic exposure in rats of 888 and 2192 times those observed in man receiving the recommended human dose of 1 mg/day. All exposure calculations were based on calculated $AUC_{(0\text{-}24\ hr)}$ for animals and mean $AUC_{(0\text{-}24\ hr)}$ for man (0.05 μg•hr/mL).

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

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

In sexually mature male rabbits treated with finasteride at 80 mg/kg/day (4344 times the human exposure) for up to 12 weeks, no effect on fertility, sperm count, or ejaculate volume was seen. In sexually mature male rats treated with 80 mg/kg/day of finasteride (488 times the human exposure), there were no significant effects on fertility after 6 or 12 weeks of treatment; however, when treatment was continued for up to 24 or 30 weeks, there was an apparent decrease in fertility, fecundity, and an associated significant decrease in the weights of the seminal vesicles and prostate. All these effects were reversible within 6 weeks of discontinuation of treatment. No drug-related effect on testes or on mating performance has been seen in rats or rabbits. This decrease in fertility in finasteride-treated rats is secondary to its effect on accessory sex organs (prostate and seminal vesicles) resulting in failure to form a seminal plug. The seminal plug is essential for normal fertility in rats but is not relevant in man.

*Pregnancy*

*Teratogenic Effects: Pregnancy Category X*

See CONTRAINDICATIONS.

PROPECIA is not indicated for use in women.

Administration of finasteride to pregnant rats on gestational days 6-20 at doses ranging from 100 μg/kg/day to 100 mg/kg/day (1-684 times the human exposure, estimated) resulted in dose-dependent development of hypospadias in 3.6 to 100% of male offspring. Pregnant rats produced male offspring with decreased prostatic and seminal vesicular weights, delayed preputial separation, and transient nipple development when given finasteride at ≥30 μg/kg/day (0.2 times the human exposure, estimated) and decreased anogenital distance when given finasteride at ≥3 μg/kg/day (0.02 times the human exposure, estimated). The critical period during which these effects can be induced in male rats has been defined to be days 16-17 of gestation. The changes described above are expected pharmacological effects of drugs belonging to the class of Type II 5α-reductase inhibitors and are similar to those reported in male infants with a genetic deficiency of Type II 5α-reductase. No abnormalities were observed in female offspring exposed to any dose of finasteride *in utero*.

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

No evidence of malformations has been observed in rabbit fetuses exposed to finasteride *in utero* from days 6-18 of gestation at doses up to 100 mg/kg/day (1908 times the recommended human dose of 1 mg/day, based on body surface area comparison). However, effects on male genitalia would not be expected since the rabbits were not exposed during the critical period of genital system development.

The *in utero* effects of finasteride exposure during the period of embryonic and fetal development were evaluated in the rhesus monkey (gestation days 20-100), a species more predictive of human development than rats or rabbits. Intravenous administration of finasteride to pregnant monkeys at doses up to 800 ng/day (at least 250 times the highest estimated exposure of pregnant women to finasteride

from semen of men taking 1 mg/day, based on body surface area comparison) resulted in no abnormalities in male fetuses. In confirmation of the relevance of the rhesus model for human fetal development, oral administration of a 2 mg/kg/day dose of finasteride to pregnant monkeys resulted in external genital abnormalities in male fetuses. No other abnormalities were observed in male fetuses and no finasteride-related abnormalities were observed in female fetuses at any dose.

*Nursing Mothers*

PROPECIA is not indicated for use in women.

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

*Pediatric Use*

PROPECIA is not indicated for use in pediatric patients.

Safety and effectiveness in pediatric patients have not been established.

*Geriatric Use*

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

## ADVERSE REACTIONS

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

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

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

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

| | PROPECIA N=945 | Placebo N=934 |
|---|---|---|
| Decreased Libido | 1.8 | 1.3 |
| Erectile Dysfunction | 1.3 | 0.7 |
| Ejaculation Disorder *(Decreased Volume of Ejaculate)* | 1.2 *(0.8)* | 0.7 *(0.4)* |
| Discontinuation due to drug-related sexual adverse experiences | 1.2 | 0.9 |

Integrated analysis of clinical adverse experiences showed that during treatment with PROPECIA, 36 (3.8%) of 945 men had reported one or more of these adverse experiences as compared to 20 (2.1%) of 934 men treated with placebo (p=0.04). Resolution occurred in men who discontinued therapy with PROPECIA due to these side effects and in most of those who continued therapy. The incidence of each of the above adverse experiences decreased to ≤0.3% by the fifth year of treatment with PROPECIA.

In a study of finasteride 1 mg daily in healthy men, a median decrease in ejaculate volume of 0.3 mL (-11%) compared with 0.2 mL (–8%) for placebo was observed after 48 weeks of treatment. Two other studies showed that finasteride at 5 times the dosage of PROPECIA (5 mg daily) produced significant median decreases of approximately 0.5 mL (-25%) compared to placebo in ejaculate volume, but this was reversible after discontinuation of treatment.

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

*Postmarketing Experience for PROPECIA (finasteride 1 mg)*

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

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

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

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

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

| | Year 1 (%) | | Years 2, 3 and 4* (%) | |
|---|---|---|---|---|
| | Finasteride, 5 mg | Placebo | Finasteride, 5 mg | Placebo |
| Impotence | 8.1 | 3.7 | 5.1 | 5.1 |
| Decreased Libido | 6.4 | 3.4 | 2.6 | 2.6 |
| Decreased Volume of Ejaculate | 3.7 | 0.8 | 1 5 | 0.5 |
| Ejaculation Disorder | 0.8 | 0.1 | 0 2 | 0.1 |
| Breast Enlargement | 0.5 | 0.1 | 1.8 | 1.1 |
| Breast Tenderness | 0.4 | 0.1 | 0.7 | 0.3 |
| Rash | 0.5 | 0.2 | 0.5 | 0.1 |

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

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

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

The relationship between long-term use of finasteride and male breast neoplasia is currently unknown. During a 4- to 6-year placebo- and comparator-controlled 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. In another 4-year, placebo-controlled 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.

In a 7-year placebo-controlled trial that enrolled 18,882 healthy men, 9060 had prostate needle biopsy data available for analysis. In the PROSCAR group, 280 (6.4%) men had prostate cancer with Gleason scores of 7-10 detected on needle biopsy vs. 237 (5.1%) men in the placebo group. Of the total cases of prostate cancer diagnosed in this study, approximately 98% were classified as intracapsular (stage T1 or T2). The clinical significance of these findings is unknown. This information from the literature (Thompson IM, Goodman PJ, Tangen CM, et al. The influence of finasteride on the development of prostate cancer. *N Engl J Med* 2003;349:213-22) is provided for consideration by physicians when PROSCAR is used as indicated. PROSCAR is not approved to reduce the risk of developing prostate cancer.

## OVERDOSAGE

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

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

PROPECIA® (Finasteride) Tablets, 1 mg

## DOSAGE AND ADMINISTRATION

The recommended dosage is 1 mg orally once a day.

PROPECIA may be administered with or without meals.

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

## HOW SUPPLIED

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

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

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

*Storage and Handling*

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

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

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

Issued March 2011

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# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# NDA 20-788/S-017

# MEDICAL REVIEW(S)

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

| | |
|---|---|
| **Submission date:** | July 16, 2010 |
| **Supplement number:** | SLR17 |
| **SDN/ eCTD #:** | 190 / 21 |
| **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:** | Helm |
| **Clinical:** | Woitach/Kettl |
| **Review date:** | November 22, 2010 |
| **In DARRTS:** | December 9, 2010 |

**Regulatory Background:**
On July 16, 2010 Merck Research Laboratories submitted a changes being effected supplement (CBE-0) for the inclusion of the term "depression" in the *ADVERSE REACTIONS Postmarketing Experience for PROPECIA (finasteride 1mg)* section of the Package Circular and corresponding possible side effects section of the Patient Package Circular. The sponsor proposes this labeling change based on results of a search of the Worldwide Adverse Experience System (WAES) database conducted in patients treated with finasteride 0.2 mg and 1 mg tablets (PROPECIA) using terms related to depression/ suicide.

The Division of Dermatology and Dental Products (DDDP) consulted the Office of Surveillance and Epidemiology, Division of Pharmacovigilance I (OSE/DPV I) to provide an assessment of the sponsor's request to add "depression" to the Propecia product label. DPVI analyzed all reports of depression-related or suicide-related events associated with finasteride (Propecia and Proscar) submitted to FDA's Adverse Event Reporting System (AERS) database from respective approval dates to September 25, 2010. A number of depression-related and suicide-related cases were identified associated with use of finasteride. DPVI recommends reporting "depression" and "suicide thoughts and behavior" in the Post marketing Experience section of labeling for both finasteride products (Propecia and Proscar) and concludes a possible association between finasteride and these events, but could not assess causality from these reports. See Dr. Namita Kothary's review from November 16, 2010.

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 DDDP approved finasteride 1 mg (Propecia, NDA 20788) on December 19, 1997 for the treatment of androgenetic alopecia in men. Generic

versions are available for both products. The current product labels for finasteride (Proscar and Propecia) do not include depression-related or suicide-related adverse events. The sponsor has not submitted a similar labeling supplement to DRUP for the addition of the term "depression" to Proscar (finasteride 5 mg) labeling.

**Review:**

***Summary of Sponsor-submitted cases:***

The sponsor conducted a search of the Worldwide Adverse Experience System (WAES) database on 06-May-2010 for postmarketing reports received from HCPs, including regulatory agencies, and consumers in patients treated with finasteride 0.2 mg and 1 mg tablets (PROPECIA) from product launch (11-Sep-1997) through 30-Apr-2010. MedDRA preferred terms searched included depression, depressed mood, depressive symptom, major depression, depression suicidal, apathy, crying, anhedonia, feeling of despair, suicidal ideation, suicide attempt, and completed suicide. A total of 283 spontaneous reports were identified (38 serious and 245 non-serious). Of the 283 total reports, 120 were submitted by HCPs including regulatory agencies and the remaining 163 reports were received from consumers. Six representative reports deemed by the sponsor to be of clinical significance are presented below:

- WAES 0605GBR00130 describes a 43 year old white male with a wheat allergy that led to drowsiness who on 04-Apr-2005, was placed on therapy with finasteride 1 mg daily for the treatment of male pattern hair loss. There was no concomitant therapy. In September 2005 the patient experienced depressive episodes and mood swings. On 30-Apr-2006 therapy with finasteride was discontinued. The reporting physician stated the patient had "depressive episodes like dropping into a hole and never had depressive episodes or mood swings before finasteride, or since stopping but had the depressive episodes and mood swings several times when on finasteride – feeling negative about everything". Laboratory tests including thyroid function, testosterone levels, vitamin B12 levels and liver function were all normal before treatment with finasteride and during the time period of the depressive episodes and mood swings (dates, values and normal ranges not reported). The patient recovered since stopping finasteride.

- WAES 0606USA02062 describes a 32 year old male who on 19-Jan-2006 was placed on therapy with finasteride 1 mg daily for the treatment of male pattern alopecia. There was no concomitant medication. On 19-Jan-2006, after the first dose of finasteride, the patient experienced swollen face and hot flash. Three weeks after initiation of finasteride, the patient experienced depression tendency with generalized malaise. The patient's symptoms gradually exacerbated, and he experienced a lapse of memory or hypomnesia. On 23-Feb-2006, finasteride was discontinued. One to two weeks after discontinuation of finasteride, his lapse of memory improved. Three to four weeks after discontinuation, malaise and depression

tendency ameliorated. On an unspecified date in 2006, the patient recovered from the face edema and facial hot flush.

- WAES 0608USA05314 describes a 41 year old male with no known drug allergies and a history of appendectomy who in January 2006, was placed on therapy with finasteride 1 mg daily to prevent hair loss (duration not reported). There was no concomitant medication. In approximately February 2006, the patient experienced feeling very lethargic, general lack of energy and feeling depressed. The patient mentioned that he had never experienced depression prior to this. The patient sought medical attention and there were no diagnostic and/or laboratory tests performed. In February 2006, therapy with finasteride was discontinued and was not reintroduced. The reporter noted that the patient improved after stopping therapy and as of 04-Oct- 2006 was recovered.

- WAES 0209ITA00041 describes a 32 year old male who was placed on therapy with finasteride, 1 mg daily for the treatment of alopecia (duration not reported). Subsequently the patient experienced depression, described by the physician as a "transient humor disorder" which affected the normal patient's life. Therapy with finasteride was interrupted and the patient recovered from depression. Subsequently therapy with finasteride was restarted and on 10-Jan-2002 the patient experienced depression again. Six months after the first drug administration therapy with finasteride was discontinued. Subsequently the patient recovered from depression.

- WAES 98040274 describes a male physician who was placed on therapy with finasteride 1 mg daily for the treatment of hair loss (duration unknown). He became depressed and tired after being on finasteride for about one and one half to two weeks. He discontinued and restarted therapy twice, and then decided not to continue. The symptoms occurred three times. Subsequently he recovered.

- WAES 0607ITA00002 describes a 27 year old male with a history of anxiety depression, for which he had been treated and recovered in 2004, who in January 2006 was placed on therapy with finasteride 1 mg daily for the treatment of alopecia. In April 2006, the patient experienced anxiety depression symptoms and he decided to interrupt therapy with finasteride; subsequently he recovered from anxiety depression. He than restarted therapy with finasteride and subsequently experienced again anxiety depression; when therapy with finasteride was interrupted he recovered from the AE. The patient reported that during the following two months he interrupted and restarted therapy several times, and in every occasion he experienced again anxiety depression from which he recovered as soon as he stopped the treatment.

The sponsor has received a total of 283 reports of depression and depression-related terms since market introduction and 21% of these report a positive dechallenge, and 5% reported a positive rechallenge.

*Reviewer comment: It appears the sponsor has identified additional cases (283 vs. 159) which were not identified in OSE's AERS search (discussed below). It is this reviewer's opinion, the representative cases submitted by the sponsor are suggestive of drug-related depression based on a temporal relationship. Many of the reports retrieved by the sponsor and OSE describe cases of new onset of depression in otherwise healthy individuals. This could suggest causality. However, due to the prevalence of depression in the population, it could also be the first presentation of the disease and definitive causality cannot be assessed.*

*Additionally, there are a number of cases in which depression is reported in individuals with a history of depression or other risk factors for depression (as in the last case, WAES 0607ITA00002). In these patients it is unclear if the drug contributes to depression in a predisposed individual or if the adverse event is simply a manifestation of the cyclical nature of the disease.*

The sponsor provided additional information to attempt to understand the rates of depression reported. Their review notes that based on an estimated total exposure of approximately (b) (4) patient-years the reporting rate of depression in patients on PROPECIA is (b) (4) events/100,000 patient-years of exposure through 30-Apr-2010. The sponsor provides reported estimates of the incidence of depressive disorders to range from 2.8 to 14.7 per 1000 person years.

*Reviewer comment: This reviewer concurs with the sponsor's assessment that although these rates are not directly comparable, it does give some context as to the low occurrence of depressive disorders observed. However, this reviewer cannot exclude the possibility of a causal association in a subset of individuals.*

***Summary of OSE/DPV I consult:***
DPV I conducted a PubMed literature search for case reports of depression-related or suicide-related adverse events associated with finasteride and did not identify additional case reports in the medical literature which were not reported in AERS.

A search of the AERS database by OSE retrieved a total of 159 depression-related or suicide-related reports out of 10,035 total adverse event reports for finasteride. Of these, 19 reports were excluded from further analysis and one report described two separate cases. DPV analyzed 141 cases of depression-related or suicide-related adverse events associated with finasteride. Approximately half (n=71) were associated with the use of Propecia. Some cases reported more than one event. Depression-related events for Propecia included: Depression (66), Depressed Mood (3), Anhedonia (1), Major Depression (1), and Feeling of despair (1) Suicide-related events for Propecia included: Suicidal Ideation (11), Completed Suicide (2), Suicide Attempt (1), and Intentional

Overdose (1). AERS search results categorized by drug product are described in the table below:

**Table 1. Characteristics of finasteride and depression-related or suicide-related AERS cases received by FDA from marketing to September 25, 2010 (n=141), based on reported finasteride product**

| | Propecia or finasteride 1 mg (n=71) | Proscar or finasteride 5 mg (n=67) | Unknown finasteride product (n=3) |
|---|---|---|---|
| Origin | US (55) Foreign (16) | US (49) Foreign (18) | US (3) |
| Gender | Male (69) NS (2) | Male (64) Female (1) NS (2) | Male (2) Female (1) |
| Age (years) | Mean: 32 Median: 30<br>Range: 16 – 56 *(n=57)* | Mean: 65 Median: 70<br>Range: 16 – 88 *(n=51)* | Reported ages: 24, 48, 51 *(n=3)* |
| Report year | 1996-2000 (23) 2001-2005 (9)<br>2006-2010 (39) | approval-1995 (32) 1996-2000 (20)<br>2001-2005 (5) 2006-2010 (10) | 2006-2010 (3) |
| Report type | Expedited (27) Direct (27) Periodic (17) | Expedited (29) Direct (5) Periodic (33) | Expedited (1) Direct (2) |
| Duration of finasteride therapy | Mean: 10 months Median: 3.3 months<br>Range: 4 days – 5.7 years *(n=45)* | Mean: 1.2 years Median: 4.2 months<br>Range: 1 day – 23.2 years *(n=35)* | Reported values: 3-4 months (1)<br>11 months (1) *(n=2)* |
| Time to onset of event from start of therapy | Mean: 6 months Median: 3 months<br>Range: same day – 3.5 years *(n=43)* | Mean: 3.9 months Median: 3 months<br>Range: same day – 2.2 years *(n=38)* | Reported values: 1-2 months (1)<br>2-3 months (1) *(n=2)* |
| Indications | Alopecia (53) Prevention of alopecia (2)<br>NS (16) | BPH (33) Enlarged prostate (4)<br>Alopecia (2) Prostate adenoma (2)<br>Other* (5) NS (21) | Alopecia (1) Prevention of alopecia (1)<br>NS (1) |
| Depression-related adverse events (n=131)† | Depression (66) Depressed Mood (3)<br>Anhedonia (1) Major Depression (1)<br>Feeling of despair (1) | Depression (57) Anhedonia (1)<br>Decreased interest (1) Dysphoria (1)<br>Major Depression (1) | Depression (1) Depressed Mood (1)<br>Major Depression (1) |
| Suicide-related adverse events (n=29)† | Suicidal Ideation (11), Completed Suicide (2), Suicide Attempt (1), Intentional Overdose (1) | Completed Suicide (6), Suicide Attempt (6), Suicidal Ideation (4), Intentional Overdose (1) | Completed Suicide (1) |
| Action taken for finasteride (DC, RC)‡ | Discontinued (41), Continued (7), NS (23)<br>+DC (11), -DC (19), +RC (3) | Discontinued (34), Continued (14), NS (19)<br>+DC (20), -DC (4), +RC (1) | Discontinued (1), Continued (1), NS (1)<br>-DC (1), +RC (1) |
| Confounding factors§ | Medical conditions (17), Medications (9) | Medical conditions (20), Medications (25) | Medical conditions (1), Medications (1) |
| Primary Outcome | DE (2) HO (4) DS (6) LT (7)<br>RI (6) OT (27) NI (19) | DE (6) HO (13) DS (3) LT (2)<br>OT (15) NI (28) | DE (1) OT (2) |

DE= Death DS=Disability HO=Hospitalization LT=Life-threatening NS=Not stated NI=No serious outcome reported OT=Other RI=Required intervention

* Other indications include 1 each of hypertension, acne, prostatism, prostatitis, prostatic disorder + dysuria

† A case may report more than one depression-related or suicide-related adverse event

‡ +DC=Positive dechallenge (events improved within one year [11 cases] or after an unknown amount of time [20 cases] of discontinuing finasteride); -DC=Negative dechallenge (events ongoing despite discontinuing finasteride); +RC=Positive rechallenge (finasteride reintroduced and events recurred, event onset details not provided in these four cases)

§ **Potentially confounding medical conditions**: depression (17), anxiety (5), diabetes (5), smoking (5), surgery (5), acne (3), alcohol use (2), cerebrovascular disorders (2), dementia (2), attention deficit hyperactivity disorder (1),blindness (1), cirrhosis (1), dysthymia (1), genital herpes (1), hysterectomy (1), marijuana use (1), osteoarthritis (1), panic attacks (1), Parkinson's disease (1), post-traumatic stress disorder (1), "psychogenic stress reaction" (1), psychosis (1), sexual dysfunction (1), thyroid disorder (1)

**Potentially confounding medications**: medications for psychiatric disorders (16; selective serotonin reuptake inhibitors-6, benzodiazepines-5, trazodone-2, bupropion-2, haloperidol-2, buspirone-1, unspecified antidepressant-1, unspecified anti-anxiety agent-1), atenolol (2), amantadine (1), atorvastatin (1), captopril (1), ciprofloxacin (2), clomiphene (1), cyclobenzaprine (1), diclofenac (1), digoxin (2), diltiazem (2), doxazosin (1), enalapril (1), estrogens (1), gabapentin (1), indoramin (1), levetiracetam (1), levothyroxine (1), lisinopril (1), lovastatin (1), metolazone (1), metoprolol (1), naproxen (2), nifedipine (3), omeprazole (2), ramipril (1), SMX/TMP (1), simvastatin (2), simvastatin/ezetimibe (1), terazosin (3), topiramate (1), valproic acid (1), warfarin (1)

Source: Table 1 DVP I review (11/16/10)

Of the 71 Propecia-associated reports, some information regarding patient disposition was included. 41 patients discontinued treatment and 7 patients continued treatment. 11 cases reported a positive dechallenge (improved within 1 year), 3 cases reported a positive rechallenge, 19 cases reported a negative dechallenge.

*Reviewer comment: This reviewer concurs with the DPV reviewer that limited information in AERS reporting, makes it difficult to independently assess the course of events and determine causality. The number of positive dechallenge/ rechallenge cases is suggestive of drug-related depression. However, as stated above, because the clinical course of depression may be cyclical and the etiology of depression is multifactorial, a determination for the relationship between Propecia and depression cannot be definitively made.*

The sponsor is proposing only the addition of "depression" to the post-marketing section of the label. DPV also searched for suicide-related reports likely because major

depression is the psychiatric diagnosis most commonly associated with suicide. Results include reports showing Suicidal Ideation and depression (11), Suicide Ideation (1), Completed Suicide (2), Suicide Attempt/ Intentional Overdose (1).

OSE's Division of Epidemiology conducted a drug use review that estimates approximately (b) (4) prescriptions were dispensed and (b) (4) patients received Propecia based on data from US outpatient retail pharmacies from 2002-2009, inclusive. An additional (b) (4) prescriptions of generic finasteride were dispensed in the same time period. Of those approximately (b) (4) were indicated for "Alopecia" resulting in approximately an additional (b) (4) prescriptions for low dose finasteride.

In this same time period, DPV identified 21 domestic (US) adverse event cases reported for Propecia that included 21 cases of depression of which 5 also reported suicidal ideation and 1 also reported completed suicide.

*Reviewer comment: The number of suicide ideation, attempts and completed suicide is lower than would be expected in this patient population. The National Center for Injury Prevention & Control's Web-based Injury Statistics Query and Reporting System (WISQARS) database ranks suicide as the 4th leading cause of death (1997-2007) in males age 16-56 of age (19,597) 7.9%*

*Assessment of suicidal behavior has been conducted in epidemiologic studies which queried a sample population as part of 2 National Institutes of Health studies. Results are shown in the table below:*

**Lifetime Rates of Suicide Attempts/ Suicidal Ideation**
**In the Full NLAES and NESARC Samples**

| | NLAES[a] (n = 42 862) % (95% CI [c]) | NESARC [b] (n = 43 093) % (95% CI [c]) | OR (95% CI [d]) |
|---|---|---|---|
| Total suicidal ideation | 9.7 (9.32–10.01) | 8.4 (7.82–8.93) | 0.78 (0.72–0.85) |
| Suicidal ideation without suicide attempts | 7.6 (7.26–7.87) | 6.1 (5.73–6.58) | 0.69 (0.63–0.75) |
| Suicide attempt among those with suicidal ideation | 21.7 (20.31–23.23) | 26.6 (24.91–28.27) | 1.50 (1.32–1.71) |
| Suicide attempt | 2.4 (2.26–2.59) | 2.4 (2.16–2.56) | 1.02 (0.90–1.15) |

[a]In the National Longitudinal Alcohol Epidemiologic Survey (NLAES): among those that reported a suicide attempt (N= 1086), 150 individuals (13.8%) reported no suicidal ideation.
[b]In the National Epidemiological Survey on Alcohol and Related Conditions (NESARC): among those that reported a suicide attempt (N= 1074), 62 individuals (5.8%) reported no suicidal ideation.
[c]CI, confidence interval.
[d]Odds ratio controlled for sex, race, age, income, education, urbanicity, region and major depression.

*The 2 reported cases of completed suicide contain limited information and one case is confounded with other with potential life stressors. This reviewer is unable to make an assessment of causality based on these 2 cases of completed suicide. The relationship between depression potentially associated with Propecia and suicidality is difficult to assess. Publications report a difference in the nature of drug-induced depression and major depression. It is possible that the drug-induced depression does not present with the same risk for suicide as major depression.*

*Suicide has been reported with use of Propecia* (b) (4) [redacted]

***Summary of literature***

Medical literature suggests a possible association between depression and finasteride based on biological plausibility. 5alpha-reductase inhibitors (5ARIs) reduce the conversion of testosterone to 5α-dihydrotestosterone (DHT). Finasteride preferentially targets the Type II isozyme of 5 alpha-reductase found in the prostate, seminal vesicles, epididymides, hair follicles, and liver. Since finasteride can cross the blood-brain barrier, it also has the potential to affect 5 alpha-reductase activity in the central nervous system. Animal studies suggest that finasteride affects 5 alpha-reductase in the brain and inhibits the conversion of progesterone to allopregnanolone. Allopregnanolone targets $GABA_A$-receptors, and may therefore have an effect on mood and behavior.

There are also reports of retrospective and prospective uncontrolled studies which suggest a link between finasteride and depression. In a retrospective case series of 23 Italian patients who used finasteride to treat alopecia, 19 patients developed moderate-severe depression. The events occurred at least one month after starting finasteride and resolved within three days to three weeks of discontinuing therapy. Two of the 19 patients reported a positive rechallenge, with the events occurring within two weeks of restarting finasteride. None of the patients reported a history of psychiatric or neurological disorder, or the use of drugs that may affect mood. Investigators could find no correlation between reported dissatisfaction with hair stabilization or sexual dysfunction.

In another larger, prospective, uncontrolled study, 144 men in Iran used finasteride 1 mg daily to treat alopecia. Subjects with mood disorders or other chronic disease were excluded. Depressed mood and anxiety was assessed using self-administered questionnaires. A small but, statistically significant difference was demonstrated on a

depression scale, but not an anxiety scale after treatment with finasteride as compared to before treatment.

*Reviewer comment: Although interpretation of these studies is limited based on study design, these studies support an association between finasteride and depression. This reviewer has been unable to find literature demonstrating a link between suicidal behavior and finasteride.*

**Conclusion:**
Taking into consideration the biologic plausibility, the spontaneously reported cases and medical literature, this reviewer concurs with including the term "depression" in the post-marketing section of the prescribing information and as a possible side-effect in the patient package insert. (b) (4)

**Proposed Propecia Labeling regarding depression:**

**Prescribing information**
*Postmarketing Experience for PROPECIA (finasteride 1 mg)*
Breast tenderness and enlargement; **depression**; hypersensitivity reactions including rash, pruritus, urticaria, and swelling of the lips and face; and testicular pain. See *Controlled Clinical Trials and Long-Term Open Extension Studies for PROSCAR* (finasteride 5 mg) in the Treatment of Benign Prostatic Hyperplasia*.

(b) (4)

**Recommended Regulatory Action:** Approval of the supplemental labeling request with labeling as proposed by the sponsor.

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

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## References:

Duskova M, Hill M, Matouskova M, Starka L. Finasteride treatment and neuroactive steroid formation. Prague Medical Report 2009;110:222-30.

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Chang SH. Dutasteride and finasteride drug use review. RCM# 2010-1830. December 1, 2010.

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/s/

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AMY S WOITACH
12/09/2010

DAVID L KETTL
12/09/2010

Concur with DDDP medical officer review that adding depression (b) (4) to the label is warranted. (b) (4)

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# NDA 20-788/S-017

# OTHER REVIEW(S)

**Department of Health and Human Services**
**Public Health Service**
**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Surveillance and Epidemiology**

Date: November 16, 2010

To: Susan Walker, M.D., F.A.A.D., Director,
Division of Dermatology and Dental Products (DDDP),
Office of New Drugs (OND)

Through: Mark Avigan, M.D., C.M., Director,
Division of Pharmacovigilance I (DPV I)
and
Ida-Lina Diak, Pharm.D., Safety Evaluator Team Leader, DPV I

From: Namita Kothary, PharmD, Safety Evaluator, DPV I

Subject: Depression-related and suicide-related adverse events

Drug Name(s): Finasteride (Propecia, Proscar, and multiple generics)

Application Type Number and Applicant/sponsor:

| Drug | Application Type, Number (Sponsor) |
|---|---|
| Propecia 1 mg tablet | NDA 20788 (Merck) |
| Finasteride 1 mg tablets | ANDAs 76436, 76905, 77335, 78371, 90060, (generics) |
| Proscar 5 mg tablet | NDA 20180 (Merck) |
| Finasteride 5 mg tablets | ANDAs 76340, 76437, 76511, 77251, 77578, 77914, 78341, 78900, 90061, 90121 (generics) |

OSE RCM #: 2010-1649

## CONTENTS

## EXECUTIVE SUMMARY

This review describes post-marketing cases of depression-related and suicide-related adverse events in the Adverse Event Reporting System (AERS) database associated with finasteride 1 mg oral tablets (Propecia) and finasteride 5 mg oral tablets (Proscar). An association between the use of finasteride and depression-related or suicide-related adverse events is possible based on the AERS cases we reviewed and information available in the medical literature. Therefore, we agree with the sponsor's assessment to add depression to the Adverse Events, Postmarketing Experience section of the label. We also identified cases of suicide-related adverse events, which further support this potential association with finasteride. A relationship between finasteride exposure as a causal or contributory factor and depression-related and suicide-related events is difficult to assess based on the limited information provided in the cases and the presence of confounding factors (i.e. medical conditions associated with depression/suicide, use of medications labeled for depression/suicide); however, we identified cases of positive dechallenge and positive rechallenge that support a possible association. Whether these cases were marked by fluctuations in depression/suicidality or drug effects associated with finasteride is not certain.

Based on this review, OSE recommends the following changes to the labels for currently available formulations of finasteride (Propecia, Proscar, and their corresponding generics):

- Updating the Adverse Events, Postmarketing Experience section to reflect the potential risk for depressive symptoms

(b) (4)

We will also continue monitoring the AERS database for adverse events associated with finasteride. If additional safety concerns emerge regarding depression-related or suicide-related events, we may consider consulting the Division of Psychiatry Products, request additional information and analyses from the sponsor, or recommend other regulatory actions as warranted.

# 1 INTRODUCTION

This review describes post-marketing cases of depression-related and suicide-related adverse events in the Adverse Event Reporting System (AERS) database associated with finasteride 1 mg oral tablets (Propecia) and finasteride 5 mg oral tablets (Proscar).

## 1.1 BACKGROUND

In July 2010, the FDA received a Changes Being Effected labeling supplement from the sponsor regarding the addition of the term "depression" to the Adverse Reactions, Postmarketing Experience section of the Propecia Package Insert and the Possible Side Effects section of the Propecia Patient Package Insert.[1] The Division of Dermatology and Dental Products (DDDP) consulted the Division of Pharmacovigilance I (DPV I) to provide an assessment of the sponsor's request to add "depression" to the Propecia product label. However, since finasteride is also available as Proscar, we expanded the search to include any orally administered finasteride product.

Finasteride inhibits 5alpha-reductase and the subsequent conversion of testosterone to dihydrotestosterone (DHT). It preferentially targets the Type II isozyme of 5alpha-reductase found in the prostate, seminal vesicles, epididymides, hair follicles, and liver. Since finasteride can cross the blood-brain barrier, it also has the potential to affect 5alpha-reductase activity in the central nervous system. Animal studies suggest that finasteride affects 5alpha-reductase in the brain and inhibits the conversion of progesterone to allopregnanolone. Allopregnanolone targets $GABA_A$-receptors, and may therefore have an effect on mood and behavior.[2-5] Additionally, the product labels for both finasteride products include decreased libido and other adverse events related to sexual dysfunction, which may also be associated with depressive symptoms.[2,3,6]

## 1.2 REGULATORY HISTORY

Two finasteride products are currently available in the US. The FDA approved finasteride 5 mg (Proscar, NDA 20180) on June 19, 1992 for the treatment of symptomatic benign prostatic hyperplasia (BPH) and finasteride 1 mg (Propecia, NDA 20788) on December 19, 1997 for the treatment of androgenetic alopecia in men. Generic versions are available for both products.[7]

## 1.3 PREVIOUS OSE REVIEWS RELATED TO PSYCHIATRIC EVENTS

OSE has not completed any post-marketing safety reviews of depression-related or suicide-related adverse events associated with finasteride.

## 1.4 PRODUCT LABELING

The current product labels for finasteride (Proscar and Propecia) do not include depression-related or suicide-related adverse events.[2,3]

## 2 METHODS AND MATERIALS

### 2.1 AERS SELECTION OF CASES

We searched the AERS database on September 25, 2010 using the following criteria:

- Drug terms: finasteride, Propecia, Proscar (including associated trade, active, and verbatim names)
- MedDRA adverse event search terms: Depression- excluding suicide and self injury (SMQ, narrow search), Suicide/Self Injury (SMQ, narrow search)
- Time period: from market approval to September 25, 2010

**Case definition:** We included cases that met the following definitions based on reported adverse event terms as well as information provided in the case narratives.

> Suicide-related: Cases that reported a temporal relationship between finasteride and one or more of the following MedDRA Preferred Terms- Completed suicide, Depression suicidal, Intentional overdose, Intentional self-injury, Multiple drug overdose intentional, Poisoning deliberate, Self injurious behavior, Self-injurious ideation, Suicidal behavior, Suicidal ideation, Suicide attempt
>
> Depression-related: Cases that reported a temporal relationship between finasteride and one or more of the following MedDRA Preferred Terms- Activation syndrome, Adjustment disorder with depressed mood, Adjustment disorder with mixed anxiety depressed mood, Agitated depression, Anhedonia, Antidepressant therapy, Childhood depression, Decreased interest, Depressed mood, Depression, Depression postoperative, Depressive symptom, Dysphoria, Dysthymic disorder, Electroconvulsive therapy, Feeling guilty, Feeling of despair, Feelings of worthlessness, Major depression, Menopausal depression, Postpartum depression

The AERS search retrieved 159 reports out of 10,035 total adverse event reports for finasteride. We did not include 19 reports in the case series for the following reasons:

- Duplicate reports (8)
- Depression-related or suicide-related events related to other situational factors in the patient's life (4). The reported situational factors include:
  - *"clinical worsening of depression […] secondary to situational changes"*
  - *"patient had retired […] reactive depression resolved with counseling and employment"*
  - *"reactive depression due to the problematical situation at work"*
  - *"after the voluntary abortion, the patient experienced reactive depression"*
- Depression-related or suicide-related events not reported (3)
- Medication error (3; filled in error-2, name confusion between Proscar and Zocor-1}
- Unclear if the patient was exposed to finasteride (1)

Of the remaining 140 cases, one report described two separate cases; this is reflected in the case count for the remainder of the document. Section 3.1 describes 141 cases of depression-related or suicide-related adverse events associated with finasteride.

### 2.2 LITERATURE SEARCH

We searched the medical literature (PubMed@FDA) on September 24, 2010 for case reports of depression-related or suicide-related adverse events associated with finasteride using the search string "(finasteride OR Propecia OR Proscar) and (depress* OR suicid*)."

## 3 RESULTS

### 3.1 AERS SEARCH RESULTS (N=141)

Table 1 describes the 141 unduplicated AERS cases of depression-related or suicide-related events associated with finasteride. Appendix A contains line-listing summaries of these cases.

**Table 1. Characteristics of finasteride and depression-related or suicide-related AERS cases received by FDA from marketing to September 25, 2010 (n=141), based on reported finasteride product**

| | Propecia or finasteride 1 mg (n=71) | Proscar or finasteride 5 mg (n=67) | Unknown finasteride product (n=3) |
|---|---|---|---|
| Origin | US (55) Foreign (16) | US (49) Foreign (18) | US (3) |
| Gender | Male (69) NS (2) | Male (64) Female (1) NS (2) | Male (2) Female (1) |
| Age (years) | Mean: 32 Median: 30<br>Range: 16 – 56 *(n=57)* | Mean: 65 Median: 70<br>Range: 16 – 88 *(n=51)* | Reported ages: 24, 48, 51 *(n=3)* |
| Report year | 1996-2000 (23) 2001-2005 (9)<br>2006-2010 (39) | approval-1995 (32) 1996-2000 (20)<br>2001-2005 (5) 2006-2010 (10) | 2006-2010 (3) |
| Report type | Expedited (27) Direct (27) Periodic (17) | Expedited (29) Direct (5) Periodic (33) | Expedited (1) Direct (2) |
| Duration of finasteride therapy | Mean: 10 months Median: 3.3 months<br>Range: 4 days – 5.7 years *(n=45)* | Mean: 1.2 years Median: 4.2 months<br>Range: 1 day – 23.2 years *(n=35)* | Reported values: 3-4 months (1)<br>11 months (1) *(n=2)* |
| Time to onset of event from start of therapy | Mean: 6 months Median: 3 months<br>Range: same day – 3.5 years *(n=43)* | Mean: 3.9 months Median: 3 months<br>Range: same day – 2.2 years *(n=38)* | Reported values: 1-2 months (1)<br>2-3 months (1) *(n=2)* |
| Indications | Alopecia (53) Prevention of alopecia (2)<br>NS (16) | BPH (33) Enlarged prostate (4)<br>Alopecia (2) Prostate adenoma (2)<br>Other* (5) NS (21) | Alopecia (1) Prevention of alopecia (1)<br>NS (1) |
| Depression-related adverse events (n=131)† | Depression (66) Depressed Mood (3)<br>Anhedonia (1) Major Depression (1)<br>Feeling of despair (1) | Depression (57) Anhedonia (1)<br>Decreased interest (1) Dysphoria (1)<br>Major Depression (1) | Depression (1) Depressed Mood (1)<br>Major Depression (1) |
| Suicide-related adverse events (n=29)† | Suicidal Ideation (11), Completed Suicide (2), Suicide Attempt (1), Intentional Overdose (1) | Completed Suicide (6), Suicide Attempt (6), Suicidal Ideation (4), Intentional Overdose (1) | Completed Suicide (1) |
| Action taken for finasteride (DC, RC)‡ | Discontinued (41), Continued (7), NS (23)<br>+DC (11), -DC (19), +RC (3) | Discontinued (34), Continued (14), NS (19)<br>+DC (20), -DC (4), +RC (1) | Discontinued (1), Continued (1), NS (1)<br>-DC (1), +RC (1) |
| Confounding factors§ | Medical conditions (17), Medications (9) | Medical conditions (20), Medications (25) | Medical conditions (1), Medications (1) |
| Primary Outcome | DE (2) HO (4) DS (6) LT (7)<br>RI (6) OT (27) NI (19) | DE (6) HO (13) DS (3) LT (2)<br>OT (15) NI (28) | DE (1) OT (2) |

DE= Death DS=Disability HO=Hospitalization LT=Life-threatening NS=Not stated NI=No serious outcome reported OT=Other RI=Required intervention

* Other indications include 1 each of hypertension, acne, prostatism, prostatitis, prostatic disorder + dysuria

† A case may report more than one depression-related or suicide-related adverse event

‡ +DC=Positive dechallenge (events improved within one year [11 cases] or after an unknown amount of time [20 cases] of discontinuing finasteride); -DC=Negative dechallenge (events ongoing despite discontinuing finasteride); +RC=Positive rechallenge (finasteride reintroduced and events recurred, event onset details not provided in these four cases)

§ **Potentially confounding medical conditions**: depression (17), anxiety (5), diabetes (5), smoking (5), surgery (5), acne (3), alcohol use (2), cerebrovascular disorders (2), dementia (2), attention deficit hyperactivity disorder (1),blindness (1), cirrhosis (1), dysthymia (1), genital herpes (1), hysterectomy (1), marijuana use (1), osteoarthritis (1), panic attacks (1), Parkinson's disease (1), post-traumatic stress disorder (1), "psychogenic stress reaction" (1), psychosis (1), sexual dysfunction (1), thyroid disorder (1)

**Potentially confounding medications**: medications for psychiatric disorders (16; selective serotonin reuptake inhibitors-6, benzodiazepines-5, trazodone-2, bupropion-2, haloperidol-2, buspirone-1, unspecified antidepressant-1, unspecified anti-anxiety agent-1), atenolol (2), amantadine (1), atorvastatin (1), captopril (1), ciprofloxacin (2), clomiphene (1), cyclobenzaprine (1), diclofenac (1), digoxin (2), diltiazem (2), doxazosin (1), enalapril (1), estrogens (1), gabapentin (1), indoramin (1), levetiracetam (1), levothyroxine (1), lisinopril (1), lovastatin (1), metolazone (1), metoprolol (1), naproxen (2), nifedipine (3), omeprazole (2), ramipril (1), SMX/TMP (1), simvastatin (2), simvastatin/ezetimibe (1), terazosin (3), topiramate (1), valproic acid (1), warfarin (1)

### 3.2 LITERATURE SEARCH RESULTS

We did not identify additional case reports of depression-related or suicide-related adverse events associated with finasteride in the medical literature.

## 4 DISCUSSION

An association between the use of finasteride and depression-related or suicide-related adverse events is possible based on the AERS cases we reviewed and information available in the medical literature. However, this association is difficult to characterize due to the limited information provided in the cases and the presence of confounding factors (i.e. medical conditions associated with depression/suicide, use of medications labeled for depression/suicide). Propecia is primarily used for the FDA-approved indication of androgenetic alopecia, which affects 30% of men 30 years and older and 50% of men 50 years and older.[10] Proscar is primarily used for the FDA-approved indication of BPH, which affects 40% of men in their fifties and 90% of men in their eighties.[11] Given the different patient populations, there were no unexpected differences observed between Propecia and Proscar in the AERS cases. Therefore, we will discuss the 141 cases together, regardless of the specific finasteride product.

The sponsor estimates the worldwide total exposure of approximately (b) (4) patient-years of treatment with Propecia from market introduction through April 30, 2010. A separate OSE drug use review estimates approximately (b) (4) prescriptions were dispensed and (b) (4) patients received finasteride based on data from US outpatient retail pharmacies for both finasteride products combined from 2002-2009, inclusive.[12] In this same time period, we identified 31 domestic (US) adverse event cases that reported depression-related events (23), suicide-related events (2), or both (6).

Two-thirds of the cases (94/141) reported serious outcomes, including nine cases of death due to completed suicide. All nine cases of completed suicide were difficult to assess due to limited information provided in the case (7), history of depression (2), use of other medications associated with depression or suicide (3), or the reporting health care professional stating that they felt the events were not related to finasteride (4); however, we cannot exclude that finasteride may have contributed to the events. The remaining serious outcomes included hospitalization (17), disability (9), life-threatening (9), required intervention (6), or "other serious" / medically significant outcome (44).

Approximately one-fifth (33/141) of the cases reported a positive dechallenge or rechallenge; however, these cases provided limited information, making it difficult for us to independently assess the course of events. Approximately 41% (31/76) of the cases in which finasteride was discontinued reported a positive dechallenge (i.e., events improved after discontinuing therapy); 28 of these cases reported depression-related events and the remaining three cases reported both depression-related and suicide-related events. Four cases reported a positive rechallenge; all four of these cases reported depression-related events. However, none of the positive rechallenge cases reported sufficient detail (e.g., times to onset and resolution) for us to assess the events. Additionally, the clinical course of depression may be cyclical. Therefore, despite the reported positive dechallenges and positive rechallenges, it is difficult to determine the role of finasteride.

Approximately 40% (55/141) of the cases were potentially confounded by a medical condition associated with depression/suicide (38) and/or the use of a medication labeled for depression/suicide (35). Of the 38 cases that were potentially confounded based on medical history, 20 cases reported a history of psychiatric disorders (depression-11, other psychiatric disorders-3, depression and other psychiatric disorders-6). Four of these 20 cases, as well as the remaining 18 cases, reported potentially confounding medical conditions that may be associated with depression (see Table 1 for details).

Of the 35 cases that were potentially confounded based on the use of concomitant medications, 33 cases reported the use of a medication with depression-related or suicide-related events in the product label, and the remaining two reported the use of unspecified medications related to psychiatric disorder (anti-anxiety-1, antidepressant-1). Sixteen of these 35 cases reported medications used for depression as well as other psychiatric disorders,(selective serotonin reuptake inhibitors-6, benzodiazepines-5, trazodone-2, bupropion-2, haloperidol-2, buspirone-1, unspecified antidepressant-1, unspecified anti-anxiety agent-1). Five of these 16 cases, as well as the remaining 19 cases, reported other medications with depression-related or suicide-related events in the product label (see Table 1 for details).

The medical literature also suggests a possible association between depression and finasteride based on biological plausibility (i.e. inhibition of 5alpha-reductase and subsequent conversion of progesterone to allopregnanolone, which targets $GABA_A$-receptors may have an effect on mood and behavior) and experience in humans.[2-5,8,9] In a retrospective case series of 23 Italian patients who used finasteride to treat alopecia, 19 developed moderate-severe depression.[8] The events occurred at least one month after starting finasteride and resolved within three days to three weeks of discontinuing therapy. Two of the 19 patients reported a positive rechallenge, with the events occurring within two weeks of restarting finasteride. None of the patients reported a history of psychiatric or neurological disorder, or the use of drugs that may affect mood. In another larger, prospective, uncontrolled study, 144 men in Iran used finasteride 1 mg daily to treat alopecia.[9] Depression was assessed using the Beck Depression Inventory (BDI) and Hospital Anxiety and Depression Scale (HADS) assessment tools.[a] Scores on the BDI were higher after two months of treatment with finasteride compared to baseline (12.80 vs. 12.11, $p<0.001$). Scores on the HADS were also higher after two months of treatment with finasteride compared to baseline for the depression component (4.61 vs. 4.04, $p=0.005$), but not for the anxiety component (6.60 vs. 6.24, $p=0.061$). Although both of these studies have limitations, they suggest that finasteride may be associated with depression.

Based on the AERS cases, biological plausibility, and medical literature, an association between finasteride and depression-related and suicide-related adverse events is possible. Although our analysis was limited by the quantity and quality of information provided in the cases, we cannot exclude that finasteride may have contributed to the reported events.

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[a] The BDI is a 21-item self-administered tool in which each item is scored from 0-3. Scores on the BDI are interpreted as follows: ≤9 (normal), 10-15 (minimal depressive state), 16-31 (mild depression), 32-47 (moderate depression), ≥47 (severe depression). The HADS is a 14-item self-administered tool used to assess depression (7 items) and anxiety (7 items). Each item is scored from 0-3 and then totaled separately for depression and anxiety. Scores on the HADS are interpreted as follows: 0-7 (normal), 8-10 (mild), 11-15 (moderate), 16-21 (severe).[6]

## 5 CONCLUSION

We agree with the sponsor's assessment to add depression to the Adverse Events, Postmarketing Experience section of the label. We also identified cases of suicide-related adverse events, which further support the potential association with finasteride. A relationship between finasteride exposure as a causal or contributory factor and depression-related and suicide-related events is difficult to assess based on the limited information provided in the cases and the presence of confounding factors (i.e. medical conditions associated with depression/suicide, use of medications labeled for depression/suicide); however, we identified cases of positive dechallenge and positive rechallenge that support a possible association. Whether these cases were marked by fluctuations in depression/suicidality or drug effects associated with finasteride is not certain.

## 6 RECOMMENDATIONS

Based on this review, OSE recommends the following changes to the labels for currently available formulations of finasteride (Propecia, Proscar, and their corresponding generics):

- Updating the Adverse Events, Postmarketing Experience section to reflect the potential risk for depressive symptoms

(b) (4)

We will also continue monitoring the AERS database for adverse events associated with finasteride. If additional safety concerns emerge regarding depression-related or suicide-related events, we may consider consulting the Division of Psychiatry Products, request additional information and analyses from the sponsor, or recommend other regulatory actions as warranted.

## 7 REFERENCES


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# 8 APPENDICES

**Appendix A.** Line listing of AERS cases of depression-related and suicide-related adverse events associated with finasteride, received by the FDA from market approval to September 25, 2010 (n=141)

| | |
|---|---|
| ADHD | Attention deficit hyperactivity disorder |
| AU | Australia |
| BPH | Benign prostatic hyperplasia |
| CA | Canada |
| D | Direct report |
| DC | Dechallenge |
| DE | Germany |
| DE | Death |
| E | Expedited (15-day) report |
| F | Female |
| FR | France |
| HO | Hospitalization |
| IE | Ireland |
| IL | Israel |
| IT | Italy |

| | |
|---|---|
| JP | Japan |
| LT | Life-threatening |
| M | Male |
| NI | No serious outcome reported |
| OD | Overdose |
| P | Periodic report |
| PTSD | Post traumatic stress disorder |
| RC | Rechallenge |
| RI | Required intervention |
| SE | Sweden |
| SI | Slovenia |
| TURP | Transurethral resection of the prostate |
| UK | United Kingdom |
| US | United States of America |
| SMX/TMP | Sulfamethoxazole / trimethoprim |

## 8.1 APPENDIX A. LINE LISTING OF AERS CASES OF DEPRESSION-RELATED AND SUICIDE-RELATED ADVERSE EVENTS ASSOCIATED WITH FINASTERIDE, RECEIVED BY THE FDA FROM MARKET APPROVAL TO SEPTEMBER 25, 2010 (N=141)

**PROPECIA OR FINASTERIDE 1 MG**

| ISR# | Report Country, Type, FDA initial received date | Age (years) / Gender | Primary Outcome | Indication | Duration of therapy | Depression-related or Suicide-related Adverse Events | Time to event from start of therapy | Relevant Medical History | Concomitant medications labeled for depression or suicide | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| 1. 3109655 | US, D (1998) | 51 / M | LT | Alopecia | 10 days | Depression | 8 days | None | None | |
| 2. 3133482 | US, E (1998) | 53 / M | DS | --- | 4.5 months | Depression, suicidal ideation | Within 4 months | --- | alprazolam, cyclobenzaprine | |
| 3. 3173825 | US, E (1998) | 47 /M | DE | Alopecia | 3.5 months | Completed suicide | 3.5 months | None | None | Medical examiner did not think finasteride played a role. |
| 4. 3370220 | US, P (1999) | --- / M | NI | Alopecia | --- | Depression | --- | --- | --- | |
| 5. 3372112 | US, P (1999) | 37 / M | NI | Alopecia | --- | Depression | 7 months | None | --- | |
| 6. 3380493 | US, P (1999) | 44 / M | NI | Alopecia | 4 months | Depression | 1.4 months | --- | None | Positive DC. |
| 7. 3385848 | US, P (1999) | 41 / M | NI | --- | --- | Depression | Same year | --- | omeprazole | |
| 8. 3385876 | US, P (1999) | 32 / M | NI | Prevention of alopecia | 4 days | Depression | 1 day | --- | --- | |
| 9. 3390883 | US, P (1999) | 41 / M | NI | Alopecia | 3 months | Depression | Same year | --- | None | Positive DC. |
| 10. 3390893 | US, P (1999) | 30 / M | NI | --- | --- | Depression | 2-4 months | --- | --- | |
| 11. 3390919 | US, P (1999) | 35 / M | NI | Alopecia | --- | Depression | Within 6 months | --- | --- | |
| 12. 3397139 | US, P (1999) | 32 / M | NI | --- | 1-3 months | Depression | Within 3 months | --- | None | |
| 13. 3397159 | US, P (1999) | 56 / M | NI | Alopecia | --- | Depression | 19 days | Anxiety, depression | fluoxetine | |
| 14. 3537765 | US, E (2000) | 45 / M | OT | Alopecia | --- | Depression | 1 year | None | --- | |
| 15. 3557009 | US, P (2000) | 47 / M | NI | Alopecia | --- | Depression | 5-7 months | --- | None | |
| 16. 3557014 (2) | US, P (2000) | --- / M | NI | --- | --- | Depression | --- | Depression | --- | |
| 17. 3557014 (1) | US, P (2000) | --- / M | NI | --- | --- | Depression | --- | Depression | --- | |
| 18. 3557021 | US, P (2000) | 36 / M | NI | --- | --- | Depression | --- | --- | --- | |
| 19. 3559187 | US, P (2000) | --- / M | NI | --- | --- | Depression | --- | --- | --- | |
| 20. 3559789 | US, P (2000) | --- / M | NI | Alopecia | --- | Depression | Same month | Diabetes | atorvastatin | |
| 21. 3560222 | US, P (2000) | --- / M | NI | Alopecia | --- | Depression | --- | --- | None | |
| 22. 3612967 | US, E (2000) | 21 / M | NI | Alopecia | --- | Depression | 1-5 weeks | Acne | None | |

| ISR# | Report Country, Type, FDA initial received date | Age (years) / Gender | Primary Outcome | Indication | Duration of therapy | Depression-related or Suicide-related Adverse Events | Time to event from start of therapy | Relevant Medical History | Concomitant medications labeled for depression or suicide | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| 23. 3667518 | US, E (1999) | 48 / M | OT | Alopecia | --- | Anhedonia, depression | 4 months | --- | estrogens, levothyroxine | |
| 24. 3813866 | DE, E (2001) | ---/ M | HO | Alopecia | --- | Depression, suicidal ideation | 1 year | Smoking, "psycho-genic stress reaction" | --- | |
| 25. 3977095 | US, E (2002) | 16 / M | LT | Alopecia | 1.7 months | Suicidal ideation, depression | 1 month | --- | --- | |
| 26. 3983252 | IT, E (2002) | 32 / M | DS | Alopecia | --- | Depression | --- | --- | --- | Positive DC and RC. |
| 27. 4040374 | US, E (2003) | 24 / M | LT | Alopecia | 3.3 months | Depression | --- | None | None | |
| 28. 4126899 | UK, E (2003) | 23 / M | OT | --- | 6 months | Depression, suicidal ideation | 6-10 weeks | --- | --- | |
| 29. 4598592 | US, D (2005) | 19 / --- | RI | Alopecia | --- | Depression | --- | Acne, smoker, alcohol use | --- | |
| 30. 4603742 | US, D (2005) | 24 / M | OT | Prevention of alopecia | 3.8 months | Depression | --- | --- | --- | |
| 31. 4604914 | US, D (2005) | 19 / M | OT | Alopecia | --- | Depression | --- | None | --- | |
| 32. 4735877 | US, D (2005) | 37 / M | OT | Alopecia | 5.4 months | Depression | Same day | None | None | |
| 33. 4928824 | UK, D (2006) | 21 / M | OT | Alopecia | 4 months | Depression | 3 months | --- | --- | |
| 34. 5131762 | JP, E (2006) | 32 / M | OT | Alopecia | 5.1 weeks | Depression | 3 weeks | --- | None | Positive DC. |
| 35. 5214923 | US, D (2007) | 53 / M | OT | Alopecia | 3 months | Depression | --- | --- | --- | |
| 36. 5339568 | US, E (2007) | --- / M | OT | --- | --- | Depressed mood | --- | None | --- | J Clin Endocrinol Metab 2007; 92(5):1659-65. |
| 37. 5456316 | US, E (2007) | 20 / M | OT | Alopecia | 4 years | Depression | --- | Acne, clinodactyl surgery | topiramate | Main events: possible pseudotumor cerebri, anxiety, vision changes |
| 38. 5647745 | SI, E (2007) | 27 / M | DS | Alopecia | 5 years | Depression, suicidal ideation | Same year | Thyroid disorder | --- | Positive DC. |
| 39. 5664534 | US, D (2008) | 27 / M | OT | Alopecia | 2 years | Depression | 2.4 years | Marijuana use | --- | Depression secondary to gynecomastia. |
| 40. 5689836 | US, D (2008) | 33 / --- | OT | --- | 4 months | Depression | 3.8 months | --- | --- | |
| 41. 5775164 | US, D (2008) | 34 / M | OT | Alopecia | 2 years | Depression | 2 years | --- | --- | |

| ISR# | Report Country, Type, FDA initial received date | Age (years) / Gender | Primary Outcome | Indication | Duration of therapy | Depression-related or Suicide-related Adverse Events | Time to event from start of therapy | Relevant Medical History | Concomitant medications labeled for depression or suicide | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| 42. 5787832 | US, D (2008) | 28 / M | OT | Alopecia | 4 days | Depression, suicidal ideation | --- | Anxiety | unspecified anxiety therapy | Positive DC. |
| 43. 5837706 | AU, E (2008) | 26 / M | DS | Alopecia | 7.1 months | Depression | 7 months | --- | --- | |
| 44. 5897774 | US, D (2008) | 21 / M | LT | Alopecia | 2 months | Depression | 2 months | None | --- | |
| 45. 5941323 | US, D (2008) | 40 / M | OT | Alopecia | 19 days | Depressed mood, feeling of despair | --- | --- | --- | |
| 46. 5988743 | US, D (2008) | 28 / M | RI | Alopecia | 3.7 months | Depression | --- | None | --- | |
| 47. 5991015 | US, E (2008) | 40 / M | OT | Alopecia | --- | Depression, suicidal ideation | 2 weeks | Genital herpes, vocal cord surgery | None | Intermittent finasteride use for "several years." |
| 48. 6073991 | US, D (2009) | 25 / M | OT | Alopecia | 8 days | Depression, suicidal ideation | Within 8 days | None | None | |
| 49. 6137041 | US, D (2009) | 27 / M | OT | Alopecia | 2-4 years | Depression | 3-4 years | None | --- | Positive DC. |
| 50. 6148311 | UK, E (2009) | 39 / M | OT | Alopecia | 1.4 months | Depression | Same day | --- | None | Positive DC. |
| 51. 6188013 | US, D (2009) | 24 / M | NI | Alopecia | 1.2 months | Depression | 1.2 months | ADHD, depression, anxiety | fluoxetine, bupropion | |
| 52. 6233283 | JP, E (2009) | 42 / M | OT | --- | --- | Intentional overdose | --- | --- | --- | |
| 53. 6277822 | US, D (2009) | 21 / M | LT | Alopecia | 11 days | Depression | --- | Alcohol use | trazodone, clomiphene | Positive RC. |
| 54. 6303644 | US, D (2009) | 23 / M | DS | Alopecia | 1 year | Depression, suicidal ideation | 1 year | Depression, family history of depression | --- | Events secondary to sexual dysfunction. |
| 55. 6317707 | US, D (2009) | 35 / M | HO | Alopecia | 2.5 months | Depression | --- | None | --- | |
| 56. 6327303 | DE, E (2009) | 18 / M | HO | Alopecia | 6 months | Depression | 6-7 months | --- | --- | Positive DC. |
| 57. 6329572 | US, D (2009) | 23 / M | OT | Alopecia | 2 months | Depression | 3 months | --- | --- | Positive RC. |
| 58. 6346130 | US, E (2009) | --- / M | DE | Alopecia | --- | Completed suicide, depression | --- | --- | --- | |
| 59. 6371159 | US, E (2009) | 34 / M | HO | Alopecia | 2.3 months | Depression | 16 days | None | None | |
| 60. 6439631 | IT, D (2009) | 26 / M | RI | Alopecia | 3 months | Depression | --- | Smoking | --- | Positive DC. |
| 61. 6538048 | US, D (2010) | 28 / M | RI | Alopecia | 4 days | Depression | 11 days | None | None | |
| 62. 6569774 | US, D (2010) | 31 / M | RI | Alopecia | 5.7 years | Depression | 3.5 years | None | None | |
| 63. 6579617 | US, D (2010) | --- / M | RI | --- | 4.3 years | Depression | --- | None | None | |
| 64. 6658198 | CA, E (2010) | ---/ M | OT | --- | 6 months | Depression | --- | --- | --- | |

| ISR# | Report Country, Type, FDA initial received date | Age (years) / Gender | Primary Outcome | Indication | Duration of therapy | Depression-related or Suicide-related Adverse Events | Time to event from start of therapy | Relevant Medical History | Concomitant medications labeled for depression or suicide | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| 65. 6754264 | CA, E (2010) | ---/ M | LT | --- | --- | Depression, suicide attempt | --- | --- | --- | |
| 66. 6754276 | CA, E (2010) | ---/ M | LT | --- | 1 week | Depressed mood, depression, suicidal ideation | --- | --- | --- | |
| 67. 6815255 | US, D (2010) | 24 / M | OT | Alopecia | 1.4 years | Depression | 7 months | None | --- | Positive DC. |
| 68. 6877181 | US, D (2010) | 27 / M | OT | Alopecia | 1 month | Depression | --- | None | None | |
| 69. 6888921 | IL, E (2010) | ---/ M | DS | Alopecia | --- | Major depression | --- | --- | None | Depression due to baldness. |
| 70. 6965734 | US, E (2010) | 29 / M | OT | Alopecia | 1.5 years | Depression, suicidal ideation | 1 year | Smoking | --- | |
| 71. 6968723 | IT, E (2010) | 28 / M | OT | Alopecia | 4 days | Depression | 4 days | --- | --- | |

**PROSCAR OR FINASTERIDE 5 MG**

| ISR# | Report Country, Type, FDA initial received date | Age (years) / Gender | Primary Outcome | Indication | Duration of therapy | Depression-related or Suicide-related Adverse Events | Time to event from start of therapy | Relevant Medical History | Concomitant medications labeled for depression or suicide | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| 72. 931411 | US, E (1993) | 87 / M | HO | BPH | --- | Depression | 1-3 months | Dementia | SMX/TMP | |
| 73. 931727 | US, E (1993) | 88 / M | HO | BPH | --- | Depression | 4-6 months | Depression | alprazolam, haloperidol | |
| 74. 950329 | CA, E (1993) | 67 / M | DE | BPH | --- | Suicide attempt, suicide completed | --- | --- | --- | Also reported acetaminophen OD. |
| 75. 959238 | US, P (1993) | 73 / M | NI | BPH | --- | Depression | Within 1 month | None | metoprolol, digoxin | |
| 76. 961097 | US, P (1993) | ---/ M | OT | BPH | 1 month | Depression | 1 month | None | None | Positive DC. |
| 77. 961113 | US, P (1993) | 75 / M | NI | BPH | --- | Depression | 6 months | None | --- | |
| 78. 961119 | US, P (1993) | ---/ M | OT | BPH | 11 days | Depression | 7 days | None | None | Positive DC. |
| 79. 1357073 | US, P (1993) | 82 / M | OT | BPH | 2.4 months | Depression | 1.9 months | None | --- | |
| 80. 1357075 | US, P (1993) | 60 / M | OT | BPH | 5 days | Depression | 4 days | None | --- | Positive DC. |
| 81. 1380349 | US, P (1993) | 52 / M | OT | BPH | --- | Depression | --- | None | --- | Positive DC. |
| 82. 1380499 | US, P (1993) | 72 / M | OT | BPH | --- | Depression | 4.2 months | None | diazepam | |
| 83. 1415838 | US, P (1994) | 77 / M | NI | BPH | 4-5 months | Depression | 4-5 months | None | None | Positive DC. |
| 84. 1418493 | US, P (1994) | --- / M | NI | --- | --- | Depression | --- | None | --- | |
| 85. 1455056 | US, P (1994) | --- / M | NI | --- | --- | Depression | 11 months | None | --- | |

| ISR# | Report Country, Type, FDA initial received date | Age (years) / Gender | Primary Outcome | Indication | Duration of therapy | Depression-related or Suicide-related Adverse Events | Time to event from start of therapy | Relevant Medical History | Concomitant medications labeled for depression or suicide | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| 86. 1457845 | US, P (1994) | 64 / M | NI | Enlarged prostrate | 1.3 - 1.5 years | Depression | 1.1 - 1.3 years | None | None | Positive DC. |
| 87. 1482624 | US, P (1994) | 85 / M | NI | BPH | 2.2 months | Depression | 5.1 months | None | None | |
| 88. 1483839 | US, E (1994) | 65 / M | LT | --- | 2.5 months | Depression | 2 months | --- | --- | Positive DC. |
| 89. 1486571 | US, P (1994) | 75 / M | NI | BPH | 10 months | Depression | --- | None | warfarin, naproxen | |
| 90. 1491371 | US, P (1994) | 72 / M | NI | BPH | --- | Depression | --- | Depression | trazodone | |
| 91. 1491474 | US, P (1994) | 69 / M | NI | --- | 9.7 months | Depression | --- | None | diazepam, temazepam | |
| 92. 1491569 | US, P (1994) | 54 / M | NI | --- | --- | Depression | --- | --- | --- | |
| 93. 1505729 | UK, E (1994) | 86 / M | DE | Prosatism | 1.7 months | Major depression, suicide attempt, suicide completed | Same year | Anxiety, psychosis, depression | None | Physician reported, "finasteride possibly aggravated his depression." |
| 94. 1516078 | SE, E (1994) | 74 / M | HO | BPH | 14 days | Depression | 8 days | None | None | |
| 95. 1521562 | US, P (1994) | --- / M | NI | --- | --- | Depression | --- | None | --- | Positive DC. |
| 96. 1530188 | US, P (1994) | 75 / M | NI | --- | --- | Depression | --- | None | --- | |
| 97. 1538618 | US, P (1994) | --- / M | NI | --- | --- | Depression | --- | None | --- | |
| 98. 1543826 | US, E (1995) | ---/M | DE | --- | --- | Suicide attempt, Completed suicide | 6.2 months | Diabetes | alprazolam, enalapril | Physician reported "no apparent relationship to any drug side effect." |
| 99. 1576993 | US, E (1995) | 83 / M | DE | --- | --- | Completed suicide | 2.2 - 2.3 months | None | --- | Physician reported suicide was "unrelated to Proscar." |
| 100. 1608663 | FR, E (1995) | 80 / M | HO | Prostate adenoma | --- | Depression | 3-5 months | Depression | --- | |
| 101. 1615668 | US, P (1995) | 74 / M | NI | BPH | 1-3 months | Depression | --- | Major depression, degenerative dementia | paroxetine, buspirone, haloperidol, amantadine, digoxin | |
| 102. 1615874 | US, P (1995) | --- / M | NI | BPH | --- | Depression | --- | None | atenolol, nifedipine | |

| ISR# | Report Country, Type, FDA initial received date | Age (years) / Gender | Primary Outcome | Indication | Duration of therapy | Depression-related or Suicide-related Adverse Events | Time to event from start of therapy | Relevant Medical History | Concomitant medications labeled for depression or suicide | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| 103. 1626011 | US, P (1995) | 65 / M | NI | BPH | 1 year | Depression | --- | None | --- | Positive DC. |
| 104. 1805745 | US, P (1996) | --- / M | NI | --- | 6-7 months | Depression | 5 months | None | --- | Positive DC. |
| 105. 1806047 | US, P (1996) | 65 / M | NI | BPH | --- | Depression | --- | None | --- | Positive DC. |
| 106. 1809547 | US, P (1996) | 63 / M | NI | --- | 10 months | Depression | 6-7 months | None | terazosin | Positive DC. Depression due to inability to ejaculate. |
| 107. 1809913 | US, P (1996) | 58 / M | NI | BPH | --- | Depression | 4 months | None | doxazosin | |
| 108. 1809952 | US, P (1996) | 35 / M | NI | --- | --- | Depression | 1.5 months | Depression | unspecified antidepressant | |
| 109. 1810548 | US, P (1996) | 74 / M | NI | BPH | up to 2 months | Depression | Within 2 months | None | terazosin, diclofenac, nifedipine | Positive DC and RC. |
| 110. 1903899 | US, D (1997) | 63 / M | HO | Enlarged prostrate | --- | Depression | --- | None | None | Positive DC. |
| 111. 1908731 | US, E (1997) | 16 / F | OT | --- | --- | Intentional overdose, suicide attempt | --- | None | --- | |
| 112. 1985940 | US, P (1997) | 78 / M | NI | --- | 6.1 months | Depression | --- | None | None | Positive DC. |
| 113. 1996121 | US, E (1997) | 79 / M | HO | BPH | at least 3 weeks | Depression | 3.4 months | --- | ciprofloxacin | |
| 114. 2012951 | US, P (1997) | --- / M | NI | BPH | 10 months | Depression | --- | None | None | Positive DC. |
| 115. 3026126 | UK, E (1998) | 77 / M | HO | BPH | --- | Depression | --- | --- | --- | |
| 116. 3105112 | FR, E (1998) | 72 / M | DE | BPH | 2.4 years | Completed suicide, depression | 1.3 - 2.3 years | Cerebro-vascular disorder, cirrhosis | None | Physician felt events were not related to finasteride. |
| 117. 3360715 | UK, E (1999) | 20 / M | OT | Acne | --- | Depression | 3 months | --- | --- | Positive DC. |
| 118. 3364088 | US, P (1999) | --- / M | NI | --- | --- | Depression | --- | Depression | --- | |
| 119. 3364393 | US, P (1999) | --- / M | NI | BPH | 6 months | Depression | within 6 months | Urethral stricture and surgery | --- | |
| 120. 3389318 | US, D (1999) | 63 / M | HO | Enlarged prostate | 1 year | Depression | --- | panic attacks, depression | --- | |

| ISR# | Report Country, Type, FDA initial received date | Age (years) / Gender | Primary Outcome | Indication | Duration of therapy | Depression-related or Suicide-related Adverse Events | Time to event from start of therapy | Relevant Medical History | Concomitant medications labeled for depression or suicide | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| 121. 3403058 | US, E (1999) | 76 / M | LT | BPH | 2.5 - 8.5 months | Depression | 3 weeks – 6 months 3 weeks | Osteo-arthritis, TURP, sexual dysfunction smoking | diltiazem, simvastatin, terazosin | Main event: seizures. |
| 122. 3406076 | DE, E (1999) | ---/ M | HO | BPH | --- | Depression, suicide attempt | --- | Parkinson's Disease | --- | |
| 123. 3477812 | UK, E (1999) | 75 / M | HO | BPH | --- | Depression | Up to 2 months | None | naproxen, nifedipine, atenolol, captopril | |
| 124. 3675249 | US, E (2001) | 40 / M | HO | --- | 1 day | Suicide attempt | Same day | PTSD, depression | valproic acid | |
| 125. 4269681 | US, E (2004) | 78 / M | DE | --- | --- | Completed suicide | --- | Depression, stroke, diabetes | lovastatin, lisinopril, gabapentin | Am J Emer Med 2003;21(5):353-421 |
| 126. 4300854 | UK, E (2003) | 28 / M | OT | Hypotrichosis | --- | Depression, suicidal ideation | 1 month | None | none | Positive DC. |
| 127. 4352396 | FR, E (2004) | 77 / M | HO | Prostatic adenoma | --- | Depression | --- | Diabetes, colectomy | paroxetine | Main event: nephrotic syndrome |
| 128. 4602182 | UK, E (2005) | 70 / M | DS | BPH | 7.8 months | Depression | Within the month | --- | None | |
| 129. 5065703 | UK, E (2006) | 49 / M | DS | Hyper-tension | 23.2 years | Dysphoria | --- | None | indoramin | Positive DC. |
| 130. 5926790 | UK, E (2008) | ---/ M | OT | --- | --- | Depression, suicidal ideation | Same day | Blind, diabetes, depression | ramipril, ciprofloxacin, omeprazole | |
| 131. 6249337 | IE, E (2009) | 26 / M | OT | Alopecia | 3-16 months | Depression, suicidal ideation | --- | --- | --- | |
| 132. 6318891 | UK, E (2009) | 64 / M | OT | BPH | 4 months | Depression | Within the month | None | diltiazem, simvastatin | Positive DC. |
| 133. 6403936 | US, D (2009) | 54 / M | DS | BPH | 3.4 - 3.6 years | Depression | 3-5 months | Dysthymia | bupropion | |
| 134. 6539734 | UK, E (2010) | ---/ M | OT | --- | 3.9 months | Decreased interest | --- | --- | --- | |
| 135. 6635359 | US, D (2010) | 68 / M | NI | Enlarged prostrate | 7.2 months | Anhedonia, depression | 1.5 months | Depression, anxiety | sertraline | |
| 136. 6736395 | CA, E (2010) | --- / --- | OT | --- | --- | Depression | --- | --- | --- | |

| ISR# | Report Country, Type, FDA initial received date | Age (years) / Gender | Primary Outcome | Indication | Duration of therapy | Depression-related or Suicide-related Adverse Events | Time to event from start of therapy | Relevant Medical History | Concomitant medications labeled for depression or suicide | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| 137. 6859762 | US, D (2010) | 58 / M | OT | Prostatitis | 1-3 months | Depression | Within 1 month | --- | --- | |
| 138. 6906742 | US, E (2010) | 57 / M | HO | Prostatic disorder, dysuria | 4 days | Suicidal ideation | --- | --- | --- | Main event: renal failure |

**UNKNOWN FINASTERIDE PRODUCT**

| ISR# | Report Country, Type, FDA initial received date | Age (years) / Gender | Primary Outcome | Indication | Duration of therapy | Depression-related or Suicide-related Adverse Events | Time to event from start of therapy | Relevant Medical History | Concomitant medications labeled for depression or suicide | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| 139. 5358554 | US, D (2007) | 24 / M | OT | Prevention of alopecia | 2-4 months | Depressed mood, depression | 2-3 months | --- | --- | "Going through some major life changes" |
| 140. 5480510 | US, D (2007) | 48 / F | OT | Alopecia | 11.2 months | Major depression | 1-2 months | Hysterectomy | --- | |
| 141. 6344976 | US, E (2009) | 51 /M | DE | --- | --- | Completed suicide | --- | --- | levetiracetam, sertraline, simvastatin / ezetimibe, metolazone | Clinical Toxicology 2007;45:815-917. |

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**Mail: OSE-DPV**
**Janet Anderson, RPM**

FROM:
Amy Woitach, Clinical Reviewer, DDDP/ODE III, 301.796.4078
David Kettl, Clinical Team Leader, DDDP/ODE III, 301.796.2105
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| DATE | IND NO. | NDA NO. | TYPE OF DOCUMENT | DATE OF DOCUMENT |
|---|---|---|---|---|
| July 29, 2010 | | 020788 | CBE-0 Labeling Supplement | July 16, 2010 |

| NAME OF DRUG | PRIORITY CONSIDERATION | CLASSIFICATION OF DRUG | DESIRED COMPLETION DATE |
|---|---|---|---|
| Propecia® (finasteride) Tablet,1mg | | | October 13, 2010 |

NAME OF FIRM: Merck, Sharp and Dohme, Corp.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- X LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

| STATISTICAL EVALUATION BRANCH | STATISTICAL APPLICATION BRANCH |
|---|---|
| ☐ TYPE A OR B NDA REVIEW<br>☐ END OF PHASE II MEETING<br>☐ CONTROLLED STUDIES<br>☐ PROTOCOL REVIEW<br>☐ OTHER (SPECIFY BELOW): | ☐ CHEMISTRY REVIEW<br>☐ PHARMACOLOGY<br>☐ BIOPHARMACEUTICS<br>☐ OTHER (SPECIFY BELOW): |

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:
A Changes Being Effected (CBE-0) labeling supplement, NDA 020788 Propecia, S-017, was submitted July 16, 2010 and provides for the addition of the term, depression, to the ADVERSE REACTIONS, Postmarketing Experience section of the Package Insert and the corresponding "Possible side effects" section of the Patient Package Insert. Please conduct a search of the AERS database for cases reporting depression or suicide-related adverse events associated with the use of finasteride and provide an assessment regarding the sponsor's request to add "depression" to the product label.

This supplement submission can be found at the following EDR location:
\\CDSESUB1\EVSPROD\NDA020788\020788.enx

| SIGNATURE OF REQUESTER | METHOD OF DELIVERY (Check one)<br>X DARRTS ☐ MAIL ☐ HAND |
|---|---|
| SIGNATURE OF RECEIVER | SIGNATURE OF DELIVERER |

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|---|---|---|---|
| NDA-20788 | SUPPL-17 | MERCK RESEARCH LABORATORIES DIV MERCK CO INC | PROPECIA |

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/s/

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JEANNINE M HELM
07/29/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020788/S-017

**CBE-0 SUPPLEMENT**

Merck Sharp & Dohme Corp.
Attention: Siyoung Ahn
Manager, Regulatory Affairs
126 East Lincoln Avenue
P.O. Box 2000, RY33-208
Rahway, NJ 07065-0900

Dear Ms. Ahn:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Propecia™ (finasteride) Tablet, 1 mg

NDA Number: 020788

Supplement Number: S-017

Date of Supplement: July 16, 2010

Date of Receipt: July 16, 2010

This supplemental application, submitted as a "Changes Being Effected" supplement, proposes the following changes: Addition of the term, depression, to the **ADVERSE REACTIONS**, Postmarketing Experience section of the Package Insert (b) (4)

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Division of Dermatology and Dental Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have questions, call me, Regulatory Project Manager, at (301) 796-0637.

Sincerely,

*{See appended electronic signature page}*

Jeannine M. Helm
Regulatory Project Manager
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|---|---|---|---|
| NDA-20788 | SUPPL-17 | MERCK RESEARCH LABORATORIES DIV MERCK CO INC | PROPECIA |

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/s/

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JEANNINE M HELM
09/02/2010