CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-180/S-029

Trade Name: Proscar Tablets

Generic Name: finasteride

Sponsor: Merck & Company, Inc

Approval Date: April 23, 2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-180/S-029

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-180/S-029

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-180/S-029

Merck & Company
Attention: Vivian Fuh, M.D.
P.O. Box 2000
Mail Drop: RY 33-200
Rathway, NJ 07065

Dear Dr. Fuh:

Please refer to your supplemental new drug application dated September 24, 2003, received September 25, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for PROSCAR™ (finasteride 5 mg).

Your submission of April 13, 2004 constituted a complete response to our March 24, 2004 action letter.

This "Changes Being Effected" supplemental new drug application provides for proposed changes to the **ADVERSE REACTIONS** section of the label to include information from the Prostate Cancer Prevention Trial (PCPT), sponsored by the U.S. National Cancer Institute (NCI), and coordinated by the Southwest Oncology Group (SWOG) regarding prostate cancers with Gleason scores of 7 to 10, as reported in the July 17, 2003 New England Journal of Medicine publication.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling.

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. 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/S-029." Approval of this submission by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for this application.

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 Jennifer Mercier, Regulatory Health Project Manager, at (301) 827-4244.

Sincerely,

{See appended electronic signature page}

Daniel Shames, M.D.
Director
Division of Reproductive and Urologic Drug Products (HFD-580)
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

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

/s/

Daniel A. Shames
4/23/04 05:08:16 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-180/S-029

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-180/S-029

Merck & Company
Attention: Vivian Fuh, M.D.
P.O. Box 2000
Mail Drop: RY 33-200
Rathway, NJ 07065

Dear Dr. Fuh:

Please refer to your supplemental new drug application dated September 24, 2003, received September 25, 2003, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for PROSCAR™ (finasteride 5 mg).

This "Changes Being Effected" supplemental new drug application provides for proposed changes to the **ADVERSE REACTIONS** section of the label to include information from the Prostate Cancer Prevention Trial (PCPT), sponsored by the U.S. National Cancer Institute (NCI), and coordinated by the Southwest Oncology Group (SWOG) regarding prostate cancers with Gleason scores of 7 to 10, as reported in the July 17, 2003 New England Journal of Medicine publication.

We completed our review of this application, and it is approvable. Before this application may be approved, however, you must submit draft labeling revising the label as follows:

1. Amend the actual wording of the label revision to clarify:
   a. That Proscar™ is not approved [ ] prostate cancer, and
   b. That this new information is intended for consideration by prescribers [ ] [ ] when Proscar™ is used as indicated, and
   c. That the source of this new safety information is the literature (and should include the citation for that specific article in labeling).

2. Agree to submit relevant efficacy and safety databases from PCPT as soon as possible, so that the Division may further evaluate the information related to this specific issue.

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.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

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.

If you have any questions, call Jennifer Mercier, Regulatory Health 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

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

/s/

Daniel A. Shames
3/25/04 04:13:42 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-180/S-029

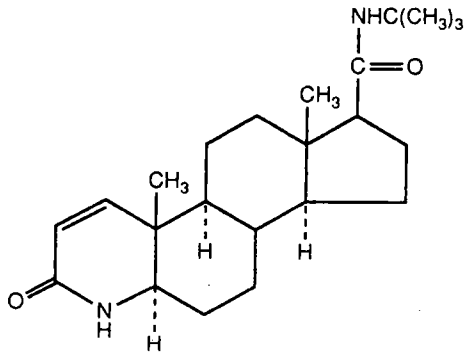
LABELING

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, hydroxypropyl methylcellulose, 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 ($t_{½}$ ~ 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

* Registered trademark of MERCK & CO., Inc.

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 6-24 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 man (n=6), a mean of 39% (range, 32-46%) of the dose was excreted in the urine in the form of metabolites; 57% (range, 51-64%) was excreted in the feces.

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 $AUC_{(0\text{-}24\ hr)}$ 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 (8.7)	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

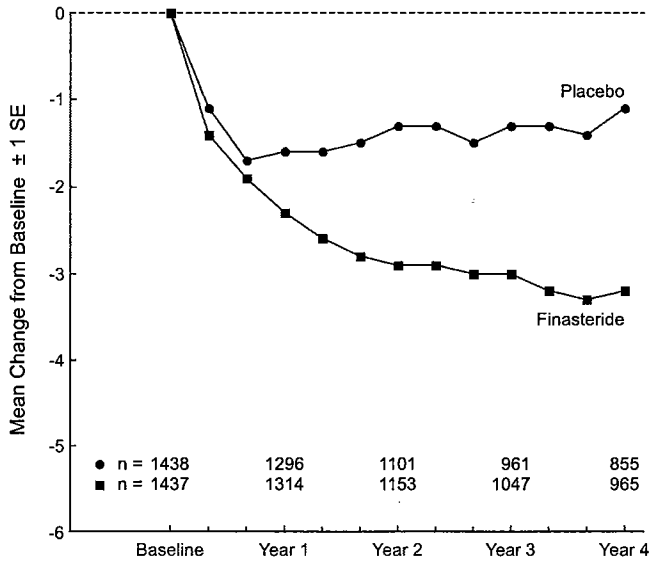
examination, were randomized into the study (1524 to finasteride, 1516 to placebo) and 3016 patients were evaluable for efficacy. 1883 patients completed the 4-year study (1000 in the finasteride group, 883 in the placebo group).

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 6 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.

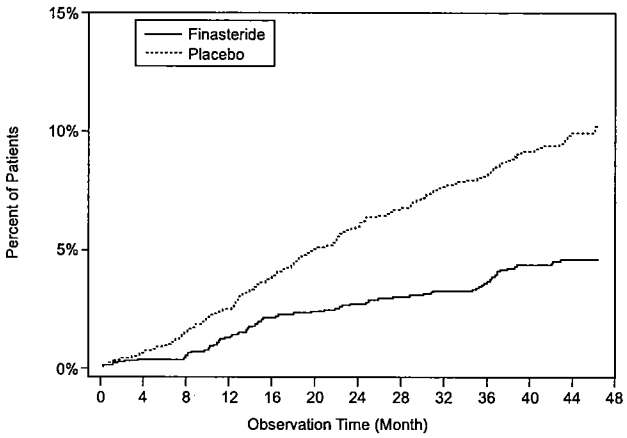
Table 1
All Treatment Failures in PLESS

	Patients (%) *				
Event	**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

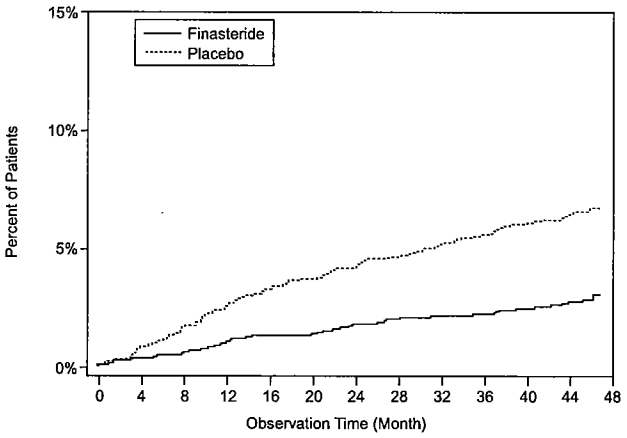
Compared with placebo, PROSCAR was associated with a significantly lower risk for acute urinary retention or the need for BPH-related surgery [13.2% for placebo vs 6.6% for PROSCAR; 51% reduction in risk, 95% CI: (34 to 63%)]. Compared with placebo, PROSCAR was associated with a significantly lower risk 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



Placebo Group				
No. of events, cumulative	37	89	121	152
No. at risk, per year	1503	1454	1374	1314
Finasteride Group				
No. of events, cumulative	18	40	49	69
No. at risk, per year	1513	1483	1438	1410

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



Placebo Group				
No. of events, cumulative	36	61	81	99
No. at risk, per year	1503	1454	1398	1347
Finasteride Group				
No. of events, cumulative	14	25	32	42
No. at risk, per year	1513	1487	1449	1421

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.

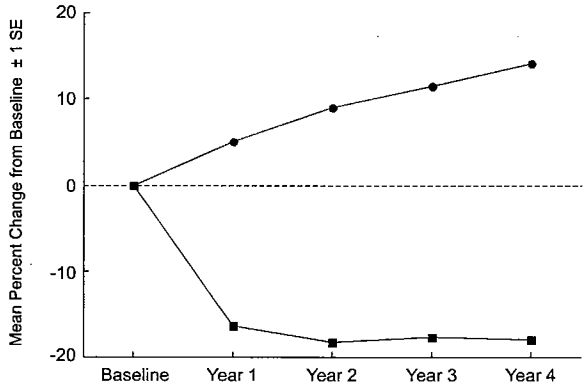
There was a clear difference between treatment groups in maximum urinary flow rate in favor of PROSCAR by month 4 (1.0 vs 0.3 mL/sec) which was maintained throughout the study. In the earlier 1-year studies, increase in maximum urinary flow rate was comparable to PLESS and was maintained through the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



Placebo (●) n =	155	136	119	98	85
Finasteride (■) n =	157	144	130	116	102

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.

Medical Therapy of Prostatic Symptoms

The Medical Therapy of Prostatic Symptoms (MTOPS) Trial was a double-blind, randomized, placebo-controlled, multicenter, 4- to 6-year study (average 5 years) in 3047 men with symptomatic BPH, who were randomized to receive PROSCAR 5 mg/day (n=768), doxazosin 4 or 8 mg/day (n=756), the combination of PROSCAR 5 mg/day and doxazosin 4 or 8 mg/day (n=786), or placebo (n=737). All participants underwent weekly titration of doxazosin (or its placebo) from 1 to 2 to 4 to 8 mg/day. Only those who tolerated the 4 or 8 mg dose level were kept on doxazosin (or its placebo) in the study. The participant's final tolerated dose (either 4 mg or 8 mg) was administered beginning at end-Week 4. The final doxazosin dose was administered once per day, at bedtime.

The mean patient age at randomization was 62.6 years (±7.3 years). Patients were Caucasian (82%), African American (9%), Hispanic (7%), Asian (1%) or Native American (<1%). The mean duration of BPH symptoms was 4.7 years (±4.6 years). Patients had moderate to severe BPH symptoms at baseline with a mean AUA symptom score of approximately 17 out of 35 points. Mean maximum urinary flow rate was 10.5 mL/sec (±2.6 mL/sec). The mean prostate volume as measured by transrectal ultrasound was

36.3 mL (±20.1 mL). Prostate volume was ≤20 mL in 16% of patients, ≥50 mL in 18% of patients and between 21 and 49 mL in 66% of patients.

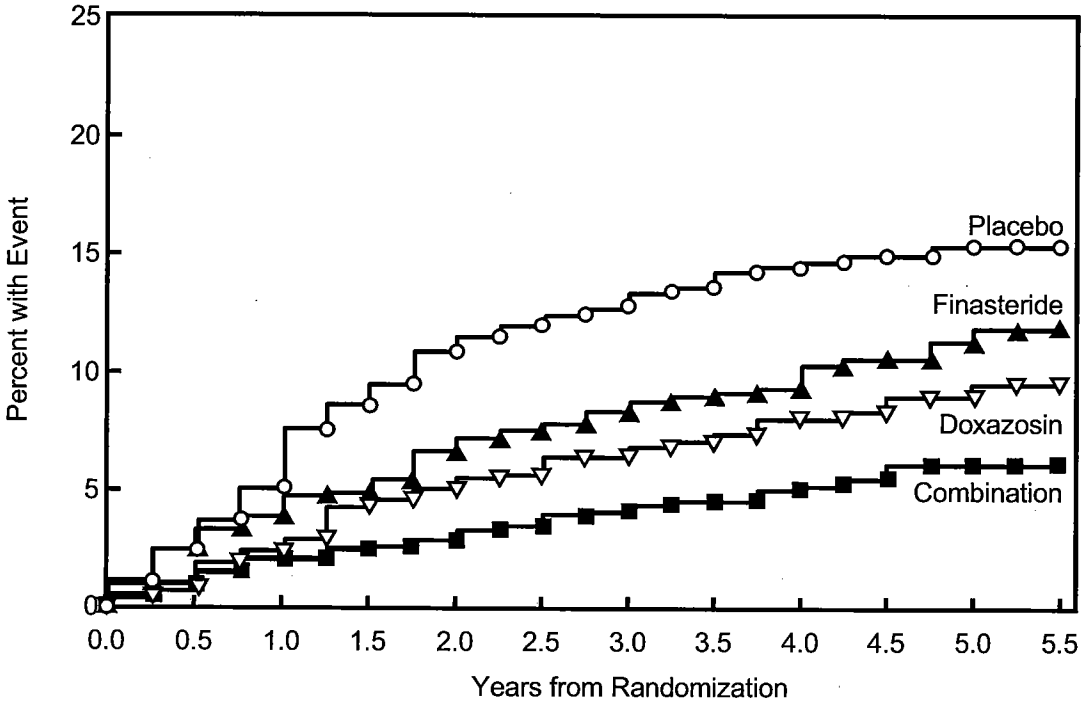
The primary endpoint was a composite measure of the first occurrence of any of the following five outcomes: a ≥4 point confirmed increase from baseline in symptom score, acute urinary retention, BPH-related renal insufficiency (creatinine rise), recurrent urinary tract infections or urosepsis, or incontinence. Compared to placebo, treatment with PROSCAR, doxazosin, or combination therapy resulted in a reduction in the risk of experiencing one of these five outcome events by 34% ($p=0.002$), 39% ($p<0.001$), and 67% ($p<0.001$), respectively. Combination therapy resulted in a significant reduction in the risk of the primary endpoint compared to treatment with PROSCAR alone (49%; $p\leq0.001$) or doxazosin alone (46%; $p\leq0.001$). (See Table 2.)

Table 2
Count and Percent Incidence of Primary Outcome Events by Treatment Group in MTOPS

Event	Treatment Group				
	Placebo N=737 N (%)	Doxazosin N=756 N (%)	Finasteride N=768 N (%)	Combination N=786 N (%)	Total N=3047 N (%)
AUA 4-point rise	100 (13.6)	59 (7.8)	74 (9.6)	41 (5.2)	274 (9.0)
Acute urinary retention	18 (2.4)	13 (1.7)	6 (0.8)	4 (0.5)	41 (1.3)
Incontinence	8 (1.1)	11 (1.5)	9 (1.2)	3 (0.4)	31 (1.0)
Recurrent UTI/urosepsis	2 (0.3)	2 (0.3)	0 (0.0)	1 (0.1)	5 (0.2)
Creatinine rise	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total Events	128 (17.4)	85 (11.2)	89 (11.6)	49 (6.2)	351 (11.5)

The majority of the events (274 out of 351; 78%) was a confirmed ≥4 point increase in symptom score, referred to as symptom score progression. The risk of symptom score progression was reduced by 30% ($p=0.016$), 46% ($p<0.001$), and 64% ($p<0.001$) in patients treated with PROSCAR, doxazosin, or the combination, respectively, compared to patients treated with placebo (see Figure 5). Combination therapy significantly reduced the risk of symptom score progression compared to the effect of PROSCAR alone ($p<0.001$) and compared to doxazosin alone ($p=0.037$).

Figure 5
Cumulative Incidence of a 4-Point Rise in AUA Symptom Score by Treatment Group



Treatment with PROSCAR, doxazosin or the combination of PROSCAR with doxazosin, reduced the mean symptom score from baseline at year 4. Table 3 provides the mean change from baseline for AUA symptom score by treatment group for patients who remained on therapy for four years.

Table 3
Change From Baseline in AUA Symptom Score
by Treatment Group at Year 4 in MTOPS

	Placebo N=534	Doxazosin N=582	Finasteride N=565	Combination N=598
Baseline Mean (SD)	16.8 (6.0)	17.0 (5.9)	17.1 (6.0)	16.8 (5.8)
Mean Change AUA Symptom Score (SD)	-4.9 (5.8)	-6.6 (6.1)	-5.6 (5.9)	-7.4 (6.3)
Comparison to Placebo (95% CI)		-1.8 (-2.5, -1.1)	-0.7 (-1.4, 0.0)	-2.5 (-3.2, -1.8)
Comparison to Doxazosin alone (95% CI)				-0.7 (-1.4, 0.0)
Comparison to Finasteride alone (95% CI)				-1.8 (-2.5, -1.1)

The results of MTOPS are consistent with the findings of the 4-year, placebo-controlled study PLESS (see CLINICAL PHARMACOLOGY, *Clinical Studies*) in that treatment with PROSCAR reduces the risk of acute urinary retention and the need for BPH-related surgery. In MTOPS, the risk of developing acute urinary retention was reduced by 67% in patients treated with PROSCAR compared to patients treated with placebo (0.8% for PROSCAR and 2.4% for placebo). Also, the risk of requiring BPH-related invasive therapy was reduced by 64% in patients treated with PROSCAR compared to patients treated with placebo (2.0% for PROSCAR and 5.4% for placebo).

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.

PROSCAR administered in combination with the alpha-blocker doxazosin is indicated to reduce the risk of symptomatic progression of BPH (a confirmed ≥4 point increase in AUA symptom score).

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.)

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 BPH studies, PROSCAR did not appear to alter the rate of prostate cancer detection, and 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 $AUC_{(0\text{-}24\ hr)}$ for animals and mean $AUC_{(0\text{-}24\ hr)}$ 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 $\geq$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- to 3-fold above control) has been demonstrated in both rodent species treated with high doses of finasteride. No drug-related Leydig cell changes were seen in either rats or dogs treated with finasteride for 1 year at doses of 20 mg/kg/day and 45 mg/kg/day (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 4 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 4
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.

Medical Therapy of Prostatic Symptoms (MTOPS) Study

The incidence rates of drug-related adverse experiences reported by ≥2% of patients in any treatment group in the MTOPS Study are listed in Table 5.

The individual adverse effects which occurred more frequently in the combination group compared to either drug alone were: asthenia, postural hypotension, peripheral edema, dizziness, decreased libido, rhinitis, abnormal ejaculation, impotence and abnormal sexual function (see Table 5). Of these, the incidence of abnormal ejaculation in patients receiving combination therapy was comparable to the sum of the incidences of this adverse experience reported for the two monotherapies.

Combination therapy with finasteride and doxazosin was associated with no new clinical adverse experience.

Four patients in MTOPS reported the adverse experience breast cancer. Three of these patients were on finasteride only and one was on combination therapy. (See ADVERSE REACTIONS, *Long-Term Data*.)

The MTOPS Study was not specifically designed to make statistical comparisons between groups for reported adverse experiences. In addition, direct comparisons of safety data between the MTOPS study and previous studies of the single agents may not be appropriate based upon differences in patient population, dosage or dose regimen, and other procedural and study design elements.

Table 5 Incidence ≥ 2% in One or More Treatment Groups Drug-Related Clinical Adverse Experiences in MTOPS				
Adverse Experience	Placebo (N=737) (%)	Doxazosin 4 mg or 8 mg* (N=756) (%)	Finasteride (N=768) (%)	Combination (N=786) (%)
Body as a whole				
Asthenia	7.1	15.7	5.3	16.8
Headache	2.3	4.1	2.0	2.3
Cardiovascular				
Hypotension	0.7	3.4	1.2	1.5
Postural Hypotension	8.0	16.7	9.1	17.8
Metabolic and Nutritional				
Peripheral Edema	0.9	2.6	1.3	3.3
Nervous				
Dizziness	8.1	17.7	7.4	23.2
Libido Decreased	5.7	7.0	10.0	11.6
Somnolence	1.5	3.7	1.7	3.1
Respiratory				
Dyspnea	0.7	2.1	0.7	1.9
Rhinitis	0.5	1.3	1.0	2.4
Urogenital				
Abnormal Ejaculation	2.3	4.5	7.2	14.1
Gynecomastia	0.7	1.1	2.2	1.5
Impotence	12.2	14.4	18.5	22.6
Sexual Function Abnormal	0.9	2.0	2.5	3.1

*Doxazosin dose was achieved by weekly titration (1 to 2 to 4 to 8 mg). The final tolerated dose (4 mg or 8 mg) was administered at end-Week 4. Only those patients tolerating at least 4 mg were kept on doxazosin. The majority of patients received the 8-mg dose over the duration of the study.

Long-Term Data

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.

During the 4- to 6-year placebo- and comparator-controlled MTOPS 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 relationship between long-term use of finasteride and male breast neoplasia is currently unknown.

In a 7-year placebo-controlled trial that enrolled 18,882 healthy men, 9060 had prostate needle biopsy data available for analysis. In the PROSCAR group, 280 (6.4%) men had prostate cancer with Gleason scores of 7-10 detected on needle biopsy vs. 237 (5.1%) men in the placebo group. Of the total cases of prostate cancer diagnosed in this study, approximately 98% were classified as intracapsular (stage T1 or T2). The clinical significance of these findings is unknown. This information from the literature (Thompson IM, Goodman PJ, Tangen CM, et al. The influence of finasteride on the development of prostate cancer. *N Engl J Med* 2003;349:213-22) is provided for consideration by

physicians when PROSCAR is used as indicated (see INDICATIONS AND USAGE). PROSCAR is not approved to reduce the risk of developing prostate cancer.

Post-Marketing Experience

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

DOSAGE AND ADMINISTRATION

The recommended dose is 5 mg orally once a day.

PROSCAR can be administered alone or in combination with the alpha-blocker doxazosin (see CLINICAL PHARMACOLOGY, *Clinical Studies*).

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. 3094 — 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

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-180/S-029

MEDICAL REVIEW

NDA 20-180 SLR 029 **DRAFT (M.H.)**

Medical Officer's Memorandum: Labeling Supplemental/Changes Being Effected

Date submitted: September 24, 2003
Date received: September 25, 2003
Date memo complete: March 25, 2004

Sponsor: Merck Research Laboratories
Drug product: Proscar™ (finasteride 5mg)
Dose: 5mg orally once daily
Indication: For the treatment of symptomatic benign prostatic hyperplasia (BPH) in men with an enlarged prostate to: 1) improve symptoms, 2) reduce the risk of acute urinary retention, and 3) reduce the risk of the need for BPH-related surgery.

Regarding: Additional verbiage has been added to the Proscar label in the **Adverse Reactions** section in the "***Long-Term Data***" subsection. The new safety information that serves as the basis for this change was derived from the Prostate Cancer Prevention Trial (PCPT). The entire CBE is as follows:

> "In a 7-year placebo-controlled trial that enrolled 18,882 healthy men, 9060 had prostate needle biopsy data available for analysis. In the PROSCAR group, 280 (6.4%) men had prostate cancer with Gleason scores of 7-10 detected on needle biopsy vs. 237 (5.1%) men in the placebo group. Of the total cases of prostate cancer diagnosed in this study, approximately 98% were classified as intracapsular (stage T1 or T2). The clinical significance of these findings is unknown."

1. Executive summary: The purpose of this memo is to provide my recommendation to the Division Director that this SLR (#029) should receive an **approvable** action. The approvable letter should state that in order for the Division to provide its final approval, the sponsor should:

1. Amend the actual wording of the label revision to clarify:
   a. That Proscar™ is not approved [ ] prostate cancer, and
   b. That this new information is intended for consideration by prescribers [ ] [ ] when Proscar™ is used as indicated, and
   c. That the source of this new safety information is the literature (and include the citation for that specific article in labeling).
2. Agree to submit relevant efficacy and safety databases from PCPT as soon as possible, so that the Division may further evaluate the information related to this specific issue.

2. Regulatory and clinical background:
Proscar is a Type [ ] 5-alpha-reductase inhibitor indicated for the treatment of symptomatic benign prostatic hyperplasia (BPH) in men with an enlarged prostate to: 1) improve symptoms, 2) reduce the risk of acute urinary retention, and 3) reduce the risk of the need for BPH-related surgery. It was first approved in 1992 for the treatment of signs and symptoms of BPH (with an enlarged prostate) and in 1998 the original indication was expanded to include the reduction in risk of AUR and need for BPH-related surgery.

In 1994, randomization was initiated for the Prostate Cancer Prevention Trial (PCPT). This was a Phase 4 study sponsored by the National Cancer Institute (NCI) and coordinated by the Southwest Oncology Group (SWOG). Merck & Company, Inc provided the study drug and placebo and the infrastructure to distribute the study drug to the many investigative sites in PCPT.

According to the sponsor's submission: "It was hypothesized that finasteride, an inhibitor of steroid 5α-reductase, the enzyme that converts testosterone to the more potent androgen dihydrotestosterone, would reduce the risk of the development of prostate cancer. The primary endpoint of the study was the period prevalence of prostate cancer during the 7 years of treatment in the trial. The study was designed with 92% power (α-level 0.05) to detect a 25% reduction in the period prevalence of prostate cancer, based upon an expected prevalence of 6% in the placebo group, and an assumption that 60% of the participants would have their prostate cancer status ascertained either by a "for cause" or (an) end-of-study biopsy."

The sponsor further stated: "The Data Safety Monitoring Board recommended early termination of the study in Feb-2003, after an interim analysis of data demonstrating that the objective of the study had been met and on the basis of the sensitivity analyses that the conclusions of the study were unlikely to change with additional prostate biopsies. The study was terminated on 12-Mar-2003 by SWOG and the NCI."

The sponsor continues: "The results of the PCPT were published on 17-Jul-2003 in the New England Journal of Medicine (NEJM).[1] The study demonstrated a 25% reduction in the period prevalence of prostate cancer with finasteride treatment. However, it was observed that prostate cancers with a Gleason score of 7 to 10 were more common in men treated with finasteride (6.4%) than in men treated with placebo (5.1%). The clinical significant of this finding is unknown."

Based upon this latter finding, the sponsor now proposes to add "*a description of these results*" to the prescribing information. The sponsor states that the enclosed "Clinical Overview" provides a "review of the key findings of the PCPT that were described in the NEJM publication" and that this overview provides support for the proposed labeling changes. The submitted overview document is 6 pages in length.

> **Reviewer's comment**: This reviewer agrees that a description of this particular issue should be a added to the Proscar labeling as soon as possible; however, the Agency is not able to conduct an independent review of this issue without the appropriate efficacy and safety databases. This sort of data has not yet been provided. Sponsor acknowledged in a teleconference that they were not yet prepared to submit this sort of data to the Agency. The information in the "clinical overview" is not sufficient for FDA to conduct a substantive review of this particular issue. However, based on potential clinical significance, this reviewer recommends that the NEJM article may serve as the basis of this particular labeling change at this time. The label should clearly reflect the fact that this information is derived from the NEJM article and should not imply that this particular information has been "verified" or "validated" by a detailed Agency review. In fact, the problem itself may be the same, better, or worse after our detailed review. The sponsor should be asked to submit the relevant databases from PCPT as soon as possible so that we may review this particular issue in greater detail.

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[1] Thompson IM, Goodman PJ, Tangen CM, Lucia MS, Miller GJ, Ford LG et al.: The influence of finasteride on the development of prostate cancer. N Engl J Med 2003;349(3): 211-20.

3. Review of the "overview" document:
On pages 6 through 11 of this SLR, sponsor provides a brief overview of efficacy, safety and benefits/risks evaluation for this particular issue from the PCPT. Sponsor first provided a synopsis of the study design followed by a summary of the study efficacy results. Herein, selected items are briefly highlighted so that the reader may place the proposed labeling revision into clinical context:

3.1 Design
The PCPT was a randomized, placebo-controlled, 7-year study of the effect of finasteride 5mg daily on reducing the risk of prostate cancer. The study was conducted at 221 sites across the U.S. and enrolled men aged 55 years of age or older with a normal digital rectal examination and a serum PSA of 3.0 ng/mL or lower. Study participants underwent yearly DRE and serum PSA and were seen in clinic every 6 months. During the study, participants were recommended to undergo needle biopsy of the prostate if they had abnormal findings on DRE or if the serum PSA was greater than 4 ng/mL. Serum PSA was measured centrally and was reported to investigators after mathematical adjustment for finasteride effect (multiplication by 2). Prostate biopsies triggered by abnormal DRE or PSA were called "for-cause" biopsies. Otherwise, at the completion of 7 years of treatment, all participants who did not already have a diagnosis of prostate cancer (including those with a negative "for-cause" biopsy) underwent an "end-of-study" biopsy.

> **Reviewer's comment**: The mechanisms by which serum PSA was adjusted for "finasteride effect" will eventually require further clarification. Another review issue will be whether multiplication by 2 is an appropriate correction factor for all serum PSA levels, all age groups, patients without BPH, etc, and finally, whether this correction factor added bias to the study, or in some way acted as a means of cancer detection.

3.2 Study subjects and conduct
Of the 24,482 men who entered the study, 18,882 were randomized to either finasteride or placebo. Of the 18,882 men, 92% were White, 4% were African American, and 4% were of Other ethnicity. The median age was 63 years (range 55 to 86). The prostate cancer status was known at the end of the study in 9989 men (4847 men and 5142 men in the finasteride and placebo groups, respectively). Results from 9060 men (4368 men and 4692 men in the finasteride and placebo groups, respectively) were included in the analysis reported in the NEJM article.

> **Reviewer's comment**: The reason for excluding patients from the analysis is not described in this overview. This is one major reason that submission of complete datasets are required for a substantive review by FDA.

Among the men included in the analysis, 1639 in the finasteride group and 1934 in the placebo group had a for-cause biopsy, and 3652 in the finasteride group and 3820 in the placebo group had an end-of-study biopsy.

3.3 Efficacy results
Of the 9060 men included in the final analysis, prostate cancer was detected in 803 of the 4368 men in the finasteride group (18.4%) versus 1147 of the 4692 in the placebo group (24.4%). The sponsor notes here that the estimated relative risk reduction was 24.8% (95% confidence interval, 18.6 to 30.6% ; $p<0.001$). According to the sponsor, the number of cases of prostate cancer detected during the course of the study in a biopsy performed for cause (and elevated PSA or abnormal DRE) OR in a biopsy at the end of the study was higher (again, for *both* types of

biopsies) in the finasteride group. According to the sponsor, subgroup analysis by age, ethnicity, family history of prostate cancer, and baseline PSA revealed risk reduction as a consequence of active treatment in all subgroups. Finally, sponsor reports that most of the cancers detected were classified as T1 or T2 or clinically localized ("intracapsular") tumors. Of the 803 and 1147 cancers detected in the finasteride and placebo groups, 97.7% and 98.4% were classifed as T1 or T2, respectively.

> **Reviewer's comment**: The word "intracapsular" implies that a pathological examination was conducted. It is more likely that sponsor means localized by clinical staging, not pathologically intracapsular by pathological examination. This too will need to be clarified, both in the context of a substantive review and for the labeling revision under consideration.

3.4 Safety results

In the overview document, sponsor focuses on the Gleason score findings as the primary safety concern from PCPT. Some background information on the Gleason grade scoring system for prostate cancer is provided. As sponsor states, the Gleason system is the most widely used grading system for prostate cancer. It is based on architectural pattern, not cytological features. And, the overall score is based upon the sum of the most predominant and second most predominant, not the highest grade tumor seen. The histological patterns are graded on a 1 to 5 scale with 1 being the most differentiated and 5 being least differentiated. Thus, the overall scoring is 2 to 10.

Table 5 of the NEJM article provides data on the Gleason scores for the prostate cancers detected in PCPT. In the overview, sponsor summarizes this information as follows: Prostate cancer with a Gleason score of 6 was the most commonly detected prostate cancer in both groups; 388 of 4368 men in the finasteride group (8.9%) and 658 of 4692 men (14.0%) in the placebo group. Sponsor states: "There was a reduction in the number of Gleason scores 2-6 tumors in the fiansteride treated men." However, "there was a higher number of cancers with a Gleason score 7-10 in the finasteride group." Overall, 280 of 4368 men (6.4%) in the finasteride group had such tumors compared to 237 of 4692 men (5.1%) in the placebo group. The sponsor states "The clinical significance of this observation of a higher prevalence of cancers with a Gleason score of 7 to 10 in the finasteride group is not known at present."

The sponsor then presents approximately 2 full pages on possible explanations for this observation. These include: "artificial upgrading" of Gleason grade by the anti-androgen hormonal effect; stimulation of the growth of prostate cancers with higher grade features by finasteride; and slowing of the development or growth of prostate cancer with lower Gleason scores by finasteride without an effect on the higher Gleason score tumors. Sponsor states,

> "Efforts are underway to further evaluate the findings of PCPT and the cancers with Gleason scores 7 to 10. SWOG is conducting ongoing studies to characterize the biopsy specimens from PCPT in terms of biomarkers. As discussed previously, radical prostatectomy specimens from men diagnosed with prostate cancer in PCPT are also being examined. These results are expected within the coming year and will be reported to regulatory agencies as appropriate.
>
> Merk & Co, Inc are currently in the process of evaluating the PCPT database; the initial work is to replicate the analyses reported in the NEJM publication Additional analyses are planned to further characterize the men who were diagnosed with prostate cancer and with Gleason score 7 to 10 prostate cancer"

Finally, in terms of other safety results, sponsor states that the adverse events profile reported in the NEJM article was consistent with the known existing safety database for Proscar.

4. Sponsor's summary and proposal for action

The sponsor acknowledges the higher prevalence of prostate cancers with Gleason scores of 7 to 10 in the finasteride-treated men in PCPT. However, they conclude that the etiology and clinical significance of these findings are unknown. They state that studies of prostate cancer speciments from PCPT and long-term follow-up of patients in this study may "shed further light on this issue".

Sponsor summates by stating:

> *"It is important to describe the currently known findings from PCPT in the Adverse Reactions/Side Effects section of the prescribing information, and text has been propsoed which details the Gleason 7 to 10 score data. However, given the clinical significance of these findings is unknown, in the context of the established efficacy and safety profile of finasteride in the treatment of BPH, the benefit/risk profile of finasteride remains favorable."*

Reviewer's comment: In general, this reviewer concurs with sponsor and agrees with the fundamental objective and substance of this labeling revision. However, the labeling revision should be further clarified to indicate:

1. That Proscar™ is *not* approved [ ] prostate cancer, and
2. That this new information is intended for consideration by prescribers [ ] [ ] when Proscar™ is used *as indicated*, and
3. That the source of this new safety information is *the literature* (and that the citation for that specific article be included in labeling).

Finally, this reviewer recommends a substantive review of actual data from PCPT for this specific issue and recommends that sponsor submit relevant efficacy and safety databases from PCPT as soon as possible, so that the Division may further evaluate the information related to this specific issue.

Therefore, in my opinion, this SLR is approvable pending the clarifications stipulated above and the sponsor's agreement to submit actual data as described above.

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/s/

Mark S. Hirsch
3/31/04 04:53:31 PM
MEDICAL OFFICER

Daniel A. Shames
4/1/04 06:08:57 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-180/S-029

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-180/S-029

Merck & Co., Inc.
Attention: Vivian Fuh, M.D.
Director, Regulatory Affairs
P.O. Box 2000
Mail Drop: RY 32-605
Rahway, NJ 07065

Dear Dr. Fuh:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Proscar ™ (finasteride) 5 mg tablets.

We also refer to the meeting between representatives of your firm and the FDA on November 23, 2004. The purpose of the meeting was to discuss the results of the Prostate Cancer Prevention Trial (PCPT).

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Martin Kaufman, D.P.M., M.B.A., Regulatory Health Project Manager, at (301) 827-4234.

Sincerely,

{See appended electronic signature page}

Mark Hirsch, M.D.
Medical Team Leader
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	November 23, 2004
TIME:	11:00 am – 12:30 pm
LOCATION:	Conference Room 'C' Parklawn Building
APPLICATION:	NDA 20-180
DRUG NAME:	Proscar® (finasteride)
TYPE OF MEETING:	Type C
MEETING CHAIR:	Mark Hirsch, M.D.
MEETING RECORDER:	Martin Kaufman, D.P.M., M.B.A.

FDA ATTENDEES:
Julie Beitz, M.D., Deputy Director, Office of Drug Evaluation III, HFD-103
Daniel Shames, M.D., Director, Division of Reproductive and Urologic Drug Products (DRUDP), HFD-580
Richard Pazdur, M.D., Director, Division of Oncology Drug Products (DODP), HFD-150
Grant Williams, M.D., Deputy Director, DODP, HFD-150
Mark Hirsch, M.D., Medical Team Leader, DRUDP, HFD-580
George Benson, M.D., Medical Team Leader, DRUDP, HFD-580
Harry Handelsman, D.O., Medical Officer, DRUDP, HFD-580
Edvardas Kaminskas, M.D., Medical Officer, DODP, HFD-150
Mike Welch, Ph.D., Biostatistics Team Leader, Division of Biometrics II (DB II), HFD-715
Katherine Meaker, M.S., Statistician, DB II, HFD-715
Martin Kaufman, D.P.M., M.B.A., Regulatory Health Project Manager, DRUDP, HFD-580

EXTERNAL CONSTITUENT ATTENDEES:
Yael Cohen, M.D., Associate Director, Clinical Research, Merck Research Labs (MRL)
Anastasia Daifotis, M.D., Vice President, Clinical Research, MRL
Norman Heyden, R.Ph., M.S., Clinical Associate, Clinical Research, MRL
Keaven Anderson, Ph.D., Executive Director, Biostatistics, MRL
Alexandra Carides, Ph.D., Associate Director, Biostatistics, MRL
Brian Mayhew, B.A., Global Regulatory Policy, MRL
Vivian Fuh, M.D., F.A.C.P., Director, Regulatory Affairs, MRL
Martin H. Himmel, M.D., M.P.H., Senior Director, Regulatory Affairs, MRL
Robert Silverman, M.D., Ph.D., F.A.C.P., Senior Director, Regulatory Affair, MRL
Leslie Ford, M.D., Associate Director, Division of Cancer Prevention, National Cancer Institute, National Institutes of Health

BACKGROUND:
The Prostate Cancer Prevention Trial (PCPT) was a double-blind, placebo-controlled, 7-year study to determine whether finasteride could reduce the prevalence of prostate cancer among healthy men. The primary endpoint was tissue diagnosis of prostate cancer during the 7 study years, and the primary objective was to assess the difference in the histologically proven prevalence of carcinoma of the prostate between the finasteride and placebo groups. Secondary endpoints included prostate cancer Gleason score and clinical stage, prostate cancer specific mortality, benign prostatic hypertrophy (BPH) severity, and urinary and sexual functions. The

study was managed by the Southwest Oncology Group (SWOG), and funded by the National Cancer Institute (NCI). The primary results of the study, published in the July, 2003, edition of the New England Journal of Medicine (NEJM), showed a 24.8% reduction in prostate cancer detected in men in the finasteride group compared to men in the placebo group. However, high-grade tumors (Gleason score ≥7) were more common in the finasteride group (6.4% of 4368 men) than in the placebo group (5.1% of 4692 men).

On September 24, 2003, the sponsor submitted Supplement 029 to NDA 20-180 requesting changes to the Adverse Reactions section of the Proscar® label which incorporated information from the PCPT. The Division issued an Approvable Letter for this supplement on March 25, 2004. In its response to the Approvable Letter, the sponsor agreed to submit relevant efficacy and safety databases from the PCPT for further evaluation. The sponsor requested this meeting to discuss the reported results of the PCPT, to update the Division on the on-going efforts to understand the reported findings, and to discuss plans for providing the additional information requested in the March 25, 2004, Action Letter.

MEETING OBJECTIVES:

1. To review the PCPT study design, objectives and results as reported in the NEJM.
2. To acquaint the Division with the on-going efforts to understand the reported findings.
3. To discuss plans for providing the additional information requested in the March 25, 2004, Action Letter.

DISCUSSION POINTS:

- Since the actual data have not yet been submitted, the Division prefaced its remarks by stating that only high level, overview comments could be provided at this time. For more detailed comments, the dataset would need to be reviewed.
- The sponsor made a presentation which summarized the analyses of the PCPT dataset (attachment).
- The presentation provided an overview of the PCPT, analyses concerning the high-grade tumors, and proposed hypotheses for the increase in high Gleason score tumors in the finasteride group.
- The analyses to understand the high-grade tumors included the following:
    1. The time-course of high-grade cancers
    2. The potential of finasteride to cause histopathologic changes that could result in prostate cancer appearing to have an elevated Gleason score.
    3. Other measures of tumor aggressiveness.
    4. Detection bias resulting from finasteride induced shrinkage of the prostate.
    5. Detection bias resulting from over-adjustment of the PSA in the finasteride arm.
    6. Analyses of Gleason scores and pathologic staging of all available prostatectomy specimens.
- The following hypotheses were proposed to understand the increase in Gleason scores:
    1. Finasteride induces development of high-grade prostate cancer by changing the hormonal milieu.
    2. Finasteride alters the morphology of prostate cancer cells, similar to the effects of androgen deprivation therapy, such that they resemble higher grade tumors.
    3. Finasteride causes a detection bias with regard to the higher grade cancers by shrinking the prostate.
- There was a discussion of the information presented by the sponsor.

- The Division acknowledged the importance of the PCPT study and the issues raised by it.
- Both DRUDP and DODP emphasized that the sponsor had presented only hypotheses to explain the increased prevalence of high-grade Gleason score tumors in men who developed prostate cancer in the finasteride arm of the study. Acceptance of any of the hypotheses would require that it be supported by adequate data.
- The sponsor expressed its concern that the language in the current Proscar® label does not provide a complete picture of the PCPT results.
- If the sponsor plans to make a claim for [redacted] supplement will need to be submitted to DODP. Labeling revisions to the current Proscar® label will continue to be submitted to DRUDP. Any labeling that showed a [redacted]
- The Division requested clarification on whether the data that will be submitted are complete or only the data that are currently available. The sponsor responded that their submission is based on the SWOG dataset they received in January, 2004. They are not aware of every analysis that SWOG is doing, however, there is a follow-up study looking at Gleason grade 7 data.

Sponsor's Questions:

Question 1: [redacted]

Question 2: [redacted]

Question 3: ***MRL continues to believe that the clinical significance of these findings is unknown.*** [redacted]

ACTION ITEMS:

- Meeting minutes to the sponsor in thirty days.

ATTACHMENTS/HANDOUTS:

- Slides of sponsor's presentation.

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confidential commercial

information from

Administrative + Correspondence: Memorandum of Meeting Minutes (11/23/04)

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/s/

Mark S. Hirsch
12/23/04 02:33:45 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-180/S-029

Merck & Co., Inc.
Attention: Vivian Fuh, M.D.
Director, Regulatory Affairs
P.O. Box 2000
Mail Drop: RY 32-605
Rahway, NJ 07065

Dear Dr. Fuh:

Please refer to your supplemental new drug application dated September 24, 2003, received September 25, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Proscar ™ (finasteride) 5 mg tablets.

We also refer to your October 13, 2004, correspondence, received October 18, 2004, requesting a meeting to discuss the results of the Prostate Cancer Prevention Trial (PCPT).

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type C meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000). The meeting is scheduled for:

Date:	November 23, 2004
Time:	11:00 am – 12:30 pm
Location:	Conference Room 'C' Parklawn Building 5600 Fishers Lane Rockville, MD 20857

CDER participants: Julie Beitz, M.D., Deputy Director, Office of Drug Evaluation III, HFD-103
Daniel Shames, M.D., Director, Division of Reproductive and Urologic Drug Products (DRUDP), HFD-580
Donna Griebel, M.D., Deputy Director, DRUDP, HFD-580
Mark Hirsch, M.D., Medical Team Leader, DRUDP, HFD-580
Harry Handelsman, D.O., Medical Officer, DRUDP, HFD-580
Lynnda Reid, Ph.D., Pharmacology/Toxicology Team Leader, DRUDP, HFD-580
Moo-Jhong Rhee, Ph.D., Chemistry Team Leader, Division of New Drug Chemistry (DNDC II), @ DRUDP, HFD-580

Ameeta Parekh, Ph.D., Clinical Pharmacology Team Leader, Division of Pharmaceutical Evaluation II (DPE II), HFD-870
Dhruba Chatterjee, Ph.D., Clinical Pharmacologist, DPE II, HFD-870
Swapan De, Ph.D., Chemist, DNDC II, @ DRUDP, HFD-580
Mike Welch, Ph.D., Biostatistics Team Leader, Division of Biometrics II (DB II), HFD-715
Katherine Meaker, M.S., DB II, HFD-715
Jennifer Mercier, Chief, Project Management Staff, DRUDP, HFD-580
Martin Kaufman, D.P.M., M.B.A., Regulatory Health Project Manager, HFD-580

Please have all attendees bring photo identification and allow 15-30 minutes to complete security clearance. If there are additional attendees, email that information to me at KaufmanM@cder.fda.gov so that I can give the security staff time to prepare temporary badges in advance. Upon arrival at FDA, give the guards either of the following numbers to request an escort to the conference room: Martin Kaufman, (301) 827-4234; the division secretary, (301) 827-4260.

Provide the background information for this meeting (three copies to the supplemental NDA and 22 desk copies to me) at least two weeks prior to the meeting. If the materials presented in the information package are inadequate to justify holding a meeting, or if we do not receive the package by November 9, 2004, we may cancel or reschedule the meeting.

If you have any questions, call Martin Kaufman, D.P.M., M.B.A., Regulatory Health Project Manager, at (301) 827-4234.

Sincerely,

{See appended electronic signature page}

Jennifer Mercier
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Jennifer L. Mercier
10/25/04 02:32:44 PM