CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-180/S-020

Name: Proscar Tablets

Generic Name: finasteride

Sponsor: Merck & Company, Inc

Approval Date: 06/26/2003

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APPLICATION NUMBER:

NDA 20-180/S-020

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APPLICATION NUMBER:

NDA 20-180/S-020

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-180\S-020

Merck & Co., Inc.
Attention: Vivian Fuh, M.D,
Director, Regulatory Affairs
P.O. Box 2000, RY 33-200
Rahway, NJ 07065-0900

Dear Dr. Fuh:

Please refer to your supplemental new drug application (NDA 20-180/SLR 020) dated November 9, 1998 and received on November 10, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for PROSCAR™ (finasteride 5 mg).

We also acknowledge receipt of your subsequent submissions to NDA 20-180/SLR 020 dated May 8, 2000, May 16, 2001, December 6, 2002, and January 3, 2003 as well as the following submissions to IND 28,422 for PROSCAR™ dated as follows:

Serial #530 (June 24, 2002/June 25, 2002)
Serial #533 (July 29, 2002/July 30, 2002)
Serial #534 (August 19, 2002/August 20, 2002)
Serial #535 (September 20, 2002/September 23, 2002)
Serial #536 (September 20, 2002/September 23, 2002)
Serial #537 (October 4, 2002/October 5, 2002)
Serial #538 (October 28, 2002/October 29, 2002)
Serial #539 (November 11, 2002/November 12, 2002)
Serial #540 (December 13, 2002/December 16, 2002)
Serial #541 (December 16, 2002/December 17, 2002)
Serial #543 (December 30, 2002/December 31, 2002)

Reference is also made to our Approvable letter, dated April 24, 2003, for NDA 20-180 SLR 020. This letter informed you that supplement 020 was approvable pending your agreement to add appropriate language to the PROSCAR™ labeling regarding the male breast cancer issue.

Reference is also made to our recent Approval letter, dated September 9, 2003, sent to you for NDA 20-180 SLR 027, which contained a revised package insert (PI) and patient package insert (PPI) that proposed the following:

1. Changes in the Labeling Section of the approved NDA to include isolated reports of male breast cancer in the ADVERSE REACTIONS, Long-Term Treatment.
2. Changes in the Information for Patients subsection of PRECAUTIONS to encourage physicians to instruct patients to promptly report any changes in their breasts, such as lumps, pain or nipple discharge, to their physician.
3. Changes consistent with those proposed in the PI under the "What you need to Know while taking PROSCAR" section of the PPI.

Based on this approval of NDA 20-180/ S 027, your supplement application NDA 20-180/S 020 is also approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. The FPL must be identical to the package insert and patient package insert labeling approved for NDA 20-180/S 027 on September 9, 2003. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-180/SLR 020." Approval of this submission by FDA is not required before the labeling is used.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

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 Jean King, M.S., R.D., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Daniel Shames, M.D.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Daniel A. Shames
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-180/S-020

APPROVABLE LETTER(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-180

Merck & Co., Inc.
Attention: Vivian Fuh, M.D.
Director, Regulatory Affairs
P.O. Box 2000
RY 33-200
Rahway, NJ 07065-0900

Dear Dr. Fuh:

Please refer to your supplemental new drug application (NDA 20-180/SLR 020) dated November 9, 1998 and received on November 10, 1998, submitted under section 505(b)/pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for PROSCAR™ (finasteride 5 mg).

We also acknowledge receipt of your subsequent submission to NDA 20-180/SLR 020 dated May 8, 2000, May 16, 2001, December 6, 2002, and January 3, 2003 as well as the following submissions to IND 28,422 for PROSCAR™ dated as follows:

Serial #530 (June 24, 2002/June 25, 2002)
Serial #533 (July 29, 2002/July 30, 2002)
Serial #534 (August 19, 2002/August 20, 2002)
Serial #535 (September 20, 2002/September 23, 2002)
Serial #536 (September 20, 2002/September 23, 2002)
Serial #537 (October 4, 2002/October 5, 2002)
Serial #538 (October 28, 2002/October 29, 2002)
Serial #539 (November 11, 2002/November 12, 2002)
Serial #540 (December 13, 2002/December 16, 2002)
Serial #541 (December 16, 2002/December 17, 2002)
Serial #543 (December 30, 2002/December 31, 2002)

Reference is also made to our regulatory letter, dated December 20, 2002, sent to you for NDA 20-180 SLR 020. In this letter, we informed you that supplement 020 was approvable pending resolution of the male breast cancer issue. We have completed our review of the male breast cancer issue and in that regard, also make reference to your serial submissions to IND 28,422 (#530, #533, #534, #535, #536, #537, #538, #539, #540, #541, and #543). Supplemental labeling revision 020 remains approvable pending your agreement to add the following language to the PROSCAR™ label:

1. In the General Precautions section, as a new third paragraph:

[redacted]

2. In the Information for Patients section as a new additional paragraph:

[redacted]

In addition, all previous revisions, as reflected in the most recently approved package insert, must be included. To facilitate review of your submission, provide a highlighted or marked-up copy that shows the changes.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes before approval of this supplemental application.

If you have any questions, call Jean King, M.S., R.D., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Daniel Shames, M.D.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Daniel A. Shames
4/24/03 03:25:47 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-180/S-020

APPROVABLE LETTER

Merck & Co. Inc.
Attention: Tamra Goodrow, Ph.D.
Associate Director
Regulatory Affairs
Sumneytown Pike
P.O. Box 4
West Point, PA 19486

Dear Dr. Goodrow:

Please refer to your supplemental new drug application dated November 9, 1998, received November 10, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Proscar® (finasteride).

This supplemental new drug application provides for changes in the labeling to upgrade and provide consistency between the Proscar® and Propecia® label.

We have completed the review of this application, as amended, and it is approvable with the modifications in the attached marked-up version of your label. The labeling should be identical in content to the enclosed labeling (text for the package insert, text for the patient package insert). Before this application may be approved, however, it will be necessary for you to address the following:

> The FDA is currently reviewing the reported cases of male breast cancer findings and their possible implications for the approved indications, as well as your proposed language, submitted in this "prior approval" supplement. Revisions to the labeling submitted on November 9, 1998, may be required as a result of these ongoing reviews.

Likewise should any other information relating to the safety or effectiveness of these drugs become available, revision of the labeling may be required. All previous revisions, as reflected in the most recently approved package insert, must be included. To facilitate review of your submission, provide a highlighted or marked-up copy that shows the changes.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

If you have any questions, call Kassandra Sherrod, R.Ph., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Daniel Shames, M.D.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

18 page(s) of draft labeling has been removed from this portion of the review.

Approvable Letter

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/s/

Donna Griebel
12/20/02 02:11:22 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-180/S-020

LABELING

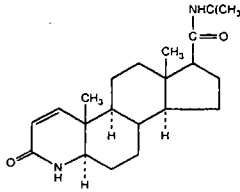
MERCK & CO., INC.
Whitehouse Station, NJ 08889, USA

PROSCAR®
(FINASTERIDE)
TABLETS

DESCRIPTION

PROSCAR* (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.

PROSCAR (finasteride) tablets for oral administration are film-coated tablets that contain 5 mg of finasteride and the following inactive ingredients: hydrous lactose, microcrystalline cellulose, pregelatinized starch, sodium starch glycolate, hydroxypropyl cellulose LF, hydroxypropylmethyl cellulose, titanium dioxide, magnesium stearate, talc, docusate sodium, FD&C Blue 2 aluminum lake and yellow iron oxide.

CLINICAL PHARMACOLOGY

The development and enlargement of the prostate gland is dependent on the potent androgen, 5α-dihydrotestosterone (DHT). Type II 5α-reductase metabolizes testosterone to DHT in the prostate gland, liver and skin. DHT induces androgenic effects by binding to androgen receptors in the cell nuclei of these organs.

Finasteride is a competitive and specific inhibitor of Type II 5α-reductase with which it slowly forms a stable enzyme complex. Turnover from this complex is extremely slow ($t_{1/2}$ ~ 30 days). This has been demonstrated both *in vivo* and *in vitro*. Finasteride has no affinity for the androgen receptor. In man, the 5α-reduced steroid metabolites in blood and urine are decreased after administration of finasteride.

In man, a single 5-mg oral dose of PROSCAR produces a rapid reduction in serum DHT concentration, with the maximum effect observed 8 hours after the first dose. The suppression of DHT is maintained throughout the 24-hour dosing interval and with continued treatment. Daily dosing of PROSCAR at 5 mg/day for up to 4 years has been shown to reduce the serum DHT concentration by approximately 70%. The median circulating level of testosterone increased by approximately 10-20% but remained within the physiologic range.

Adult males with genetically inherited Type II 5α-reductase deficiency also have decreased levels of DHT. Except for the associated urogenital defects present at birth, no other clinical abnormalities related to Type II 5α-reductase deficiency have been observed in these individuals. These individuals have a small prostate gland throughout life and do not develop BPH.

In patients with BPH treated with finasteride (1-100 mg/day) for 7-10 days prior to prostatectomy, an approximate 80% lower DHT content was measured in prostatic tissue removed at surgery, compared to placebo; testosterone tissue concentration was increased up to 10 times over pretreatment levels, relative to placebo. Intraprostatic content of prostate-specific antigen (PSA) was also decreased.

In healthy male volunteers treated with PROSCAR for 14 days, discontinuation of therapy resulted in a return of DHT levels to pretreatment levels in approximately 2 weeks.

In patients treated for three months, prostate volume, which declined by approximately 20%, returned to close to baseline value after approximately three months of discontinuation of therapy.

Pharmacokinetics

Absorption

In a study of 15 healthy young subjects, the mean bioavailability of finasteride 5-mg tablets was 63% (range 34-108%), based on the ratio of area under the curve (AUC) relative to an intravenous (IV) reference dose. Maximum finasteride plasma concentration averaged 37 ng/mL (range, 27-49 ng/mL) and was reached 1-2 hours postdose. Bioavailability of finasteride was not affected by food.

Distribution

Mean steady-state volume of distribution was 76 liters (range, 44-96 liters). Approximately 90% of circulating finasteride is bound to plasma proteins. There is a slow accumulation phase for finasteride after multiple dosing. After dosing with 5 mg/day of finasteride for 17 days, plasma concentrations of finasteride were 47 and 54% higher than after the first dose in men 45-60 years old (n=12) and ≥70 years old (n=12), respectively. Mean trough concentrations after 17 days of dosing were 6.2 ng/mL (range, 2.4-9.8 ng/mL) and 8.1 ng/mL (range, 1.8-19.7 ng/mL), respectively, in the two age groups. Although steady state was not reached in this study, mean trough plasma concentration in another study in patients with BPH (mean age, 65 years) receiving 5 mg/day was 9.4 ng/mL (range, 7.1-13.3 ng/mL; n=22) after over a year of dosing.

Finasteride has been shown to cross the blood brain barrier but does not appear to distribute preferentially to the CSF.

In 2 studies of healthy subjects (n=69) receiving PROSCAR 5 mg/day for 8-24 weeks, finasteride concentrations in semen ranged from undetectable (<0.1 ng/mL) to 10.54 ng/mL. In an earlier study using a less sensitive assay, finasteride concentrations in the semen of 16 subjects receiving PROSCAR 5 mg/day ranged from undetectable (<1.0 ng/mL) to 21 ng/mL. Thus, based on a 5-mL ejaculate volume, the amount of finasteride in semen was estimated to be 50- to 100-fold less than the dose of finasteride (5 µg) that had no effect on circulating DHT levels in men (see also 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

In healthy young subjects (n=15), mean plasma clearance of finasteride was 165 mL/min (range, 70-279 mL/min) and mean elimination half-life in plasma was 6 hours (range, 3-16 hours). Following an oral dose of ^{14}C-finasteride in men (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.

The mean terminal half-life of finasteride in subjects ≥70 years of age was approximately 8 hours (range, 6-15 hours; n=12), compared with 6 hours (range, 4-12 hours; n=12) in subjects 45-60 years of age. As a result, mean AUC (0-24 hr) after 17 days of dosing was 15% higher in subjects ≥70 years of age than in subjects 45-60 years of age (p=0.02).

Special Populations

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

Gender: Finasteride pharmacokinetics in women are not available.

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*, PRECAUTIONS, *Geriatric Use* and DOSAGE AND ADMINISTRATION.

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 values 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 BPH patients 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 PROSCAR in those 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 metabolism enzyme system. Compounds that have been tested in man have included antipyrine, digoxin, propranolol, theophylline, and warfarin, and no clinically meaningful interactions were found.

Mean (SD) Pharmacokinetic Parameters in Healthy Young Subjects (n=15)	
	Mean (± SD)
Bioavailability	63% (34-108%)*
Clearance (mL/min)	165 (55)
Volume of Distribution (L)	76 (14)
Half-Life (hours)	6.2 (2.1)

*Range

Mean (SD) Noncompartmental Pharmacokinetic Parameters After Multiple Doses of 5 mg/day in Older Men		
	Mean (± SD)	
	45-60 years old (n=12)	≥70 years old (n=12)
AUC (ng•hr/mL)	389 (98)	463 (186)
Peak Concentration (ng/mL)	46.2 (6.7)	48.4 (14.7)
Time to Peak (hours)	1.8 (0.7)	1.8 (0.6)
Half-Life (hours)*	6.0 (1.5)	8.2 (2.5)

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

Clinical Studies

PROSCAR 5 mg/day was initially evaluated in patients with symptoms of BPH and enlarged prostates by digital rectal examination in two 1-year, placebo-controlled, randomized, double-blind studies and their 5-year open extensions.

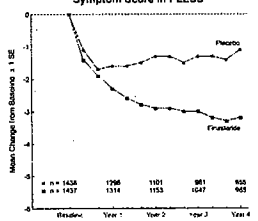
PROSCAR was further evaluated in the PROSCAR Long-Term Efficacy and Safety Study (PLESS), a double-blind, randomized, placebo-controlled, 4-year, multicenter study. 3040 patients between the ages of 45 and 78, with moderate to severe symptoms of BPH and an enlarged prostate upon digital rectal examination, were randomized into the study (1524 to finasteride, 1516 to placebo) and 3016 patients were evaluable for efficacy. 1883 patients completed the 4-year study (1000 in the finasteride group, 883 in the placebo group).

Effect on Symptom Score

Symptoms were quantified using a score similar to the American Urological Association Symptom Score, which evaluated both obstructive symptoms (impairment of size and force of stream, sensation of incomplete bladder emptying, delayed or interrupted urination) and irritative symptoms (nocturia, daytime frequency, need to strain or push the flow of urine) by rating on a 0 to 5 scale for six symptoms and a 0 to 4 scale for one symptom, for a total possible score of 34.

Patients in PLESS, had moderate to severe symptoms at baseline (mean of approximately 15 points on a 0-34 point scale). Patients randomized to PROSCAR who remained on therapy for 4 years had a mean (± 1 SD) decrease in symptom score of 3.3 (± 5.8) points compared with 1.3 (± 5.6) points in the placebo group. (See Figure 1.) A statistically significant improvement in symptom score was evident at 1 year in patients treated with PROSCAR vs placebo (-2.3 vs -1.6), and this improvement continued through Year 4.

Figure 1
Symptom Score in PLESS



Results seen in earlier studies were comparable to those seen in PLESS. Although an early improvement in urinary symptoms was seen in some patients, a therapeutic trial of at least 8 months was generally necessary to assess whether a beneficial response in symptom relief had been achieved. The improvement in BPH symptoms was seen during the first year and maintained throughout an additional 5 years of open extension studies.

Effect on Acute Urinary Retention and the Need for Surgery

In PLESS, efficacy was also assessed by evaluating treatment failures. Treatment failure was prospectively defined as BPH-related urological events or clinical deterioration, lack of improvement and/or the need for alternative therapy. BPH-related urological events were defined as urological surgical intervention and acute urinary retention requiring catheterization. Complete event information was available for 92% of the patients. The following table (Table 1) summarizes the results.

PROSCAR®
(FINASTERIDE)
TABLETS

Circular Number 9556705

PROSCAR®
(FINASTERIDE)
TABLETS

Circular Number 9556705

PROSCAR®
(FINASTERIDE)
TABLETS

Circular Number 9556705

PROSCAR®
(FINASTERIDE)
TABLETS

Circular Number 9556705

PROSCAR®
(FINASTERIDE)
TABLETS

9556705

Table 1
All Treatment Failures in PLESS

Event	Patients (%) *				
	Placebo N=1503	Finasteride N=1513	Relative Risk**	95% CI	P Value**
All Treatment Failures	37.1	26.2	0.68	(0.57 to 0.79)	<0.001
Surgical Interventions for BPH	10.1	4.6	0.45	(0.32 to 0.63)	<0.001
Acute Urinary Retention Requiring Catheterization	6.6	2.8	0.43	(0.28 to 0.66)	<0.001
Two consecutive symptom scores ≥20	9.2	6.7			
Bladder Stone	0.4	0.5			
Incontinence	2.1	1.7			
Renal Failure	0.5	0.6			
UTI	5.7	4.9			
Discontinuation due to worsening of BPH, lack of improvement, or to receive other medical treatment	21.8	13.3			

*patients with multiple events may be counted more than once for each type of event
**Hazard ratio based on log rank test

Compared with placebo, PROSCAR was associated with a significantly lower risk for acute urinary retention or the need for BPH-related surgery [13.2% for placebo vs 6.6% for PROSCAR; 51% reduction in risk, 95% CI: (34 to 63%)]. Compared with placebo, PROSCAR was associated with a significantly lower risk for surgery [10.1% for placebo vs 4.6% for PROSCAR; 55% reduction in risk, 95% CI: (37 to 68%)] and with a significantly lower risk of acute urinary retention [6.6% for placebo vs 2.8% for PROSCAR; 57% reduction in risk, 95% CI: (34 to 72%)]; See Figures 2 and 3.

Figure 2
Percent of Patients Having Surgery for BPH, including TURP

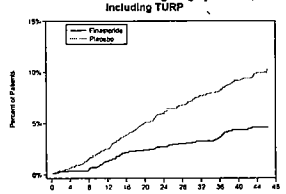
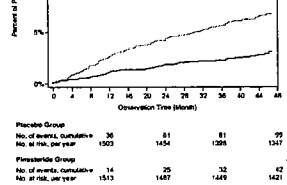


Figure 3
Percent of Patients Developing Acute Urinary Retention (Spontaneous and Precipitated)



Effect on Maximum Urinary Flow Rate

In the patients in PLESS who remained on therapy for the duration of the study and had evaluable urinary flow data, PROSCAR increased maximum urinary flow rate by 1.9 mL/sec compared with 0.2 mL/sec in the placebo group.

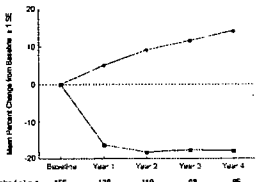
There was a clear difference between treatment groups in maximum urinary flow rate in favor of PROSCAR by month 4 (1.0 vs 0.3 mL/sec) which was maintained throughout the study. In the earlier 1-year studies, increase in maximum urinary flow rate was comparable to PLESS and was maintained through the first year and throughout an additional 5 years of open extension studies.

Effect on Prostate Volume

In PLESS, prostate volume was assessed yearly by magnetic resonance imaging (MRI) in a subset of patients. In patients treated with PROSCAR who remained on therapy, prostate volume was reduced compared with both baseline and placebo throughout the 4-year study. PROSCAR decreased prostate volume by 17.9% (from 55.9 cc at baseline to 45.8 cc at 4 years) compared with an increase of 14.1% (from 51.3 cc to 58.5 cc) in the placebo group (p<0.001). (See Figure 4.)

Results seen in earlier studies were comparable to those seen in PLESS. Mean prostate volume at baseline ranged between 40-50 cc. The reduction in prostate volume was seen during the first year and maintained throughout an additional five years of open extension studies.

Figure 4
Prostate Volume in PLESS



Prostate Volume as a Predictor of Therapeutic Response

A meta-analysis combining 1-year data from seven double-blind, placebo-controlled studies of similar design, including 4491 patients with symptomatic BPH, demonstrated that, in patients treated with PROSCAR, the magnitude of symptom response and degree of improvement in maximum urinary flow rate were greater in patients with an enlarged prostate at baseline.

Summary of Clinical Studies

The data from these studies, showing improvement in BPH-related symptoms, reduction in treatment failure (BPH-related urological events), increased maximum urinary flow rates, and decreasing prostate volume, suggest that PROSCAR arrests the disease process of BPH in men with an enlarged prostate.

INDICATIONS AND USAGE

PROSCAR is indicated for the treatment of symptomatic benign prostatic hyperplasia (BPH) in men with an enlarged prostate to:

-Improve symptoms
-Reduce the risk of acute urinary retention
-Reduce the risk of the need for surgery including transurethral resection of the prostate (TURP) and prostatectomy.

CONTRAINDICATIONS

PROSCAR is contraindicated in the following:

Hypersensitivity to any component of this medication.

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

WARNINGS

PROSCAR is not indicated for use in pediatric patients (see PRECAUTIONS, *Pediatric Use*) or women (see also WARNINGS, EXPOSURE OF WOMEN — RISK TO MALE FETUS; PRECAUTIONS, *Information for Patients* and *Pregnancy*; and HOW SUPPLIED).

EXPOSURE OF WOMEN — RISK TO MALE FETUS

Women should not handle crushed or broken PROSCAR 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. PROSCAR 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 CONTRAINDICATIONS; PRECAUTIONS, *Information for Patients* and *Pregnancy*; and HOW SUPPLIED).

9556705
PROSCAR® (Finasteride) Tablets

PRECAUTIONS

General

Prior to initiating therapy with PROSCAR, appropriate evaluation should be performed to identify other conditions such as infection, prostate cancer, stricture disease, hypotonic bladder or other neurogenic disorders that might mimic BPH.

Patients with large residual urinary volume and/or severely diminished urinary flow should be carefully monitored for obstructive uropathy. These patients may not be candidates for finasteride therapy.

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

Effects on PSA and Prostate Cancer Detection

No clinical benefit has been demonstrated in patients with prostate cancer treated with PROSCAR. Patients with BPH and elevated PSA were monitored in controlled clinical studies with serial PSAs and prostate biopsies. In these studies, PROSCAR did not appear to alter the rate of prostate cancer detection. The overall incidence of prostate cancer was not significantly different in patients treated with PROSCAR or placebo.

PROSCAR causes a decrease in serum PSA levels by approximately 50% in patients with BPH, even in the presence of prostate cancer. This decrease is predictable over the entire range of PSA values, although it may vary in individual patients. Analysis of PSA data from over 3000 patients in PLESS confirmed that in typical patients treated with PROSCAR for six months or more, PSA values should be doubled for comparison with normal ranges in untreated men. This adjustment preserves the sensitivity and specificity of the PSA assay and maintains its ability to detect prostate cancer.

Any sustained increases in PSA levels while on PROSCAR should be carefully evaluated, including consideration of non-compliance to therapy with PROSCAR.

Percent free PSA (free to total PSA ratio) is not significantly decreased by PROSCAR. The ratio of free to total PSA remains constant even under the influence of PROSCAR. If clinicians elect to use percent free PSA as an aid in the detection of prostate cancer in men undergoing finasteride therapy, no adjustment to its value appears necessary.

Information for Patients

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

Physicians should inform patients that the volume of ejaculate may be decreased in some patients during treatment with PROSCAR. This decrease does not appear to interfere with normal sexual function. However, impotence and decreased libido may occur in patients treated with PROSCAR (see ADVERSE REACTIONS).

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).

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

Drug/Laboratory Test Interactions

In patients with BPH, PROSCAR has no effect on circulating levels of cortisol, estradiol, prolactin, thyroid-stimulating hormone, or thyroxine. No clinically meaningful effect was observed on the plasma lipid profile (i.e., total cholesterol, low density lipoproteins, high density lipoproteins and triglycerides) or bone mineral density. Increases of about 10% were observed in luteinizing hormone (LH) and follicle-stimulating hormone (FSH) in patients receiving PROSCAR, but levels remained within the normal range. In healthy volunteers, treatment with PROSCAR did not alter the response of LH and FSH to gonadotropin-releasing hormone indicating that the hypothalamic-pituitary-testicular axis was not affected.

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

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 have included antipyrine, digoxin, propranolol, theophylline, and warfarin and no clinically meaningful interactions were found.

Other Concomitant Therapy: Although specific interaction studies were not performed, PROSCAR was concomitantly used in clinical studies with acetaminophen, acetylsalicylic acid, α-blockers, angiotensin-converting enzyme (ACE) inhibitors, analgesics, anti-convulsants, beta-adrenergic blocking agents, diuretics, calcium channel blockers, cardiac nitrates, HMG-CoA reductase inhibitors, nonsteroidal anti-inflammatory drugs (NSAIDs), benzodiazepines, H_2 antagonists 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 111 and 274 times those observed in man receiving the recommended human dose of 5 mg/day. All exposure calculations were based on calculated AUC (0-24 hr) for animals and mean AUC (0-24 hr) for man (0.4 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 (228 times the human exposure). In mice at a dose of 25 mg/kg/day (23 times the human exposure, estimated) and in rats at a dose of ≥40 mg/kg/day (39 times the human exposure) an increase in the incidence of Leydig cell hyperplasia was observed. A positive correlation between the proliferative changes in the Leydig cells and an increase in serum LH levels (2-3 fold above control) has been demonstrated in both rodent species treated with high doses of finasteride. No drug-related Leydig cell changes were seen in either rats or dogs treated with finasteride for 1 year at doses of 20 mg/kg/day and 45 mg/kg/day (30 and 350 times, respectively, the human exposure) or in mice treated for 19 months at a dose of 2.5 mg/kg/day (2.3 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. These concentrations correspond to 4000-5000 times the peak plasma levels in man given a total dose of 5 mg. 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 (228 times the human exposure) as determined in the carcinogenicity studies.

In sexually mature male rabbits treated with finasteride at 80 mg/kg/day (543 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 (61 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 and is not relevant in man.

Pregnancy

Pregnancy Category X

See CONTRAINDICATIONS.

PROSCAR is not indicated for use in women.

Administration of finasteride to pregnant rats at doses ranging from 100 µg/kg/day to 100 mg/kg/day (1-1000 times the recommended human dose of 5 mg/day) resulted in dose-dependent development of hypospadias in 3.6 to 100% of male offspring. Pregnant rats produced male offspring with decreased prostatic and seminal vesicular weights, delayed preputial separation and transient nipple development when given finasteride at ≥30 µg/kg/day (≥3/10 of the recommended human dose of 5 mg/day) and decreased anogenital distance when given finasteride at ≥3 µg/kg/day (≥3/100 of the recommended human dose of 5 mg/day). The critical period during which these effects can be induced in male rats has been defined to be days 16-17 of gestation. The changes described above are expected pharmacological effects of drugs belonging to the class of Type II 5α-reductase inhibitors and are similar to those reported in male infants with a genetic deficiency of Type II 5α-reductase. No abnormalities were observed in female offspring exposed to any dose of finasteride *in utero*.

No developmental abnormalities have been observed in first filial generation (F_1) male or female offspring resulting from mating finasteride-treated male rats (80 mg/kg/day; 61 times the human exposure) with untreated females. Administration of finasteride at 3 mg/kg/day (30 times the recommended human dose of 5 mg/day) during the late gestation and lactation period resulted in slightly decreased fertility in F_1 male offspring. No effects were seen in female offspring. No evidence of malformations has been observed in rabbit fetuses exposed to finasteride *in utero* from days 6-18 of gestation at doses up to 100 mg/kg/day (1000 times the recommended human dose of 5 mg/day). However, effects on male genitalia would not be expected since the rabbits were not exposed during the critical period of genital system development.

The *in utero* effects of finasteride exposure during the period of embryonic and fetal development were evaluated in the rhesus monkey (gestation days 20-100), a species more predictive of human development than rats or rabbits. Intravenous administration of finasteride to pregnant monkeys at doses as high as 800 ng/day (at least 60 to 120 times the highest estimated exposure of pregnant women to finasteride from semen of men taking 5 mg/day) resulted in no abnormalities in male fetuses. In confirmation of the relevance of the rhesus model for human fetal development, oral administration of a dose of finasteride (2 mg/kg/day; 20 times the recommended human dose of 5 mg/day or approximately 1-2 million times the highest estimated exposure to finasteride from semen of men taking 5 mg/day) to pregnant monkeys resulted in external genital abnormalities in male fetuses. No other abnormalities were observed in male fetuses and no finasteride-related abnormalities were observed in female fetuses at any dose.

Nursing Mothers

PROSCAR is not indicated for use in women.

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

Pediatric Use

PROSCAR is not indicated for use in pediatric patients.

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Of the total number of subjects included in PLESS, 1480 and 105 subjects were 65 and over and 75 and over, respectively. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients. No dosage adjustment is necessary in the elderly (see CLINICAL PHARMACOLOGY, *Pharmacokinetics* and *Clinical Studies*).

ADVERSE REACTIONS

PROSCAR is generally well tolerated; adverse reactions usually have been mild and transient.

4-Year Placebo-Controlled Study

In PLESS, 1524 patients treated with PROSCAR and 1516 patients treated with placebo were evaluated for safety over a period of 4 years. The most frequently reported adverse reactions were related to sexual function. 3.7% (57 patients) treated with PROSCAR 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

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

Phase III Studies and 5-Year Open Extensions

The adverse experience profile in the 1-year, placebo-controlled, Phase III studies, the 5-year open extensions, and PLESS were similar.

Long-Term Treatment

There is no evidence of increased adverse experiences with increased duration of treatment with PROSCAR. 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 finasteride but no cases in men not treated with finasteride. During the 4-year, placebo-controlled PLESS study that enrolled 3040 men, there were 2 cases of breast cancer in placebo-treated men, but no cases were reported in men treated with finasteride.

The following additional adverse effects have been reported in post-marketing experience:

- hypersensitivity reactions, including pruritus, urticaria, and swelling of the lips and face
- testicular pain.

OVERDOSAGE

Patients have received single doses of PROSCAR up to 400 mg and multiple doses of PROSCAR up to 80 mg/day for three months without adverse effects. Until further experience is obtained, no specific treatment for an overdose with PROSCAR can be recommended.

Significant lethality was observed in male and female mice at single oral doses of 1600 mg/m² (500 mg/kg) and in female and male rats at single oral doses of 2360 mg/m² (400 mg/kg) and 5900 mg/m² (1000 mg/kg), respectively.

DOSAGE AND ADMINISTRATION

The recommended dose is 5 mg orally once a day.

PROSCAR may be administered with or without meals.

No dosage adjustment is necessary for patients with renal impairment or for the elderly (see CLINICAL PHARMACOLOGY, *Pharmacokinetics*).

HOW SUPPLIED

No. 3084 — PROSCAR tablets 5 mg are blue, modified apple-shaped, film-coated tablets, with the code MSD 72 on one side and PROSCAR on the other. They are supplied as follows:

NDC 0006-0072-31 unit of use bottles of 30
NDC 0006-0072-58 unit of use bottles of 100
NDC 0006-0072-28 unit dose packages of 100
NDC 0006-0072-82 bottles of 1000.

Storage and Handling

Store at room temperatures below 30°C (86°F). Protect from light and keep container tightly closed.

Women should not handle crushed or broken PROSCAR 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 (see WARNINGS, EXPOSURE OF WOMEN — RISK TO MALE FETUS, and PRECAUTIONS, *Information for Patients* and *Pregnancy*).

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

Issued July 2003
Printed in USA

7819308

PROSCAR® (Finasteride) Tablets
Patient Information about PROSCAR® (Prahs-car)

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

PROSCAR* is for use by men only.

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

Why your doctor has prescribed PROSCAR

Your doctor has prescribed PROSCAR because you have a medical condition called benign prostatic hyperplasia or BPH. This occurs only in men.

What is BPH?

BPH is an enlargement of the prostate gland. After age 50, most men develop enlarged prostates. The prostate is located below the bladder. As the prostate enlarges, it may slowly restrict the flow of urine. This can lead to symptoms such as:

- a weak or interrupted urinary stream
- a feeling that you cannot empty your bladder completely
- a feeling of delay or hesitation when you start to urinate
- a need to urinate often, especially at night
- a feeling that you must urinate right away.

In some men, BPH can lead to serious problems, including urinary tract infections, a sudden inability to pass urine (acute urinary retention), as well as the need for surgery.

Treatment options for BPH

There are three main treatment options for symptoms of BPH:

- **Program of monitoring or "Watchful Waiting".** If a man has an enlarged prostate gland and no symptoms or if his symptoms do not bother him, he and his doctor may decide on a program of monitoring which would include regular checkups, instead of medication or surgery.
- **Medication.** Your doctor may prescribe PROSCAR for BPH. See **"What PROSCAR does"** below.
- **Surgery.** Some patients may need surgery. Your doctor can suggest several different surgical procedures for BPH. Which procedure is best depends on your symptoms and medical condition.

There are two main treatment options to reduce the risk of serious problems due to BPH:

- **Medication.** Your doctor may prescribe PROSCAR for BPH. See **"What PROSCAR does"** below.
- **Surgery.** Some patients may need surgery. Your doctor can suggest several different surgical procedures for BPH. Which procedure is best depends on your symptoms and medical condition.

What PROSCAR does

PROSCAR lowers levels of a key hormone called DHT (dihydrotestosterone), which is a major cause of prostate growth. Lowering DHT leads to shrinkage of the enlarged prostate gland in most men. This can lead to gradual improvement in urine flow and symptoms over the next several months. PROSCAR will help reduce the risk of developing a sudden inability to pass urine and the need for surgery. However, since each case of BPH is different, you should know that:

- Even though the prostate shrinks, you may NOT notice an improvement in urine flow or symptoms.
- You may need to take PROSCAR for six (6) months or more to see whether it improves your symptoms.
- Therapy with PROSCAR may reduce your risk for a sudden inability to pass urine and the need for surgery.

What you need to know while taking PROSCAR

- **You must see your doctor regularly.** While taking PROSCAR, you must have regular checkups. Follow your doctor's advice about when to have these checkups.
- **About side effects.** Like all prescription drugs, PROSCAR may cause side effects. Side effects due to PROSCAR may include impotence (an inability to have an erection) or less desire for sex.

  Some men taking PROSCAR may have changes or problems with ejaculation, such as a decrease in the amount of semen released during sex. This decrease in the amount of semen does not appear to interfere with normal sexual function. In some cases these side effects went away while the patient continued to take PROSCAR.

  In addition, some men may have breast enlargement and/or tenderness. You should promptly report to your doctor any changes in your breasts such as lumps, pain or nipple discharge. Some men have reported allergic reactions such as rash, itching, hives, and swelling of the lips and face. Rarely, testicular pain has been reported.

You should discuss side effects with your doctor before taking PROSCAR and anytime you think you are having a side effect.

- **Checking for prostate cancer.** Your doctor has prescribed PROSCAR for symptomatic BPH and not for cancer — but a man can have BPH and prostate cancer at the same time. Doctors usually recommend that men be checked for prostate cancer once a year when they turn 50 (or 40 if a family member has had prostate cancer). These checks should continue while

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you take PROSCAR. PROSCAR is not a treatment for prostate cancer.

- **About Prostate-Specific Antigen (PSA).**

  Your doctor may have done a blood test called PSA. PROSCAR can alter PSA values. For more information, talk to your doctor.

- **A warning about PROSCAR and pregnancy.**

  PROSCAR is for use by MEN only.
  Women who are or may potentially be pregnant must not use PROSCAR. They should also not handle crushed or broken tablets of PROSCAR.

  If a woman who is pregnant with a male baby absorbs the active ingredient in PROSCAR after oral use or through the skin, it may cause the male baby to be born with abnormalities of the sex organs.

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

PROSCAR® (Finasteride) Tablets

If a woman who is pregnant comes into contact with the active ingredient in PROSCAR, a doctor should be consulted.

Remember, these warnings apply only when the woman is pregnant or could potentially be pregnant.

How to take PROSCAR

Follow your doctor's advice about how to take PROSCAR. You must take it every day. You may take it with or between meals. To avoid forgetting to take PROSCAR, it may be helpful to take it at the same time every day.

Do not share PROSCAR with anyone else; it was prescribed only for you.

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

FOR MORE INFORMATION ABOUT 'PROSCAR' AND BPH, TALK WITH YOUR DOCTOR.
IN ADDITION, TALK TO YOUR PHARMACIST OR OTHER HEALTH CARE PROVIDER.

Issued July 2003

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-180/S-020

MEDICAL REVIEW(S)

Date of submission – November 9, 1998
Date completed - October 29, 1999

Medical Officer Review of sNDA-Labeling Supplement

NDA 20 180 [Proscar], SLR #002, supplement 020
Sponsor – Merck Research Laboratories

Background – The sponsor submitted this supplement in response to a phase IV commitment at the time of the approval of PROPECIA [finasteride 1 mg] December 19, 1997 "to upgrade and provide consistency with the PROSCAR label and the PROPECIA label." A major supplemental labeling revision for PROSCAR was approved by DRUDP in March 1998.

The Division of Dermatological and Dental Drug Products is also reviewing this submission.

The sponsor states that the three guiding principles for the revision were:

- To ensure that all information that applied to finasteride 1 mg or 5 mg, independent of support of the indications, was as consistent as possible.
- To always retain wording in a given label if this wording was present as the result of a specific request from the reviewing division.
- To make editorial changes to:
  - conform with current USP or Merck guidelines
  - Increased clarity
  - Lessen redundancy

The submission includes the cover letter and ten attachments:

- Draft package circulars and draft patient information for PROSCAR and PROPECIA, side by side, with annotated revisions
- Clean running text [draft] for PROSCAR and PROPECIA package circulars and patient information
- Summary of revisions for PROSCAR and PROPECIA package circulars and patient information

Sponsor-Proposed changes to PROSCAR label

The sponsor has included a Summary of Revisions [see attachment] for the label which includes 24 proposed changes in the DESCRIPTION, CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, OVERDOSAGE, AND HOW SUPPLIED sections.

The sponsor states that "no significant changes" were made in the following sections: INDICATIONS AND USAGE, CONTRAINDICATIONS, WARNINGS, OVERDOSAGE, DOSAGE AND ADMINISTRATION, and HOW SUPPLIED.

Reviewer comment -The changes proposed in the DESCRIPTION, WARNINGS, ADVERSE REACTIONS, OVERDOSAGE, and HOW SUPPLIED sections have been reviewed and the proposed labeling changes are acceptable. [see Summary of Revisions, attachment]

The CLINICAL PHARMACOLOGY section:

- Adds multiple dose PK results to harmonize with data from the PROPECIA label and replace single dose PK information.
- [redacted]
- [redacted]

The PRECAUTIONS, Information for Patients section adds information to clarify the risk associated with the handling of the drug by pregnant women

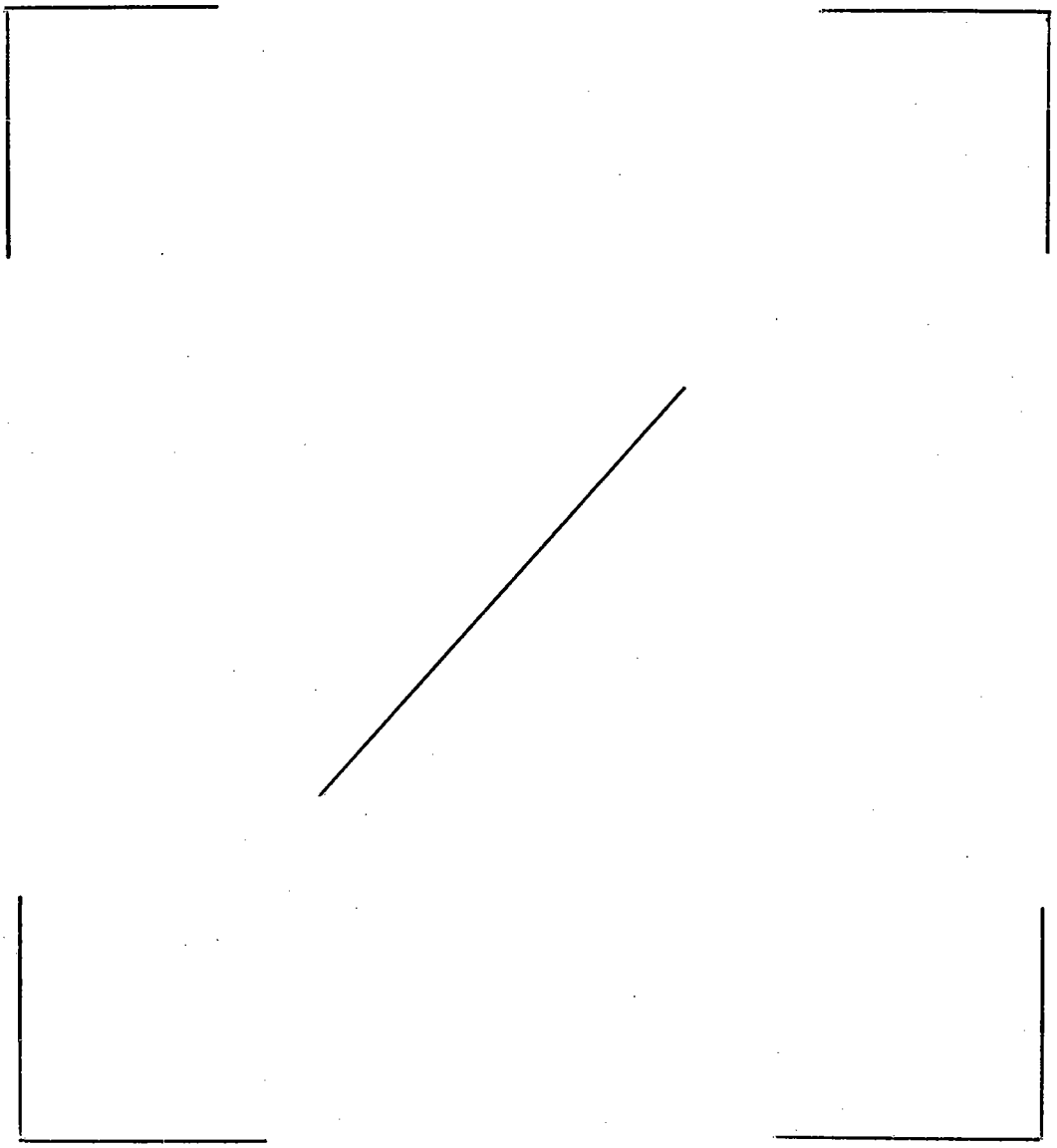
Reviewer comment – The proposed labeling changes are acceptable.

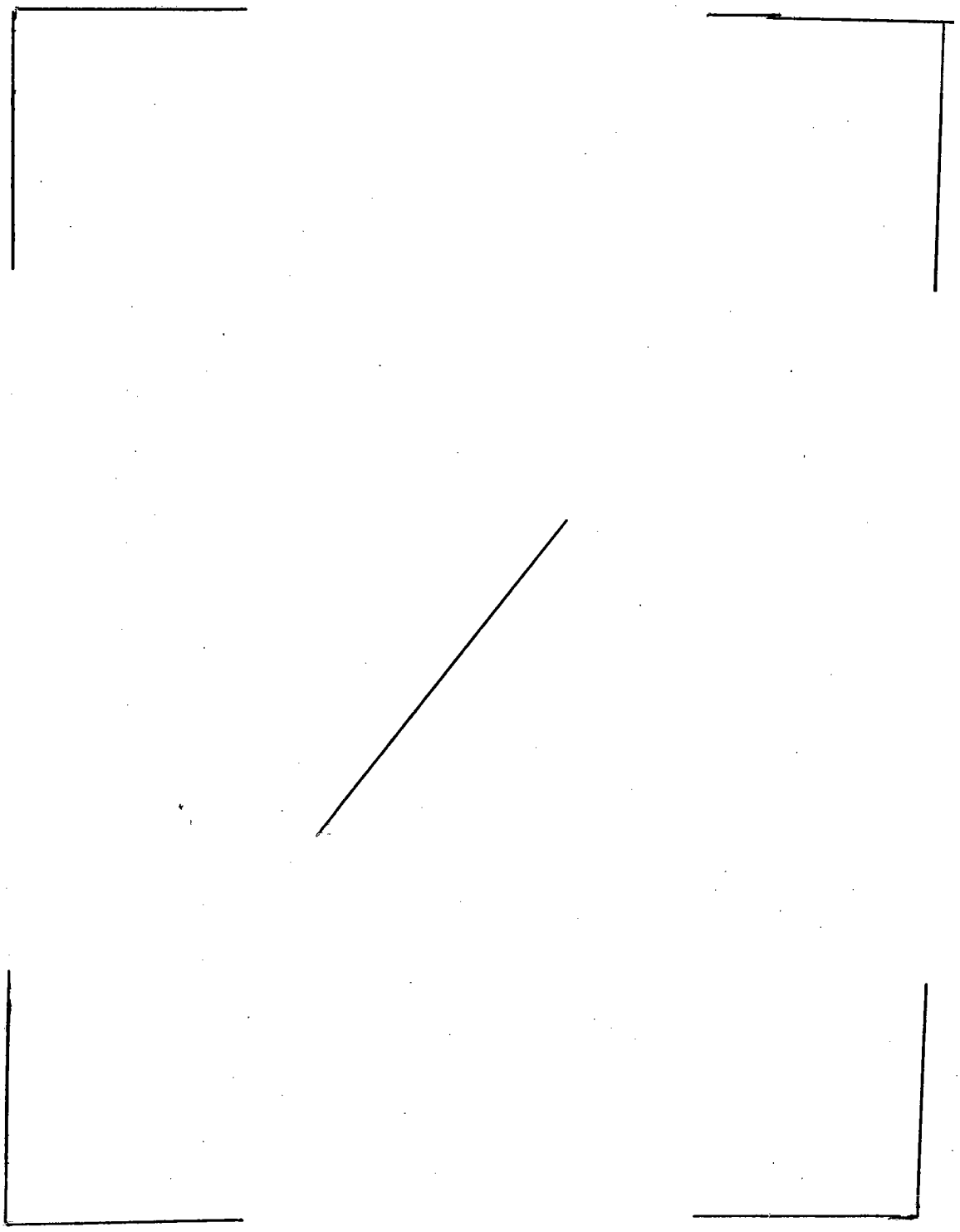
PRECAUTIONS, Drug-Laboratory Test Interactions adds information on the effects of finasteride on estradiol and prolactin.

Reviewer comment - The sponsor comments that a statistically significant change in prolactin versus placebo is noted after administration of finasteride but that the 'effect is not clinically relevant'. The summary of the primary data for this claim has been reviewed and appears to be truthful and accurate. The proposed labeling changes are acceptable.

This paragraph was relocated from the CLINICAL PHARMACOLOGY section at the time of a labeling revision March 1998. This information would seem to be most useful for referencing if located in its present location. Including duplicate information in CLINICAL PHARMACOLOGY with cross-referencing would be an acceptable alternative [as recommended by the DDDDP reviewer].

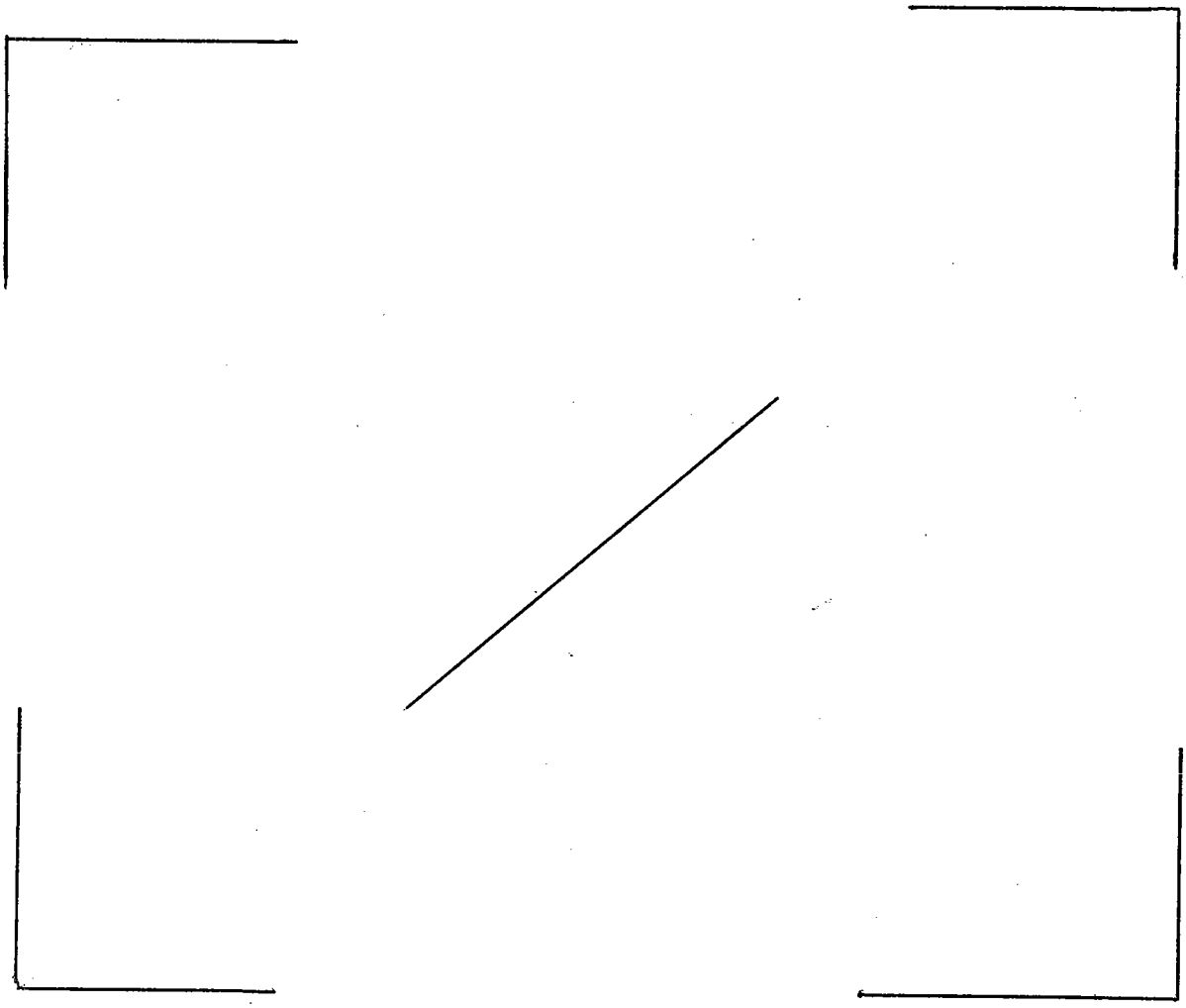
The CONTRAINDICATIONS and PRECAUTIONS sections have been reviewed and the following seven modifications are suggested. None of these changes are included in the draft labeling submitted by the sponsor.





[CURRENT APPROVED LABEL] *PRECAUTIONS, Drug/Laboratory Test Interactions*

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



7. The PRECAUTIONS, Geriatric Use section, now required under 21 CFR 201.57 (f)(10)(ii), is not included in this labeling submission.

   Reviewer comment - *The sponsor has submitted a sNDA, supplement 022, on August 25, 1999 to add a PRECAUTIONS, Geriatric Use section to the label.*

[redacted]

Recommended regulatory action – The reviewer comments will be shared with the Division of Dermatological and Dental Drug Products. The following comments should be transmitted to the sponsor in a regulatory letter. When the sponsor formally accepts the wording, an approval letter for this supplement should be issued.

The sponsor has included a Summary of Revisions for the PROSCAR package circular which includes 24 proposed changes in the DESCRIPTION, CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, OVERDOSAGE, AND HOW SUPPLIED sections.

Reviewer comment -The changes proposed in the DESCRIPTION, CLINICAL PHARMACOLOGY, WARNINGS, ADVERSE REACTIONS, OVERDOSAGE, and HOW SUPPLIED sections have been reviewed and the proposed labeling changes are acceptable. [see Summary of Revisions, attached]

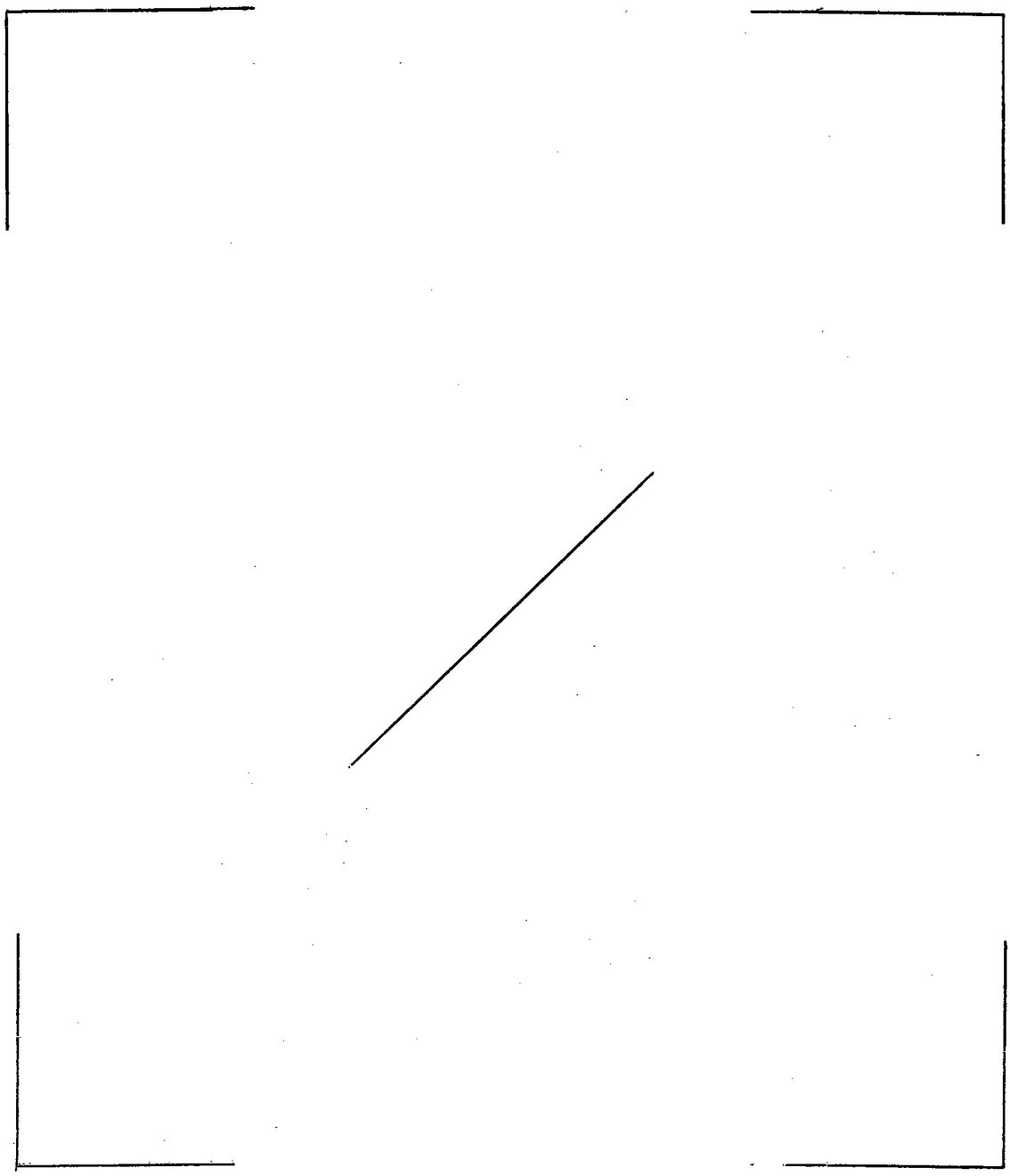
The PRECAUTIONS, Information for Patients section adds information to clarify the risk associated with the handling of the drug by pregnant women

The PRECAUTIONS, Drug-Laboratory Test Interactions section adds information on the effects of finasteride on estradiol and prolactin.

Reviewer comment-This paragraph was relocated from the CLINICAL PHARMACOLOGY section at the time of a labeling revision March 1998. This information would seem to be most useful for referencing if located in its present location. Including duplicate information in CLINICAL PHARMACOLOGY with cross-referencing would be acceptable [as recommended by the DDDDP reviewer].

The proposed labeling changes in these two paragraphs are acceptable.

[redacted]

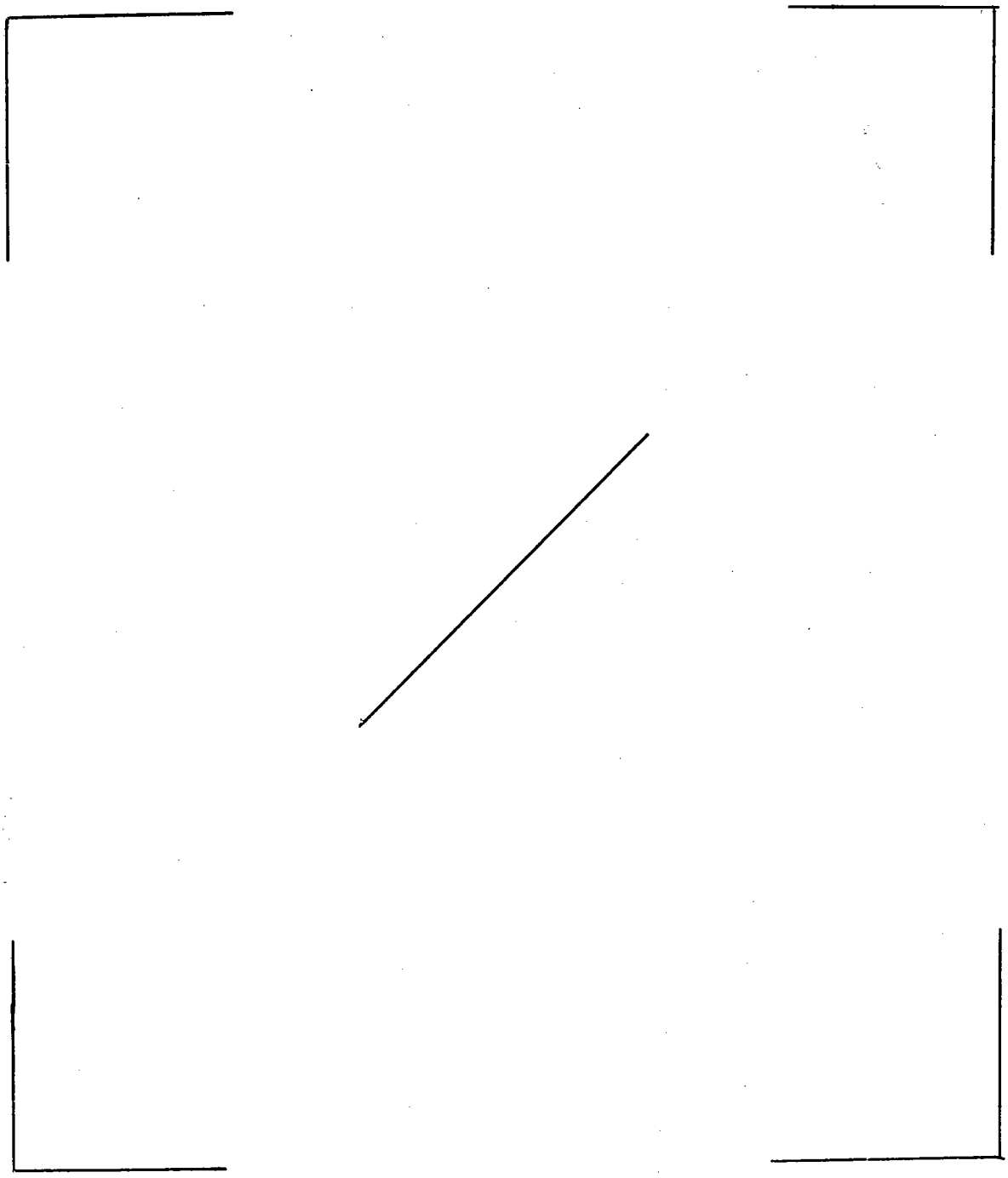


The following alternative is suggested to replace the information currently in the PROSCAR label:

[CURRENT APPROVED LABEL] *PRECAUTIONS, Drug/Laboratory Test Interactions*

Treatment with PROSCAR for 24 weeks to evaluate semen parameters in healthy male volunteers revealed no clinically meaningful effects on sperm concentration,

motility, morphology, or pH. A 0.6 ml [22.1%] median decrease in ejaculate volume with a concomitant reduction in total sperm per ejaculate was observed. These parameters remained within the normal range and were reversible upon discontinuation of therapy with an average time to return to baseline of 84 weeks.



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Reviewer comment - The sponsor has submitted a sNDA, supplement 022, on August 25, 1999 to add a PRECAUTIONS, Geriatric Use section to the label.

Norman S. Marks, M.D.
Medical Officer, Urology, HFD-580
CC: Daniel Shames, M.D.
Marianne Mann, M.D.
Evelyn Farinas
NDA 20 180, supplement 020

IND #28,422 **Serial** #530, #533, #534, #535, #536, #537, #538, #539, #540, #541, and #543
NDA #20-180 **SLR** 020

Medical Officer's Memorandum

Submitted/Received:

IND# 28,422	Serial #530 (June 24, 2002/June 25, 2002)
	Serial #533 (July 29, 2002/July 30, 2002)
	Serial #534 (August 19, 2002/August 20, 2002)
	Serial #535 (September 20, 2002/September 23, 2002)
	Serial #536 (September 20, 2002/September 23, 2002)
	Serial #537 (October 4, 2002/October 5, 2002)
	Serial #538 (October 28, 2002/October 29, 2002)
	Serial #539 (November 11, 2002/November 12, 2002)
	Serial #540 (December 13, 2002/December 16, 2002)
	Serial #541 (December 16, 2002/December 17, 2002)
	Serial #543 (December 30, 2002/December 31, 2002)
NDA 20-180	SLR 020 (November 9, 1998/November 10, 1998)
Memo completed:	April 2, 2003

Sponsor: Merck Research Laboratories (MRL)
Drug: Proscar (finasteride)
Dosage strength, formulation, route and frequency: 5 mg tablet by mouth once daily
Indication: benign prostatic hypertrophy (BPH)
Regarding: Division-proposed new precaution for the Proscar labeling regarding to potential safety issue of male breast cancer

1. Executive summary:
The purpose of this memorandum is to provide the Division Director with my recommendation regarding new labeling for a potential new safety issue with Proscar: male breast cancer. After reviewing 12 submissions by the sponsor (MRL), three new consults from the Office of Drug Safety (ODS), and three old consults from ODS, this reviewer recommends that the following new language should be added to the Proscar labeling as a new precaution in the "*General*" subsection of the **PRECAUTIONS** section:

I recommend that this specific language should be added as a new third precaution in the General Precaution section of the Proscar label that was conveyed to the sponsor as part of the December 20, 2002 Approvable letter for SLR 020.

I also recommend the addition of a new paragraph in the Information for Patients section as follows:

[ ]

This new label should then serve as the final piece in the approvable action for SLR 020, and should be conveyed via a new regulatory letter attached to supplement 020.

I also recommend that the new precaution be added to the Propecia label despite the lack of breast cancer cases with Propecia. I make this recommendation based upon the need to adequately inform [ ] men with alopecia, [ ] and their health care providers who may be considering off-label use of Propecia. [ ]

[ ]

2. Background

Proscar was approved for marketing in 1992. It is a 5-alpha-reductase inhibitor, meaning that it inhibits the intracellular conversion of testosterone (T) to dihydrotestosterone (DHT). DHT is considered the more potent of the two androgens. By reducing intracellular DHT, finasteride prevents certain androgenic effects, including effects on the prostate. This property of the compound has been exploited in men with benign prostatic hypertrophy to stop further growth of the gland and even to shrink it. This results in a modest improvement in urinary outflow signs and symptoms and in addition, has been shown to decrease the risk of going into urinary retention or needing BPH-related surgery.

One of the known adverse reactions with Proscar is male breast enlargement and breast tenderness. The pathophysiologic reason for these adverse events is not well understood. It is known that the metabolic pathway for testosterone is altered by the 5-alpha reductase enzyme inhbition, thus leading to modestly increased serum testosterone and also modestly increased serum estrogen. Since breast tissue is known to be sensitive to changes in serum testosterone, and changes in serum estradiol, it is plausible to believe that the benign breast changes seen after administration of Proscar are pathophysiologically related to treatment.

The question now arises as to the potential relationship between cancerous changes of the male breast and treatment with fiansteride. Such a link has heretofore not been made. In the ten-year postmarketing period for finasteride, there have been several spontaneous adverse event reports of male breast cancer. Based upon the spontaneous nature of the reports, as well as other factors, it has not been possible to draw the conclusion that the development of breast cancer is linked to treatment with finasteride.

3. Brief discussion of the relevant issues

3.1 The MTOPS Study results

On June 5, 2002, Dr. Leroy Nyberg, Director of Urology Programs, Division of Kidney, Urologic and Hematologic Diseases, at the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK) of the National Institute of Health (NIH) informed the Division of a potential safety finding following the unblinding of study data from a clinical trial being conducted under his IND #43,564. The study is known as MTOPS, or the Medical Treatment of Prostatic Symptoms. In this randomized, placebo-controlled trial in which over 3000 BPH patients were randomized to placebo, finasteride-only, doxazosin-only, or the combination, there were 4 new cases of male breast cancer reported. Three of these were reported during the trial and one was reported immediately after the study closed. The three cases reported during the trial had been randomized to the finasteride-only group (N=2) or to the finasteride/doxazosin combination group (N=1). The fourth case, reported after the trial closed, had also been in the finasteride-only group.

In this report, Dr, Nyberg submitted the following items:

1. Brief information for each of the 4 breast cancer cases reported in MTOPS (1-page)
2. A copy of an eMAIL transmission from Dr. Joanne Walstreicher of Merck Research Laboratories to Dr. Nyberg (dated June 2, 2002) containing a summary document which she refers to as "a report prepared in the year 2000 on breast cancer cases" (11-pages)
3. A copy of a letter to the editor of the New England Journal published on September 12, 1996 from Drs. Wysowski and Fourcroy, in which two patients taking finasteride were diagnosed with breast cancer (2-pages)
4. A copy of an eMAIL transmission from Oliver Bautista of the George Washington University Biostatistics Center to Dr. Nyberg (dated June 3, 2002) comparing breast cancer incidences in MTOPS to the incidences in other Merck-sponsored clinical trials that was shared with Dr. Bautista by Dr. Waldstreicher (1-page)

To summarize this submission:

1. The four MTOPS cases were males, aged 70 to 81 years. Two patients were Black, one was White and one was Asian. Time on finasteride ranged from 1.8 years to 5.0 years.

2. Dr. Waldstreicher's "report from the year 2000" notes the following:
   a. There were 27 cases reported in the post-marketing period as of the year 2000 and an additional 7 cases since then (6 in men and 1 in a woman). Of the original 27 cases, 5 were from clinical trials (3 drug and 2 placebo) and 22 were from marketed use.
   b. Merck states that the expected incidence of breast cancer in men of the same age range as BPH users is [redacted] per 100,000 person-years. In their clinical trials, they quote incidences of 16.1 per 100,000 person-years for drug and 20.4 per 100,000 person-years for placebo. They believe the increased incidences in both groups are due to the increased monitoring in clinical trials.
      - Of the 5 controlled cases, 4 came from placebo-controlled studies (2 drug and 2 placebo) and 1 from an open-label extension.
      - All 4 cases from placebo-controlled studies presented as a breast lump.

   c. Based on the expected background incidence, Merck postulates that approximately 295 cases of male breast cancer should have been reported in the post-marketing period and only 22 were reported as of the year 2000.

- Of the 22 cases, five had inadequate information to assess time on finasteride.
- Of the 22 cases, one patient had a previous history of breast cancer.
- Of the 22 cases, six developed cancer within 1 year of starting finasteride and one was on therapy for only 1 month.
- Of the 22 cases, one patient was diagnosed 21 months after starting finasteride but actually noted a breast lump after only 4 months on treatment

d. Merck concludes that:
   - Reports of breast cancer in controlled trials are few and balanced between drug and placebo.
   - The number of reports in the post-marketing period are "low" and do not suggest any association between fiunasteride use and an increased risk of breast cancer. In fact, the reported rate is well below the expected incidence in this age group of men.
   - While finasteride has been associated with an "infrequent" occcurrence of benign breast complaints (tenderness and enlargement), a casual relationship has never been established between these complaints and breast cancer in men. These complaints might actually lead to increased breast monitoring and enhanced detection of breast cancer.
   - Life-long carcinogenecity studies in rodents did not reveal a signal for breast cancer.
   - Breast cancer has not been reported in men with the genetic syndrome of 5-alpha reductase deficiency.
   - Finasteride does not alter the serum testosterone to estradiol ratio.
   - In summary, there is no evidence from clinical studies, pre-clinical studies, or the post-marketing operiod of a link between therapy with finasteride and the development of breast cancer.

3. Dr. Oliver N. Bautista reports that the incidence of breast cancer was 44.7 per 100,00 person-years , at least "double" that reported by Merck in their position paper.

4. In their 1996 New England journal abstract, Drs. Wysowski and Fourcroy summarize the postmarketing reports of gynecomastia and breast cancer seen with Proscar from marketing in June 1992 to February 1995. They conclude that finasteride alters the testosterone to estradiol ratio and thus leads to gynecomastia. (Merck does not agree that this ratio is altered). The authors also conclude that gynecomastia has been associated with breast cancer in men. (Merck does not agree that there is any such link). Authors conclude that "whether finsteride and breast cancer in men are related is unknown at this time, and continued surveillance is required."

3.2. Consults received from OPDRA prior to MTOPS results

1. The Division has received three previous consults from on this same matter prior to Dr. Nyberg's safety report, as follows:

    a. In April 1995, Lanh Green described 234 cases of gynecomastia and two cases of breast cancer in the postmarketing period for Proscar. She concluded that the labeling contained references to breast tenderness and enlargement but not to male breast carcinoma.
    b. In March 2001, Drs Toyer and Uhl described 24 unduplicated cases of male breast cancer in Proscar users reported in the post-marketing period. Using IMS health data, they reported calculated reporting rates of [ ] per 100,00 for all men, [ ] for men less than age 65 years, and [ ] for men >age 65. They compared these rates to the SER database where they found incidence rates of 1.0 per 100, 000 for all men, 0.5 per 100,000 for men less than age 65, and 5.4 per 100,000 for men >65. They concluded that

        "Based on the number of adverse event reports retrieved from AERS and the IMS drug use data, a signal does not exist noting a cause and effect between finasteride use and breast cancer in men".
    c. In October 2001, Drs. Toyer, Boxwell and Beitz were asked to "update" the Division on the number of cases of breast cancer reported with finasteride. Dr. Toyer identified 3 new cases compared with her previous search and stated:

        "none of these cases are compelling".

        Also, she stated:

        "In the previous review, the crude calculated reporting rate for this age category was [ ] per 100,00 men. The SEER expected incidence for this age category was 5.4 per 100,00 men. The addition of these three new cases, including one domestic case, would probably not substantially change the U.S. crude calculated reporting rate."

        Finally, the consult concluded:

        "As noted in previous reviews, OPDRA has been unable to establish a clear cause and effect between finasteride use and breast cancer in men."

        Reviewer's comment: Of note, OPDRA's final consult to the Division was received less than 7 months prior to Dr. Nyberg's safety report from MTOPS

3.3. Initial communication with Merck following MTOPS safety report

On June 17, 2002, this reviewer contacted Merck in regard to the potential safety issue of male breast cancer in MTOPS. Merck informed the Division that they were aware of the issue (having been notified by Dr. Nyberg on June 5, 2003) and were in the process of conducting an extensive review and analysis of all cases of male breast cancer from both clinical trials and post-marketing expereince with Proscar and Propecia. On June 24, 2002, Merck provided a "report summarizing the findings of their review" in **Serial #530** to IND#24,822. The results of this report (a 30-page document) are summarized below:

1. In controlled clinical trials with finasteride, reports of breast cancer have been few and balanced between treatment groups. In the PLESS trial, for instance, which randomized 3000 patients to finasteride or placebo for 4 years, two (2) cases were reported with in the placebo group and none in the drug group. There was one (1) case of breast cancer ("a recurrence in the contralateral breast") in a "short-term" placebo-controlled clinical trial (involving Permixon). There were four (4) cases in the MTOPS study. There were two (2) cases in open-label extension studies.

2. The National Cancer Institute informed Merck that there is "no excess" of breast cancer reports in their ongoing and blinded Prostate Cancer Prevention Trial (PCPT), although exact numbers were not provided.

3. Review and analysis of post-marketing data does not suggest an association between the use of finasteride and development of male breast cancer due to:

    a) the relatively few reports (N=28) and
    b) the relatively low incidence in the treated group compared to the background incidence ([ ] cases per 100,000 patient-years worldwide [ ] for the United States only] compared to [ ] cases per 100,000 men aged 45 years and older, and [ ] cases per 100,000 men aged 60 and older).

4. No cases of male breast cancer have been reported with Propecia (finasteride 1 mg)

Taken all together, Merck states "there does not appear to be an association between treatment with finasteride and an increased risk for development of breast cancer."

Other points of interest from this report are as follows:

1. Four women receiving finasteride reported breast cancer; three of these women were receiving finasteride for the treatment of hair loss and two were noted to be post-menopausal.

[redacted]

2. Merck was continuing to seek out data regarding the risk of finasteride upon development of breast cancer, including specific numbers of patients with the

condition in PCPT (Note: ultimately found out to be 1 and 1, placebo and drug groups, respectively).

3. Merck also intended to conducting a retrospective analysis of this issue using the UK General Practice Research Database.
4. Merck also intended to continue to review, on an ongoing basis, all reports of breast cancer in patients being treated with finasteride.
5. When MTOPS and PLESS were compared for the incidences of breast cancer, the following results were noted:

   MTOPS (N=3047):
   Placebo = 0 cases, 0.0 cases per 100,000 patient-years
   Finasteride = 4 cases, 56.5 cases per 100,00 patient-years (95% CI = 1.1, 111.8)

   PLESS (N=3040)
   Placebo = 2 cases, 44.8 cases per 100,000 patient-years (95% CI = 0.0, 106.9)
   Finasteride = 0 cases, 0.0 cases per 100,000 patient-years

   From this data, the sponsor concluded "there is no compelling evidence to suggest a difference in breast cancer rate between men treated with finasteride 5mg or men treated with placebo."

6. The ongoing PCPT trial, in which 18,882 patients have been randomized to drug or placebo for a 7-year period. The study is intended to end in the year 2004. The sponsor of the trial is the Southwest Oncology Group (SWOG). Dr. Charles Coltman, acting as PCPT principal investigator and representing SWOG, informed Merck that "there is no excess of breast cancer among patients treated with finasteride." However, Dr. Coltman did not make the exact number of cases available to Merck.

7. The sponsor combined all available cases from both controlled and uncontrolled clinical trials of at least one year in duration (as in Table 4 of this submission). The following data was submitted:

   Finasteride exposed: **6 cases**, no combined incidence rate provided
   Placebo exposed: 2 cases, no combined incidence rate provided.

   The sponsor provided only a final statistical analysis of this combined data as follows: "M-H estimate of RR = 1.72; 95% CI = (0.35, 8.47); p value =0.485".

   The sponsor's textual description of this analysis is: "While the number of events is too small to provide any definitive conclusions, the incidence on finasteride is not statistically significantly different from that on placebo ($p > 0.4$) taking into account all of the placebo-controlled clinical trials of greater than one-year in length."

   Reviewer's comments

   1. **I do not agree that the 7th finasteride case (a recurrence in the contralateral breast in a placebo-controlled Permixon trial) should be excluded from this analysis.**
   2. **Without additional clarification from sponsor and my Biometrics collegues it remains unclear to this reviewer how this analysis was conducted.**

8. The sponsor combined all available data from only the controlled trials of at least one year duration (as in Table 3 of this submission). The following data was provided:

   Finasteride exposed: **4 cases**, no combined incidence rate provided
   Placebo exposed: 2 cases, no combined incidence rate provided.

   The sponsor provided only a final statistical analysis of this combined data as follows: "M-H estimate of RR = 1.91; 95% CI = (0.35, 10.42); p value =0.445".

   Reviewer's comments

   1. **Again, I do not agree that the 5th finasteride case (a recurrence in the contralateral breast in a placebo-controlled Permixon trial) should be excluded from this analysis.**
   3. **Again, without additional clarification from sponsor and my Biometrics collegues it remains unclear to this reviewer how this analysis was conducted.**

9. Sponsor provided an additional analysis of incidence rates by exposure time interval (Year 0-1, Year 1-2, Year 2-3, etc) for the combined analysis (controlled and uncontrolled of at least one year's duration). The data is as follows:

   Finasteride exposed:

Year 0-1	Cases=0	**Rate= 0**
Year 1-2	Cases=2	Rate=30.7 per 100,000 pt-yrs (95% CI = 0, 73.2)
Year 2-3	Cases=0	Rate=0
Year 3-4	Cases=1	Rate=30.1 per 100,000 pt-yrs (95% CI = 0, 89.1)
Year 4-5	Cases=2	Rate=75.1 per 100,000 pt-yrs (95% CI = 0, 179.2)
Year 5+	Cases=1	Rate=56.6 per 100,000 pt-yrs (95% CI = 0, 167.4)

   Placebo exposed:

Year 0-1	Cases=1	Rate=14.5 per 100,000 pt-yrs (95% CI = 0, 42.8)
Year 1-2	Cases=1	Rate=22.9 per 100,000 pt-yrs (95% CI = 0, 67.7)
Year 2-3	Cases=0	Rate=0
Year 3-4	Cases=0	Rate=0
Year 4-5	Cases=0	Rate=0
Year 5+	Cases=0	Rate=0

   The sponsor concludes from this data that: "The number of events is too small to permit any definitive conclusions."

   Reviewer's comments:

   1. **I still do not agree that the 7th finasteride case (the "recurrence") should be excluded from this analysis.**
   2. **There are differences between drug and placebo in Years 3-4, 4-5 and 5+. While the numbers may be small, these are differences. I think this provides some support to the argument of a potential linkage to drug**

3.4. Regulatory proceedings following the initial Merck submission

On July 8 and July 11, 2002, the Agency sought additional information on several individual adverse event reports that described breast lumps or masses, gynecomastia, or other breast-related growths. The intent of this request was to seek out additional cases of breast cancer from those reports that might reflect cancer and not non-malignant lesions.

In Merck's response of July 29, 2002 (**Serial 533**) they state that no additional cases of breast cancer were uncovered. According to Merck this is probably because these were all cases of gynecomastia, not cancer. Merck does acknowledge difficulty in obtaining additional details from consumers and health care providers. There is some information of note in this submission:

1. The document describes 10 individual post-marketing reports for **Propecia**. All 10 reports involved an adverse event of breast lump or mass. Three reports came from health care professionals and 7 directly from consumers. Age was reported in 7 cases and ranged from 29 years to 59 years. Duration of finasteride therapy (in the 7 cases with such information) ranged from 2 to 18 months. In three cases there was a mass described just below the nipple. Mamography or biopsy information was available in only 3 patients as follows:

   •In the first patient (WAES 00060818), ultrasound showed a 1.8 cm irregular region in the left retroareolar region. Since the lesion appeared to decrease in size over 2 months time, the surgeon deferred biopsy.

   •In the second patient (WAES 000062019) a 36-year old male developed gynecomastia and a breast mass after 18 months of finasteride. He required biopsy, which a pharmacist reported as "negative".

   •In the third patient (WAES 00064495), a 56 year old physician developed unilateral breast enlargement and tenderness after 16 months on finasteride. Ultrasound showed a "small subareolar mass which suggested inflammation and not tumor". Biopsy was not undertaken."

   Reviewer's comment: I believe that these cases could represent breast cancer. [redacted] **At a minimum, these types of cases should be noted in the Propecia label.** [redacted]

On July 23, July 31 and August 8, 2002, the Agency sought additional information from Merck regarding Serial 530. The intent of these requests was to obtain additional information so that the Agency might conduct its own analysis of breast cancer incidence in controlled clinical trials. In their response, Serial 536, dated August 19, 2002, Merck submitted some additional information requested by ODS, but nevertheless they stated:

> *"Also provided in the response, is a discussion of the information provided in this and the June 24, 2002 report, with particular attention to possible additional analyses.*

Considering the limited number of cases, MRL believes that it has already thoroughly analyzed the data and that additional analyses would not provide greater insight."

In this document, Merck makes their case that additional analysis will be fruitless. They believe strongly that the results from MTOPS are "chance" (direct quote). They believe that the results from PLESS and PCPT are more telling, especially those from PCPT. They re-iterate that pre-clinical and clinical data does not provide evidence of an association. Of note, they believe that one of the cases (the patient with pre-existing breast cancer in the Permixon trial after 4 months on finasteride) should always be excluded from such analyses.

Reviewer's comment:

1. **The sponsor's argument that the results of MTOPS are "chance", may or may not be correct. Currently, I cannot be sure it was chance.**
2. **The sponsor's argument the Permixon case (the recurrence) should always be excluded is based upon unsupported speculation that it couldn't be related.**

On August 28 and September 4 2002, the Agency requested additional Forms 3500A for 34 patients with reports of breast-related adverse experiences. These were submitted by sponsor in **Serial 536** (September 20, 2002).

On September 20, 2002, Merck submitted **Serial 535**. This document conveys their 33-page technical report of a recent observational retrospective study using the UK General Practice Research Database (GPRD). The GPRD essentially contains electronic patient records of 614 general practices throughout the UK. It has been used as a database for these sorts of research efforts and is purported to adequately reflect female breast cancer incidences in the UK. First, sponsor chose criteria to define male breast cancer in the database. These were strict, such that having cancer was necessary. Then, the sponsor compared the male breast cancer incidences between the GPRD and the UK national registries. Then, the sponsor pulled out all patients who had been prescribed finasteride in the GPRD and calculated the breast cancer incidence in this population and compared it to the larger GPRD population. Additional analysis were performed to assess the impact of time on finasteride and time from finasteride to diagnosis.

The GPRD appeared to reflect the national registries very well. The sponsor found 3 cases out of 9,314 men on finasteride. They found 76 cases in the general male GPRD population out of 1,347,734 eligible men aged 35 years and older. They compared these incidences and came up with a "median unbiased estimate of the common incidence rate ratio comparing the breast cancer rate among men exposed to finasteride to the rate in the general male population of the GPRD (of) 3.4 (95% CI: 0.8, 9.3)." The p-value for the difference was not significant (p=0.083). Thus, they conclude that the hypothesis that the incidence rate among those exposed to finasteride was the same as the background rate in the general male population of the GPRD was "not rejected."

Additional conclusions by Merck included the fact that the three finasteride cases were noted not very long after starting treatment and after not very much treatment.

Reviewer's comment: Rather than being comforted by these results, I believe that they support MTOPS in some way. Specifically, I believe that there is some difference between finasteride and non-finasteride groups, although it is not statistically significant. I believe that statistical significance is not required to conclude that there is a potential safety issue.

On August 29, August 30, September 12 and September 13, 2002, the Agency and sponsor communicated via either teleconference or letter so that ODS could obtain all necessary information to conduct its own analysis of the issue. Additional information was submitted by Merck in **Serial 537** on October 4, 2002. In this submission, Merck urged the Agency to include the PCPT results in any contemplated analysis and in fact, believed that any analysis without PCPT would be biased. Merck suggested several means of analysis that would include PCPT.

3.5 Consults from ODS to the review Divisions (including MTOPS)

3.5.1 The September 26, 2002 ODS consult

On September 26, 2002, Drs. Wysowski and Beitz signed off on a formal consult from ODS providing the ODS opinion and recommendation on this matter.

Dr. Wysowski's consult re-iterated the number of cases in controlled trials (total off 11 cases – 7 drug, 3 placebo and 1 recurrence with drug). She also re-iterated the total number from the postmarketing databases (N=28, 14 domestic). The consult also listed new information for dutasteride, another 5-alpha-reductase inhibitor. There have been 3 cases reported for this drug (two drug and one placebo).

In terms of the controlled trial database, Dr. Wysowski concluded: "there is an excess number of male breast cancer cases in randomized clinical trials." However, she also stated that additional information from the MTOPS and PLESS trials were requested of sponsor and had not yet arrived. When these data were in-house, Dr. Wysowski commented that Dr. Yi Tsong would conduct a "time-to-event analysis" and such analysis would be ready within one month after receipt of this information.

In terms of the post-marketing reports, Dr. Wysowski calculated that the reporting rate for male breast cancer in finasteride users is[ ] cases per 100,000 person-years in the entire adult male population. In the 60-64 year old age group, the reporting rate was[ ] per 100,000 person-years. She contrasted these rates with the U.S. reported rates of 1.1 per 100,000 person-years in the larger group, and 3.0 per 100,000 in the older group only. She concluded that these close comparisons are "supportive of an association between male breast cancer and Proscar" since there is substantial underreporting to the FDA, especially for diseases like cancer with a long latency period.

Additional comments by Dr. Wysowski included her discussion of potential pathophysiological mechanism, reports of gynecomastia, and reports of several women who had taken finasteride and reported breast cancer. All of this leads her to conclude that there is:

> "evidence of an effect of finasteride on breast tissue growth and proliferation and *possible* induction or promotion of malignancy."
>
> **Reviewer's comment: I agree in large part with Dr. Wysowski's comments except in her belief that finasteride lowers serum testosterone (T). It has, in fact, been shown to modestly increase serum T. Also, at the time of this consult, I expressed concern that the current calculated reporting rates appeared greater than those calculated not long ago by Dr. Toyer. And, the comparisons to US registry figures were much closer than had previously been told to the Division by ODS. The actual number of cases has changed little since then. This discrepancy was later addressed in an additional consult (see below).**

Ms. Farinas added a section to this review in which she collated and described the postmarketing reports. She states: "Despite the temporal association, none of the 29 cases provide sufficient information to make a causality assessment." Nevertheless, she summates by stating:

> "There appears to be an emerging signal from the AERS reports and from the clinical trial data presented in the June 2002 Merck assessment based on the number of reports in

each database of men developing breast cancer in association with the use of Proscar." Additionally, she comments that these issues should be labeled, with special emphasis upon the fact that the word gynecomastia is not currently in the label.

3.5.2 The October 8, 2003 ODS Consult

On October 8, 2003, Drs. Beitz and Wysowski signed off on a consult to the review Divisions concerning their intepretation of the GPRD retrospective study submitted by Merck (as above). ODS felt that despite some methodological limitations, the study still showed an increased risk in finasteride users. This was for the overall risk, as well as the risk in the first two years of follow-up and the risk after the second year of follow-up. They believed that the lack of statistical significance did not obviate the notable increase in the finasteride group and the potential for causation. In addition, ODS did not agree that limited exposure time implied an impossibility of drug causality, since even short exposures to certain tumor promotors may be risky.

Reviewer's comment: I agree entirely with these ODS comments regarding the GPRD study.

3.6 Additional regulatory proceedings after the initial ODS consults

On October 4, October 10, October 22, and November 13, 2002 Drs. Wysowski and Tsong communicated with Merck in order to request and to discuss additional information from other Phase 3 Proscar trials that was necessary for the Agency's analysis.

In response to these requests, on October 28, 2002, Merck submitted **Serial 538** containing extensive information from several of the Phase 3 Proscar trials. Also, on November 11, 2002, in **Serial 539**, Merck submitted case report forms for two patients from open-label extension trials, in whom breast cancer had been reported. Finally, on December 13, 2002, in **Serial 540**, Merck submitted additonal information from several Phase 3 Proscar trials.

3.7 Additional consults from ODS after they received additional materials from sponsor

3.7.1 November 14, 2002 meeting
On November 14, 2002, reviewers from DRUDP and from DDDP, met with reviewers from the ODS and Office of Biostatistics in order to: "continue discussion of the safety issues and safety reviews of finasteride completed by the Office of Drug Safety and Office of Biostatistics"

Dr. Yi Tsong presented his analysis of 8 breast cancer cases from Proscar trials. This analysis excluded the two cases from PCPT. It also excluded the "recurrent" case from the Permixon trial. In sum, Dr. Tsong found an "excess number of male breast cancer cases in exposed subjects, but the differences in rates were not statistically significant". He also noted that the pattern of diagnosis was different between groups: patients on placebo were diagnosed sooner after study initiation and patients on drug were diagnosed in "later years of the study". He concluded that:

> "Larger and longer studies would be required to determine if an association exists between male breast cancer and finasteride use."

Dr. Wysowski presented her analysis of the 14 domestic post-marketing reports and her recommendation to add a new [ ] to the Proscar label, a new Precaution to the Propecia label [ ]

It was decided that Dr. Tsong's analysis would be incomplete without taking into consideration the PCPT information and that the group would meet again after such analysis had been completed.

3.72. The December 18 and 19, 2002 ODS consults and meeting

3.7.2.1. Consult from Dr. Beitz
In this consult, Dr. Beitz informed the review Divisions that the March 5, 2001 and October 25, 2001 consults underestimated the crude reporting rate for breast cancer in men taking finasteride. The actual number of Proscar prescriptions in the relevant six-year period was [ ] not [ ] as previously believed. When this error is corrected, the crude reporting rate is actually [ ] cases per 100,000 prescriptions, not [ ] cases per 100,000 men as presented presented previously.

In fact, when the person-time exposure is calculated using 30 days per prescription, then the calculated domestic reporting rate for the previous consults should have been [ ] cases per 100,000 person-years, a figure very similar to Dr. Wysowski's quoted rate of [ ] cases per 100,000 person-years.

In this consult, ODS stresses that it is better to rely on results from the controlled databases than the postmarketing calculations. In this regard, ODS tallied all cases from controlled trial with both finasteride and dutasteride and they derived the following incidence rates: [ ] cases per 100,000 person-years for drug (finasteride combined with dutasteride) compared to 24.1 cases per 100,000 person-years for placebo. When the data from PCPT is added in to this mix, the figures become: [ ] cases per 100,000 person-years for drug versus 6.3 cases per 100,000 person-years for placebo. Comparing these two rates, Dr. Beitz states that the "ratio of the cumulative incidence density rates is 2.03 with a p-value of 0.23."

Reviewer's comment: I do not agree that the dutasteride data can or should be combined with the finasteride data. Nevertheless, the differences between drug and placebo are consistent with differences in MTOPS and the GPRD retrospective study.

3.7.2.2. Draft consult from Drs Tsong and Zhang to Dr. Wysowski

The draft consult from Drs Tsong and Tsong dated December 18, 2002, describes the attempt to combine all data from Phase 3 Proscar trials, MTOPS, PCPT and the dutasteride trials and draw conclusions about relative risk for breast cancer incidence. Dr. Tsong makes it clear that this exercise was difficult and fraught with limitations.

His results focused on an annual hazard rate analysis. The hazard rate in the placebo group "stayed 20-45 cases per 100,000 person-years in the first 3 years of the 4-year data. There were no cases beyond the third year." On the other hand, finasteride/dutasteride-treated subjects "had the similar hazard rate as the placebo group in the first two years of exposure. There was no cases in the third year and then it increased to over [ ] cases per 100,00 patient-years in the 5th and 6th years." Over all the years, the finasteride/dutasteride ratio of cumulative incidence rates was 1.418 with a binomial test p-value of 0.60." Dr. Tsong states:

> "If male breast cancer is finasteride/dutasteride-associated, the hazard was not short-term".

When the PCPT data was introduced, the hazard rate was "largely reduced" in both placebo and finasteride groups. Dr. Tsong cannot explain this finding.

In addition, Dr. Tsong reported (also reported by Dr. Beitz in her consult) that the "over-the-year incidence densities were 24.07 per 100,00 person-years for placebo and [ ] person-years in the drug groups (finasteride/dutasteride combined without PCPT). When PCPT was added to the mix, the incidence densities were 6.3 per 100,000 person-years for the placbo group and [ ] per 100,000 person-years for the finasteride group. He states:

> "These rates are higher than the male breast cancer rates of the general population and the reporting rate estimated by AERS."

He concludes by saying:

> "The analysis showed about a 1.4 to 2-fold higher risk of male breast cancer in the men exposed to 5-alpha reductase inhibitors compared with placebo; however, the differences were not statistically signficant."

Reviewer's comments:

1. **I still do not concur with the concept of pooling finasteride and dutasteride in these analyses.**
2. **I find Dr. Tsong's draft consult difficult to interpret, especially his methods section.**
3. **Nevertheless, Dr. Tsong's conclusion is consistent with those from his previous review without PCPT, from MTOPS, and from the retrospective GPRD study.**

3.7.2.3 Final meeting between HFD-580, HFD-540 and ODS/Biostatistics

At this December 19, 2002 meeting, Dr. Tsong presented his analysis to the group and described its limitations and potential findings. He re-iterated the results stated in his December 18, 2002 draft consult. Dr. Wysowski again stressed the need to add a [ ] to the Proscar label and to revise the Propecia [ ] labels. Dr. Hirsch agreed that some labeling revisions were warranted but did not agree to specific language or label section. Additional consultation with the Divison Director was necessary.

Of note, on December 16, 2002, Merck submitted **Serial #541** requesting a meeting to discuss the Agency's analysis of the various items that Merck had submitted.

4. Reviewer's overall conclusions

The results of MTOPS cannot be disregarded as simple "chance". This reviewer acknowledges that PCPT is the largest and longest controlled trial available to us and the results to date are reassuring. However, we cannot ignore the MTOPS outcome. This is especially true when other factors are considered and these include:

1. **The known adverse reactions of breast enlargement and breast tenderness with Proscar.**
2. **The known effect of Proscar on increasing serum estradiol in healthy men.**
3. **The potential for testosterone to estrogen ratio to perhaps be altered in some men, especially those with low serum testosterone.**
4. **Twenty-eight (14 domestic) post-marketing reports of male breast cancer over a 10-year period, with a crude domestic rate similar to the background rate. We must acknowledge underreporting in the current US post-marketing voluntary reporting system.**
5. **The GPRD retrospective study which calculated an increased incidence of male breast cancer for finasteride users over non-users.**
6. **The basic conclusions from Dr. Tsong's analyes (with and without PCPT) that incidences are higher in the drug group than in the placebo group although the differences are not statistically significant.**

Therefore, if the MTOPS results can't be ignored and there is additional data to support this safety finding, then, at a minimum, the results of MTOPS and the results from post-marketing should be conveyed to consumers in some prominent part of the Proscar label.

I would recommend similar labeling for Propecia, at the discretion of DDDP. [ ]

5. Recommended regulatory action:

The following comment should be conveyed to sponsor by regulatory letter to NDA 20-180 SLR 020.

"Reference is made to our regulatory letter to you dated December 20, 2002 for NDA 20-180 SLR 020. In this letter we informed you that supplement 020 was approvable pending resolution of the male breast cancer issue. We have completed our review of the male breast cancer issue and in that regard, also make reference to your serial submissions to IND#28,422 (#530, #533, #534, #535, #536, #537, #538, #539, #540, #541, and #543). Supplemental labeling revision 020 remains approvable pending your agreement to add the following language to the Proscar label:

In the General Precautions section, as a new third paragraph:

In the Information for Patients section as a new additional paragraph:

Mark S. Hirsch M.D.
Medical Team Leader
DRUDP
Arch IND#28,422 and Arch NDA 20-180
cc: HFD-580/Div File
cc: HFD-580/DShames/JKing
cc: HFD-103/JBeitz

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

/s/

Mark S. Hirsch
4/6/03 09:33:30 AM
MEDICAL OFFICER

Daniel A. Shames
4/8/03 11:26:46 AM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-180/S-020

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Vivian L. Fuh, M.D.
Director
Regulatory Affairs

Merck & Co., Inc.
P.O. Box 2000, RY 33-200
Rahway NJ 07065-0900
Tel 732 594 0374
Fax 732 594 1030
vivian_fuh@merck.com

December 2, 2003

Daniel Shames, MD, Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III (CDER)
c/o Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

MERCK
Research Laboratories

Dear Dr. Shames:

NDA 20-180: PROSCAR™ (Finasteride 5 mg)

FINAL PRINTED LABELING For Approved Supplemental/NDA S-020

Reference is made to the Supplemental/New Drug Application cited above. Reference is also made to the Agency's Approval letter of September 23, 2003 requesting Final Printed Labeling identical to the labeling submitted for S-027 on September 9, 2003.

As indicated on the attached Form FDA 356h, this submission provides Final Printed Labeling for the approved supplemental New Drug Application for PROSCAR. The Statement of Organization following this letter describes the sections contained in this application.

With this submission is the following item:

Labeling

Final Printed Package Circular (#9556705)
Final Printed PPI (#7819308)

This submission is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the January 1999, *Guidance for Industry – Providing Regulatory Submissions in Electronic Format – NDAs.* As an attachment to this letter, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., is providing 1 Compact Disk (CD) which contains the submission. All documents requiring signatures for certification are included as paper for archival purposes.

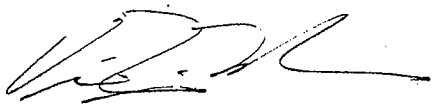
All of the information is contained on 1 CD and is not more than 100 MB. We have taken precautions to ensure that the contents of this CD are free of computer viruses (Norton Anti-Virus 7.51, Symantec Corp., 2000) and we authorize the use of anti-virus software, as appropriate.

A list of reviewers from the Division of Reproductive and Urologic Drug Products who should be provided access to this electronic submission on their desktops may be obtained from Ms. Jennifer Mercier, Regulatory Project Manager, Division of Reproductive and Urologic Drug Products.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

If you have any questions or need additional information, please contact Vivian Fuh, MD, (732-594-0374), or in her absence, David Altarac, MD, MPA (732-594-0135).

Sincerely,



Vivian Fuh, MD
Director,
Regulatory Affairs

Enclosure: CD

Federal Express

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STATEMENT OF ORGANIZATION

NDA 20-180: PROSCAR ™ (Finasteride 5 mg)
FINAL PRINTED LABELING For Approved Supplemental NDA S-020

This submission contains the following paper and/or electronic information:

ITEM(s)	DESCRIPTION	Contents on Archival CD	Archival Copy	Paper Review Copies
1	Administrative Data containing Archival CD	Yes	Blue Binder (1 volume)	No
2	Labeling	Yes	No	No

TOTAL VOLUMES: 1

(NOTE: The total number of volumes above equals the total number of volumes received by FDA - archival plus paper review copies. The total number of volumes entered on the 356H is the total number of volumes contained in the archival copy)

Vivian L. Fuh, M.D.
Director
Regulatory Affairs

Merck & Co., Inc.
P.O. Box 2000, RY 33-200
Rahway NJ 07065-0900
Tel 732 594 0374
Fax 732 594 1030
vivian_fuh@merck.com

May 2, 2003

MERCK
Research Laboratories

Daniel Shames, MD, Acting Director
Division of Reproductive and Urologic Drug Products
c/o Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

Dear Dr. Shames:

NDA 20-180/S-020: PROSCAR™ (Finasteride 5 mg)
INTENT TO AMEND

Reference is made to the above supplemental New Drug Application submitted on November 9, 1998. Reference is also made to the December 20, 2002 Approvable Letter for S-020 from Dr. Daniel Shames, Director, Division of Reproductive and Urologic Drug Products, Food and Drug Administration. Final reference is made to the April 24, 2003 letter from Dr. Shames, containing additional proposed labeling language for PROSCAR.

In accordance with 21 CFR 314.110, the purpose of this letter is to notify the Agency of our intent to file an amendment to the above referenced supplemental application for PROSCAR. This supplemental new drug application was initiated in response to a Phase IV commitment outlined in the approval letter for PROPECIA™, to "Commit to work with the FDA (Division of Dermatologic and Dental Drug Products and Division of Reproductive and Urologic Drug Products) on the labeling to upgrade and provide consistency between the PROSCAR and PROPECIA labels." As of today, we have not received comments to this supplement from the Division of Dermatologic and Dental Drug Products. However, as their response is required in order to finalize this application, we will again contact the Division to check on their status of their review.

This submission is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the January 1999, *Guidance for Industry – Providing Regulatory Submissions in Electronic Format – NDAs.* As an attachment to this letter, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., is providing 1 Compact Disk (CD) which contains the submission. All documents requiring signatures for certification are included as paper for archival purposes.

All of the information is contained on 1 CD and is not more than 100 MB. We have taken precautions to ensure that the contents of this CD are free of computer viruses (Norton Anti-Virus 7.51, Symantec Corp., 2000) and we authorize the use of anti-virus software, as appropriate.

A list of reviewers from the Division of Reproductive and Urologic Drug Products who should be provided access to this electronic submission on their desktops may be obtained from Ms. Jean King, Regulatory Project Manager, Division of Reproductive and Urologic Drug Products.

We consider the filing of this amendment to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

If you have any questions or need additional information, please contact Vivian Fuh, MD, (732-594-0374), or in her absence, David Altarac, MD (732-594-0135).

Sincerely,

Vivian Fuh, MD
Director
Regulatory Affairs

Enclosure: CD
Federal Express

Desk Copies: Jean King, HFD-580, Parklawn Building, Room 17B-45
Federal Express #2

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Vivian Fuh, MD, Director, Regulatory Affairs
Tel 732 594 0374
Fax 732 594 1030
Email: vivian_fuh@merck.com

Merck & Co., Inc.
P.O. Box 2000
Rahway NJ 07065-0900

January 3, 2003

MERCK
Research Laboratories

Daniel Shames, MD, Acting Director
Division of Reproductive and Urologic Drug Products
c/o Central Document Room
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20852

Dear Dr. Shames:

NDA 20-180/S-020: PROSCAR™ (Finasteride 5 mg)
INTENT TO AMEND

Reference is made to the above supplemental New Drug Application submitted on November 9, 1998. Reference is also made to the December 20, 2002 Approvable Letter for S-020, from Dr. Daniel Shames, Director, Division of Reproductive and Urologic Drug Products, Food and Drug Administration. This letter was received via U.S. Mail by Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., on December 31, 2002.

In accordance with 21 CFR 314.110, the purpose of this letter is to notify the Agency of our intent to file an amendment to the above referenced supplemental application for PROSCAR™.

This submission is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the January 1999, *Guidance for Industry – Providing Regulatory Submissions in Electronic Format – NDAs.* As an attachment to this letter, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc., is providing 1 Compact Disk (CD) which contains the submission. All documents requiring signatures for certification are included as paper for archival purposes.

All of the information is contained on 1 CD and is not more than 100 MB. We have taken precautions to ensure that the contents of this CD are free of computer viruses (Norton Anti-Virus 7.51, Symantec Corp., 2000) and we authorize the use of anti-virus software, as appropriate.

We consider the filing of this amendment to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

If you have any questions or need additional information, please contact Vivian Fuh, MD, (732-594-0374), or in her absence, David Altarac, MD (732-594-0135).

Sincerely,

Vivian Fuh, MD
Director
Regulatory Affairs

Enclosure: CD
Federal Express

Desk Copies: Jean King, HFD-580, Parklawn Building, Room 17B-45
Federal Express #2
Kassandra Sherrod, HFD-640, Metro Park North 2, Room 113
Federal Express #3

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Division of Reproductive and Urologic Drug Products

REGULATORY PROJECT MANAGER LABELING REVIEW

Application Number: NDA 20-180/S-020

Name of Drug: Proscar® (finasteride)

Sponsor: Merck & Co., Inc.

Material Reviewed:

Submission Date(s): November 9, 1998
Receipt Date(s): November 10, 1998

Background

The Sponsor submitted this supplement in response to a phase IV commitment at the time of approval of PROPECIA on December 19, 1997 to upgrade and provide consistency between the PROSCAR label.

General

The Sponsor has made 24 proposed changes to the label in the DESCRIPTION, CLINICAL PHARMACOLOGY, WARNINGS,PRECAUTIONS,ADVERSE REACTIONS, OVERDOSAGE, AND HOW SUPPLIED sections.

The changes have been included in the approved label dated January 30, 2001(SLR022) and patient information insert approved dated January 17, 2001(SLR019).

Strike through=deleted by Sponsor
Double underline=added by sponsor
Double Strike through=deleted by DRUDP
Underline=added by DRUDP

21 page(s) of draft labeling has been removed from this portion of the review.

Administrative + Correspondence (Labeling Review)

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

/s/

Kassandra C. Sherrod
12/20/02 09:18:14 AM
CSO

Margaret Kober
12/20/02 05:57:54 PM
CSO