CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-180/S-026

Trade Name: Proscar Tablets

Generic Name: finasteride

Sponsor: Merck & Company, Inc

Approval Date: April 12, 2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-180/S-026

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-180/S-026

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-180/S-026

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

Dear Dr. Fuh:

Please refer to your supplemental new drug application dated June 12, 2003, received June 12, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for PROSCAR® (finasteride) tablets 5 mg.

We acknowledge receipt of your submissions dated September 24, November 11, December 17, 2003, February 20, and April 12, 2004 (facsimile).

This supplemental new drug application provides for the use of PROSCAR® administered in combination with the alpha-blocker doxazosin is indicated to reduce the risk of symptomatic progression of BPH (a confirmed $\geq$ 4 point increase in AUA symptom score).

We have 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 (text for the package insert, text for the patient package insert).

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-026." 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.

In addition, submit three copies of the introductory promotional materials that you propose to use for this new regimen. Submit all proposed materials in draft or mock-up form, not final print. Send one

copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

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) 827-4260.

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:
Physician Insert
Patient Package Insert

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
4/12/04 03:49:10 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-180/S-026

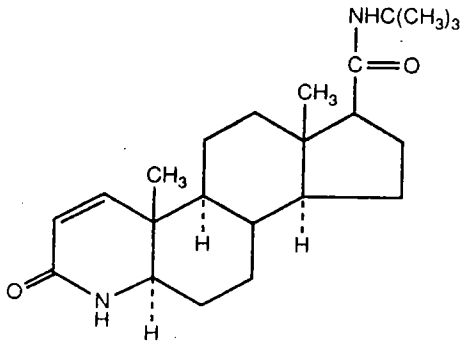
LABELING

PROSCAR®
(FINASTERIDE)
TABLETS

DESCRIPTION

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

Finasteride is 4-azaandrost-1-ene-17-carboxamide, *N*-(1,1-dimethylethyl)-3-oxo-,(5□,17□)-. 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, 5□-dihydrotestosterone (DHT). Type II 5□-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 5□-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 5□-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 5□-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 5□-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

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*Registered trademark of MERCK & CO., Inc.

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 □g) 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 (0-24 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

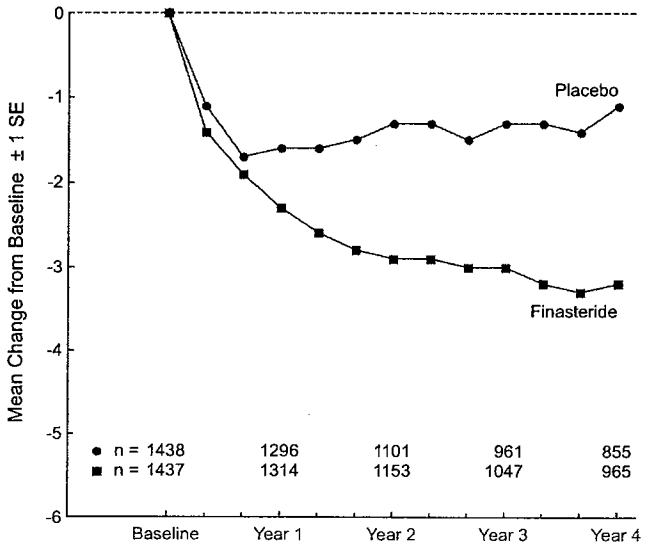
Mean (SD) Noncompartmental Pharmacokinetic Parameters After Multiple Doses of 5 mg/day in Older Men		
	Mean (± SD)	
	45-60 years old (n=12)	≥70 years old (n=12)
AUC (ng•hr/mL)	389 (98)	463 (186)
Peak Concentration (ng/mL)	46.2 (8.7)	48.4 (14.7)
Time to Peak (hours)	1.8 (0.7)	1.8 (0.6)
Half-Life (hours)*	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.

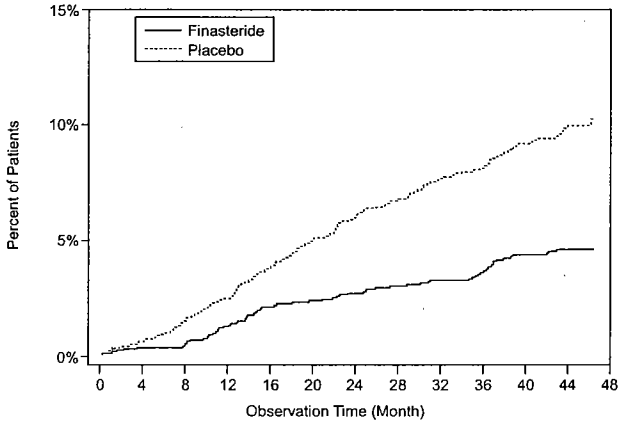
Table 1
All Treatment Failures in PLESS

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

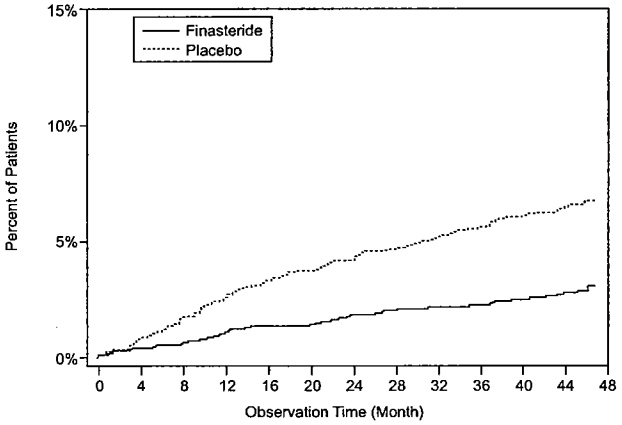
Compared with placebo, PROSCAR was associated with a significantly lower risk for acute urinary retention or the need for BPH-related surgery [13.2% for placebo vs 6.6% for PROSCAR; 51% reduction in risk, 95% CI: (34 to 63%)]. Compared with placebo, PROSCAR was associated with a significantly lower risk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



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.

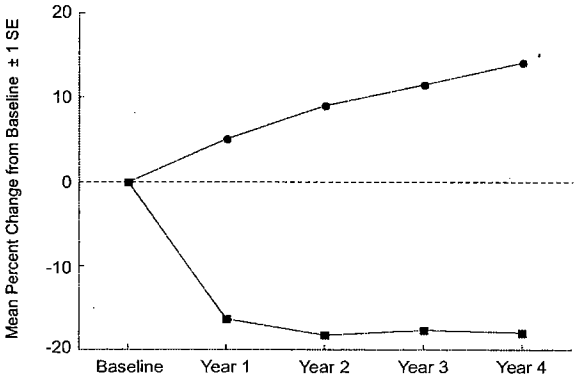
There was a clear difference between treatment groups in maximum urinary flow rate in favor of PROSCAR by month 4 (1.0 vs 0.3 mL/sec) which was maintained throughout the study. In the earlier 1-year studies, increase in maximum urinary flow rate was comparable to PLESS and was maintained through the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

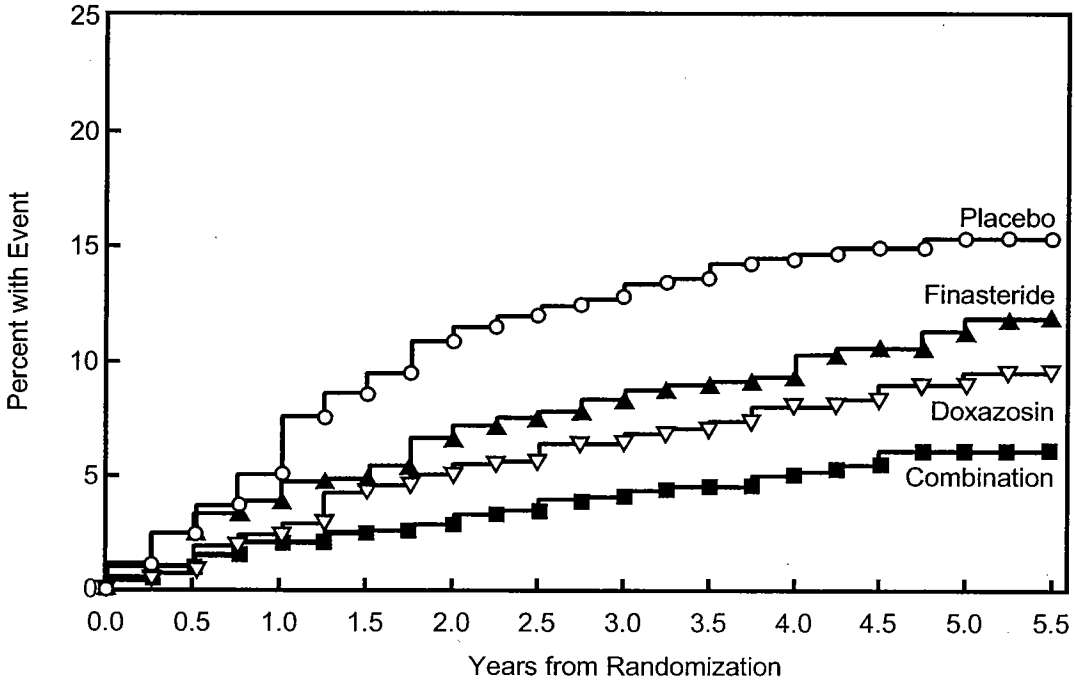
The primary endpoint was a composite measure of the first occurrence of any of the following five outcomes: a ≥4 point confirmed increase from baseline in symptom score, acute urinary retention, BPH-related renal insufficiency (creatinine rise), recurrent urinary tract infections or urosepsis, or incontinence. 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≤0.001) or doxazosin alone (46%; p≤0.001).(See Table 2.)

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

	Treatment Group				
Event	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 5□-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, □-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 □g•hr/mL).

In a 19-month carcinogenicity study in CD-1 mice, a statistically significant (p□0.05) increase in the incidence of testicular Leydig cell adenomas was observed at 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 □g/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 □g/kg/day (□3/10 of the recommended human dose of 5 mg/day) and decreased anogenital distance when given finasteride at □3 □g/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 5□-reductase inhibitors and are similar to those reported in male infants with a genetic deficiency of Type II 5□-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 4mg or 8mg* (N=756) (%)	Finasteride (N=768) (%)	Combination (N=786) (%)
Body as a whole				
Asthenia	7.1	15.7	5.3	16.8
	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.

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

Issued
Printed in USA

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

*Registered trademark of MERCK & CO., INC.

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 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.

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.

Your doctor may prescribe PROSCAR along with another medicine, an alpha-blocker called doxazosin, to help you better manage your BPH symptoms.

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.

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-180/S-026

MEDICAL REVIEW

NDA 20-180 (S-026)

Date submitted: June 12, 2003
Date received: June 13, 2003
MOR draft completed: December 29, 2003
MOR final completed: December 29, 2003

Medical Officer's Review of NDA Supplement (DRAFT)

Sponsor:	Merck Research Laboratories POB 2000 Rahway NJ 07065
Drugs:	Generic: finasteride, doxazosin Trade: Proscar® 5 mg, Cardura® 4 or 8 mg.
Route of administration:	Oral
Dosage form:	Tablets
Strength:	Finasteride 5 mg, doxazosin 4 or 8 mg.
Dosing Regimen:	Once daily, in combination.
Proposed indication:	[ ]
Related NDAs:	For the indication: "treatment of symptomatic benign prostatic hyperplasia". NDA 20-180 (Merck & Co. "Proscar") NDA 20-371 (Pfizer Inc. "Cardura")

Harry Handelsman, DO
Medical Officer

Mark Hirsch, MD
Clinical Team Leader

Executive Summary:

I. Recommendations

In the opinion of this reviewer, from a clinical perspective, the safety and efficacy of the combination of finasteride and doxazosin has been established, and should be approved for the indication [redacted]

II. Summary of Clinical Findings

II.A Brief Overview of the Clinical Program

The Medical Therapy of Prostatic Symptoms (MTOPS) study, sponsored by the NIH was a double-blind, randomized, placebo-controlled, multicenter, 4-6 year trial to evaluate the safety and efficacy of finasteride 5 mg/day and doxazosin 4 or 8 mg/day (titrated from 1 mg to 4 or 8 mg over a 3-week period), alone or in combination, in the treatment of BPH in 3047 patients.

II.B Efficacy

The results of the trial demonstrated finasteride and doxazosin alone or in combination was effective in delaying the clinical progression of BPH. Combination therapy was more effective than either drug alone. In addition, finasteride (but not doxazosin) alone or in combination with doxazosin reduced the relative risk of developing acute urinary retention. The effects of the combination on the need for BPH invasive therapy was essentially the same as that of finasteride alone, i.e., risk-reduction in BPH-related surgery.

II.C Safety

The safety and tolerability profile of the combination of agents was generally consistent with the profiles of the individual drugs. A notable exception was that this combination demonstrated an additive effect on the incidence of ejaculation disorder.

Reviewer's comment: *This reviewer believes that in view of the fact that extensive data on safety are available for the individual agents, and no further safety concerns were evidenced in the trial, it would appear that the demonstrated improved efficacy of the combination represents a clear clinical benefit vis a vis BPH symptoms. However, more recent available evidence concerning finasteride and the subsequent development of higher grade prostatic cancer (despite a lower incidence), might lead one to temper ones' enthusiasm for any increased exposure to its use.*

II.D Dosing, Regimen, and Administration Issues.

The sponsor believes that the proposed doses had the best balance between efficacy and safety in achieving the effects on symptomatic BPH.

II.E Use in Special Populations.

Gender: The combination of finasteride and doxazosin is indicated in the treatment of symptomatic BPH and is not indicated for use in women.

Pediatric: The safety and effectiveness in pediatric patients has not been established, and is not indicated for use in this population. Sponsor has requested a waiver for pediatric studies.

Elderly: Data from clinical trials and clinical experience have indicated no overall differences in safety and effectiveness in subjects 65 and over and 75 and over. No dosage adjustment is necessary in the elderly.

Race/Ethnicity: The effect of race/ethnicity on the pharmacokinetics of this combination has not been studied.

Table of Contents

Clinical Review

1. Introduction and Background

1.1 Trade name of drugs, class, proposed indication, dose and regimen.

Proscar® is a 5α-reductase inhibitor indicated for the treatment of symptomatic BPH, at a recommended dose of 5 mg once daily.

Cardura® is an α-adrenergic blocker indicated for both the urinary outflow obstructive and irritative symptoms associated with BPH, at a recommended dose of 1-8 mg once daily.

1.2 State of armamentarium for indication.

Beneficial medical, surgical, and non-medical treatments have included α-blockers, 5α-reductase inhibitors, transurethral resection, transurethral microwave thermotherapy, transurethral needle ablation, saw palmetto plant extracts, β-sitosterol plant extracts, and rye grass pollen extracts.

1.3 Milestones in product development.

Original NDA 20,180 (Proscar) was submitted on April 15, 1991 and approved on June 19, 1992.
Original NDA 20,371 (Cardura) was submitted on August 3, 1993 and approved on February 6, 1995.

1.4 Foreign marketing history.

Proscar has been marketed in 111 countries, and has not been rejected, withdrawn or suspended/revoked in any country.

Cardura has been marketed in 90 countries and has been [redacted]

1.5 Important issues with pharmacologically related agents.

5-α reductase inhibitors, by inhibiting the conversion of testosterone to DHT, may cause abnormalities of the external genitalia of a male fetus of a pregnant women exposed to this agent.

Inhibitors of α adrenergic receptors may cause marked hypotension with syncope, most commonly with the first dose, but also during dose increase or if therapy is interrupted for more than a few days.

2. Significant Findings from Chemistry, Pharmacology, Toxicology, and Statistics.

N/A

3. Human Pharmacokinetics and Pharmacodynamics.

N/A

4. Description of Clinical Data and Sources.

The following materials from the NDA were reviewed: 1) Description and analysis of clinical study MK-0906. 2) Integrated summary of safety. 3) Integrated summary of efficacy. 4) Adverse events data.

5. Clinical Review Methods.

The single clinical trial MK-096 was reviewed in detail. Reviews of the Integrated Summaries of safety and efficacy were conducted.

Full documentation related to financial disclosure has not been received.

DSI inspection has been determined to be unnecessary.

6. Integrated Review of Efficacy.

6.1. Introduction

Evidence of efficacy comes from a single clinical trial enrolling 3,097 participants randomized to one of four medical therapy groups.

6.2. General Approach

The focus of the efficacy review is the single trial, MK-096, conducted at 18 centers in the United States beginning in December, 1993 and completing randomization in March, 1998.

6.3 Brief Review of Clinical Trial MK-096.

Prior to the first screening visit (SV1), potential participants underwent pre-screening procedures to identify screening candidates who then underwent the following in order to determine eligibility:

1) AUA symptom score, impact index, QOL and sexual function questionnaires.
2) History and physical exam including digital rectal exam, vital signs, and urinalysis.
3) PSA, chemistry and hematological analyses.

Candidates successfully satisfying the inclusion/exclusion criteria listed below (study design), had the following performed at SV2:

1) AUA symptom score, impact index, and QOL questionnaire.
2) MOS-36 health survey.
3) Prostatitis questionnaire.
4) Vital signs.
5) Urinary flow rate and post void residual.
6) Transrectal ultrasound (TRUS).
7) Analysis for testosterone, DHT, and luteinizing hormone, and needle biopsy for those selected for the prostate substudy;

Objectives

The objective of the trial and the primary efficacy endpoint was achieving a reduction in the time to clinical progression of BPH, defined as the first occurrence of any of the following:

1) Acute urinary retention.
2) Renal insufficiency.
3) Recurrent UTI or sepsis.
4) Incontinence or increased AUA symptom score.

Study Design

Eligible participants with BPH were randomly assigned to one of the following groups:

1) Finasteride and doxazosin placebo.
2) Doxazosin and finasteride placebo.
3) Doxazosin and finasteride.
4) Finasteride placebo and doxazosin placebo.

Inclusion Criteria.

1) Age 50 or older.
2) Peak urinary flow rate between 4-15 ml/sec. and voided volume of at least 125 ml.
3) AUA symptom score ≥ 8 and ≤ 30.
4) Signed informed consent.

Exclusion Criteria.

1) Prior intervention for BPH.
2) Prior experimental intervention for prostate disease or enrolled in current study.
3) Previous reaction to finasteride, α-blockers, or quinazolines.
4) Use of α-blocker within a year of randomization.
5) Use of phenylephrine, pseudoephedrine, imipramine, or anticholinergic/cholinergic medication within 4 weeks of screening.
6) Prior use of anabolic steroids, estrogen, androgen or androgen suppressant. Use of cimetidine within 3 months of screening.
7) Inability to urinate.
8) Supine BP < 90/70 mmHg.
9) Clinically significant renal or hepatic impairment.
10) PSA > 10 ng/ml.
11) Daily use of a pad or incontinence device.
12) MI, TIA, CVA, or unstable angina within 6 months of screening.
13) History of orthostatic hypotension or significant fainting spells.
14) History of bladder or prostate cancer, pelvic radiation or surgery, urethral stricture or BPH surgery.
15) Active urinary tract disease or cystoscopy or prostate biopsy within 1 month of screening.
16) Primary neurological disorder known to affect bladder function.
17) Bacterial prostatitis or 2 UTIs within a year of screening.

18) A bleeding disorder making biopsy impossible.
19) Cancer, other than skin cancer, not considered cured.
20) Psychiatric illness.
21) Alcoholism or drug abuse that might affect compliance.
22) Serious medical condition likely to affect completion of study.

Safety was evaluated by clinical laboratory tests and reported adverse events monitored throughout the study.

Efficacy Results

Primary Outcomes

As noted in the following, Table 1, there were a total of 351 primary outcome events in the study population, with all active treatment groups exhibiting a significantly longer time to clinical progression than placebo. Seventy-eight percent of the events were a consequence of a confirmed 4-point or greater rise in the AUA symptom score, followed by 12% for acute urinary retention, 9 % for incontinence, and 1 % for recurrent UTI/sepsis. There were no reports of increased creatinine or renal insufficiency.

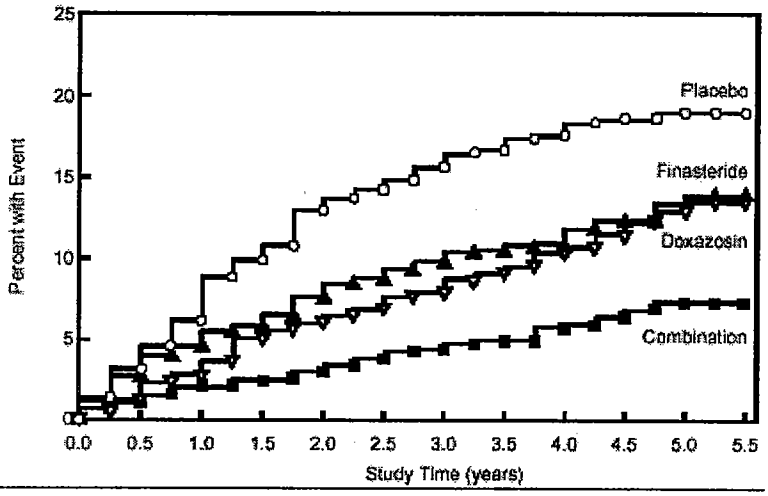
Table 1

Event	Placebo N=737 (%)	Doxizosin N=756 (%)	Finasteride N=768 (%)	Combination N=786 (%)	Total N=3047(%)
AUA ≥ 4 points	100 (13.6)	59 (7.8)	74 (9.6)	41 (5.2)	274 (9.0)
Acute 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)
Recur.UTI/Sepsis	2 (0.3)	2 (0.3)	0 (0.0)	1 (0.1)	5 (0.2)
> creatinine	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 time to BPH progression in the treatment groups is shown in Figure 1 where the active treatments alone or in combination exhibited significant reductions in the progression of BPH. The cumulative incidence of a 4-point rise in AUA symptom score, and of acute urinary retention by treatment groups are seen in figures 2 and 3 respectively.

Figure 1

Cumulative Incidence of BPH Progression by Treatment Group

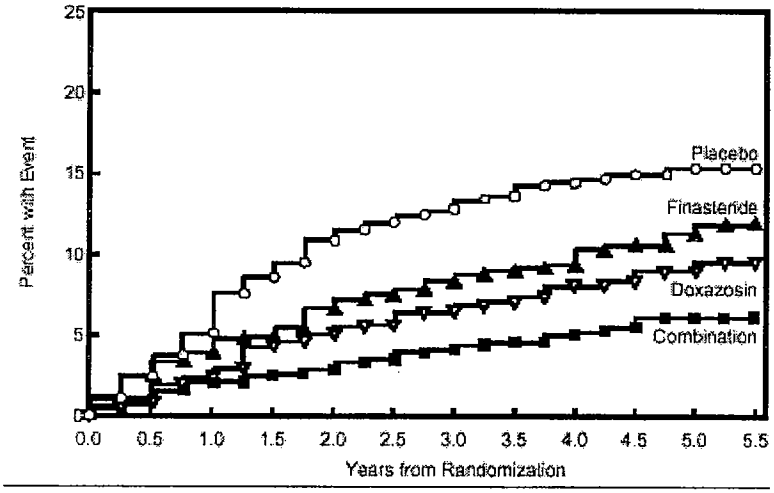


Compared with the placebo group risk reduction for progression of BPH were doxazosin 39%, finasteride 34%, and the combination 67% (Table 2).

The most common and second most common outcome events are seen in Figures 2 and 3 respectively.

Figure 2

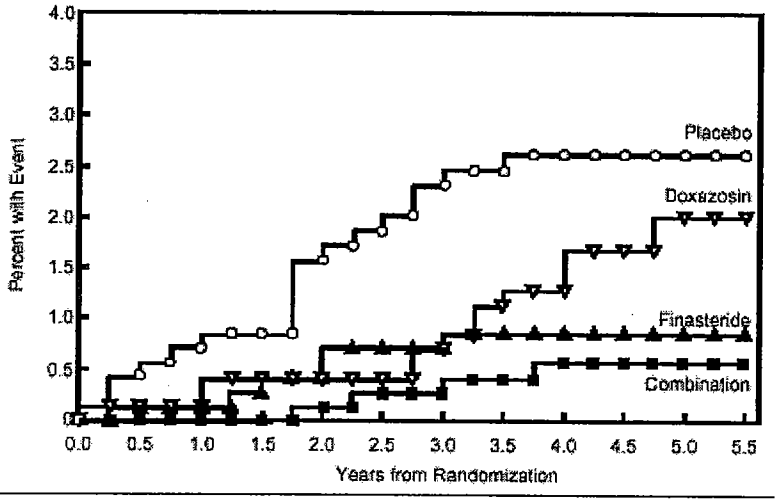
Cumulative Incidence of a 4-Point Rise in AUA Symptom Score by Treatment Group



The risk of symptom score progression was significantly reduced by 30 %, 46 % and 64 % in the finasteride, doxazosin, and combination groups respectively.

Figure 3

Cumulative Incidence of Acute Urinary Retention by Treatment Group



The risk of developing acute urinary retention was reduced by 67 %, 31 %, and 79 % in the finasteride, doxazosin, and combination groups respectively. As seen in Table 2, only the finasteride and combination groups were significantly different than placebo.

Table 2

Between-Treatment Group Comparison of the Risk Reduction (95% CI) in BPH Progression, 4-Point or Greater Increase in AUA Symptom Score, and Acute Urinary Retention

Outcome	Treatment Comparison					
	Doxazosin vs. Placebo	Finasteride vs. Placebo	Combination vs. Placebo	Combination vs. Doxazosin	Combination vs. Finasteride	Finasteride vs. Doxazosin
BPH Progression	39% (20%, 54%) p=0.0002	34% (14%, 50%) p=0.0018	67% (54%, 76%) p<0.0001	46% (23%, 62%) p=0.0004	49% (28%, 64%) p<0.0001	-7% (-44, 20%). p=0.6518
4-Point Rise in AUA Symptom Score	46% (25%, 60%) p=0.0001	30% (6%, 48%) p=0.0156	64% (48%, 75%) p<0.0001	34% (2%, 55%) p=0.0369	48% (24%, 64%) p=0.0006	-27% (-79%, 9%). p=0.1683
Acute Urinary Retention	31% (-39%, 66%) p=0.2963	67% (18%, 87%) p=0.0114	79% (40%, 93%) p=0.0013	70% (10%, 90%) p=0.0214	37% (-120%, 82%) p=0.4644	53% (-22%, 83%) p=0.1123

For the active-versus-placebo comparison, p<0.0157 was considered statistically significant. For the active-versus-active comparison, p<0.0167 was considered statistically significant.

Secondary Outcomes--- BPH-related Invasive Therapy

The risk of requiring BPH-related invasive therapy compared with placebo was reduced by 64 %, 3 %, and 67 % in the finasteride, doxazosin, and combination groups,

respectively (Table 3). Again, only finasteride and the combination had significant reductions in risk compared with placebo.

Table 3

Relative Risk Reduction (95% CI) of BPH Invasive Therapy, BPH Invasive Therapy or BPH Progression, and BPH Invasive Therapy or Acute Urinary Retention

Outcome	Treatment Comparison					
	Doxazosin vs. Placebo	Finasteride vs. Placebo	Combination vs. Placebo	Combination vs. Doxazosin	Combination vs. Finasteride	Finasteride vs. Doxazosin
BPH Invasive Therapy	3% (-48%, 37%)	64% (34%, 80%)	67% (40%, 82%)	67% (39%, 82%)	10% (-86%, 56%)	63% (34%, 79%)
BPH Progression OR BPH Invasive Therapy	34% (15%, 48%)	39% (20%, 53%)	66% (54%, 75%)	49% (30%, 63%)	44% (22%, 60%)	8% (-20%, 31%)
Acute Urinary Retention OR BPH Invasive Therapy	14% (-29%, 43%)	63% (37%, 78%)	74% (53%, 86%)	71% (46%, 84%)	30% (-41%, 66%)	58% (27%, 75%)

Secondary Outcomes--- AUA symptom score, Max. urine flow rate, Prostate vol.

All active treatment groups showed improvements in AUA symptom score, which were similar between finasteride and doxazosin, and larger in the combination.

The improvement in urinary flow rate was similar between doxazosin and the combination, and, was larger than finasteride or placebo, which were also similar.

As expected, only finasteride alone or in combination resulted in lowered prostate volume.

These results are seen in Table 4.

Table 4

Baseline and Change From Baseline to Year 5 or Last Observation in AUA Symptom Score, Maximum Urinary Flow Rate (Q_{max}), and Prostate Volume by Treatment Group

Event	Treatment Group			
	Placebo (N=737)	Doxazosin (N=756)	Finasteride (N=768)	Combination (N=786)
AUA Symptom Score				
Baseline Mean (SD)	16.8 (6.0)	17.0 (5.9)	17.1 (6.0)	16.8 (5.8)
Mean Change (SD) From Baseline[1]	-5.0 (5.9)	-6.2 (6.3)	-6.0 (6.3)	-7.2 (6.6)
Between-Treatment Group Comparison p-values versus				
Doxazosin	<0.001			
Finasteride	0.002	0.536		
Combination	<0.001	0.002	<0.001	
Maximum Urinary Flow Rate (Q_{max}, mL/sec)				
Baseline Mean (SD)	10.5 (2.7)	10.3 (2.6)	10.5 (2.6)	10.6 (2.5)
Mean Change (SD) From Baseline[1]	2.7 (6.7)	4.0 (7.7)	3.1 (6.3)	4.1 (6.6)
Between-Treatment Group Comparison p-values versus				
Doxazosin	0.001			
Finasteride	0.233	0.013		
Combination	<0.001	0.784	0.002	
Prostate Volume (cc)				
Baseline Mean (SD)	35.2 (18.9)	36.9 (21.6)	36.9 (20.6)	36.4 (19.2)
Baseline Median	30.6	31.1	31.0	31.4
Median % Change from Baseline[1]	24.0	25.2	-13.3	-9.5
Mean % Change (SD) from Baseline[2]	28.4 (35.3)	30.3 (36.5)	-4.5 (38.2)	-1.5 (36.3)
Between-Treatment Group Comparisons of mean percent changes				
Doxazosin	0.307			
Finasteride	<0.001	<0.001		
Combination	<0.001	<0.001	0.113	

[1] Change from baseline at Year 5.
[2] Change from baseline to last observation.

6.4 Efficacy Conclusions.

This clinical trial demonstrated that combination therapy was more effective than finasteride or doxazosin alone in reducing the risk of BPH progression. Finasteride, alone or in combination with doxazosin (not doxazosin alone), reduced the risk of acute urinary retention and BPH-related surgery. Finasteride or doxazosin alone or in combination positively impacted AUA symptom score and maximum urinary flow rate. Doxazosin or placebo treatment was associated with an increased prostate volume (normal disease progression) while finasteride, alone or in combination with doxazosin, reduced prostate volume consistent with the mechanism of action of finasteride.

7. Integrated Review of Safety.

7.1 Brief Statement of Findings

Safety evaluations include clinical and laboratory AE's and clinical and endpoint measurements. A total of 2840/3047 (93.2%) patients reported AE's, with almost equal numbers in all the treatment groups including the placebo group. AE's occurred most frequently in the urogenital, body as a whole, nervous, and cardiovascular systems. AE's reported with an incidence > 5 % are listed in Table 5.

Table 5

Number (%) of Patients With Specific Clinical Adverse Experiences (Incidence ≥5.0% in One or More Treatment Groups) by Body System

Adverse Experience	Placebo (N=737) N (%)	Doxazosin (N=756) N (%)	Finasteride (N=768) N (%)	Combination (N=786) N (%)	Grand Total (N=3047) N (%)
Total number of patients with adverse experience	675 (91.6)	708 (93.7)	712 (92.7)	745 (94.8)	2840 (93.2)
Body As A Whole	**414 (56.2)**	**488 (64.6)**	**457 (59.5)**	**509 (64.8)**	**1868 (61.3)**
Accidental Injury	73 (9.9)	63 (8.3)	67 (8.7)	66 (8.4)	269 (8.8)
Asthenia	72 (9.8)	147 (19.4)	56 (7.3)	162 (20.6)	437 (14.3)
Back Pain	79 (10.7)	81 (10.7)	97 (12.6)	101 (12.8)	358 (11.7)
Chest Pain	34 (4.6)	55 (7.3)	39 (5.1)	43 (5.5)	171 (5.6)
Flu Syndrome	48 (6.5)	54 (7.1)	58 (7.6)	62 (7.9)	222 (7.3)
Headache	40 (5.4)	47 (6.2)	34 (4.4)	36 (4.6)	157 (5.2)
Hernia	37 (5.0)	50 (6.6)	51 (6.6)	59 (7.5)	197 (6.5)
Infection	82 (11.1)	74 (9.8)	72 (9.4)	90 (11.5)	318 (10.4)
Pain	137 (18.6)	138 (18.3)	126 (16.4)	133 (16.9)	534 (17.5)
Cardiovascular	**218 (29.6)**	**284 (37.6)**	**241 (31.4)**	**291 (37.0)**	**1034 (33.9)**
Postural Hypotension	81 (11.0)	148 (19.6)	92 (12.0)	166 (21.1)	487 (16.0)
Metabolic And Nutritional	**135 (18.3)**	**160 (21.2)**	**161 (21.0)**	**178 (22.6)**	**634 (20.8)**
Peripheral Edema	23 (3.1)	32 (4.2)	26 (3.4)	47 (6.0)	128 (4.2)
Musculoskeletal	**149 (20.2)**	**147 (19.4)**	**173 (22.5)**	**143 (18.2)**	**612 (20.1)**
Arthralgia	32 (4.3)	38 (5.0)	35 (4.6)	25 (3.2)	130 (4.3)
Arthritis	31 (4.2)	32 (4.2)	46 (6.0)	32 (4.1)	141 (4.6)
Nervous	**279 (37.9)**	**348 (46.0)**	**314 (40.9)**	**395 (50.3)**	**1336 (43.8)**
Dizziness	80 (10.9)	162 (21.4)	86 (11.2)	206 (26.2)	534 (17.5)
Hypertension	72 (9.8)	58 (7.7)	80 (10.4)	48 (6.1)	258 (8.5)
Libido Decreased	50 (6.8)	57 (7.5)	86 (11.2)	99 (12.6)	292 (9.6)
Respiratory	**218 (29.6)**	**201 (26.6)**	**210 (27.3)**	**234 (29.8)**	**863 (28.3)**
Dyspnea	20 (2.7)	34 (4.5)	21 (2.7)	46 (5.9)	121 (4.0)
Pharyngitis	47 (6.4)	50 (6.6)	46 (6.0)	45 (5.7)	188 (6.2)
Rhinitis	54 (7.3)	49 (6.5)	50 (6.5)	55 (7.0)	208 (6.8)
Sinusitis	29 (3.9)	36 (4.8)	34 (4.4)	39 (5.0)	138 (4.5)
Skin And Appendages	**134 (18.2)**	**118 (15.6)**	**140 (18.2)**	**153 (19.5)**	**545 (17.9)**
Rash	44 (6.0)	43 (5.7)	44 (5.7)	50 (6.4)	181 (5.9)

Table 5 (Cont.)

Adverse Experience	Placebo (N=737) N (%)	Doxazosin (N=756) N (%)	Finasteride (N=768) N (%)	Combination (N=786) N (%)	Grand Total (N=3047) N (%)
Urogenital	**456 (61.9)**	**447 (59.1)**	**477 (62.1)**	**510 (64.9)**	**1890 (62.0)**
Abnormal Ejaculation	29 (3.9)	40 (5.3)	64 (8.3)	118 (15.0)	251 (8.2)
Dysuria	34 (4.6)	39 (5.2)	34 (4.4)	29 (3.7)	136 (4.5)
Hematuria	63 (8.5)	60 (7.9)	42 (5.5)	50 (6.4)	215 (7.1)
Impotence	115 (15.6)	130 (17.2)	164 (21.4)	198 (25.2)	607 (19.9)
Prostatic Carcinoma	63 (8.5)	56 (7.4)	41 (5.3)	63 (8.0)	223 (7.3)
Prostatic Disorder	52 (7.1)	57 (7.5)	43 (5.6)	47 (6.0)	199 (6.5)
Prostatic Specific Antigen Increase	116 (15.7)	116 (15.3)	109 (14.2)	122 (15.5)	463 (15.2)
Urinary Frequency	86 (11.7)	59 (7.8)	70 (9.1)	42 (5.3)	257 (8.4)
Urinary Tract Infection	62 (8.4)	46 (6.1)	37 (4.8)	37 (4.7)	182 (6.0)
Urination Impaired	38 (5.2)	31 (4.1)	31 (4.0)	21 (2.7)	121 (4.0)

There were no clinically meaningful differences in the incidence of AE's between treatment groups except for those consistent with the well described AE profile of both finasteride and doxazosin, i.e., impotence, decreased libido, and abnormal ejaculation; and dizziness, postural hypotension, asthenia, peripheral edema, and dyspnea respectively.

A total of 1816 patients (59.6 %) had drug related AE's, including 342 (46.4 %) treated with placebo. The highest incidence of these AE's was seen in the doxazosin alone or combination groups. Drug-related and serious AE's seen in $\geq$ 2 % and $\geq$ 1 % of patients are described in Tables 6 and 7 respectively.

There were only 32 patients (1.1 %) who reported serious drug-related AE's, and the differences between the treatment groups, including placebo, were not clinically meaningful.

A total of 133 patients died during the 6 year trial. There were no significant differences in the numbers of deaths between the treatment groups, including placebo. These deaths were reviewed by the Clinical Review Committee which concluded that none of the deaths were drug-related.

The incidence of sexual AE's is described in Table 8.

Table 8
Incidence of Sexual Adverse Experiences
by Treatment Group

	Incidence							
	Placebo N=737		Doxazosin N=756		Finasteride N=768		Combination N=786	
Adverse Experience	n	%	n	%	n	%	n	%
Impotence								
Overall	115	15.6	130	17.2	164	21.4	198	25.2
On or Before Year 1	71	9.6	79	10.4	111	14.5	149	19.0
Post Year 1	48	6.5	55	7.3	61	7.9	51	6.5
Libido Decreased								
Overall	50	6.8	57	7.5	86	11.2	99	12.6
On or Before Year 1	37	5.0	45	6.0	67	8.7	81	10.3
Post Year 1	12	1.6	13	1.7	23	3.0	18	2.3
Abnormal Ejaculation								
Overall	29	3.9	40	5.3	64	8.3	118	15.0
On or Before Year 1	18	2.4	34	4.5	46	6.0	97	12.3
Post Year 1	11	1.5	7	0.9	20	2.6	24	3.1

Breast tenderness and enlargement are additional AE's associated with use of finasteride, and their incidence in this study is seen in Table 9.

Table 9

Incidence of Breast-Related Adverse Experiences[†] by Treatment Group

Adverse Experience	Percent Incidence							
	Placebo N=737		Doxazosin N=756		Finasteride N=768		Combination N=786	
	n	%	n	%	n	%	n	%
Gynecomastia/Breast Enlargement[‡]								
Overall	6	0.8	9	1.2	19	2.5	16	2.0
On or Before Year 1	4	0.5	4	0.5	12	1.6	14	1.8
Post Year 1	3	0.4	5	0.7	7	0.9	2	0.3
Breast Pain[§]								
Overall	1	0.1	5	0.7	11	1.4	14	1.8
On or Before Year 1	0	0.0	1	0.1	7	0.9	10	1.3
Post Year 1	1	0.1	4	0.5	5	0.7	6	0.8
Breast Carcinoma[¶]								
Overall	0	0.0	0	0.0	3	0.4	1	0.1
On or Before Year 1	0	0.0	0	0.0	0	0.0	0	0.0
Post Year 1	0	0.0	0	0.0	3	0.4	1	0.1
Breast Neoplasm[#*]								
Overall	1	0.1	1	0.1	1	0.1	3	0.4
On or Before Year 1	1	0.1	1	0.1	0	0.0	1	0.1
Post Year 1	0	0.0	0	0.0	1	0.1	2	0.3
Mastitis[§]								
Overall	0	0.0	0	0.0	0	0.0	1	0.1
On or Before Year 1	0	0.0	0	0.0	0	0.0	1	0.1
Post Year 1	0	0.0	0	0.0	0	0.0	0	0.0

† In EOS report, some breast adverse experiences (breast pain, breast neoplasm, breast enlargement, and mastitis) were erroneously classified as female. See Tables 8-8 and 8-9 in [1]. Since women were not randomized into this study, this encoding error is inconsequential and has been corrected here.

‡ Classified as female in EOS Report: 1 in finasteride group and 2 in combination group.

§ Classified as female in EOS Report: 1 in placebo group, 1 in doxazosin group, 3 in finasteride group, and 6 in combination group.

* Classified as female in EOS Report: 1 in placebo group, 1 in finasteride group, 3 in combination group.

¶ Classified as female in EOS Report: 1 in combination group.

Encoding was performed using the COSTART dictionary. Breast neoplasms are considered benign while breast carcinomas are malignant.

Tables 10 and 11 display the incidence of doxazosin associated hypotension, syncope and edema, and asthenia and CNS AE's respectively.

Table 10

Incidence of Hypotension, Syncope, and Edema Adverse Experiences by Treatment Group

Adverse Experience	Incidence							
	Placebo N=737		Doxazosin N=756		Finasteride N=768		Combination N=786	
	n	%	n	%	n	%	n	%
Postural Hypotension								
Overall	81	11.0	148	19.6	92	12.0	166	21.1
On or Before Year 1	31	4.2	74	9.8	33	4.3	96	12.2
Post Year 1	57	7.7	89	11.8	64	8.3	101	12.8
Peripheral Edema								
Overall	23	3.1	32	4.2	26	3.4	47	6.0
On or Before Year 1	9	1.2	23	3.0	14	1.8	27	3.4
Post Year 1	14	1.9	14	1.9	12	1.6	25	3.2
Hypotension								
Overall	9	1.2	34	4.5	15	2.0	17	2.2
On or Before Year 1	2	0.3	19	2.5	6	0.8	11	1.4
Post Year 1	7	0.9	16	2.1	9	1.2	6	0.8
Edema								
Overall	12	1.6	18	2.4	19	2.5	23	2.9
On or Before Year 1	4	0.5	7	0.9	5	0.7	10	1.3
Post Year 1	9	1.2	12	1.6	15	2.0	14	1.8
Syncope								
Overall	11	1.5	15	2.0	16	2.1	22	2.8
On or Before Year 1	1	0.1	8	1.1	9	1.2	12	1.5
Post Year 1	10	1.4	8	1.1	8	1.0	11	1.4

Table 11

Incidence of Asthenia and Central Nervous System Adverse Experiences by Treatment Group

Adverse Experience	Incidence							
	Placebo N=737		Doxazosin N=756		Finasteride N=768		Combination N=786	
	N	%	N	%	n	%	n	%
Asthenia								
Overall	72	9.8	147	19.4	56	7.3	162	20.6
On or Before Year 1	50	6.8	120	15.9	41	5.3	123	15.6
Post Year 1	24	3.3	36	4.8	17	2.2	52	6.6
Dizziness								
Overall	80	10.9	162	21.4	86	11.2	206	26.2
On or Before Year 1	53	7.2	123	16.3	49	6.4	158	20.1
Post Year 1	35	4.7	53	7.0	45	5.9	72	9.2
Somnolence								
Overall	14	1.9	31	4.1	14	1.8	30	3.8
On or Before Year 1	11	1.5	26	3.4	11	1.4	25	3.2
Post Year 1	4	0.5	4	0.5	3	0.4	7	0.9

Clinical and laboratory AE's are described in Table 12. Few patients experienced these AE"s, which were regarded as being due to chance and not clinically meaningful.

Table 12

Number (%) of Patients With Specific Laboratory Adverse Experiences (Incidence ≥1.0% in One or More Treatment Groups)

Adverse Experience	Placebo (N=737) N (%)	Doxazosin (N=756) N (%)	Finasteride (N=768) N (%)	Combination (N=786) N (%)	Grand Total (N=3047) N (%)
Hemic And Lymphatic	**38 (5.2)**	**47 (6.2)**	**38 (4.9)**	**56 (7.1)**	**179 (5.9)**
Anemia	12 (1.6)	25 (3.3)	13 (1.7)	23 (2.9)	73 (2.4)
Hypochromic Anemia	12 (1.6)	8 (1.1)	5 (0.7)	10 (1.3)	35 (1.1)
Thrombocytopenia	4 (0.5)	12 (1.6)	5 (0.7)	15 (1.9)	36 (1.2)
Metabolic And Nutritional	**135 (18.3)**	**160 (21.2)**	**161 (21.0)**	**178 (22.6)**	**634 (20.8)**
Creatinine increased	22 (3.0)	23 (3.0)	14 (1.8)	11 (1.4)	70 (2.3)

The postmarketing experience of finasteride and concomitant α-blockers included 369 AE reports since 1992. These are summarized in Table 13.

Table 13

Most Frequently Observed Adverse Experiences in the Postmarketing Adverse Experience Reports of Finasteride Concomitant With an α-Adrenergic Blocker

Total Number of Postmarketing Adverse Experience Reports	Number (%) of Reports With Adverse Experience	
	Concomitant α-Adrenergic Blocker With Finasteride	
	Doxazosin N=35	Any α-Adrenergic Blocker N=369
Breast Adverse Experiences		
Gynecomastia	8 (22.9)	52 (14.1)
Breast Pain	4 (11.4)	30 (8.1)
Breast Tenderness	--	11 (3.0)
Breast Enlargement	--	5 (1.4)
Sexual Adverse Experiences		
Erectile Dysfunction NOS	4 (11.4)	42 (11.4)
Libido Decreased	2 (5.7)	24 (6.5)
Semen Volume Decreased	2 (5.7)	14 (3.8)
Ejaculation Disorder NOS	1 (2.9)	6 (1.6)
Other Adverse Experiences		
Drug Ineffective	3 (8.6)	45 (12.2)
General Symptom NOS	--	16 (4.3)
Headache NOS	--	14 (3.8)
Dizziness	2 (5.7)	13 (3.5)

7.2 Safety Conclusions.

Compared with patients on placebo, finasteride-treated patients had a higher incidence of sexual and breast AE's, and doxazosin-treated patients had a higher incidence of hypotension, syncope, dizziness, edema, asthenia, and somnolence. Overall, there were no clinically relevant new or unexpected AE's.

8.0 Dosing, Regimen, and Administration Issues.

The sponsor believes that the proposed doses had the best balance between efficacy and safety in achieving the effects on symptomatic BPH.

9.0 Use in Special Populations.

Gender: The combination of finasteride and doxazosin is indicated in the treatment of symptomatic BPH and is not indicated for use in women.

Pediatric: The safety and effectiveness in pediatric patients has not been established, and is not indicated for use in this population. Sponsor has requested a waiver for pediatric studies.

Elderly: Data from clinical trials and clinical experience have indicated no overall differences in safety and effectiveness in subjects 65 and over and 75 and over. No dosage adjustment is necessary in the elderly.

Race/Ethnicity: The effect of race/ethnicity on the pharmacokinetics of this combination has not been studied.

10. Conclusions, Recommendation, and Labeling.

10.1 Conclusions Regarding Safety and Efficacy.

In the opinion of this reviewer, the submitted clinical data support the safety and efficacy of the proposed doses of the combination of finasteride and doxazosin.

10.2 Recommendation on Approvability.

From a clinical perspective, the combination of finasteride and doxazosin should be approved for the indication [ ] [ ]

10.3 Labeling.

This reviewer agrees with the proposed labeling changes which include insertion of data from the MTOPS trial documenting a reduction in time to progression of BPH (primary endpoint), including both percentages and p-values.

This reviewer finds the section "Indications and Usage" to be the same as that of the previous label, and reflects the current trial data, without indicating p-values or confidence intervals. This is acceptable.

This reviewer believes that the "Precautions" section of the proposed label changes be modified to include recent published data regarding the effects of finasteride on both the incidence and grade of prostate cancer.

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

/s/

Harry Handelsman
4/12/04 12:38:31 PM
MEDICAL OFFICER

Mark S. Hirsch
4/12/04 01:18:30 PM
MEDICAL OFFICER
I concur with the MO's recommendation to approve the supplement. For additional discussion and details, please refer to my team leader's memo.

NDA 20-180 SE8-026

Medical Team Leader's Memorandum: Review of Efficacy Supplement

Date submitted: June 12, 2003
Date received: June 13, 2003
Date of memo: April 12, 2004

Sponsor: Merck & Co., Inc
Drug: Proscar™ (finasteride)
Dose: 5mg tablets
Indication: PROSCAR, [redacted]
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.

Note to reader: Sponsor requests a change to the Proscar indication to add the words in *italics* and to add information to the Clinical Studies, Adverse Reactions, and Dosage and Administration sections of the physician package insert (PI). Brief change is also proposed for the patient package insert (PPI).

1. Executive summary: The purpose of this memo is to provide the Division Director with my recommendation for this application. Now that a final label has been negotiated, I recommend that this application receive an **approval** action. Herein, I provide my reasoning for this decision:

In my opinion, the results of the Medical Treatment of Prostate Symptoms Trial (or MTOPS) demonstrates that the combination of finasteride and doxazosin provides a clinically meaningful benefit to patients with symptomatic BPH **through additional risk reduction for symptomatic progression** [redacted]

Based upon this scientific conclusion, I believe the study results support *some* new indication for finasteride in combination with doxazosin BUT the sponsor's original proposed labeling (especially the Indications statement and the Clinical Studies section) does not accurately describe the benefits of combination treatment shown in MTOPS. Fundamentally, the original proposed labeling was unacceptable because it implied uses for the combination treatment that were not demonstrated. The proposed labeling, therefore, has been *substantially* revised prior to the final approval of this application.

Note to reader: Extensive labeling discussions were held with sponsor. These talks and correspondences have been successful in resolving all labeling issues.

The major problems with the original label (prior to label negotiations) were:

1) It overstated the efficacy of the combination therapy, implying that combination therapy adds significantly to finasteride-alone for [redacted] This was not

demonstrated in MTOPS because the study was underpowered to detect between-group differences for these infrequent outcome events.

2) The most compelling clinical benefit that was actually demonstrated in MTOPS was [ ] that fewer patients in the combination group experienced BPH symptom worsening ("symptomatic progression") of symptoms (a confirmed ≥4 point rise in AUA symptom score) compared to either the finasteride-alone group or the doxazosin-alone group. Nevertheless, it is true that relief of symptoms appeared better in the combination group than in either group alone, but this was a secondary endpoint. Analysis of this particular endpoint was also an issue of extensive discussion and the presentation in the label was finally agreed upon on April 12th.

Both of these issues, and all others, were successfully resolved through extensive labeling discussions between the review team and sponsor.

Therefore, at this point in the review of this application, now that all labeling matters have been resolved, I can recommend an approval action.

2. Materials reviewed

In conducting my secondary clinical review of this supplement, I reviewed the following documents:

1. Primary medical officer's filing memo.
2. Primary medical officer's draft review.
3. Biometrics draft review.
4. Final consult from the Division of Drug Marketing, Advertising and Consultation (DDMAC) regarding the PI.
5. Final consult from the Office of Drug Safety (ODS)/Division of Surveillance, Research and Communication Support (DSRCS) regarding the PPI.
6. Clinical pharmacology draft filing eMAIL.
7. Sponsor's proposed changes to the PI and PPI.
8. Hard-copy Volume 1 of the sNDA, with particular focus on the 52-page "Clinical Summary".
9. The "Clinical and Statistical Documentation" section of the application consisting of a total of 2 volumes. Particular focus was on the 57-page text of the "End-of-Study Report", Reference #30 (the original protocol), and Reference #51 (Assessment of breast cancer).

3. Summary of the MTOPS Trial

3.1. Design and procedures

MTOPS was a double-blind, placebo-controlled, multi-center randomized trial. It was designed to evaluate the safety and efficacy of finasteride (an inhibitor of 5-alpha-reductase) and doxazosin (an antagonist of alpha-1-adrenoceptors) on "the clinical progression of BPH." Eligible patients with symptomatic BPH were to be assigned randomly to one of 4 parallel treatment arms (finasteride 5mg + doxazosin placebo, doxazosin 4mg or 8mg + finasteride placebo, both active finasteride and active doxazosin, finasteride placebo and doxazosin placebo). Doxazosin final dose was achieved by weekly up-titration from 1mg to 2mg to 4mg to 8mg. Final tolerated dose (4mg or 8mg) was administered beginning end-Week 4. Patients not tolerating at least 4mg did not received doxazosin in the study. Randomization was stratified by clinical center.

The primary objective of the study was "to ascertain if medical therapy (finasteride and/or doxazosin) delays or prevents the progression of BPH". During the trial, participants were classified into one of the following four Categories:

1. "Clinical progression of BPH", as defined by one of the following:
   a. Acute urinary retention.
   b. Renal insufficiency due to BPH, as indicated by a 50% increase from baseline in serum creatinine to at least 1.5mg/dL, confirmed within 4 weeks.
   c. Recurrent urinary tract infections or urosepsis.
   d. Incontinence
   e. An increase from baseline in the AUA symptom score index of 4 or more points, confirmed 2 to 4 weeks later.
2. "Crossover to known invasive therapy", prior to clinical progression.
3. Non-compliance with study medication treatment regimen.
4. Completion of study

Patients who were coded as Category #1 were to be taken off their study medication, but were to continue scheduled follow-up visits, if possible. Patients coded as Category #1 in the subset "increase in AUA score" could be taken off study medications or could continue on study medications, at the discretion of the investigator, but were still to continue follow-up visits. Patients coded as Category #2 were to be taken off study medications but were to continue follow-up. Patients coded as Category #2 (crossover to invasive surgery) prior to meeting a Category #1 endpoint were to remain classified to Category #2. Patients classified as Category #3 (non-compliant with study medications) were to continue on study and would eventually be classified into one of the other 3 categories as indicated by their follow-up experience.

The primary analysis planned was for "time to clinical progression of BPH (time-to-Category #1). Patients in Categories #2, #3 and #4 were "censored" as of the date of their last completed visit. A planned supportive analysis was time to the first occurrence of clinical progression of BPH (as in Category #1) or crossover to known invasive therapy (Category #2). For this analysis, only patients in Categories #3 and #4 would be censored at the date of their last visit.

> **Reviewer's comment**: In this trial, a total of 40, 41, 15 and 14 patients "crossed-over" to invasive therapy in the placebo, doxazosin-alone, finasteride-alone and combination arms, respectively (Category #2). In retrospect, the need for invasive treatment while on BPH medications could have been an additional element of Category #1, not a separate Category. Nevertheless, according to the statistical analysis plan in protocol version #3, cross-over to invasive therapy (Category #3) was taken into account as a competing risk factor in the efficacy analysis (reader is referred to the Biometrics review for details).

Other secondary objectives were "to assess differences over time between the four treatment groups with regard to":

1. AUA Symptom Score and "Impact Index".
2. The Medical Outcomes Study (MOS) 36-Item Short Form Health Survey score.
3. Maximum urinary flow rate.

Randomized patients were scheduled for follow-up visits every 3 months for an average duration of 5 years. Baseline and follow-up visits were to include:

1. History and physical exam (including rectal exam)

2. Safety laboratories (including hematology, chemistry, serum PSA and urinalysis)
3. Uroflowmetry
4. Questionnaires for symptoms (AUA SI and Impact Index), for overall health (the MOS SF-36), for "sexual function", and for "Prostatitis" (an unspecified 4-question questionnaire).
5. Pill count for compliance.
6. Adverse event recording.
7. Concomitant medication recording.

Transrectal ultrasound (TRUS) with assessment of prostate volume was assessed at baseline and at end-of-study.

A substudy was planned and carried out, in which approximately half of the participants would undergo TRUS with needle biopsies of the prostate, prior to treatment and at their end-of-study visit (or at Year 5). This was planned in order to assess prostate volume changes over time and "to obtain additional information regarding the histopathobiology of BPH". Patients in the TRUS substudy also underwent serum hormone testing at the times of their ultrasound procedures. According to the study report, 1082 patients participated in this substudy.

A urodynamics substudy was also added to the study in the third edition of the protocol (1/97) and was subsequently discontinued "due to lack of enrollment and feasibility" (10/97). According to the study report, 220 patients participated in the urodynamics substudy prior to its termination.

It should also be noted that preceding the full-scale trial, there was a "pilot study" conducted to assess the feasibility of the full-scale trial. For the pilot study, 141 patients were recruited over 12 months at six clinical sites and were followed for an average of 6 months.

> **Reviewer's comment**: Although the Division had no input into the protocol or SAP, the general design and procedures are acceptable. In terms of the endpoint: the elements of the novel composite endpoint, clinical BPH progression, were chosen because they were considered clinically reasonable to define progression of BPH. The sponsors anticipated that most events would be the confirmed ≥4-point rise in AUA symptom score. They hoped that the other events would serve as a "catch-all" in case the symptom score outcome was "missed" in a given patient. The inherent problem of such a composite endpoint is that some individual elements are of greater clinical significance than others, and the inclusion of some elements and the omission of others can be arbitrary. Furthermore, if one element drives the results of the composite, and it is of lesser (or different) clinical significance than all other elements, then the results of the composite itself may be misleading.

3.2. Eligibility criteria

There were 4 inclusion criteria and 23 exclusion criteria. The four inclusion criteria were:

1. Male at least 50 years of age.
2. Peak urine flow rate at least 4 mL/sec but no greater than 15 mL/sec, with voided volume at least 125mL.
3. AUA symptom score greater than or equal to 8, and no greater than 30.
4. Voluntary informed consent.

The 23 exclusion criteria are listed in Dr. Handelsman's primary medical officer's review and will not be reiterated here.

Reviewer's comments:

1. The eligibility criteria were generally appropriate for a BPH study.
2. It is notable that while prostate volume itself was not an entry criterion, the protocol called for post-randomization "modified recruitment" based upon periodic review of the prostate volumes measured by TRUS in the currently enrolled patients (after 500, 100 and 1500 patients). In brief, these recruitment procedures called for:

- Limitations on further recruitment of patients with prostate volume <20cc if the lower 99% CI on the proportion of the total number of patients with prostate volume <20cc was greater than 0.25, and
- Limitations on further recruitment of patients with prostate volume >50cc if the lower 99% CI on the proportion of the total number of patients with prostate volume >50cc was greater than 0.25, and
- Adding additional patients with prostate volumes >50cc if the lower 99% CI on the proportion of the total number of patients with prostate volume >50cc was less than 0.15.

To this reviewer, this study procedure acted to ensure that at least 15% of all enrolled patients would have a prostate volume >50cc, a fairly large gland. The reviewer has no objection to the procedure but this demographic would be appropriate in labeling.

3.3. Statistical considerations

In terms of statistical considerations, the third edition of the study protocol (dated 10/13/00) described the major components of the statistical plan as follows:

"*Primary endpoint.* Survival analysis techniques (Miller, 1981) such as Kaplan-Meier survival estimates, the logrank test, and the Cox proportional hazards model to adjust for baseline or time-dependent covariates will be used to compare the treatment groups with respect to time to clinical progression of BPH." And:

"Crossover to known invasive therapy prior to clinical progression of BPH may be considered a competing risk event (Lagakos, Kim and Robbins, 1990). To account for crossover to known invasive therapy as a competing risk event, the treatment groups will be compared on the composite event as clinical progression of BPH or crossover to known invasive therapy, whichever occurs first, using the same methods described above for the clinical endpoint." And:

"*Secondary endpoints.* Longitudinal data analysis techniques will be used to analyze repeated measures data (e.g. AUA symptom score, MOS-36 Health Survey score, and maximum uroflow). Data will be compared across treatment groups using the nonparametric procedures of Wei and Lachin (1984) for two-group comparisons."

Reviewer's comment: At least in the protocol version #3, the fundamental plan to analyze the primary endpoint does not provide extensive detail about between-group comparisons. For example, this reviewer has questions about the SAP, such as: Was the sponsor planning to adjust the significance level (alpha) used for the primary analysis for multiple comparisons? What were the primary comparisons of interest? For the primary, were only active treatment group versus placebo comparisons planned or were comparisons between active-treatment groups also planned? What statistical findings were pre-defined to constitute a "regulatory or scientific win" for the combination group? Was the analysis of secondary objectives built into the overall SAP? For the secondary endpoints, were only active treatment group versus placebo comparisons planned or were

comparisons between active-treatment groups also planned? The reader is referred again to the Biometrics review for details. Nevertheless, suffice to say here that the overall lack of specificity in the SAP section makes the regulatory and scientific evaluation of this protocol, in the context of the requested labeling, challenging.

Additional important information that may answer some of these questions was found in the "Sample Size Requirement" section of the protocol. For example:

"In the full-scale trial, a total number of 2,448 participants will be needed (612 per treatment group) in order to have 80% power to detect a one-third reduction in the time to clinical progression of BPH in *an* active drug group compared to the placebo group (alpha = 0.05, two sided). This figure *includes* a Bonferroni adjustment (Miller, 1981) to control the probability of a Type 1 error for three pairwise comparisons; i.e. each treatment group versus placebo."

In determining this sample size, the sponsors assumed that the rate of progression (as defined above) would be **25%** over five years ("hazard rate in the placebo group of 5.8 percent per year"). Sponsors also assumed that the randomization period would last 2 years and that there would be 4 to 6 years of follow-up per patient. The protocol also comments on the expected incidence rates for each component of the composite, as follows:

1. Information from the Olmstead County BPH trial ("personal communication – Dr. Michael M. Lieber") indicated that 13.5% of the cohort of men between 50 and 80 years of age with an initial AUA Symptom Score of 8 or more, and an initial maximum uroflow rate of 15mL/sec or less, had an increase of 4 or more in their AUA symptoms score within 3.5 years of follow-up; this equates to an exponential cumulative incidence over five years of **19 percent.**
2. The VA study and the alpha-blocker and finasteride studies have demonstrated a **one percent** probability of (urinary) retention per year in patients managed on placebo and watchful waiting. Likewise, the probability of the development of renal insufficiency, recurrent urinary tract infection, and urosepsis is estimated to be approximately **one percent** per year.
3. There was no estimate of the rates of incontinence.

Reviewer's comment: This section of the protocol is informative because it shows that in planning the trial, sponsors anticipated that the 4-point rise in AUA score would account for most of the "BPH progression" events. Given this acknowledgement, and the lack of statistical planning for between-group comparisons for each individual component of the composite, the reviewer is even more convinced that the "BPH progression" composite is actually a measurement of "progression of BPH symptoms" and not of the other endpoints in a meaningful way. Far more patients would have been required to draw conclusions about the other elements of the composite or for Category#2 (BPH-related surgery). Does this disqualify the primary endpoint and hence the results of the study? This reviewer believes not, reasoning as follows: If the results from the primary endpoint (the composite) are clear, and one clinically meaningful element of the composite is particularly compelling, and this element "pulls" the composite (e.g., the confirmed ≥4 point rise in AUA symptom score), and it can stand alone as a public health benefit, then the results from the composite and the "driving" element may still be appropriate for labeling.

3.4. Screening, Randomization, Discontinuations, Protocol Deviations

Randomization began into the pilot phase on December 1993 and ended on November 1994. For the full-scale phase, randomization began on December 1995 and ended November 1997.

Recruitment was extended through to March 1998. By the end of randomization on March 17, 1998, 17 clinical centers had randomized a total of 3,047 participants; 116 patients in the pilot phase and 2931 during the 28 months of the full-scale phase. Of these 3,047 participants, 737 were assigned to double-placebo, 756 to doxazosin, 768 to finasteride and 786 to the combination of doxazosin/finasteride.

Of the 2,931 "full-scale" participants, 22 (0.8%) were allowed to be randomized with an exception by the Randomization Committee. Sixty-four (64) patients (2%) were randomized despite not fulfilling all eligibility criteria. A total of 11% of all participants either died (N=77) or prematurely withdrew (N= 285) before reaching a pre-defined outcome Category. In terms of death and premature discontinuation, these are depicted in Table 1:

Table 1. Reasons for premature termination

	Placebo	Doxazosin	Finasteride	Combination
Patient decision	53	44	63	37
Intercurrent illness	4	6	9	6
Moved	11	14	19	16
Death	17	13	22	25
Other reason	1	0	1	1

Over the entire study duration, over all clinical sites, 75% of MTOPS participants were ≥85% compliant to coded doxazosin. These figures were similar or slightly higher for coded finasteride. For the dose of doxazosin, participants were initially titrated weekly from 1mg to 2mg to 4mg to 8mg (once daily at bedtime) but allowed to reduce the dose to 4mg if 8mg was not tolerated. Over the entire study, the percentage of participants who were on coded 4mg doxazosin was placebo=10%, finasteride alone =11%, doxazosin alone = 25%, combination =30%.

> **Reviewer's comment**: The reader should note that most patients in this study were on doxazosin 8mg and this dose selection has implications in the interpretation of safety results.

3.5. Patient Characteristics

The mean age at randomization was 62.6 years (±7.3). Eighty-two (82%) of patients were Caucasian. The mean height and weight were 69.7 inches (±2.9) and 192 pounds (±32). Co-morbid medical conditions were common; the most commonly reported being hypertension (28.6%), gastrointestinal disease (26.3%), skin disease (20.8%), heart disease (19.4%), lung disease (11%), diabetes mellitus (8.5%), renal disease (7.1%), and neoplastic disease (5.0%). In terms of physical examination, the most commonly reported abnormalities were of urogenital origin (13.1%), followed by skin (11.8%), eyes (11.4%), HEENT (9.4%), heart (7.9%), abdomen (7.4%) and neurological (4.9%). Mean systolic and diastolic blood pressure were 135 mmHg (±17) and 82 mmHg (±8), respectively.

The mean duration of BPH symptoms was 4.7 years (±4.6). Sixty percent of patients reported that their BPH symptoms were "stable" over the past year, while 38% said their symptoms were "worsened". The mean AUA Symptom score was 16.9 (±5.9), with mean irritative and obstructive subscores of 7.6 (±2.9) and 9.4 (±4.2), respectively. The mean maximum urinary flow rate was 10.5 mL/sec (±2.6) on a mean voided volume of 240mL (±102). The mean post-void residual urine volume was 68mL (±83 mL)

Of the total of 2927 patients in the full-scale phase, 15% had a prostate volume <20cc, 17% had a prostate volume >50cc, and 67% had a prostate volume between 20 and 50cc. Mean serum PSA was 2.4 (±2.1), with 59.3% of patients having serum PSA <2.0ng/mL, 21.2% having a serum PSA between 2.0ng/mL but <4.0ng/mL, and 19.5% having a serum PSA >4.0ng/mL. Screening PSA >10ng/mL was an exclusion criteria.

3.6. Efficacy Results

As previously noted, the primary endpoint was "time to clinical progression of BPH" as defined in the composite endpoint known as "Category #1" (acute urinary retention, renal insufficiency due to BPH, recurrent UTI or urosepsis, incontinence, or "confirmed" increase from baseline in the AUA symptom score index of 4 or more points).

Reviewer's comment: Again, in order to fully understand the challenges of interpreting and labeling these results, the reader should be aware of the following:

1) In planning this study, the sponsor anticipated that about 75%-80% of the "BPH progression" events would be the "confirmed 4 point rise in AUA score" outcome, yet the primary endpoint was still the composite "clinical progression of BPH".
2) The sponsors planned comparisons between placebo and each active group, but not between active treatment groups. Therefore, the study was designed to show superiority of the combination over placebo but not to show superiority of the combination over the individual components. To this reviewer, these later comparisons would seem to be crucial in regulatory decisions regarding approval of the new combination regimen.

3.6.1. Primary endpoint: Time to clinical progression of BPH

With 100% follow-up completed, a total of 351 primary outcome events were recorded (placebo=128, doxazosin=85, finasteride=89, combination=49). Of these 351 primary outcome events, 274 events (78%) were for symptom score rise, 41 events (12%) were for retention, 31 (9%) were for incontinence, and 5 events (1%) were for recurrent UTI/urosepsis. Table 2 below demonstrates the total number of each event observed in each of the four treatment groups:

Table 2. Counts and incidences of primary outcome events

Event	Placebo (n=737) N(%)	Doxazosin (n=756) N (%)	Finasteride (n=768) N (%)	Combination (n=786) N (%)	ALL (n=3047) N (%)
4-point AUA rise	100 (13.6)	59 (7.5%)	74 (9.6%)	41 (5.2%)	274 (9.0%)
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%)
UTI/urosepsis	2 (0.3%	2 (0.3%)	0 (0.0%)	1 (0.1%)	5 (0.2%)
Creatinine rise	0	0	0	0	0
Total	128 (17.4%)	85 (11.2%)	89 (11.6%)	49 (6.2%)	351 (11.5%)

As previously stated, simple counts or simple incidence rates were not the primary endpoint. However, when these "counts" were analyzed by adjusting for patient-years of treatment, the overall incidence rates per 100 patient-years for BPH progression (all 5 outcomes included) were 4.5, 2.7, 2.9 and 1.5 for the placebo, doxazosin, finasteride and combination groups, respectively.

For the 4-point rise outcome ONLY, the incidence rates per 100 patient-years were 3.6, 1.9, 2.5, and 1.3, for the placebo, doxazosin, finasteride and combination groups, respectively.

Finally, for the urinary retention outcome ONLY, the incidence rates per 100 patient-years were 0.6, 0.4, 0.2, and 0.1, for the placebo, doxazosin, finasteride and combination groups, respectively.

The pre-defined primary efficacy analysis called for the use of survival analysis techniques (described as Kaplan-Meier survival estimates, the logrank test, and the Cox proportional hazards model) to adjust for baseline or time-dependent covariates so as to compare the treatment groups with respect to time to clinical progression of BPH. The sample size justification section stated that the study was adequately powered to detect an overall reduction of 33% in any active treatment group as compared to placebo.

Therefore, using the log-rank test, an overall test demonstrated a difference between the four treatment groups (χ^2=49.4, df=3, p<0.0001). Using the log-rank test to compare each active treatment group to placebo, the test was considered significant if the p-value was less than 0.0157. Each active treatment group was found to be significantly better than placebo (a longer time to BPH clinical progression). These pairwise comparisons are as follows:

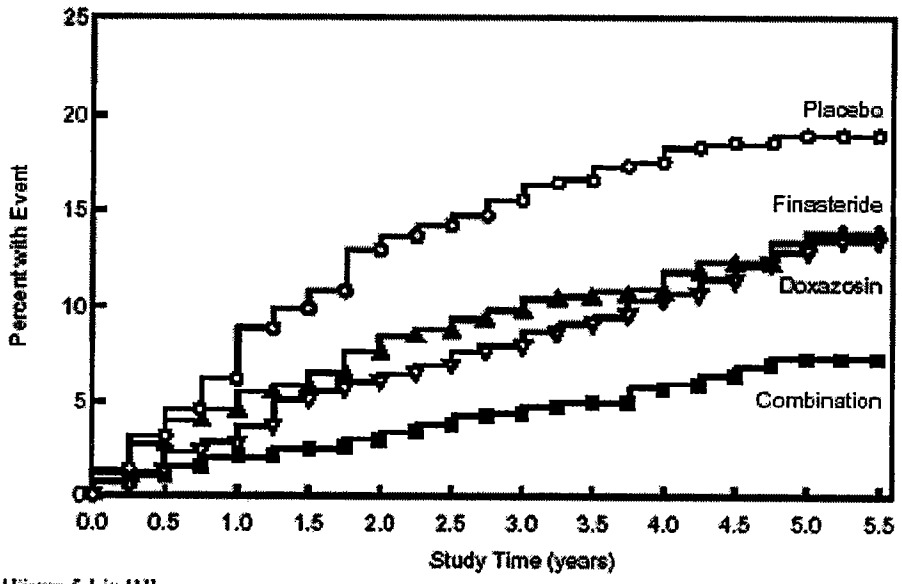
1. Doxazosin versus placebo - (χ^2=13.1, df=1, p=0.0002)
2. Finasteride versus placebo - (χ^2=9.7, df=1, p=0.0018)
3. Combination versus placebo - (χ^2=48.5, df=1, p<0.0001)

Using the Cox proportional hazards regression model to analyze the same data, the associated reductions in the risk of BPH progression (versus placebo) were 39% (95% CI = 20%, 54%) in the doxazosin group, 34% (95% CI = 14%, 50%) in the finasteride group, and 67% (95% CI = 54%, 76%) in the combination group.

Finally, figure 5-1 in the End-of-Study Report demonstrates the entire cumulative incidence distribution curves for each group (see Figure 1 below).

Figure 1

Cumulative Incidence of BPH Progression by Treatment Group



[Figure 5-1 in [1]]

Reviewer's comment: It is interesting to note that the majority of men are "BPH progression free" at the end of 4 years; specifically, placebo=83% free, doxazsoin=89% free, finasteride=89% free and combination=94%, free. The reviewer sees this as another important clinical reason not to overstate the efficacy of this combination treatment in the label; specifically, a large percentage (83%) of patients are "progression-free" after 4 years on double-placebo and even in the remaining 17%, most of the events described as BPH progression were progression of symptoms, not other sequalae.

Although the original SAP did not call for between group comparisons in the pre-defined SAP, the sponsor conducted these anyway for the primary endpoint. The report states: "The combination group *tends to* have a significantly longer time to BPH progression compared to the doxazosin and finasteride groups." For the log-rank test, combination versus doxazosin ($p=0.0004$) and combination versus finasteride ($p<0.0001$). For the proportional hazards model, combination versus doxazosin (risk reduction =46%) and combination versus finasteride (risk reduction=49%). There was no difference between finasteride and doxazosin using either test, and the curves in Figure 1 for finasteride and doxazosin virtually overlap.

3.6.2. Primary endpoint: 4-point rise in AUA symptoms score ONLY

On page 34 of the End-of-Study Report it is stated: "The MTOPS BPH progression outcome events were driven mostly by progression in symptom scores (≥4-point rise)." This element was then analyzed separately, followed by a separate analysis of the retention element.

Reviewer's comment: We agree with sponsor that the BPH progression outcome events were mostly driven by the symptom score element. We agree that separate analysis of this element is appropriate even though the reviewer finds no evidence that such an analysis was pre-defined in the original SAP. However, we find it important to analyze this primary outcome event separately because it drove the overall primary endpoint result and it has different clinical significance than the other outcomes in the composite (urinary retention, UTI, renal insufficiency or incontinence).

Therefore, the 4-point rise primary outcome event (given the name "Symptom Progression" in the End-of-Study Report) was analyzed by sponsor using the same methods as for the composite. Using the log-rank test, an overall test demonstrated a difference between the four treatment groups (χ^2=36.8, df=3, p<0.0001) for the 4-point rise endpoint. The pairwise comparisons of active treatment to placebo are as follows:

1. Doxazosin versus placebo - (χ^2=14.4, df=1, p=0.0001)
2. Finasteride versus placebo - (χ^2=5.8, df=1, p=0.0156)
3. Combination versus placebo - (χ^2=33.7, df=1, p<0.0001)

Reviewer's comment: Since this is an unplanned exploratory analysis, the p-value for significance is not clear. In fact, it is not clear how these particular p-values should be used in the context of regulatory decision-making. This reviewer concludes that it is probably best not to rely too heavily on the exact p-values in making regulatory decisions about these comparisons.

Using a Cox proportional hazards regression model to analyze the same data, the associated reductions in the risk of "symptomatic progression" (versus placebo) were 46% (95% CI = 25%, 60%) in the doxazosin group, 30% (95% CI = 6%, 48%) in the finasteride group, and 64% (95% CI = 48%, 75%) in the combination group.

Finally, figure 5-3 in the End-of-Study Report demonstrates a comparison between groups for the entire cumulative incidence distribution curves for the 4-point rise outcome event (see Figure 2 below).

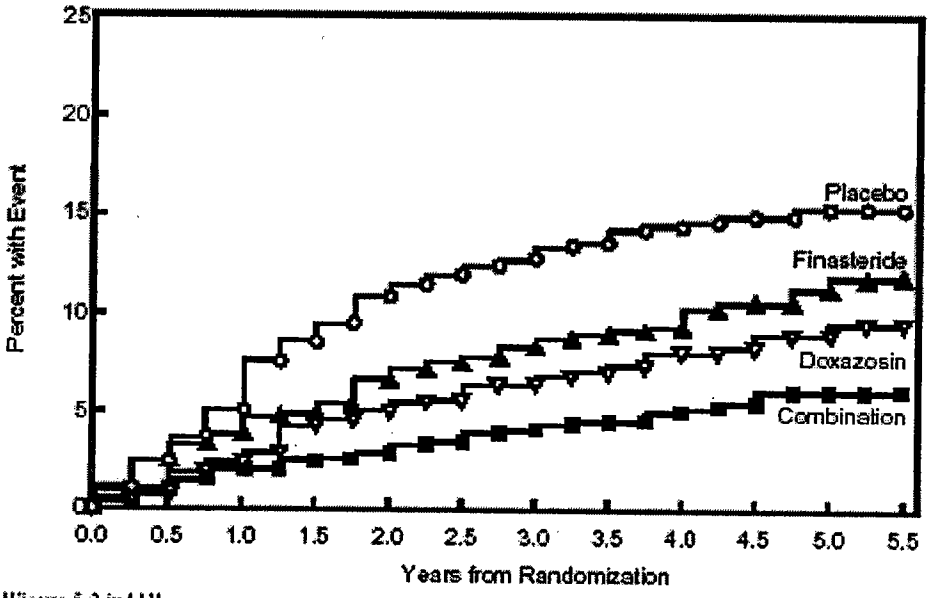
Again, although not originally planned, the sponsor conducted between active-treatment group comparisons for the 4-point rise outcome event. For the log-rank test, combination versus doxazosin (**p=0.0369**) and combination versus finasteride (p=0.0006). For the proportional hazards model, combination versus doxazosin (**risk reduction =34%; 95%CI= 2%, 55%**) and combination versus finasteride (risk reduction=48%; 95%CI=24%, 64%). In the comparison of monotherapies, (finasteride vs doxazosin), the log rank test yields a p-value of 0.1683 and the proportional hazards ratio method yields a risk reduction of –27% (95% CI=-79%, 9%).

Reviewer's comment: Thus, for the 4-point rise endpoint, the effect of doxazosin drives the benefit of the combination, but there is *at least some* additional benefit of the combination over doxazosin alone. This is seen in the comparison of combination to doxazosin alone where the proportional hazards model yields a reduction in risk of 34%, (95% CI 2% and 55%) and the comparison of combination to finasteride yields a reduction in risk of 48% (95%CI=24%, 64%). Thus, it can be stated with 95% confidence that the additional risk reduction for progression of symptoms offered by the combination over doxazosin alone is greater than zero and is substantially better than finasteride alone. This reviewer believes that 95% confidence intervals are acceptable for this comparison without adjustment since such is standard for testing a combination

therapy versus its individual components (personal communication: Biometrics Team Leader). Therefore, in my opinion, combination was shown to be better for preventing "progression of symptoms" than either component alone and both components were shown to be better than placebo. This is the fundamental reason that this reviewer can approve this supplement: the combination regimen offers a clinical benefit over either drug alone for reduction of risk of symptomatic progression.

Figure 2

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



[Figure 5-3 in [1]]

3.6.3. Primary endpoint: AUR outcome event ONLY

The sponsor presented a separate analysis of the AUR outcome event, the second most commonly reported event. In fact, symptom progression and AUR (together) accounted for over 90% of all reported outcome events.

Using the log-rank test, an overall test demonstrated a difference between the four treatment groups (χ^2=13.6, df=3, p=0.0034) for AUR endpoint. The pairwise comparisons of active treatment to placebo are as follows:

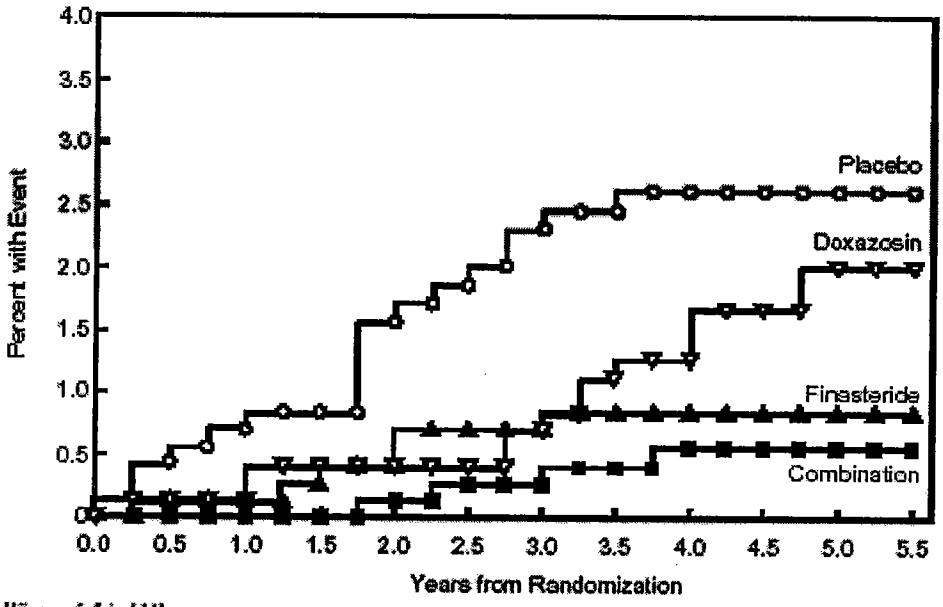
4. Doxazosin versus placebo - (χ^2=1.0, df=1, p=0.2963)
5. Finasteride versus placebo - (χ^2=6.3, df=1, p=0.0114)
6. Combination versus placebo - (χ^2=10.2, df=1, p<0.0013)

Using a Cox proportional hazards regression model to analyze the same data, the associated reductions in the risk of AUR (versus placebo) were 31% (95% CI = **-39%**, 66%) in the doxazosin group, 67% (95% CI = 18%, 87%) in the finasteride group, and 79% (95% CI = 40%, 93%) in the combination group.

Figure 5-3 in the End-of-Study Report demonstrates a comparison between groups for the entire cumulative incidence distribution curves for AUR (see Figure 3 below).

Figure 3

Cumulative Incidence of Acute Urinary Retention by Treatment Group



[Figure 5-5 in [1]]

Again, although not originally planned, the sponsor conducted between active-treatment group comparisons for the AUR event. For the log-rank test, combination versus doxazosin (p=0.0214) and combination versus finasteride (p=0.4644). For the proportional hazards model, combination versus doxazosin (risk reduction =70%; 95%CI= 10%, 90%) and combination versus finasteride (risk reduction=37%; 95%CI= **-120%**, 82%). In the comparison of monotherapies, (finasteride vs doxazosin), the log rank test yields a p-value of 0.1123 and the proportional hazards ratio method yields a risk reduction of 53% (95% CI=-22%, 82%).

The sponsor acknowledges that "Considering the small number of events observed in the active therapy groups, pairwise comparisons of these groups are less precise; the power to detect statistically significant difference are small".

Reviewer's comments: It is clear that finasteride drives the success of the combination therapy for the AUR endpoint. In fact, with these numbers of events, these data do not clearly support a contributing role of doxazosin in the combination therapy for AUR. Specifically, doxazosin-alone did not differentiate itself clearly from placebo (lower bound of the 95% CI for reduction in risk - doxazosin versus placebo = -39%) and combination did not differentiate itself clearly from finasteride (lower bound of the 95% CI for reduction in risk combination versus finasteride = -120%). This is likely a consequence of an insufficient sample size thereby yielding insufficient numbers of AUR events. On the other hand, there is a "hint" of potential benefit of the combination over the individual components. Nevertheless, since doxazosin was not clearly shown to contribute to the benefit of the combination for the AUR outcome, this reviewer cannot

definitively conclude that adding doxazosin to finasteride is necessary if the goal of therapy is only to reduce the risk of AUR.

3.6.4. Secondary endpoint: BPH-related invasive therapy

As previously discussed, the "cross-over" to an invasive therapy was Category #2 of the original patient classification schema and was not included in the primary endpoint composite (clinical progression of BPH). However, secondary analyses were conducted to analyze the difference between groups for Category #2 alone, and for *either* Category #1 (BPH clinical progression event) or Category #2 (cross-over to invasive therapy).

A total of 110 invasive therapy events for BPH were observed in MTOPS (placebo=40, doxazosin=41, finasteride=15, and combination=14). When these "counts" were analyzed by adjusting for patient-years of treatment, the overall incidence rates per 100 patient-years were 1.3, 1.3, 0.5 and 0.4 for the placebo, doxazosin, finasteride and combination groups, respectively.

The sponsor also analyzed this specific outcome using the same methods as for the analysis of the primary endpoint (including Kaplan-Meier survival estimates, the logrank test, and the Cox proportional hazards model). Using the log-rank test, an overall test demonstrated a difference between the four treatment groups (χ^2=27.2, df=3, p<0.0001). Using the log-rank test to compare each active treatment group to placebo, the pairwise comparisons are as follows:

1. Doxazosin versus placebo - (χ^2=0.0, df=1, p=0.8686)
2. Finasteride versus placebo - (χ^2=12.4, df=1, p=0.0004)
3. Combination versus placebo - (χ^2=14.6, df=1, p=0.0001)

Using the Cox proportional hazards regression model to analyze the same data, the associated reductions in the risk of BPH-related invasive therapy (versus placebo) were 3% (95% CI = -48%, 37%) in the doxazosin group, 64% (95% CI = 34%, 80%) in the finasteride group, and 67% (95% CI = 40%, 82%) in the combination group.

Finally, figure 6-1 in the End-of-Study Report demonstrates the entire cumulative incidence distribution curves for each group.

The sponsor again conducted between active-group comparisons for this secondary endpoint. The report states: "The risk of BPH invasive therapy in the finasteride group is not significantly different compared to combination therapy. The risk of BPH invasive therapy in the doxazosin group is significantly higher than finasteride and combination groups (p<0.001). The increased risk starts at year 3, causing the doxazosin group cumulative incidence of BPH invasive therapy to approach and exceed the placebo group BPH invasive therapy cumulative incidence at year 5."

For the log-rank test, combination versus doxazosin (p=0.0001) and combination versus finasteride (p=0.7731). For the proportional hazards model, combination versus doxazosin risk reduction was 67% (95% CI, 39%, 82%) and combination versus finasteride was 10% (95% CI, -86%, 56%). The cumulative incidence figure (Figure 6-1) reveals that the curves for combination and finasteride virtually overlap and the curve for doxazosin actually re-meets the placebo curve at year 5.

Reviewer's comment: In terms of reduction of risk of BPH invasive therapy, a contribution of doxazosin to the reduction in risk offered by the combination therapy was not demonstrated. The combination does not differentiate itself from finasteride and doxazosin does not differentiate itself from placebo.

3.6.6. Secondary endpoint: Change from baseline in AUA Symptom Score

The AUA Symptom Questionnaire was administered at Screening and at all quarterly follow-up visits. The AUA symptom score is the total of seven (7) items related to symptoms with each item response ranging from 0 to 5. The maximum total AUA symptom score is 35, reflecting the worst symptoms.

The End-of-Study report states: "Over the 69 months of follow-up, AUA symptoms scores were different across treatment groups. Compared to placebo, (all) active therapy groups have lower AUA symptom scores over time. Dual-therapy group has lower AUA symptom scores over time compared to each active monotherapy. Doxazosin therapy group has lower AUA symptom score over time compared to finasteride."

Reviewer's comment: The reviewer referred to Tables 6-13 and 6-14 of the End-of-Study Report where data is presented for total AUA symptom score. In these two tables, data for each treatment groups is presented at specific timepoints (at Year 1, at Year 2, at Year 3, etc) and is analyzed using the pre-defined Wai-Lachin test. The sponsor describes this test as a "longitudinal analysis method to assess the change from baseline over time"(annotated comment in sponsor's labeling proposal of April 8th). The reviewer also referred to pages 24-27 of the Clinical Summary where the data was presented in Table 6 as group mean changes-from-baseline. Finally, the reviewer also referred to the Biometrics reviewer's eMAIL communication of April 11, wherein additional analysis were conducted (an "Observed Cases at Year 4" analysis intended to validate Tables 6-13 and 6-14, and a traditional last observation carried forward [LOCF] to Year 4 analysis).

In validating the results of Tables 6-13 and 6-14 and the data in Reference 37 from the supplement, our Biometrics reviewer provided the following table (Table 3 below):

Table 3. Change-from-baseline in mean AUA symptoms score (Observed Cases at Year 4)

	Placebo N=534	Doxazosin N=582	Finasteride N=565	Combination N=598
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		-1.8 (-2.5, -1.1)	-0.7 (-1.4, -0.0)	-2.5 (-3.2, -1.8)
Comparison to Doxazosin-alone				-0.7 (-1.4, -0.0)
Comparison to Finasteride-alone				-1.8 (-2.5, -1.1)

Notes: Negative values for the comparisons represent a better reduction in AUA symptom score.
SOURCE: SAS datasets submitted November 11, 2003.

In conducting a traditional LOCF analysis of the same dataset, our Biometrics reviewer provided the following table (Table 4 below):

Table 4. Change-from-baseline in mean AUA symptom score (LOCF) to Year 4

	Placebo N=728	Doxazosin N=746	Finasteride N=755	Combination N=772
Mean Change AUA Symptom Score (SD)	-4.9 (6.1)	-6.4 (6.2)	-5.4 (5.9)	-7.1 (6.3)
Comparison to Placebo		-1.5 (-2.2, -0.9)	-0.5 (-1.1, +0.1)	-2.2 (-2.8, -1.6)
Comparison to Doxazosin-alone				-0.7 (-1.3, -0.0)
Comparison to Finasteride-alone				-1.7 (-2.3, -1.1)

Notes: Negative values for the comparisons represent a better reduction in AUA symptom score.
SOURCE: SAS datasets submitted November 11, 2003.

According to sponsor, the Wei-Lachin test of stochastic ordering was employed to make between group comparisons of the secondary endpoints, including total AUA symptom score. According to sponsor, this test assesses whether one treatment group had a consistently higher or lower change from baseline in the index measurement over time compared with another treatment group. According to sponsor, the results of this analysis show that all active treatment groups had a consistently greater reduction over time in total AUA symptom score than placebo. Further, the combination group had a consistently greater reduction over time compared to the doxazosin and finasteride monotherapy groups. P-values were provided for these comparisons in Table 7 of the Clinical Summary.

Reviewer's comments:

1. The presentation and analysis of symptom score data is consistent between the "Observed Cases at Year 4" analysis that was conducted by our Biometrics reviewer and the analysis presented in Reference 37 of the End-of-Study-Report by sponsor ("Analysis of change-from-baseline: wei-lachin test of stochastic ordering: AUA symptom score").
2. However, the data presented by Biometrics in its LOCF analysis and that the data presented by sponsor in Table 6 of their Clinical Summary differ slightly.

Table 6 of the Clinical Summary shows the mean AUA symptom scores for each group at baseline and the mean changes-from-baseline for each group. At baseline, the group mean (±SD) AUA symptom scores were 16.8 (±6.0), 17.0 (±5.9), 17.1 (±6.0), and 16.8 (±5.8), for the placebo, doxazosin, finasteride and combination groups, respectively. According to Table 6, the mean changes from baseline (±SD) were -5.0 (± 5.9), -6.2 (±6.3), -6.0 (± 6.3) and –7.2 (±6.6), for the placebo, doxazosin, finasteride and combination groups, respectively.

According to sponsor's text describing Table 6 (found on page 24 of Clinical Summary), "all three active-treatment groups showed improvements from baseline in the overall AUA symptom score". The listed p-values in Table 6 for the comparisons between placebo and doxazosin, finasteride and combination are $p<0.001$, $p=0.002$ and $p<0.001$, respectively. For active-treatment comparisons, the following are as follows:

For combination versus doxazosin, $p=0.002$
For combination versus finasteride, $p<0.001$
For finasteride versus doxazosin, $p=0.536$.

Reviewer's comments:

1. In the reviewer's opinion, reduction in symptom score is a clinically important secondary endpoint. It is a routine method used in clinical trials and clinical practice to follow patients' BPH status. Presentation of the data for this endpoint in this label is justified on a clinical basis.
2. Overall, the data and analysis for this endpoint appears to show that both treatments are better than placebo, and combination is better than either treatment. Such a conclusion is very clinically relevant and this reviewer recommends that data for this endpoint should appear in labeling.
3. Of the available data and analyses, the sponsor's repeated measures analysis at Year 4 and the Division's "Observed Cases at Year 4" are consistent. Therefore, I'd advise inserting Table 3 of this review in the label, which includes the mean-changes from baseline, comparisons between groups, and associated 95% confidence intervals.
4. [redacted]

3.7. Safety Results

In MTOPS, safety was assessed by physical examination (including rectal exam), safety laboratories (including hematology, chemistry, serum PSA and urinalysis), recording of clinical adverse experiences, and a questionnaire for sexual function. In a subgroup study, serum hormones were monitored and prostate biopsies were taken.

The most important evidence of safety for the proposed combination regimen comes from the collection of clinical adverse experiences. The End-of-Study report presents the adverse experience information adjusted for 100 patient-years. Merck transposed this to percent incidence; calculated by dividing the number of patients with a specific adverse event in each treatment group by the number of patients in that treatment group. Tables were also presented for serious adverse events, adverse events resulting in study discontinuation, and drug-related adverse events. Drug-related adverse effects were those determined by the investigator to be possibly or probably related to study drug.

> **Reviewer's comments**: Based upon the large number of patients in this trial, the prolonged duration of exposure (4 years or more), the high rate of co-morbid conditions in this middle-aged male population, and the well-known safety profiles for both individual drugs alone, this team leader focused on drug-related AEs, SAEs, and AEs of special interest only.

A total of 1816 (59.6%) of patients experienced one or more drug-related adverse experiences including 342 (46.4%) in the placebo, 491 (64.9%) in the doxazosin group, 403 (52.2%) in the finasteride group, and 580 (73.8%) in the combination groups. Table 5 below provides the percent incidences of all drug-related adverse expereinces reported by at least 2.0% of any treatment group.

Table 5 demonstrates that there are no fundamentally new clinical adverse events reported for the combination compared to either drug alone. Further, the safety profiles for each individual drug were consistent with their known safety profiles. Drug-related incidences of asthenia, dizziness, and postural hypotension were highest in the doxazosin and combination group as anticipated.

Impotence, decreased libido, and abnormal ejaculation were highest in the finasteride and combination groups, as anticipated.

Table 5. Drug-Related Clinical Adverse Experiences in MTOPS Incidence ≥ 2% in One or More Treatment Groups

Adverse Experience		Placebo (N=737) (%)	Doxazosin 4mg or 8mg* (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

**Final doxazosin was achieved by weekly titration from 1mg to 2mg to 4mg to 8mg. Only patients tolerating at least 4mg were kept on doxazosin in the study. Final doxazosin dose was administered once per day at bedtime beginning at end-Week 4. At any given time in the trial, the majority of patients were on the 8mg dose level.*

Drug-related experiences reported at higher incidence in the combination group compared to either group alone included: asthenia, postural hypotension, peripheral edema, dizziness, decreased libido, rhinitis, abnormal ejaculation, impotence and abnormal sexual function (see Table 4). Of these, the incidence of *abnormal ejaculation* was the only term reported in the combination therapy group where the percent incidence was comparable to the sum of the incidences of this adverse experience reported for the two monotherapies.

> **Reviewer's comment**: It is notable that the incidence of adverse events was fairly high in the placebo group. In assessing these safety results, the reader is cautioned that 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.

The incidence of serious adverse events was similar across treatments. Sponsor believes that small difference between groups for the incidences of myocardial infarction (lower in the

doxazosin and combination groups compared to the finasteride and placebo groups) was not clinically meaningful as the incidences for "coronary occlusion" and coronary artery disease" were similar between groups. Prostate carcinoma was lowest in the finasteride-alone arm. The incidences of serious "drug-related" adverse events was small (0.7% to 1.6% in any given treatment group) and similar between groups in terms of incidence and type of AE. No death was considered to be drug-related. One hundred twenty-seven deaths were reported as follows: 31 (4.2%) placebo; 22 (2.9%) doxazosin; 38 (4.9%) finasteride and 36 patients (4.6%) combination.

In terms of specific adverse events of particular interest, the incidences of "sexual-related", "breast-related", "orthostasis-related", and "CNS-related" clinical adverse experience deserve special mention. These are discussed herein:

Sexual-related
The incidences of impotence, decreased libido and abnormal ejaculation (both all-causality and drug-related) were highest in the first year of treatment and decreased after Year 1. The cumulative incidence of abnormal ejaculation in the combination group probably reflects an effect on ejaculation by two different mechanisms (alpha-blockade and diminished ejaculate volume) or a potentiation of one of those drug-related mechanisms.

Breast-related
Four patients in MTOPS reported the adverse experience - breast carcinoma. Three of these patients were on finasteride-only and one was on combination therapy. It is notable that in PLESS, the incidence of breast cancer was two in placebo and none on finasteride. Finally, the current count for breast cancer cases from the 19,000-patient, seven-year, Prostate Cancer Prevention Trial (PCPT) is one patient on placebo and one on active drug.

> **Reviewer's comment**: Cases of breast cancer in MTOPS and issues surrounding these cases were reviewed in great detail by the Division last year and documentation of these discussions and reviews have already been completed and archived. New labeling is already in place to describe these events. Suffice to say here that the presently available data does not allow one to draw a causal link between therapy with finasteride and the development of male breast cancer, although continued post-marketing and clinical sudy monitoring is appropriate. In addition, patients on finasteride should be encouraged to promptly report any breast tenderness, pain, enlargement, growths, nipple discharge, or lesions to their physician.

In terms of gynecomastia or breast enlargement, the drug-related incidences are described in Table 5 above. For all-causality reports the overall incidences are 0.8% for placebo, 1.2% for doxazosin, 2.5% for finasteride and 2.0% for combination. For breast pain, the corresponding overall incidences are 0.1%, 0.7%, 1.4% and 1.8% for the placebo, doxazosin, finasteride and combination groups, respectively. There was one case of "mastitis" in the combination group. There was six additional cases of benign breast lesions – one each in placebo, finasteride and doxazosin and three in the combination group.

Orthostasis-related
Postural hypotension and hypotension are known to be related to treatment with alpha-blockers. In MTOPS, the following were of note:

1. The cumulative incidence of hypotension in the placebo group was fairly high (8.0%).
2. Most patients were taking the highest recommended dose of doxazosin or its placebo (8mg)
3. For unclear reasons, the incidence of postural hypotension was slightly higher in the finasteride group than in placebo group and the incidence was highest in the combination

group. These small differences in postural hypotension probably do not reflect an effect of finasteride itself or an unexplained combination effect, as such an adverse experiences have not been reported in numerous, large, placebo-controlled clinical trials of finasteride.

CNS-related
The incidences of drug-related asthenia, dizziness and somnolence are reported in Table 5. The major issue of note is the incidence rates of dizziness and asthenia in the doxazosin-alone group, likely a consequence of the use of the higher daily dosage strengths (4mg or 8mg). Also of note is the higher incidence of drug-related dizziness in the combination group compared to doxazosin-alone, implying a possible role of finasteride. Since this has never been reported for finasteride in numerous large, controlled trials, the reviewer considers it more likely, though, that this difference is a matter of chance and not of clinical importance.

4. Relevant information from other disciplines

4.1 Office of Clinical Pharmacology and Biopharmaceutics
In an eMAIL to the review team dated August 19, 2003, Dr. Jarugula, the Clinical Pharmacology reviewer stated:

> "For biopharm, no data are submitted since both drugs are approved and no issues were identified also. I am not writing any memo at this point."

During the course of the review, additional discussions were held with the Clinical Pharmacology team leader (Dr. Parekh) and replacement Clinical Pharmacology primary reviewer (Dr. Chatterjee). The Clinical Pharmacology team re-iterated that a formal memo was not considered necessary since there were no clinical pharmacology or pharmacokinetic issues and no pharmacokinetic interaction between the two drugs in the proposed combination regimen.

4.2 Office of Biometrics

In the Executive Summary from her final (draft) review dated April 7th, Ms.. Meaker made the following summary statements:

1. "The results of that clinical trial (MTOPS) show that finasteride, in combination with the alpha-blocker doxazosin, provides additional benefit over long-term use in terms of symptoms, but not in terms of reduction of risk of acute urinary retention (AUR) versus finasteride alone."
2. "As proposed, the sponsor's wording of the (original) indication implies more than can be supported by the MTOPS trial results. The results of the MTOPS trial support the combination product for the symptoms part of the indication, [redacted] Different wording is needed in order to add a reference about the combination product to the indication statement which accurately reflects the trial results."
3. "As proposed by sponsor, most of the information regarding the MTOPS trial in this section (Clinical Studies) would not be appropriate for label or claims. This section will need to be reworded to accurately represent the MTOPS results."

Reviewer's comment: I am in general agreement with Ms. Meaker on the larger issues. At this point in labeling negotiations, I believe that all of Ms. Meaker's concerns have been addressed through revisions to the Indications and Clinical Studies sections. In an eMAIL to Ms. Mercier on April 12th, Ms. Meaker agreed to the final negotiated label.

The Biometrics (final draft) review contains commentary in one area where there is a subtle but important difference between Ms. Meaker's view and the view of others. Ms. Meaker believes that that the combination therapy group was shown to be superior only to the finasteride-alone group for the confirmed ≥4 –point rise in AUA score part of the composite. She states that combination therapy was not shown to be statistically superior to doxazosin-alone.

In this TL's memo, I have documented that combination was superior to *both* treatment groups alone for this endpoint. For example, using the log-rank test, for this specific endpoint, combination versus doxazosin yielded **p=0.0369** and combination versus finasteride yielded p=0.0006. For the proportional hazards model, the risk reduction of combination versus doxazosin was **34% (95%CI= 2%, 55%)** and versus finasteride was 48% (95%CI=24%, 64%). Thus, it can be stated with 95% confidence that the additional risk reduction for progression of symptoms offered by the combination over doxazosin alone is greater than zero and is substantially better than finasteride alone. Standard 95% confidence intervals (and a standard p-value <0.05) are acceptable for this comparison without adjustment since such testing is acceptable to the Agency when testing a combination therapy versus its individual components (personal communication: Biometrics Team Leader). Therefore, this team leader believes that the combination is *both* clinically and statistically superior to either component alone for the 4-point rise endpoint.

Finally, throughout this review, Ms. Meaker has cautioned against the inclusion of exploratory analyses, including those for secondary endpoints. These comments and cautions were considered carefully during the labeling negotiation process. Only those endpoints and analyses supported by substantial evidence were presented in the label and in general, p-values for secondary endpoints were avoided.

4.3 Division of Drug Marketing, Advertising and Consultation (DDMAC)

In her final review dated March 8, 2004, Corinne Kulick provided several comments about the original proposed PI. The clinical and Biometrics review teams evaluated these comments and instituted changes to the labeling as deemed appropriate. During labeling negotiations with sponsor, Ms. Kulick's comments were fully addressed to the satisfaction of this team leader. For example:

1. *Provide the average age of the patients in MTOPS.* – Demographics were added.

2. *Provide the baseline AUA symptom score.* – The baseline AUA symptoms score was added along with other relevant baseline BPH signs and symptoms (including prostate volume, duration of symptoms, maximum urinary flow rate).

3. *Present the data for the primary endpoint in a table format to include the actual number of events and incidence for the primary endpoint (the composite) and each component of the composite for all four treatment arms.* – Such a table was inserted.

4. *If the relative risk reduction of the primary endpoint (the composite) is included, DDMAC recommends inclusion of the relative risk reduction of each element of the composite only if there is substantial evidence to support stand alone risk reduction claims for each component.* – This advice was heeded and relative risk reductions appear only for the primary and the ≥4-point rise element.

5. *Include a statement that acknowledges that the primary endpoint- time from randomization to clinical progression of BPH- was driven by a ≥4-point confirmed increase from baseline in symptom score.* – Such a sentence was added.

6. [redacted]

7. *Include only those secondary endpoints supported by substantial evidence* – This advice was heeded. The only secondary endpoints included were: reduction in total AUA symptom score (across treatments) and BPH-related invasive therapy and AUR (for the finasteride arm ONLY). There was substantial evidence for labeling of these endpoints.

8. *Avoid redundancy between sections* – This was accomplished.

9. *Remove vague sentences in the Adverse Reactions section such as* [redacted] *Add context for these statements.* – This advise was heeded and a table of incidences was added.

10. *Replace text related to breast cancer in the "Long-Term Treatment" subsection.* – This text was replaced by sponsor in a later version of this label; and was in fact, never actually removed.

4.4 Office of Drug Safety (ODS)/Division of Surveillance, Research and Communication Support (DSRCS)

In their final review dated March 2, 2004, Ms. Best and Piazza-Hepp, provided comments and proposed revisions to the patient package insert. These included re-formatting the entire document to make it consistent with the current Medication Guide question and answer-type format (21 CFR 208) and a general comment that most PPIs are often not dispensed with each prescription.

The sponsor proposed a single sentence addition to the PPI as follows:

[redacted]

At this time, the Division did not pursue re-formatting the PPI but do acknowledge that such could be undertaken in the context of near-future labeling supplements.

The new sentence proposed by sponsor was modified to remove the [redacted] verbiage and was replaced with more acceptable language ("to help better manage your BPH").

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
4/12/04 01:14:35 PM
MEDICAL OFFICER

Daniel A. Shames
4/12/04 01:46:52 PM
MEDICAL OFFICER

NDA 20-180 (S-026)

Drug Product: Proscar (finasteride)
Sponsor: Merck Research Laboratories (MRL)
Date Submitted: June 12, 2003
Memo Completed: August 25, 2003

Medical Officer's NDA Filing Review Memo

I. Summary:

Objective:

The review is conducted to fulfill a regulatory requirement of reviewing a NDA to determine its suitability for filing under 21 CFR 314.101. This document will also serve as the basis for communicating to sponsor the potential review issues identified during this initial filing review period as required by CDER manual of policies and procedure (MaPP 6010.x)

Conclusion:

After the preliminary review of the clinical section of NDA 20-180, supplement 026, this reviewer has not identified any deficiencies that would constitute the basis for a Refuse-to-File action as described in the FDA guidance 21 CFR 314.101(d) (3).

It is the impression of this reviewer that the application submitted is sufficiently complete to permit a substantive clinical review.

II. NDA Filing Review:

Drug Product:

Finasteride is an inhibitor of Type II 5 alpha reductase, an intracellular enzyme that converts the androgen testosterone into 5 alpha dihydrotestosterone (DHT) in the prostate gland, liver and skin. The development and enlargement of prostate gland is dependent on DHT, which induces androgenic effects by binding to androgen receptors in the cell nuclei of these organs.

The mean terminal half-life of finasteride is 6-8 hours. The bioavailability is 63% (range 34-108%), and is not affected by food. The mean steady-state volume of distribution is 76 liters. Approximately 90% of circulating finasteride is bound to plasma protein.

Finasteride has been shown to cross the blood brain barrier (BBB) but does not appear to distribute through CSF.

Finasteride is metabolized by the liver, via CYP450 enzymes.
It is excreted in the urine and in feces and the mean elimination half-life in plasma is 6 hours.
An NDA for finasteride 5-mg (Proscar) for the treatment of symptomatic BPH was approved by the Agency in 1992.

The other 5-alpha reductase inhibitor approved for this indication in the US is dutasteride

Method of RTF Review:
The review is based on the three criteria proposed in FDA guidance for the filing review, which represents FDA's interpretation of 21 CFR 314.101 (d)(3):

- Omission of a section of the NDA required under 21 CFR 314.50, or presentation of a section in an incomplete manner
- Failure to include evidence of effectiveness compatible with the statue and Regulations
- Omission of critical data, information or analyses needed to evaluate effectiveness and safety or failure to provide adequate directions for use.

Filing Review Results:

1. **Does the NDA omit a section required under CFR 314.50, or was the section of the NDA presented in such a manner as to render it incomplete for the clinical review?**
   Answer: No.
   The NDA contains the critical sections in a sufficient detail as demonstrated in Table 1. Certification is provided for all the investigators involved in the MTOPS study # MK-0906, the pivotal study required by the Division to support the proposed indication.

Table .1. Checklist for the critical sections of NDA for a sufficient clinical review:

Required Sections (21 CFR 314.50)	**Location (Table of Contents)**
The proposed text of the labeling (c)(2)(I)	2
A summary of the data (c)(2)(viii)	3
The technical sections and integrated summaries (d)	
Controlled clinical studies (d)(5)(ii)	8
Integrated summary of efficacy (d)(5)(ii)	8.4.4
Integrated summary of safety (d) (5) (vi)	8.4.5
Integrated summary of the benefits and risks (d)(5) (viii)	8.6
Required case report forms and tabulations (f)	11 and 12
Financial certification or disclosure statement (k)	19

2. **Does the NDA clearly fail to include evidence of effectiveness compatible with the statute and regulations, for example:**
   a. **lack of any adequate and well-controlled studies, including use of obviously inappropriate or clinically irrelevant study endpoints**
   b. **presentation or what appears to be only a single adequate and well controlled trial without adequate explanation**
   c. **Use of a study design clearly inappropriate**

   Answer: No.
   The sponsor has provided data from one large multi-center, randomized, double-blind, placebo-controlled study conducted in the US to support the proposed indication and dosage (5-mg for finasteride and 1-8mg for doxazosin).
   The study appears to be adequate and well controlled.

   The primary endpoint used in this study was:
   Time to clinical progression of BPH, as ascertained by the first occurrence of any of the following events:

   1. Greater than 4 point rise in baseline AUA Symptom Score (confirmed by repeat score 2 to 4 weeks after first rise)
   2. Acute urinary retention
   3. Urinary incontinence
   4. Recurrent UTI/Urosepsis
   5. Renal Insufficiency due to BPH

Reviewer's Comment:
No prior agreements were made with the Division in regard to this endpoint. It is novel. We will assess the scientific and clinical support for this endpoint during this review process.
The analysis of the primary end point appears to be well-designed and comprehensive. The combination drug group (5mg finasteride plus titrated doxazosin 1mg to 8mg) appears superior to either group alone and to placebo.

3. **Does the NDA omit critical data, information or analyses needed to evaluate effectiveness and safety or provide adequate directions for use, for example:**
   a. **total patient exposure at relevant doses that is clearly inadequate to evaluate safety**
   b. **clearly inadequate evaluation for safety and/or effectiveness of the population intended to use the drug, including pertinent subsets, such as gender, age and racial subsets:**
   c. **absence of a comprehensive analysis of safety data**
   d. **absence of an analysis of data supporting the proposed dose and dose interval.**

Answer: **No.**
The patients enrolled in this clinical study met the following eligibility criteria for benign prostatic hyperplasia (BPH) (among other criteria):

1. Men at least 50 years of age
2. Peak urinary flow rate (Q_{max}) 4-15ml/sec, voided volume of >125ml.
3. American Urological Association (AUA) symptom severity score 8-30.

The NDA contains 3047 subjects who were exposed to the study medications for an average time of 5 years in a controlled trial. The summary of clinical safety data appears to be presented adequately in the ISS.

Reviewer's Comments:
1.The eligibility criteria and demographics appear appropriate for the target population. In this pivotal study, the patients were males at least 50 years of age (mean age 62 years) which is consistent with the disease distribution in the general population. The percentage of non-white population is similar to that in general population.

2.The preliminary safety data does not appear to suggest that the study drugs are associated with cardiac, renal or liver toxicity. However, the percentage of patients, who had syncope was higher in the combination group compared to the finasteride or doxazosin groups alone and to placebo.

3.This reviewer also notes a slightly higher percentage of patients reporting asthenia, postural hypotension, dizziness, abnormal ejaculation and impotence in patients on combination of finasteride and doxazosin (see Table-1 below). Importance of these findings is a review issue.

4.Additional details relevant to the study design, efficacy and safety results are described in the brief summary of the MTOPS trial that follows in section III.

Table: 1. Incidences of Specific Drug-Related Adverse Events

Adverse Events	Placebo (N=737) N (%)	Doxazosin (N=756) N (%)	Finasteride (N=768) N (%)	Combination (N=786) N (%)
Asthenia	52 (7.1)	119 (15.7)	41 (5.3)	132 (16.8)
Postural Hypotension	59 (8.0)	126 (16.7)	70 (9.1)	140 (17.8)
Dizziness	60 (8.1)	134 (17.7)	57 (7.4)	182 (23.2)
Abnormal Ejaculation	17 (2.3)	34 (4.5)	55 (7.2)	111 (14.1)
Impotence	90 (12.2)	109 (14.4)	142 (18.5)	178 (22.6)
Syncope	11 (1.5)	15 (2.0)	16 (2.1)	22 (2.8)

III. Brief Summary:
The MTOPS trial - Medical Therapy of Prostatic Symptoms

Sponsor
Merck Research Labs. (MRL)

Investigator
National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK) of NIH/with statistical supervision from GWU

Purpose of Study
To evaluate the efficacy and safety of finasteride (Type II 5alpha reductase inhibitor) and doxazosin (alpha-blocker) alone or in combination in the treatment of BPH.

Primary End Point
Reduction in time to clinical progression of BPH as defined by occurrence of greater than 4 point rise in AUA symptom score and acute urinary retention

Reviewer's Comments
1. Sponsor must support 4-point rise in AUA symptom score as reflection of progression of BPH.
2. Sponsor should justify the selection of five criteria in the composite end point called BPH progression.

Design
Multi-center, randomized, double blind, placebo-controlled study in men with BPH.

Treatment Groups
Placebo 737
Doxazosin 756
Finasteride 768
Combination (doxazosin+finasteride) 786
Total 3047

Dose
Doxazosin 1-8mg PO, QD (titrated)
Finasteride 5 mg PO, QD

Duration of Study
4-6 years (average 5 years)

Follow up during the study
Quarterly

NDA 20-180 (S-026)

Population

A total of 4394 men were screened, 1347 excluded and remaining 3047 patients were randomized across 18 clinical sites in the US
116 in the pilot study (P27, D28, F29, C32)
2931 in the main study (P710, D728, F739, C754)

Reviewer's Comment

The sponsor should explain the impact of the pilot group on overall results of the study, and if at all they should have been excluded. Also, was there an alpha spend for this test.

Criteria for inclusion

Men at least 50 years of age (mean age 63years) with BPH,
Peak urinary flow (Q_{max}) 4-15ml/sec (mean Q_{max} 10.5+/-2.6ml/sec),
Voided volume >125 ml
American Urology Association (AUA) symptom score 8-30.
Prostate volume by transrectal U/S to be <20 cm^3 in no more than 25% of patients and > 50cm^3 in no more than 25% of patients
Mean gland volume 36.3+/- 20.1
Mean serum PSA 2.4+/-2.1
Mean post-void residual volume 68.1+/-82.9ml.
Race: W 82%, B 8.9%, H 7.3%, A1.3%

Safety

Treatment emergent adverse events were collected at each quarterly visit, entered on case report forms, and detailed on the adverse event forms.

A total of 1816 (59%) patients experienced one or more adverse events considered drug related. Placebo 342 (46%), Doxazosin 491 (64.9%), Finasteride 403 (52%) and Combination 580 (73.8%). The incidences of drug-related adverse events were highest in the combination therapy.

Table 1: Patients with Selective Drug Related Adverse Events

Adverse Events	Placebo (N=737) N (%)	Doxazosin (N=756) N (%)	Finasteride (N=768) N (%)	Combination (N=786) N (%)
Asthenia	52 (7.1)	119 (15.7)	41 (5.3)	132 (16.8)
Postural Hypotension	59 (8.0)	126 (16.7)	70 (9.1)	140 (17.8)
Dizziness	60 (8.1)	134 (17.7)	57 (7.4)	182 (23.2)
Abnormal Ejaculation	17 (2.3)	34 (4.5)	55 (7.2)	111 (14.1)
Impotence	90 (12.2)	109 (14.4)	142 (18.5)	178 (22.6)
Syncope	11 (1.5)	15 (2.0)	16 (2.1)	22 (2.8)

A total of 1187 (39%) patients reported serious adverse events (SAE) as follows.
P 286 (38.8%), D297 (39.3%), F 296 (38.5%), C 308 (39.2%)

Serious adverse events occurred most frequently in cardiovascular, urogenital, body as a whole and digestive body systems.

Disease specific serious adverse events
(where P=Placebo, D=Doxazosin, F=Finasteride and C=Combination)

1. Prostate cancer P (8.5%), D (7.4%), F (5.3%), C (8.0%)
2. Bladder Cancer P 2, D7, F 4, C 7 (Individual Patients)
3. Breast Cancer P 0, D0, F 3, C 1 (Individual Patients)
4. Myocardial Infarction P (3.0%), D (1.9%), F (3.4%), C (1.9%)
5. Coronary occlusion P (2.2%), D (1.9%), F (2.7%), C (2.0%)

Deaths
Total of 133 patients died in this study
127 died prior to 11/01 P 31 (4.2%)
D 22 (2.9%)
F 38 (4.9%)
C 36 (4.6%)

6 patients died after 11/01 P 1, D 1, F 3, C 1
None of the deaths were considered drug-related.
Narratives for serious adverse events including deaths are not available

Efficacy
Combination therapy was reported to be more effective than either finasteride or doxazosin alone in reducing the risk of primary outcome of "BPH progression".
Finasteride alone or in combination with doxazosin, reduced the risk of acute urinary retention (one part of the composite primary endpoint).
Finasteride or doxazosin monotherapy or in combination positively impacted AUA symptom scores and improved the maximum urinary flow (Q_{max}).
Mean prostate volume decreased in both finasteride and in the combination therapy.

Efficacy itself was measured using the following endpoints:
1. Time to BPH Progression: Significant risk reduction in progression of BPH was seen with doxazosin 39 % RR ($p<0.001$), finasteride 34%RR ($P=0.002$) and in the combination group 67% RR ($p< 0.001$) compared to placebo.

2. Greater than 4 point rise in AUA symptom score (one part of the composite)
This "symptom score progression" was significantly reduced by 30% in finasteride, 46% with doxazosin, and by 64% with combination, compared to placebo.

3. Acute Urinary Retention (one part of the composite)

The risk of developing acute urinary retention was reduced by 67% (p=0.0114) with finasteride, 31% (p=0.2963) with doxazosin, and 79% (p=0.0013) with combination as compared to placebo.

Summary Statement

1. It is the impression of this reviewer that the application submitted is sufficiently complete to permit a substantive clinical review.
2. There are no items missing that would constitute a reason to refuse to file this supplement.

Clinical Review Issues Noted at Filing

1. Please provide information to support a 4 point rise in AUA symptom score as a reflection of progression of BPH.
2. Please provide justification for the selection of the five criteria in the composite end point called "BPH progression".
3. Please explain the impact of the pilot group on the overall results of the Study.
4. We acknowledge your intent to submit additional disclosure information in October of 2003.
5. There is slightly higher percentage of patients in the combination group who reported asthenia, postural hypotension, abnormal ejaculation, impotence and syncope then in either drug group alone or placebo. This is a review issue.
6. Clinical site inspections are a review issue. For each of 18 clinical sites, please provide the following information:

* The principal investigator and/or designated contact person, complete site address, and telephone number at each site.
* The number of subjects enrolled at each site
* The number of subjects discontinued from the study at each site
* The number of serious adverse events that occurred at each site.

Recommended regulatory action

The "clinical review issues noted at filing" should be conveyed to the sponsor in a regulatory letter.

Suresh Kaul, MD
Medical Officer, DRUDP, HFD-580

Mark Hirsch, MD
Urology Team Leader, DRUDP, HFD-580

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On Original

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/s/

Suresh Kaul
8/25/03 02:59:20 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-180/S-026

PHARMACOLOGY REVIEW

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

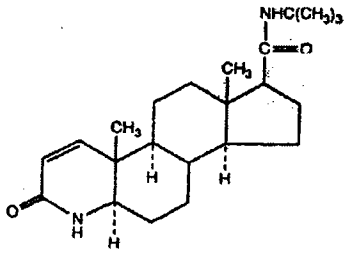
PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**20-180**
SERIAL NUMBER:	**S-026**
DATE RECEIVED BY CENTER:	**06/12/2003**
DRUG NAME:	**Proscar (finasteride)**
INDICATION:	**[redacted]**
SPONSOR:	**Merck Research Laboratories**
DOCUMENTS REVIEWED:	**electronic**
REVIEW DIVISION:	**Division of Reproductive and Urologic Drug Products (HFD-580)**
PHARM/TOX REVIEWER:	**Suzanne R. Thornton-Jones, Ph.D.**
PHARM/TOX SUPERVISOR:	**Lynnda Reid, Ph.D.**
DIVISION DIRECTOR:	**Daniel Shames, M.D.**
PROJECT MANAGER:	**Jen Mercier**

Date of review submission to Division File System (DFS): 02 March 2004

PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA NUMBER:	20-180
SEQUENCE NUMBER/DATE/TYPE OF SUBMISSION:	S026/12 June 2003
INFORMATION TO SPONSOR:	Yes (X) No ( )
SPONSOR AND/OR AGENT:	Merck Research Laboratories P.O. Box 2000, RY 33-200 Rahway, NJ 07065
MANUFACTURER FOR DRUG SUBSTANCE :	Merck and Co., Inc., West Point, PA
REVIEWER NAME:	Suzanne R. Thornton
DIVISION NAME:	DRUDP
HFD #:	580
REVIEW COMPLETION DATE:	01 March 2004
DRUG:	
TRADE NAME:	Proscar
GENERIC NAME (LIST ALPHABETICALLY):	finasteride
CODE NAME:	NA
CHEMICAL NAME:	N-(1,1-dimethylethyl)-3-oxo-4-aza-5α-androst-1-ene-17β-carboxymide
CAS REGISTRY NUMBER:	98319-26-7
MOLE FILE NUMBER:	not indicated
MOLECULAR FORMULA/MOLECULAR WEIGHT:	$C_{23}H_{36}N_2O_2$/[ ]
STRUCTURE:	



RELEVANT INDS/NDAS/DMFS:	None
DRUG CLASS:	5-alpha reductase inhibitor
CLINICAL FORMULATION:	finasteride, hydrous lactose, microcrystalline cellulose, pregelatinized starch, sodium starch glycolate, hydroxypropyl cellulose LF, hydroxypropylmethyl cellulose, titanium dioxide, magnesium stearate, docusate sodium
ROUTE OF ADMINISTRATION:	oral
PROPOSED USE: [ ]	

[Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.]

STUDIES REVIEWED WITHIN THIS SUBMISSION: None were submitted.

STUDIES NOT REVIEWED WITHIN THIS SUBMISSION: None were submitted.

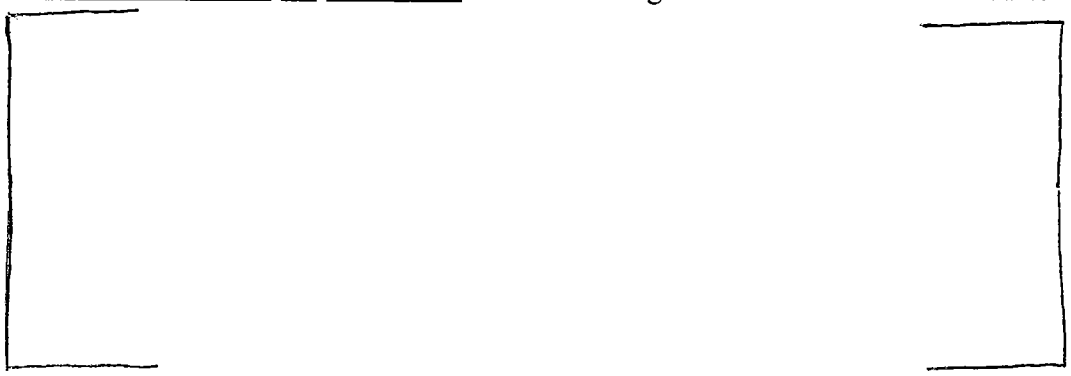
Executive Summary

I. RECOMMENDATIONS

A. RECOMMENDATION ON APPROVABILITY: From a pharmacology/toxicology standpoint, the supplement is approvable.

B. RECOMMENDATION FOR NONCLINICAL STUDIES: None at this time.

C. RECOMMENDATIONS ON LABELING: The following sentences should be added to



II. SUMMARY OF NONCLINICAL FINDINGS

A. BRIEF OVERVIEW OF NONCLINICAL FINDINGS: No non-clinical studies were submitted for review to determine any toxicities associated with co-administration of finasteride and doxazosin. It is unlikely that there will be a pharmacodynamic (PD) interaction because finasteride is an alpha reductase inhibitor while doxasozin is an alpha blocker. It is also unlikely that there will be a pharmacokinetic (PK) interaction even though they are both primarily metabolized in the liver. Finasteride is metabolized via CYP 3A4 while doxasosin is metabolized by O-demethylation. The supplement contains a clinical study, medical therapy of prostatic symptoms (MTOPS), which examined the co-administration of finasteride and doxazosin efficacy in BPH and should identify any PD and/or PK interaction issues.

B. PHARMACOLOGIC ACTIVITY: Not applicable.

C. NONCLINICAL SAFETY ISSUES RELEVANT TO CLINICAL USE:
There are no safety concerns.

III. ADMINISTRATIVE

A. REVIEWER SIGNATURE: Suzanne R. Thornton-Jones, Ph.D.
B. SUPERVISOR SIGNATURE: CONCURRENCE – Lynnda Reid, Ph.D.

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/s/

Suzanne Thornton
3/2/04 02:19:26 PM
PHARMACOLOGIST

Lynnda Reid
3/2/04 02:46:50 PM
PHARMACOLOGIST

45 DAY MEETING CHECKLIST
NDA 20-180

FILEABILITY:

On initial overview of the NDA application:

PHARMACOLOGY AND TOXICOLOGY:

(1) On its face, is the pharmacology section of the NDA organized in a manner to allow substantive review to begin? **Not applicable.**

(2) Is the pharmacology section of the NDA indexed and paginated in a manner to allow substantive review to begin? **Not applicable.**

(3) On its face, is the pharmacology section of the NDA legible so that substantive review can being? **Not applicable.**

(4) Are all required (*) and requested IND studies completed and submitted in this NDA (carcinogenicity, mutagenicity, teratogenicity*, effects on fertility*, juvenile studies, acute adult studies*, chronic adult studies*, maximum tolerated dosage determination, dermal irritancy, ocular irritancy, photocarcinogenicity, animal pharmacokinetics studies, etc)? **No non-clinical studies were conducted, but the data was for a clinical investigation.**

(5) If the formulation to be marketed is different from the formulation used in the toxicology studies, has the sponsor made an appropriate effort to either repeat the studies using the marketed product or to explain why such repetition should be required? **Not applicable.**

(6) Are the proposed labeling sections relative to pharmacology appropriate (including human dose multiples expressed in either mg/m^2 or comparative serum/plasma levels) and in accordance with 201.57? [redacted]

(7) Has the sponsor submitted all special studies/data requested by the Division during Pre-submission discussions with the sponsor? **Not applicable.**

(8) On its face, does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted rationale to justify the alternative route? **Not applicable.**

(9) Has the sponsor submitted a statement(s) that all the pivotal Pharm/Tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations? **Not applicable.**

(10)Has the sponsor submitted a statement(s) that the Pharm/Tox studies have been performed using acceptable, state-of-the-art protocols which also reflect agency animal welfare concerns? **Not applicable.**

(11) From a pharmacology perspective, is this NDA fileable? If "no", please state below why it is not. **Yes**

Suzanne R. Thornton, Ph.D. 25 August 2003
Reviewing/Supervisory Pharmacology Officer Date

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/s/

Suzanne Thornton
8/25/03 01:48:32 PM
PHARMACOLOGIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-180/S-026

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	20-180 / S-026
Drug Name:	PROSCAR ™ (finasteride 5 mg)
Indication(s):	Treatment of symptomatic benign prostatic hyperplasia (BPH)
Applicant:	Merck & Co., Inc.
Date(s):	NDA Received 6/13/03
	Data received in edr 12/7/03
	PDUFA date 4/13/04
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II
Statistical Reviewer:	Kate Meaker, M.S.
Concurring Reviewers:	Mike Welch, Ph.D.
	Ed Nevius, Ph.D.
Medical Division:	HFD-580
Clinical Team:	Harry Handelsman, M.D.
Project Manager:	Jen Mercier

Keywords: Clinical study, NDA Review, Composite endpoint

Table of Contents

1. EXECUTIVE SUMMARY

This application requests a change in the indication and label information for Proscar (finasteride) for the treatment of benign prostate hyperplasia (BPH). Proscar currently is approved for use alone for this indication. The requested label changes are based on results from the Medical Therapy of Prostatic Symptoms (MTOPS) Trial. The results of that clinical trial show that finasteride, in combination with the alpha-blocker doxazosin, provides additional benefit over long-term use in terms of symptoms, but not in terms of reduction of risk of acute urinary retention (AUR), versus finasteride-alone.

This application requests that the indication statement be changed to: PROSCAR, [redacted], is indicated for the treatment of symptomatic benign prostate hyperplasia (BPH) in men with enlarged prostate to: improve symptoms, reduce the risk of acute urinary retention, and reduce the need for surgery including transurethral resection of the prostate (TURP) an prostatectomy. The only requested change from the current indication statement is the addition of the phrase [redacted] As proposed, the sponsor's wording of the indication implies more than can be supported by the MTOPS trial results. The results of the MTOPS trial support the combination product for the symptoms part of the indication, [redacted]
Different wording is needed in order to add a reference about the combination product to the indication statement which accurately reflects the trial results.

The sponsor's primary efficacy outcome defined in the protocol is a composite endpoint referred to as time to clinical progression of BPH. The first occurrence of any of 5 events would be considered as clinical progression. These 5 events are: an increase from baseline in the AUA Symptom Severity Score of 4 or more points (confirmed on 2 visits); acute urinary retention (AUR); renal insufficiency due to BPH; recurrent urinary tract infections or urosepsis; or urinary incontinence. A subject could only have one of the five events recorded as the first occurrence. Analyses of each of the five outcomes separately were planned as secondary.

The first two items in the sponsor's composite endpoint, an increase from baseline in the AUA Symptom Severity Score of 4 or more points (confirmed on two visits), and acute urinary retention (AUR), are considered by the DRUDP Medical Officers to be most relevant to the indication for the treatment of BPH. These two outcomes, considered separately, are of primary interest to the Medical Officers in assessing efficacy for the desired label changes. The relevance of the sponsor's composite endpoint for labeling was not agreed to by the Division prior to initiation of the MTOPS study.

In the Clinical Studies section of the label, the sponsor has requested the addition of four paragraphs and a figure (Sponsor's Figure 1 from study report; see Appendix) presenting results of the MTOPS trial. Much of the information presented covers secondary endpoints or analyses not of primary interest for this indication. The sponsor also presents results for a composite endpoint, referred to as [redacted] which the

Medical Officers find inappropriate for this indication. As proposed by the sponsor, most of the information regarding the MTOPS trial in this section would not be appropriate for the label or claims. This section will need to be reworded to accurately represent the MTOPS results.

1.1 Conclusions and Recommendations

My suggestion regarding the label changes is that only information describing the study design and the two primary efficacy endpoints of interest to the Medical Officers be presented. Caution should be used to limit the conclusions or statements about the results to only what the study can support. Specifically, the combination treatment group was statistically significantly different than finasteride-alone for the AUA symptom score endpoint, [ ] [ ]. These results are summarized in terms of risk reduction in Table 2 (see Appendix). If the values from this table are included in the label, I would propose a footnote stating only that the [ ] rather than putting in the p-values. Presenting p-values for the many comparisons lends itself to misinterpretation or misunderstanding because of the need to adjust for multiple comparisons and the retrospective nature of the analyses. If a graph of the Kaplan-Meier survival curve for events over time is desired, a figure for Cumulative Incidence of a 4-point Rise in AUA Symptom Score could be shown (sponsor's Figure 2, see Appendix).

1.2 Brief Overview of Clinical Study

This application is based on a single clinical study. The Medical Therapy of Prostatic Symptoms (MTOPS) Trial was sponsored by the National Institutes of Diabetes and Digestive Diseases (NIDDK) of the National Institutes of Health (NIH). It is a multicenter, randomized, double-blind, placebo-controlled study. The objective is to evaluate the efficacy and safety of finasteride, a type II 5α-reductase inhibitor, and doxazosin, and α-adrenergic blocker, alone or in combination, in the treatment of benign prostate hyperplasia (BPH).

Subjects were men, at least 50 years old, with BPH as defined by peak urinary flow rate and AUA symptom severity score. Subjects were randomized to one of four treatment groups: placebo, finasteride alone, doxazosin alone, or finasteride and doxazosin in combination. A pilot study was conducted, randomizing 141 men, to assess the feasibility of the study. Subsequently, an additional 2931 men were randomized for the full-scale study. All 3072 men received the same treatment and assessments. Subjects were followed for an average of 5 years (range 4 to 6 years).

The sponsor's primary efficacy outcome defined in the protocol is a composite endpoint referred to as time to clinical progression of BPH. Any of 5 events would be considered as clinical progression. These are: an increase from baseline in the AUA Symptom Severity Score of 4 or more points (confirmed at 2 visits); acute urinary retention (AUR); renal

insufficiency due to BPH; recurrent urinary tract infections or urosepsis; or urinary incontinence. The sponsor's primary endpoint was defined as the time to first occurrence of any of these five outcomes. A subject could only have one of the five events recorded as the first occurrence. Analyses of each of the five outcomes separately were planned as secondary.

The first two items in the sponsor's composite endpoint, an increase from baseline in the AUA Symptom Severity Score of 4 or more points, and acute urinary retention (AUR), are considered by the DRUDP Medical Officers to be most relevant to the indication for the treatment of BPH. These two outcomes, considered separately, are of primary interest to the Medical Officers in assessing efficacy for the desired label changes. The relevance of the sponsor's composite endpoint for labeling was not agreed to by the Division prior to submission of this NDA.

1.3 Statistical Issues and Findings

The main statistical concern for this application is the difference in primary efficacy endpoints as defined in the protocol and those considered important to the Division Medical Officers. A composite endpoint which summarized 5 outcomes was planned in the protocol as the primary efficacy endpoint. Table 1 in the Appendix shows the incidence of the 5 outcomes separately, and the total for the composite. However, two of those outcomes are considered to be most important by the Division Medical Officers. These are an increase from baseline in the AUA Symptom Severity Score of 4 or more points (confirmed at 2 visits), and acute urinary retention (AUR). As shown in Table 1, overall the majority of the events observed in the trial were an increase from baseline in the AUA Symptom Severity Score (274 of 351 = 78%). The incidence of AUR was second, with 41 (12% of total) events observed. The Medical Officers prefer to analyze the incidence of each of those outcomes separately to assess efficacy for the desired indication for the [redacted]

In this study, the efficacy endpoints of interest are measured as the incidence of each specific event. Each subject could have only one of the events which are included in the sponsor's composite endpoint. The statistical methods proposed by the sponsor are appropriate for the type of endpoints being measured. The sponsor's analysis plan specified survival analysis methods (Kaplan-Meier estimates, log rank test, and Cox proportional hazards model) would be used to assess time until clinical progression of BPH for the primary endpoint.

The protocol planned to make comparisons of each of the three active treatment groups (finasteride-alone, doxazosin-alone, and finasteride/doxazosin combination) to placebo using two-sided tests. An adjustment for three pairwise multiple comparisons was planned. Five interim analyses were planned, with an additional adjustment to the overall alpha level using the Lan-DeMets approach. Comparisons between the active treatment groups were not planned as primary analyses and were not included in the interim analyses.

The results from the sponsor's analyses are shown in Table 2 in the Appendix. Both the finasteride-alone group and the combination treatment group were statistically significantly

different from placebo for both the 4-point Rise in AUA Symptom Score endpoint and the Acute Urinary Retention endpoint (all p-values ≤ 0.0156 versus the adjusted α=0.0157). The sponsor's Kaplan-Meier survival plots for each of these endpoints are shown in Figures 1, 2 and 3 in the Appendix.

In the MTOPS protocol (third edition, dated 10/13/00) the sponsor did not plan for comparisons within the active-treatment groups. In the clinical summary report submitted with this application, the sponsor performed these comparisons using a Bonferroni adjustment for 3 comparisons, resulting in an adjusted alpha level of 0.0167. As shown in Table 2, the combination treatment group is not statistically significantly different from the doxazosin group for either of the endpoints of interest (p-value=0.0369, 0.0214). The combination treatment groups is statistically significantly different from the finasteride-alone group for the 4-point Rise in AUA Symptom Score endpoint (p=0.0006) but not for the Acute Urinary Retention endpoint (p=0.4644).

The sponsor classified an event as a rise in AUA Symptom Severity Score of 4 or more points (confirmed at 2 visits). Supportive information on the efficacy for symptoms is provided by the mean change from baseline in AUA symptom score. The Medical Officers requested that this information (see Table 3 in Appendix) be added to the label because it is informative to prescribers and patients. Only descriptive values, not p-values, are reported since this a secondary endpoint.

2. INTRODUCTION

2.1 Overview

This application is based on a single clinical study. The Medical Therapy of Prostatic Symptoms (MTOPS) Trial was sponsored by the National Institutes of Diabetes and Digestive Diseases (NIDDK) of the National Institutes of Health (NIH). It is a multicenter, randomized, double-blind, placebo-controlled study. The objective is to evaluate the efficacy and safety of finasteride, a type II 5α-reductase inhibitor, and doxazosin, and α-adrenergic blocker, alone or in combination, in the treatment of benign prostate hyperplasia (BPH).

The primary endpoint planned in the protocol is a composite of five outcomes. Two of these outcomes are considered by the Medical Officers as being of primary concern for the indication of the treatment of BPH. The sponsor's composite endpoint was not agreed to by the Division as being appropriate for the label or claims. Instead, the Medical Officers would prefer to look at two of the outcomes separately. These are the incidence of a 4-point rise in AUA Symptom Score, and the incidence of acute urinary retention (AUR).

2.2 Data Sources

The data analysis was performed for NIH by the Biostatistics Center at the George Washington University. The sponsor of the application is Merck & Co. NIH provided the

clinical summary report to Merck for this submission, but the data is considered proprietary and was not released to Merck. Instead, the Biostatistics Center at the George Washington University provided limited SAS datasets and documentation to the Division to review the analyses in the Clinical Summary Report. I was able to reproduce the statistical results for the sponsor's composite endpoint and the two separate outcomes of interest to the Medical Officers.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

In this study, the efficacy endpoints are measured as the time to an event. The sponsor's primary endpoint was a composite endpoint (clinical progression of BPH) based on the time until first occurrence of any one of five possible outcomes. The DRUDP Medical Officers consider the primary endpoints to be the incidence rates for two of the specified outcomes, but analyzed separately. Each subject could have only one of the events. The statistical methods proposed by the sponsor are appropriate for the type of endpoints being measured. The sponsor's analysis plan specified survival analysis methods (Kaplan-Meier estimates, logrank test, and Cox proportional hazards model) would be used to assess time until clinical progression of BPH for the primary endpoint.

The protocol planned to make comparisons of each of the three active treatment groups (finasteride alone, doxazosin alone, and finasteride/doxazosin combination) to placebo using two-sided tests. An adjustment for three pairwise multiple comparisons was planned. Comparisons between the active treatment groups were not planned as primary analyses.

In the protocol, the power calculations only considered comparisons of each of the 3 active treatment groups to placebo. MTOPS was designed to have 80% power to detect a one-third (33%) hazard reduction in any one of the active treatment groups compared to placebo. The calculations included adjustments for multiple comparisons. It did not assess the power to detect differences between any of the active-treatment groups. The comparisons of interest for this application involve those comparisons between the active treatment groups, specifically the comparison of the combination treatment group to the finasteride-alone and doxazosin-alone treatment groups.

The sponsor classified an event as a rise in AUA Symptom Severity Score of 4 or more points (confirmed at 2 visits). Supportive information on the efficacy for symptoms is provided by the mean change from baseline in AUA symptom score. The Medical Officers requested that this information (see Table 3 in Appendix) be added to the label because it is informative to prescribers and patients. Subjects who remained on therapy through Year 4 of the study are included in the analysis. Only descriptive values, not p-values, are reported since this a secondary endpoint.

3.2 Evaluation of Safety

Each of the active treatments included in the combination product is currently approved. There were no safety issues identified for the statistical review.

4. SUMMARY AND CONCLUSIONS

4.1 Statistical Issues and Collective Evidence

This application requests changes to an approved label and is based on the results of a single study. The trial was not designed with Division concurrence to support the label changes being considered. Specifically, the planned primary endpoint is a composite of 5 outcomes, two of which the Division Medical Officers consider important for the indication. An additional issue is that the comparisons used to support the label changes, between active-treatment groups, were not planned as the primary comparisons of interest in the protocol, and the study was not powered for these comparisons.

Based on secondary analyses, the combination treatment group is statistically significantly better than the finasteride-alone group for the 4-point rise in AUA symptom score endpoint, but not for the incidence of acute urinary retention endpoint. The combination treatment group is not statistically significantly better than the doxazosin-alone group for either endpoint.

4.2 Conclusions and Recommendations

My suggestion regarding the label changes is that only information describing the study design and the two primary efficacy endpoints of interest to the Medical Officers be presented. Caution should be used to limit the conclusions or statements about the results to only what the study can support. Specifically, the combination treatment group was statistically significantly different than finasteride-alone for the AUA symptom score endpoint, [redacted]. These results are summarized in terms of risk reduction in Table 2 (see Appendix). If the values from this table are included in the label, I would propose a footnote stating only that the [redacted] rather than putting in the p-values. Presenting p-values for the many comparisons lends itself to misinterpretation or misunderstanding because of the need to adjust for multiple comparisons and the retrospective nature of the analyses. If a graph of events over time is desired, a figure for Cumulative Incidence of a 4-point Rise in AUA Symptom Score (sponsor's Figure 2, see Appendix) could be shown.

5. APPENDIX

Table 1
Count and Percent Incidence of Primary Outcome Events by Treatment group

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 (Sponsor's composite endpoint)	128 (17.4)	85 (11.2)	89 (17.4)	49 (16.2)	351 (11.5)

Source: Clinical Summary Report, Table 3, Vol. S111.1

Table 2
Between-Treatment Group Comparison of the Risk Reduction (95% CI)

Outcome	Treatment Comparisons					
	Doxazosin vs. Placebo	Finasteride vs. Placebo	Combination vs. Placebo	Combination vs. Doxazosin	Combination vs. Finasteride	Finasteride vs. Doxazosin
AUA Symptom Score – 4 point rise	46% (25%, 60%) p=0.0001	30% (6%, 48%) p=0.0156	64% (48%, 75%) p<0.0001	34% (2%, 55%) p=0.0369	48% (24%, 64%) p=0.0006	-27% (-79%, 9%) p=0.1683
Acute Urinary Retention	31% (-39%, 66%) p=0.2963	67% (18%, 87%) p=0.0114	79% (40%, 93%) p=0.0013	70% (10%, 90%) p=0.0214	37% (-120%, 82%) p=0.4644	53% (-22%, 83%) p=0.1123
BPH Progression (Sponsor's Composite endpoint)	39% (20%, 54%) p=0.0002	34% (14%, 50%) p=0.0018	67% (54%, 76%) p<0.0001	46% (23%, 62%) p=0.0004	49% (28%, 64%) p<0.0001	-7% (-44%, 54%) p=0.6518
	For the active-versus-placebo comparisons, p<0.0157 was considered statistically significant.			**For the active-versus-active comparisons, p<0.0167 was considered statistically significant.**		

Source: Clinical Summary Report, Table 4, Vol. S111.1

Table 3
Baseline and Mean Change in AUA Symptom Score at Year 4

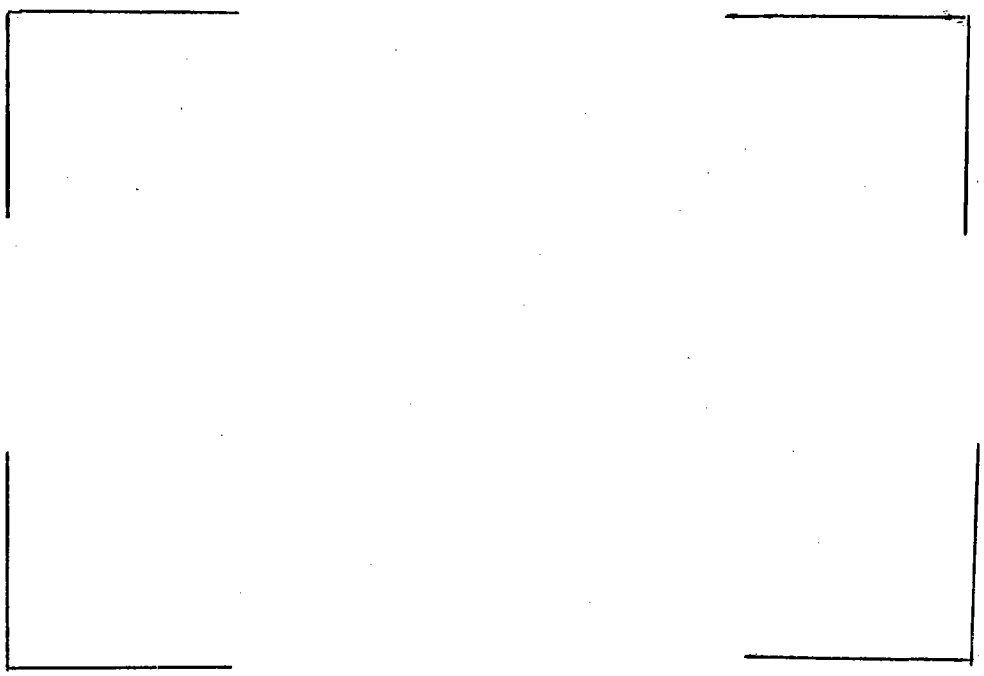
	Placebo	Doxazosin	Finasteride	Combination
Baseline Mean (SD)	N=737 16.8 (6.0)	N=756 17.0 (5.9)	N=768 17.1 (6.0)	N=786 16.8 (5.8)
AUA Symptom Score at Year 4* Mean Change (SD)	N=534 -4.9 (5.8)	N=582 -6.6 (6.1)	N=565 -5.6 (5.9)	N=598 -7.4 (6.3)
Difference vs. placebo (Nominal 95% Confidence Interval)		-1.8 (-2.5, -1.1)	-0.7 (-1.4, 0.0)	-2.5 (-3.2, -1.8)
Diff. vs. Doxazosin-alone (Nominal 95% Confidence Interval)				-0.7 (-1.4, 0.0)
Diff. vs. Finasteride-alone (Nominal 95% Confidence Interval)				-1.8 (-2.5, -1.1)

* Subjects who remained on therapy through Year 4 of study.
SOURCE: SAS datasets submitted November 11, 2003.

Sponsor's Figures from Clinical Summary Report (Vol. S111.1)

Sponsor's Figure 1 (Sponsor's composite endpoint):

Figure 1

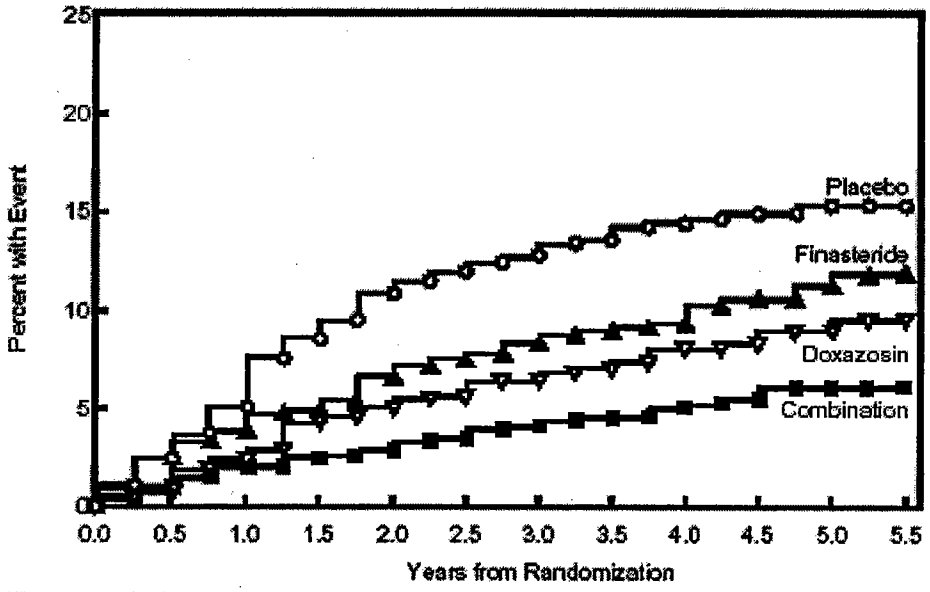


Appears This Way
On Original

Sponsor's Figure 2:

Figure 2

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



[Figure 5-3 in [1]]

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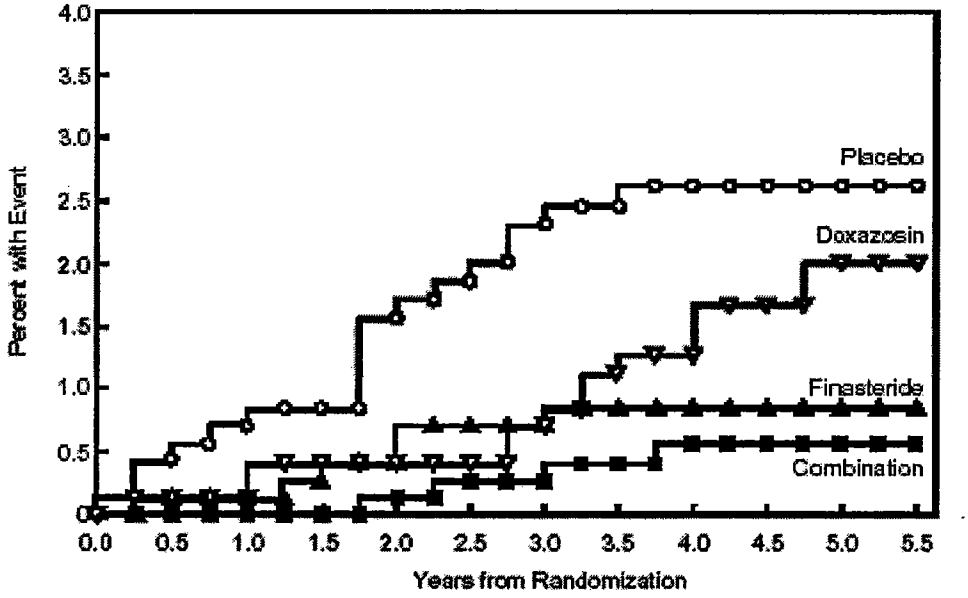
Sponsor's Figure 3:

Figure 3

Cumulative Incidence of Acute Urinary Retention by Treatment Group



[Figure 5-5 in [1]]

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

/s/

Katherine Meaker
4/12/04 12:38:31 PM
BIOMETRICS

I added a pragraph in section 1.3, 3.1 and
Table 3 in Appendix

Mike Welch
4/12/04 12:43:09 PM
BIOMETRICS

S. Edward Nevius
4/12/04 03:24:59 PM
BIOMETRICS
Concur with review.

TO: Jean King, Project Manager

FROM: Sue-Jane Wang, Ph.D.

DATE: September 5, 2003

RE: PROSCAR supplement NDA 20180 SE-08

Please request the sponsor to submit the following:

(1) Has Appendix F been submitted electronically? If so, where to locate it? If not, please submit it ASAP.

(2) SAS programs used for the primary efficacy and secondary efficacy analyses. The programs should include the algorithms used to define whether a patient is clinically progressed for each of the five criteria, i.e., what variable(s) were used in which SAS transport file(s) when referencing the five criteria. For each criterion, there should be one algorithm, which includes the variables and transport files to locate those variables.

(3) Please provide a separate dataset which include
(a) patient id
(b) treatment assignment
(c) date of randomization
(d) trial start date
(e) date of study end
(f) date of last completed visit
(g) maximum visit date
(h) reason of discontinuation
(i) yes/no as clinically progressed based on condition-1 (see definition below)
(j) yes/no as clinically progressed based on condition-2
(k) yes/no as clinically progressed based on condition-3
(l) yes/no as clinically progressed based on condition-4
(m) yes/no as clinically progressed based on condition-5
(n) the final composite score (yes/no) on whether a patient is clinically progressed
(o) trus prostate volume
(p) max flow rate
(q) aua symptom score
(r) PSA
(s) post void residual

Note: (o) to (s) are the variables used to produce Tables 5-3 and 5-4 in reference #1 (p.209 and 210).

The definition of the primary efficacy endpoint extracted from the protocol is

The primary outcome was the time to clinical progression of BPH. Clinical progression of BPH is defined by having at least one of the following conditions:

Criterion-1: Acute urinary retention defined in the Appendix F of the protocol
Criterion-2: Renal insufficiency due to BPH, as indicated by a 50% increase from baseline in serum creatinine to at least 1.5 mg/dL confirmed within 4 weeks
Criterion-3: Recurrent urinary tract infections or urosepsis defined in the Appendix F of the protocol
Criterion-4: Incontinence defined in the Appendix F of the protocol
Criterion-5: An increase from baseline in the AUA symptom score index of 4 or more points confirmed 2 to 3 weeks later

Participants who were not categorized as having clinical progression of BPH were censored as the date of their last completed visit. A supportive analysis was the time to the first occurrence of clinical progression of BPH or crossed over to known invasive therapy.

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

/s/

Sue Jane Wang
9/6/03 03:56:47 PM
BIOMETRICS

Jean, please send a request letter to the sponsor ASAP according to this internal memo. Thanks. Sue-Jane

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-180/S-026

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

'ent Information

Item 13

PATENT AND EXCLUSIVITY INFORMATION
MERCK RESEARCH LABORATORIES

1. Active Ingredient	Finasteride
2. Dosage(s)	5 mg
3. Trade Name	PROSCAR®
4. Dosage Form	Tablets
Route of Administration	Oral
5. Applicant Firm Name	Merck Research Laboratories
6. NDA Number	20-180
Approval Date	Pending Supplement
8. Exclusivity	3 years from NDA approval date; length of exclusivity - 3 years.
9. Applicable Patent Numbers	US 4,760,071, expires June 19, 2006 US 5,886,184, expires November 19, 2012 US 5,942,519, expires October 23, 2018 US 6,046,183, expires March 20, 2011

PATENT SUBMISSION FORM

Time Sensitive Patent Information pursuant to 21 C.F.R. §314.53 and/or
Patent Information pursuant to 21 C.F.R. §314.53 and §314.60
for

NDA # 20-180 - PROSCAR®

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

- Trade Name: PROSCAR®
- Active Ingredient(s): Finasteride
- Strength(s): 5 mg
- Dosage Form(s): Tablet, oral
- Date __ NDA ✓ sNDA filed: this is part of supplemental filing
- Date __ NDA ✓ sNDA approved: supplement pending

A. This section should be completed for each individual patent

U.S. Patent Number: 4,760,071

Expiration Date: 6/19/2006

Type of Patent - indicate all that apply:

1. Drug Substance (Active Ingredient) ✓ Y__ N
2. Drug Product (Composition/Formulation) ✓ Y__ N
3. Method of Use ✓ Y__ N

Name of Patent Owner: MERCK & CO., INC., Rahway, NJ

U.S. Agent (if patent owner or applicant does not reside or have place of business in the US):

B. The following declaration statement is required if the above listed patent has Composition/ Formulation or Method of Use claims.

The undersigned declares that United States Patent Number 4,760,071
covers the composition, formulation and/or method of use of PROSCAR®
(name of drug product). This product is:

- ✓ currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act
  OR
- __ the subject of this application for which approval is being sought.

A. This section should be completed for each individual patent

U.S. Patent Number: 5,886,184

Expiration Date: 11/19/2012

Type of Patent - indicate all that apply:

1. Drug Substance (Active Ingredient) ✓ Y__ N
2. Drug Product (Composition/Formulation) __ Y ✓ N
3. Method of Use __ Y ✓ N

Name of Patent Owner: MERCK & CO., INC., Rahway, NJ

U.S. Agent (if patent owner or applicant does not reside or have place of business in the US):

B. The following declaration statement is required if the above listed patent has Composition/ Formulation or Method of Use claims.

The undersigned declares that United States Patent Number 5,886,184

covers the composition, formulation and/or method of use of _____

(name of drug product). This product is:

- __ currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act

  OR

- __ the subject of this application for which approval is being sought.

A. This section should be completed for each individual patent

U.S. Patent Number: 5,942,519

Expiration Date: 10/23/2018

Type of Patent - indicate all that apply:

1. Drug Substance (Active Ingredient) __ Y ✓ N
2. Drug Product (Composition/Formulation) __ Y ✓ N
3. Method of Use ✓ Y __ N

Name of Patent Owner: MERCK & CO., INC., Rahway, NJ

U.S. Agent (if patent owner or applicant does not reside or have place of business in the US):

B. The following declaration statement is required if the above listed patent has Composition/ Formulation or Method of Use claims.

The undersigned declares that United States Patent Number 5,942,519

covers the composition, formulation and/or method of use of PROSCAR®

(name of drug product). This product is:

- ✓ currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act

  OR

- __ the subject of this application for which approval is being sought.

A. This section should be completed for each individual patent

U.S. Patent Number: 6,046,183

Expiration Date: 3/20/2011

Type of Patent - indicate all that apply:

1. Drug Substance (Active Ingredient) __ Y ✓ N
2. Drug Product (Composition/Formulation) ✓ Y __ N
3. Method of Use ✓ Y __ N

Name of Patent Owner: MERCK & CO., INC., Rahway, NJ

U.S. Agent (if patent owner or applicant does not reside or have place of business in the US):

B. The following declaration statement is required if the above listed patent has Composition/ Formulation or Method of Use claims.

The undersigned declares that United States Patent Number 6,046,183

covers the composition, formulation and/or method of use of PROSCAR®

(name of drug product). This product is:

- ✓ currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act

  OR

- __ the subject of this application for which approval is being sought.

Respectfully submitted,

By _____
CATHERINE D. FITCH
Attorney for Applicants

Merck & Co., Inc.
P.O. Box 2000 - RY60-30
Rahway, NJ 07065-0907
(732) 594- 4283

Date: May 13, 2003

A copy of the above information should be submitted to the FDA with the original application or as correspondence to an existing NDA. For patents issued after the NDA is filed or approved, the applicant is required to submit the information within 30 days of the date of issuance of the patent.

In accordance with 21 C.F.R. §314.53(d)(4), the applicant shall submit two copies of each submission of patent information to:

Central Document Room
Center For Drug Evaluation and Research
Food and Drug Administration
Park Bldg., Room 2-14
12420 Parklawn Dr.
Rockville, MD 20857

EXCLUSIVITY SUMMARY for NDA # 20-180 SUPPL # 026

Trade Name Proscar (finasteride) Tablets

Applicant Name MERCK & Company HFD-580

Approval Date April 12, 2004

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/___/ NO /_X_/

   b) Is it an effectiveness supplement? YES /_X_/ NO /___/

      If yes, what type(SE1, SE2, etc.)? SE8

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /_X_/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /___/ NO /_X_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /_X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 20-180 Proscar

NDA # 20-371 Cardura

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement

or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_**X**_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /_**X**_/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /_**X**_/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X_/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # MTOPS

Investigation #2, Study #

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /_X_/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the

NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #_1_, Study # _MTOPS

Investigation #__, Study #

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial

support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 MTOPS

IND # _____ YES /___/ ! NO /_X_/ Explain:

Investigation #2

IND # _____ YES /___/ ! NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /_X / Explain MTOPS was conducted by NIH with funding from Pfizer and Merck

! NO /___/ Explain _____

_____ ! _____

_____ ! _____

Investigation #2

YES /___/ Explain _____ ! NO /___/ Explain _____

_____	!	_____
	!	
_____	!	_____
	!	

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X_/

If yes, explain: _____

_____

_____

_____
Signature of Preparer Date
Title:

Signature of Office or Division Director Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-610/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

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/s/

Daniel A. Shames
4/12/04 03:44:20 PM

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : 20-180

Supplement Type (e.g. SE5): SE8 **Supplement Number: 026**

Stamp Date: June 12, 2003 **Action Date: April 12, 2004**

HFD 580

Trade and generic names/dosage form: **Requested Tradename** - Proscar
Generic: finasteride
dosage form: Tablets

Applicant: MERCK & Company

Therapeutic Class: S

Indication(s) previously approved: N/A

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application: 1

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).

Is there a full waiver for this indication (check one)?

☒ **Yes: Please proceed to Section A.**

☐ **No: Please check all that apply: Partial Waiver Deferred Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver: not applicable to NDA 21-513

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☒ **Other: Proscar will not be used in pediatric patients for the indication described in this supplemental NDA submission.**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

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

/s/

Jennifer L. Mercier
4/12/04 03:52:59 PM

REQUEST FOR WAIVER OF PEDIATRIC STUDIES

NDA 20-180
PROSCAR™ – (finasteride 5 mg)
Sponsor: Merck & Co., Inc
Indications: Treatment and control 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.

1. What age ranges are included in your waiver request? Entire pediatric population.

2. Reasons for waiving pediatric studies:

(a) No meaningful therapeutic benefit over existing treatments and is unlikely to be used in a substantial number of pediatric patients
(b) Studies are impossible or highly impractical because the number of patients is so small or geographically dispersed
(c) The product would be ineffective or unsafe in all pediatric age groups
(d) Attempts to develop a pediatric formulation for a specific age group have failed
(e) Disease- specific waiver indicated for the treatment of the condition in adults (please check)

___ Alzheimer's disease
___ Prostate Cancer
___ Renal cell cancer
___ Hairy cell cancer
___ Osteoarthritis
___ Uterine cancer
___ Endometrial cancer
___ Parkinson's disease
___ Arteriosclerosis
___ Infertility
___ Age- related macular degeneration
___ Breast cancer
___ Non- germ cell ovarian cancer
___ Pancreatic cancer, colorectal cancer
___ Squamous cell cancers of the oropharynx
___ Basal cell and squamous cell cancer
___ Small cell and non- small cell lung cancer
___ Amyotrophic lateral sclerosis
___Symptoms of menopause
_X_ Other (please state and justify): Benign Prostatic Hyperplasia

3. Justification for waiver (not necessary if category 2(e) is checked):
A 2 (e) waiver is requested because the indication is not relevant to the pediatric population. PROSCAR is not indicated for use in pediatric patients [PRECAUTIONS and WARNINGS sections of the current USPC for PROSCAR].

Proscar™ (Finasteride) 5mg
Item 16 - Debarment Certification

As required by §306(k)(1) of 21 U.S.C. 335a(k)(1), we hereby certify that, in connection with this application, Merck & Co., Inc. did not and will not use in any capacity the services of any person debarred under subsections 306(a) or (b) of the Act.

June 12, 2003

Vivian Fuh, MD
Director
Regulatory Affairs

Date

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
National Institutes of Health

National Institute of Diabetes and
Digestive and Kidney Diseases
Bethesda, Maryland 20892

May 8, 2003

Albert Leung, M.D.
Director, Clinical Research
Merck Research Laboratories
RY34-B152
Rahway, New Jersey 07065

Subject: Debarment Certification in the MTOPS Trial

Dear Dr. Leung:

As required by §306 (k) (1) of 21 U.S.C. 335a (k) (1), the National Institute of Diabetes and Digestive and Kidney Diseases certify that, in connection with the Medical Therapy of Prostatic Symptoms (MTOPS) Trial, we did not and will not use in any capacity the services of any person debarred under subsections 306 (a) or (b) of the Act.

Please contact me if you have any questions about this statement.

Sincerely,

John W. Kusek, Ph.D.
Director, Urologic & Kidney Clinical Trials
Division of Kidney, Urologic & Hematologic Diseases
Phone: 301.594.7735
Fax: 301.480.3510
E mail: kusekj@extra.niddk.nih.gov

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 20-180	Efficacy Supplement Type SE-8	Supplement Number 026	
Drug: Proscar® (finasteride) 5 mg.,		Applicant: Merck Research Laboratories	
RPM: Jennifer Mercier		HFD-580	Phone # 301-827-4260
Application Type: (X) 505(b)(1) ( ) 505(b)(2)		Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	3
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	April 12, 2004
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2
❖ User Fee Information	
• User Fee	(X) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(X) Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted.	( ) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted.	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified

❖ Exclusivity (approvals only)	
• Exclusivity summary	X
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!*	( ) Yes, Application #_____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	
General Information	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (X) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	X
• Most recent applicant-proposed labeling	X
• Original applicant-proposed labeling	X
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	X
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	X
• Applicant proposed	X
• Reviews	X
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	N/A
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	N/A

❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	X
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	X
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	See MO review
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	X
❖ Demographic Worksheet *(NME approvals only)*	N/A
❖ Statistical review(s) *(indicate date for each review)*	X
❖ Biopharmaceutical review(s) *(indicate date for each review)*	N/A
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	N/A
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	N/A
• Review & FONSI *(indicate date of review)*	N/A
• Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	N/A
❖ Facilities inspection (provide EER report)	Date completed: ( ) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	X
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A

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/s/

Martin Kaufman
4/12/04 03:51:31 PM

MERCK
Research Laboratories

FAX

Merck Research Laboratories
P.O. Box 2000
126 E. Lincoln Avenue
Rahway, NJ 07065

Number of Pages Including Cover Sheet: 20

Date: April 12, 2004

To:	Jennifer Mercier Food & Drug Administration	**Phone:** **Fax:**	301-827-4244 301-827-4267
From:	Vivian Fuh, M.D. Merck & Co., Inc.	**Phone:** **Fax:**	732-594-0374 732-594-1030

Subject: MTOPS Label

Attached, as requested, is the USPC & PPI with clean running text containing language as agreed upon today at the April 12, 2004 teleconference.

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

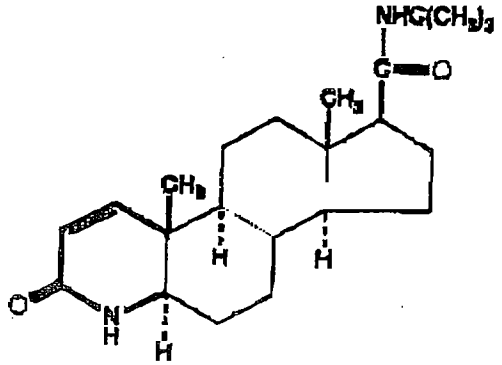
9556706

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 ($t_{½}$ ~ 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 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

* Registered trademark of MERCK & CO., Inc.

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 (0-24 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)

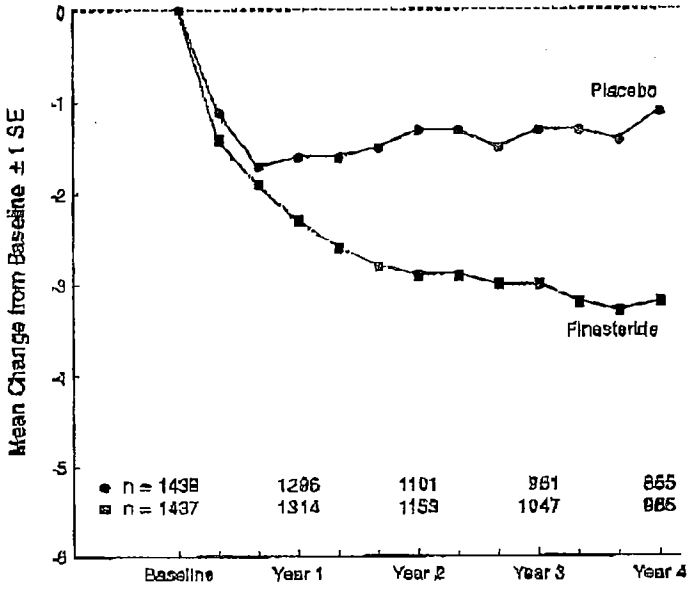
*First-dose values; all other parameters are last-dose values

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.

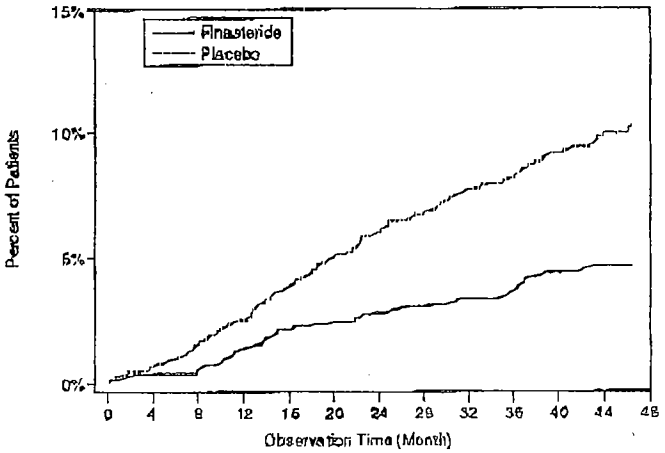
Table 1
All Treatment Failures in PLESS

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	19.3			

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

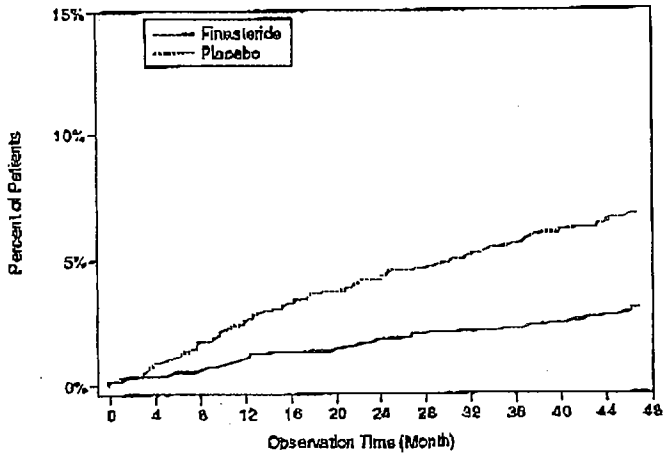
Compared with placebo, PROSCAR was associated with a significantly lower risk for acute urinary retention or the need for BPH-related surgery [13.2% for placebo vs 6.6% for PROSCAR; 51% reduction in risk, 95% CI: (34 to 63%)]. Compared with placebo, PROSCAR was associated with a significantly lower risk 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	1464	1374	1314
Finasteride Group				
No. of events, cumulative	16	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.

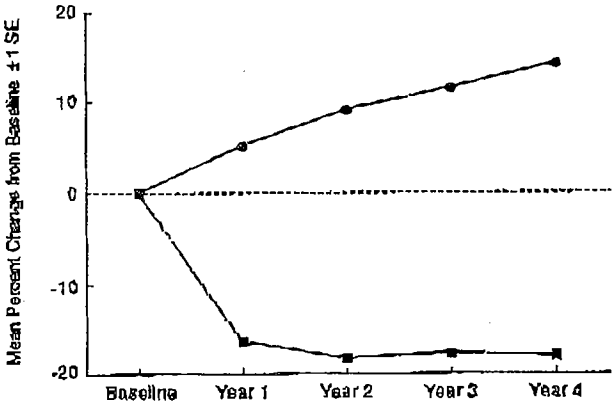
There was a clear difference between treatment groups in maximum urinary flow rate in favor of PROSCAR by month 4 (1.0 vs 0.3 mL/sec) which was maintained throughout the study. In the earlier 1-year studies, increase in maximum urinary flow rate was comparable to PLESS and was maintained through the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



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.

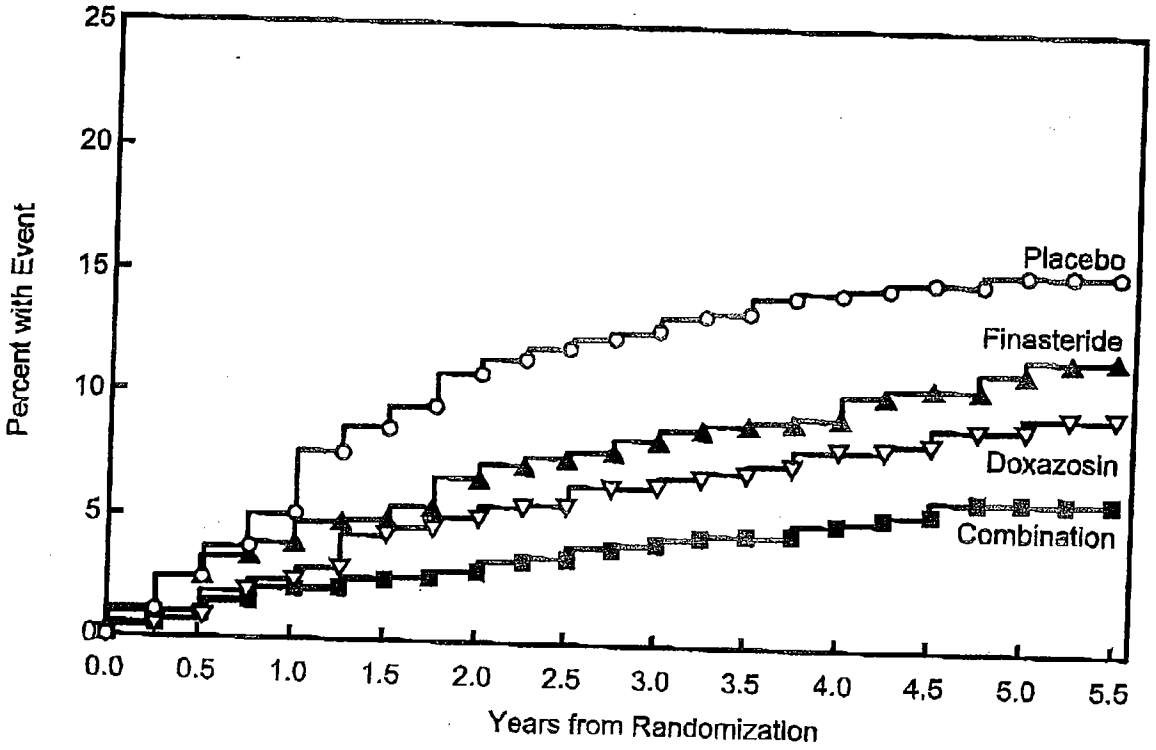
The primary endpoint was a composite measure of the first occurrence of any of the following five outcomes: a ≥4 point confirmed increase from baseline in symptom score, acute urinary retention, BPH-related renal insufficiency (creatinine rise), recurrent urinary tract infections or urosepsis, or incontinence. 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≤0.001) or doxazosin alone (46%; p≤0.001).(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 (6.9)	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 (0-24 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 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 4mg or 8mg* (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	6.0	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 8mg). The final tolerated dose (4mg or 8mg) was administered at end-Week 4. Only those patients tolerating at least 4mg 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.

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

Issued ~~August 2003~~
Printed in USA

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 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.

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.

Your doctor may prescribe PROSCAR along with another medicine, an alpha-blocker called doxazosin, to help you better manage your BPH symptoms.

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

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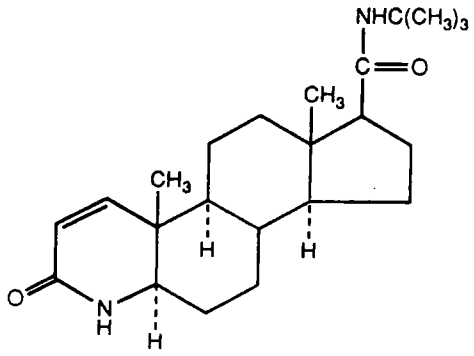
PROSCAR®
(FINASTERIDE)
TABLETS

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 ($t_{½}$ ~ 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 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.

* Registered trademark of MERCK & CO., Inc.

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 (0-24 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

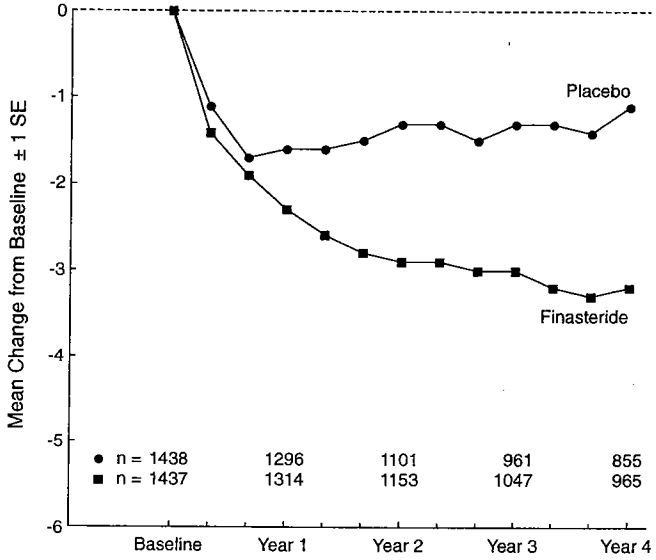
Clinical Studies
PROSCAR 5 mg/day was initially evaluated in patients with symptoms of BPH and enlarged prostates by digital rectal examination in two 1-year, placebo-controlled, randomized, double-blind studies and their 5-year open extensions.
PROSCAR was further evaluated in the PROSCAR Long-Term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

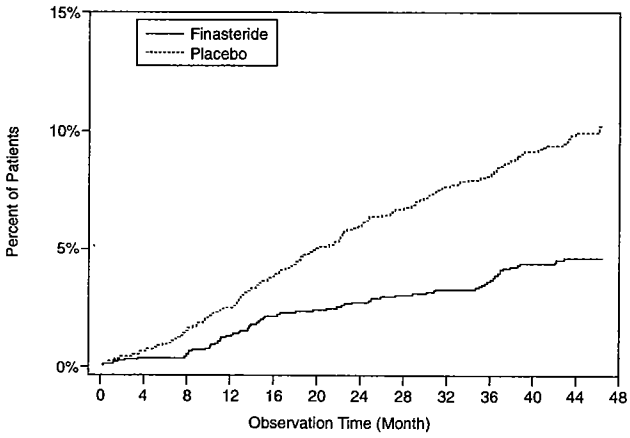
Table 1
All Treatment Failures in PLESS

	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

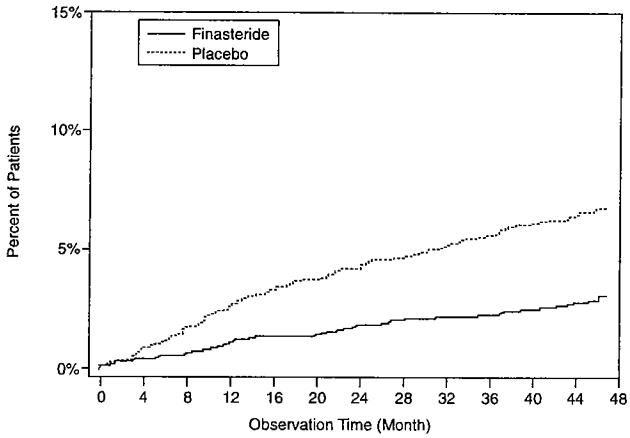
Compared with placebo, PROSCAR was associated with a significantly lower risk for acute urinary retention or the need for BPH-related surgery [13.2% for placebo vs 6.6% for PROSCAR; 51% reduction in risk, 95% CI: (34 to 63%)]. Compared with placebo, PROSCAR was associated with a significantly lower risk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

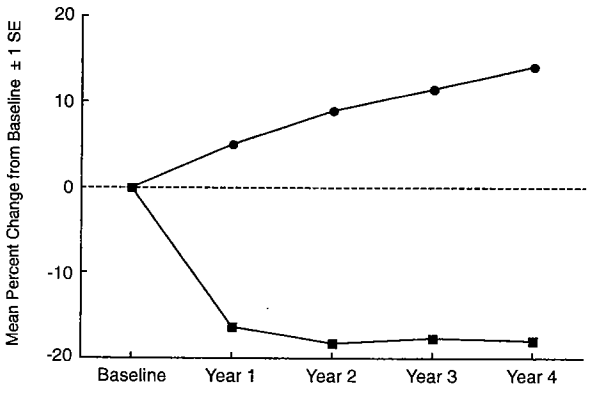
There was a clear difference between treatment groups in maximum urinary flow rate in favor of PROSCAR by month 4 (1.0 vs 0.3 mL/sec) which was maintained throughout the study. In the earlier 1-year studies, increase in maximum urinary flow rate was comparable to PLESS and was maintained through the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



	Baseline	Year 1	Year 2	Year 3	Year 4
Placebo (●) n =	155	136	119	98	85
Finasteride (■) n =	157	144	130	116	102

Prostate Volume as a Predictor of Therapeutic Response

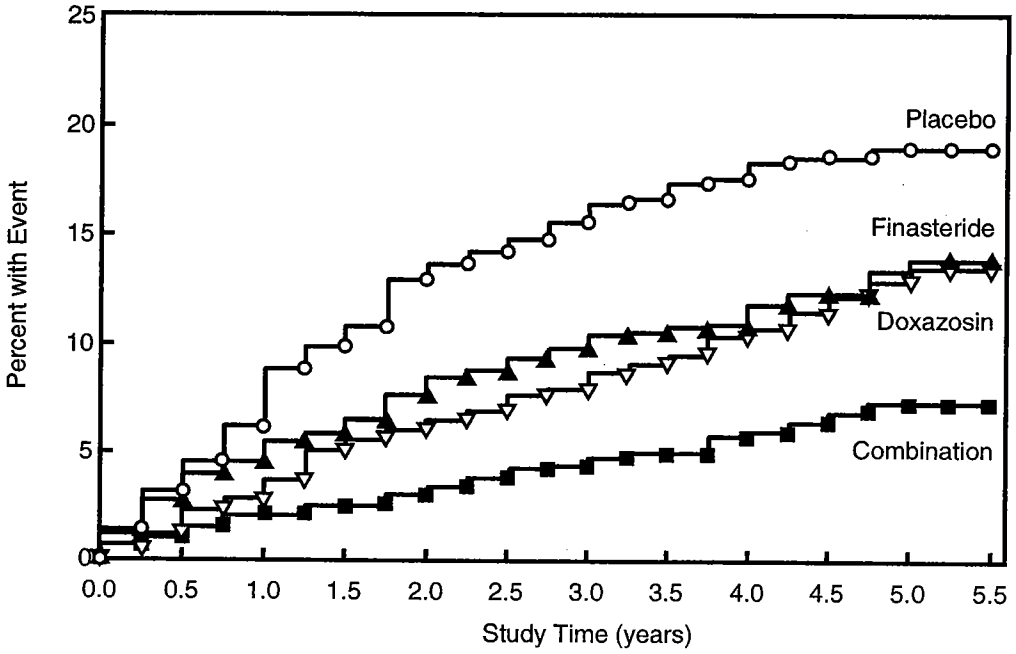
A meta-analysis combining 1-year data from seven double-blind, placebo-controlled studies of similar design, including 4491 patients with symptomatic BPH, demonstrated that, in patients treated with PROSCAR, the magnitude of symptom response and degree of improvement in maximum urinary flow rate were 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). The primary endpoint was time from randomization to clinical progression of BPH, defined as the first occurrence of any of the following events: 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 significant reduction in the risk of clinical progression of BPH by 34 ($p=0.002$), 39 ($p<0.001$), and 67% ($p<0.001$), respectively. Combination therapy reduced the risk of clinical progression of BPH to a significantly greater extent than either PROSCAR or doxazosin alone, which were not significantly different from each other (see Figure 5). The majority of the events (274 out of 351) that constituted BPH progression were confirmed ≥4 point increases in symptom score; the risk of symptom score progression was reduced by 30, 46, and 64% in the PROSCAR, doxazosin, and combination groups, respectively, compared to placebo. Acute urinary retention accounted for 41 of the 351 events of BPH progression; the risk of developing acute urinary retention was reduced by 67, 31, and 79% in the PROSCAR, doxazosin, and combination groups, respectively, compared to placebo. Only the PROSCAR and combination therapy groups were significantly different from placebo. Small cumulative numbers of events of renal insufficiency, urinary tract infection, and incontinence were reported and were of limited contribution to the primary endpoint of BPH progression.

* Titrated from 1 mg to 4 or 8 mg over a 3-week period.

Figure 5
Cumulative Incidence of Clinical Progression of BPH by Treatment Group



Secondary outcomes measured in MTOPS included the impact of treatment on BPH-related invasive therapy, symptom score, maximum urinary flow, and prostate volume. The risk of requiring BPH-related invasive therapy was reduced by 64, 3, and 67% in the PROSCAR, doxazosin, and combination groups, respectively, compared to placebo. Only the PROSCAR and combination therapy groups were significantly different from placebo. All three active treatment groups showed significant improvement in symptom score compared to placebo, and combination therapy was superior to both monotherapy treatments. The effect of combination therapy and doxazosin monotherapy on maximum urinary flow was superior to that of PROSCAR and placebo. PROSCAR and combination treatment decreased prostate volume, whereas, prostate volume increased in men treated with doxazosin or placebo.

The results of MTOPS confirm the findings of the 4-year, placebo-controlled study PLESS (see CLINICAL PHARMACOLOGY, *Clinical Studies*) that treatment with PROSCAR reduces the risk of acute urinary retention and the need for BPH-related surgery. The results of MTOPS further demonstrate that the combination of PROSCAR and doxazosin reduces the risk of BPH progression to a significantly greater extent than either therapy administered alone.

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, administered alone or in combination with the alpha-blocker doxazosin, 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).

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 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.

Medical Therapy of Prostatic Symptoms (MTOPS)

The MTOPS study compared PROSCAR 5 mg/day (n=768), doxazosin 4 or 8 mg/day (n=756), combination therapy of PROSCAR 5 mg/day and doxazosin 4 or 8 mg/day (n=786), and placebo (n=737). In this study, the safety and tolerability profile of the combination therapy was generally consistent with the profiles of the individual components. The incidence of ejaculation disorder in patients receiving combination therapy was comparable to the sum of incidences of this adverse experience for the two monotherapies.

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 PROSCAR and male breast neoplasia is currently unknown.

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*).

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

Issued Month Year
Printed in USA

XXXXXXX

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 swelling and/or tenderness. 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 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.

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.

Your doctor may prescribe PROSCAR along with another medicine, called doxazosin, to help you better control your BPH.

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 Month Year

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

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 2, 2004

TO: Dan Shames, M.D. Director
Division of Reproductive and Urologic Drug Products
HFD-580

VIA: Jennifer Mercier, Regulatory Health Project Manager
Division of Reproductive and Urologic Drug Products
HFD-580

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Gerald Dal Pan, M.D., M.H.S., Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: ODS/DSRCS Review Patient Labeling for Proscar (finasteride) Tablets, NDA 20-180/S-026

The patient labeling which follows represents the revised risk communication materials of the Patient Labeling for Proscar (finasteride) Tablets, NDA 20-180/S-026. We have simplified the wording, made it consistent with the PI, and removed other unnecessary information (the purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications, not to provide detailed information about the condition), and put it in the format that we are recommending for all patient information. Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds. These revisions are based on draft labeling submitted June 12, 2003.

Comments to the review Division are bolded, italicized, and underlined. We can provide marked-up and clean copies of the revised document in Word if requested by the review division.

We also have the following comments:

1. The review division may want to consider initiating class PPI labeling for similar BPH treatment products for labeling consistency.
   - Use the Medication Guide question and answer type format (see 21 CFR 208) as this format has research and experience to support its communication effectiveness.

- Ensure that the vocabulary and sentence structure is simplified for low literacy readers. A 6th to 8th grade reading comprehension level and a reading ease score of at least 60% is optimal for all patient materials.
- Do not list partial lists of medications. Either list all generic and tradenames, or list the name of the drug class and add a statement for the patient to check with their doctor or pharmacist if they are not sure if their medications are in a specific class. Patients feel 'safe' if a list of medications fails to include the name of their medication.
- Avoid presenting treatment options. Treatment options are constantly evolving. These discussions should take place with the healthcare provider.
- Remove any promotional language per DDMAC guidelines.

2. The PI states (PRECAUTIONS: Information for Patients section) that [ ] [ ] What mechanism does the sponsor have in place to ensure that a PPI is dispensed with each prescription? PROSCAR is not always written for or dispensed in unit of use packages and there is no requirement for PPIs to be dispensed with prescriptions. In general, pharmacies do not have space to stock bulk PPIs, nor make copies of a single PPI for dispensing purposes. The above statement should be deleted from the PI unless there is a mechanism in place for getting the PPI to patients with each prescription or refill.

Please call us if you have any questions.

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

Administrative + Correspondence
- 3/2/04 Memo

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

/s/

Jeanine Best
3/2/04 08:43:08 AM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
3/2/04 03:30:31 PM
DRUG SAFETY OFFICE REVIEWER
for Gerald Dal Pan

Meeting Minutes

Date: December 16, 2003 **Time:** 2:00 – 3:00 PM **Location:** 17B-43

Application: NDA 20-180/S-026 **Drug Name:** Proscar® (finasteride)

Indication: Benign Prostate Hyperplasia (BPH)

Type of Meeting: Status Meeting – 6-Months

Sponsor: Merck Research Laboratories

Meeting Chair: Mark Hirsch, M.D.

Meeting Recorder: Jennifer Mercier

FDA Attendees:
Mark Hirsch, M.D. – Medical Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Harry Handelsman, M.D. – Medical Officer, DRUDP (HFD-580)
Sue Jane Wang, Ph.D. – Statistician, Division of Biometrics II (DBII; HFD-715)
Jennifer Mercier – Regulatory Health Project Manager, DRUDP (HFD-580)

Meeting Objective:
To discuss the review status of the current supplement for review.

Background: The sponsor has submitted this supplement which contains the Medical Therapy of Prostatic Symptoms (MTOPS) study results. The sponsor believes the results of the MTOPS study demonstrates that finasteride and doxazosin as monotherapy [redacted] offer effective therapy in delaying the clinical progression on BPH. Because of this belief, the sponsor is seeking approval of this claim to their label.

Discussion:

Chemistry

- There is no information for the chemist to review; therefore no review will be needed for this supplement.

Pharmacology

- There is no information for the pharmacologist to review; therefore no review will be needed for this supplement.

Biopharmaceutics

- There are no issues from the biopharmaceutics reviewer and they will be submitting a brief memo for this application.

Clinical

- The clinical review is in progress.
- No clinical inspection is needed at this time.
- The clinical review may be completed by the end of January, 2004.
- Consults needed from the Division of Drug Marketing, Advertising and Communications (DDMAC) and Division of Surveillance, Research, and Communication Support (DSRCS) for the proposed PI and PPI, respectively.
- At this point, the reviewer has completed the review of the clinical summary, but not the final study report.
- The composite endpoint remains a review issue.
- Reviewer to check original application and 4 month safety update for financial disclosure information.

Statistics

- Review is in progress.
- Reviewer is waiting for sponsor to submit requested algorithms etc. (see the statistical section of the Division's letter request from all reviewers) for statistical analysis. The sponsor does not own this data and needs to obtain a contract with the owner of the data to submit. The sponsor was contacted about the timeframe and they estimated that they would be submitting the information to the NDA by December 19, 2003.
- As part of the same request, the reviewer sought a "minor dataset" to determine the impact of missing data on the results.
- Another review issue is the impact of the "pilot study" on the overall results.

Action Items:

- All reviews should be to the Medical Team Leader by March 22, 2004.
- The action package will be to the Division Director by April 5, 2004.
- PDUFA goal date for this application is April 12, 2004.

Cc:
HFD-580 – Hirsch/Handelsman/Wang/Mercier

Drafted: December 16, 2003
Initialed: Wang12.5.03/Handelsman12.15.03/Hirsch12.19.03
Final: December 24, 2003

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/s/

Mark S. Hirsch
12/31/03 02:17:22 PM

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

INFORMATION REQUEST LETTER

Dear Dr. Fuh:

Please refer to your supplemental new drug application (NDA 20-180/S 026) dated and received June 12, 2003, submitted under section 505(b)/pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for PROSCAR™ (finasteride 5 mg) for the treatment of benign prostatic hyperplasia (BPH). We have completed our filing review of your application and have identified the following issues:

Clinical

The application is fileable. However, the following are areas of concern and requests for additional clarifying information:

1. Please provide information to support a 4-point rise in American Urological Association (AUA) symptom severity score as a reflection of progression of BPH.

2. Provide justification for the selection of the five criteria in the composite end point called "BPH progression".

3. Explain the impact of the pilot group on the overall results of the study.

4. We acknowledge your intent to submit additional financial disclosure information in October, 2003.

5. There is a slightly higher percentage of patients in the combination group who reported asthenia, postural hypotension, abnormal ejaculation, impotence and syncope than in either drug group alone or placebo. This is a review issue.

6. For each of the 18 clinical sites, please provide the following information:

   - The principal investigator and/or designated contact person, complete site address, and telephone number at each site.
   - The number of subjects enrolled at each site.
   - The number of subjects discontinued from the study at each site.
   - The number of serious adverse events that occurred at each site.

7. We also acknowledge receipt of your supplemental submission (NDA 20-180/S 027) on August 15, 2003. This "Changes Being Effected" supplement proposed labeling changes to include isolated reports of male breast cancer in the ADVERSE REACTIONS, Long-Term Treatment

and for changes in the Information for Patients subsection of PRECAUTIONS to encourage physicians to instruct patients to promptly report any changes in heir breasts, such as lumps, pain or nipple discharge, to their physician.

NDA 20-180/S 027 was approved on September 9, 2003. You must submit revised labeling to 20-180/S 026 based on NDA 20-180/S 027 final printed labeling (FPL).

Clinical Pharmacology and Biopharmaceutics

The application is fileable. No review issues noted at time of filing.

Pharmacology/Toxicology

The application is fileable. However, the following review issue, which is not an impediment to NDA filing, has been identified:

1. [redacted]

Chemistry

The application is fileable. No review issues noted at time of filing.

Statistics

The application is fileable. However, the following are areas of concern and requests for additional clarifying information:

1. Please clarify whether Appendix F has been submitted electronically? If so, please verify the location of Appendix F within the electronic submission. If Appendix F was not submitted electronically, please do so as soon as possible.

2. Please submit electronically the SAS programs used for the primary efficacy and secondary efficacy analyses. The programs should include the variables/files extracted from SAS transport files and criteria used in the algorithms for defining an event. The programs should also include those algorithms used to perform statistical tests not defined in the SAS software. The algorithms, used to define whether a patient is clinically progressed for each of the five criteria (i.e., what variable(s) were used in which SAS transport file(s) when referencing the five criteria) and the algorithms not defined in the SAS software should also be submitted as a separate document.

3. Please provide a separate dataset which includes the following:

   (a) Patient id
   (b) Treatment assignment
   (c) Date of randomization
   (d) Trial start date
   (e) Date of study end
   (f) Date of last completed visit
   (g) Maximum visit date
   (h) Reason of discontinuation

(i) Yes/no as clinically progressed based on condition-1 (see definition below)
(j) Yes/no as clinically progressed based on condition-2
(k) Yes/no as clinically progressed based on condition-3
(l) Yes/no as clinically progressed based on condition-4
(m) Yes/no as clinically progressed based on condition-5
(n) The final composite score (yes/no) on whether a patient is clinically progressed
(o) Trus prostate volume
(p) Max flow rate
(q) AUA symptom score
(r) PSA
(s) Post void residual

Note: (o) to (s) are the variables used to produce Tables 5-3 and 5-4 in reference #1 (p.209 and 210).

If you have any questions, please call Jean King, 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; HFD-580
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Daniel A. Shames
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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:

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

Name of Drug Product:	PROSCAR™ (finasteride, 5 mg)
NDA Number:	NDA 20-180
Supplement number:	026
Review Priority Classification:	Standard (S)
Date of supplement:	June 12, 2003
Date of receipt:	June 12, 2003

This supplemental application provides additional clinical studies in support of proposed changes to the Labeling Sections of the approved New Drug Application for PROSCAR, including but not limited to the following:

1. Under the "Clinical Studies, Prostate Volume as a Predictor of Therapeutic Response" section, you have proposed the addition of clinical data from the Medical Therapy of Prostatic Symptoms (MTOPS) Trial.
2. Under the "Indications and Usage" section, you have proposed a modification to the indication that Proscar, [ ], is indicated for the treatment of symptomatic benign prostatic hyperplasia.
3. Under the "Adverse Reactions: section, you have proposed the addition of safety and tolerability information from the MTOPS, including a proposed statement that "the

relationship between long-term use of Procar and male breast neoplasia is currently unknown".

4. Under the "Dosage and Administration" section, you have proposed reiterating that "Proscar can be administered alone or in combination with the alpha-blocker doxazosin".

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 11, 2003 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be April 12, 2004.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Document Room 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

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

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph.
Chief, Regulatory Project Management
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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