

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***

**20-180/S-022**

***Trade Name:*** Proscar 5mg

***Generic Name:*** finasteride

***Sponsor:*** Merck & Company, Inc

***Approval Date:*** 01/30/2001

***Indications:*** For the treatment of symptomatic benign prostatic hyperplasia (BPH) in men with an enlarged prostate.

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*APPLICATION NUMBER:*

**20-180/S-022**

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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**20-180/S-022**

**APPROVAL LETTER**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville MD 20857

NDA 20-180/S-022

Merck & Co, Inc.  
Attention: Tamra L. Goodrow, Ph.D.  
Associate Director, Regulatory Affairs-Domestic  
Sumneytown Pike  
P.O. Box 4, BLA-20  
West Point, PA 19486

Dear Dr. Goodrow:

Please refer to your supplemental new drug application dated August 24, 1999, received August 25, 1999, 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 April 14 and May 8, 2000.

This supplemental new drug application provides for revisions to the Clinical Pharmacology and Precautions sections to comply with the provisions listed under the Geriatric Use Ruling [21 CFR 201.57(f)(10)(ii)].

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert).

Please 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 ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format - NDAs (January 1999). For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-180/S-022." Approval of this submission by FDA is not required before the labeling is used.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

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Page 2

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

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2  
FDA  
5600 Fishers Lane  
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Evelyn R. Farinas, R.Ph., M.G.A., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

Susan Allen, M.D., M.P.H.  
Director  
Division of Reproductive and Urologic Drug Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosure

/s/

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Susan Allen

1/30/01 11:59:37 AM

**CENTER FOR DRUG EVALUATION AND RESEARCH**

***APPLICATION NUMBER:***

**20-180/S-022**

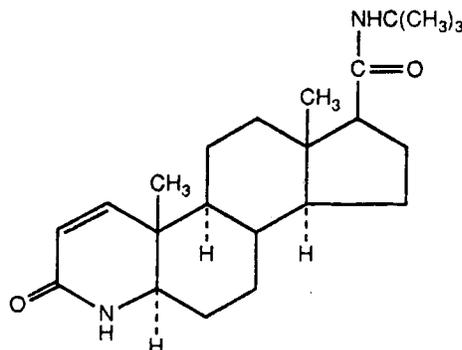
**LABELING**

**PROSCAR®**  
**(FINASTERIDE)**  
TABLETS

**DESCRIPTION**

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

Finasteride is 4-azaandrost-1-ene-17-carboxamide, *N*-(1,1-dimethylethyl)-3-oxo-, (5 $\alpha$ ,17 $\beta$ )-. The empirical formula of finasteride is C<sub>23</sub>H<sub>36</sub>N<sub>2</sub>O<sub>2</sub> 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 $\alpha$ -dihydrotestosterone (DHT). Type II 5 $\alpha$ -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 $\alpha$ -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 $\alpha$ -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 $\alpha$ -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 $\alpha$ -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  $\geq 70$  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  $\mu$ 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 5 $\alpha$ -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 <sup>14</sup>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  $\geq 70$  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  $\geq 70$  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 <sup>14</sup>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).

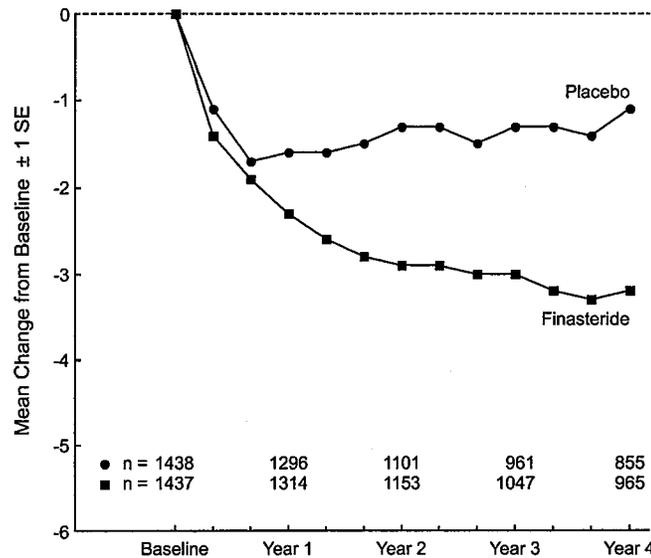
**Effect on Symptom Score**

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 ( $\pm$ 1 SD) decrease in symptom score of 3.3 ( $\pm$  5.8) points compared with 1.3 ( $\pm$  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 .

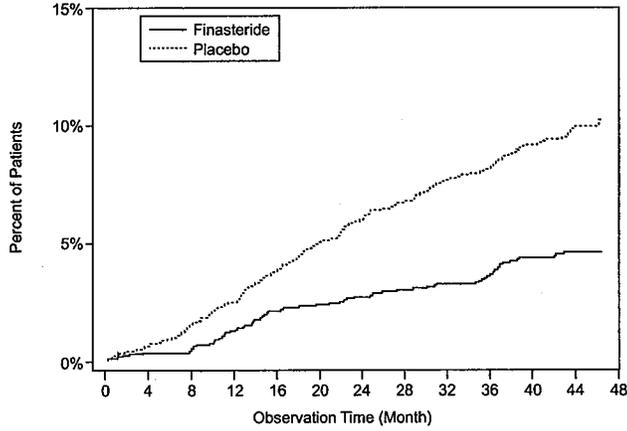
Table 1 All Treatment Failures in PLESS					
Event	Patients (%) *		Relative Risk**	95% CI	P Value**
	Placebo N=1503	Finasteride N=1513			
All Treatment Failures	37.1	26.2	0.68	(0.57 to 0.79)	<0.001
Surgical Interventions for BPH	10.1	4.6	0.45	(0.32 to 0.63)	<0.001
Acute Urinary Retention Requiring Catheterization	6.6	2.8	0.43	(0.28 to 0.66)	<0.001
Two consecutive symptom scores $\geq 20$	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**



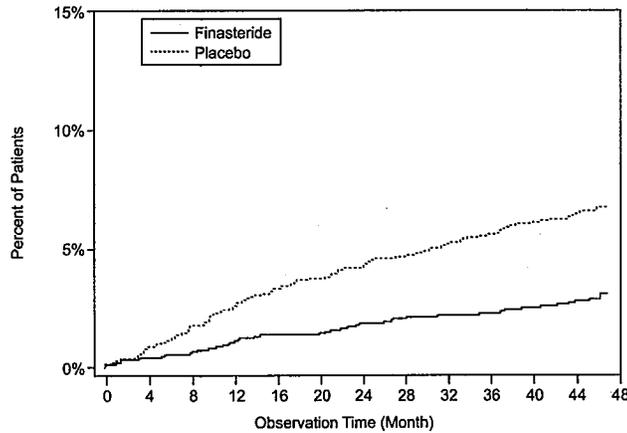
**Placebo Group**

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.

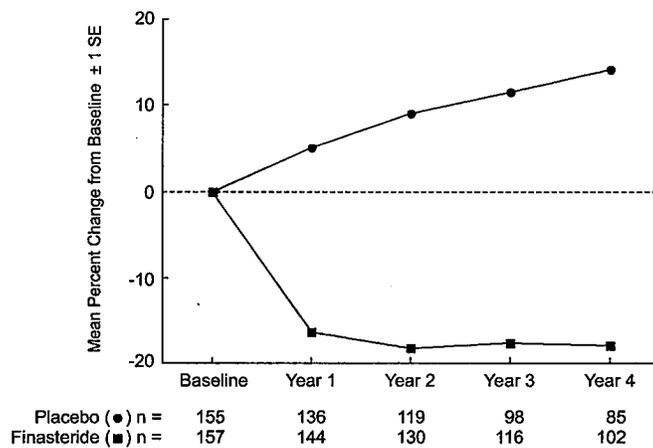
There was a clear difference between treatment groups in maximum urinary flow rate in favor of PROSCAR by month 4 (1.0 vs 0.3 mL/sec) which was maintained throughout the study. In the earlier 1-year studies, increase in maximum urinary flow rate was comparable to PLESS and was maintained through the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



*Prostate Volume as a Predictor of Therapeutic Response*

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

*Summary of Clinical Studies*

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

**INDICATIONS AND USAGE**

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

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

**CONTRAINDICATIONS**

PROSCAR is contraindicated in the following:

Hypersensitivity to any component of this medication.

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

## 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,  $\alpha$ -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<sub>2</sub> 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  $\mu\text{g} \cdot \text{hr/mL}$ ).

In a 19-month carcinogenicity study in CD-1 mice, a statistically significant ( $p \leq 0.05$ ) increase in the incidence of testicular Leydig cell adenomas was observed at a dose of 250 mg/kg/day (228 times the human exposure). In mice at a dose of 25 mg/kg/day (23 times the human exposure, estimated) and in rats at a dose of  $\geq 40$  mg/kg/day (39 times the human exposure) an increase in the incidence of Leydig cell hyperplasia was observed. A positive correlation between the proliferative changes in the Leydig cells and an increase in serum LH levels (2-3 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  $\geq 30$  µg/kg/day ( $\geq 3/10$  of the recommended human dose of 5 mg/day) and decreased anogenital distance when given finasteride at  $\geq 3$  µg/kg/day ( $\geq 3/100$  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 $\alpha$ -reductase inhibitors and are similar to those reported in male infants with a genetic deficiency of Type II 5 $\alpha$ -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<sub>1</sub>) 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<sub>1</sub> 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  $\geq 1\%$  and greater than placebo over the 4 years of the study. In years 2-4 of the study, there was no significant difference between treatment groups in the incidences of impotence, decreased libido and ejaculation disorder.

	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.

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

#### DOSAGE AND ADMINISTRATION

The recommended dose is 5 mg orally once a day.

PROSCAR may be administered with or without meals.

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

#### HOW SUPPLIED

No. 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

#### 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

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WARNINGS, EXPOSURE OF WOMEN — RISK TO MALE FETUS, and PRECAUTIONS, *Information for Patients and Pregnancy*).

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

Issued  
Printed in USA

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**20-180/S-022**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

**Division of Reproductive and Urologic Drug Products**

**Regulatory Project Manager Labeling Review**

**Application Number:** NDA 20-180/S-022  
**Name of Drug:** Proscar (finasteride)  
**Sponsor:** Merck & Co. Inc.  
**Material Reviewed:** Proposed label changes to the approved label  
**Submission Dates:** August 24, 1999  
**Receipt Dates:** August 25, 1999

**Background and Summary Description:**

Sponsor is proposing changes to the **CLINICAL PHARMACOLOGY** and **PRECAUTIONS** sections to comply with the Geriatric Use ruling (21 CFR 201.57). The intent of the final rule is to provide information on the safe and effective use of drugs in patients aged 65 and older. The Geriatric Use subsection should include what is known about the effects of a drug in the elderly and list any limitations, hazards or monitoring associated with geriatric use. The Geriatric Use ruling does not require that the sponsor conduct additional clinical studies. The proposed label was submitted electronically in accordance with the January 1999 Guidance (Guidance for Industry – Providing Regulatory Submissions in Electronic Format – NDAs). A list of references was provided in support of the proposed changes. The sponsor is also requesting a categorical exclusion for the requirements to prepare an Environmental Assessment under 21 CFR 25.31(a) because this supplement will not increase the use of the active moiety. A brief labeling history was included indicating that (at the time of submission) there were  supplements pending approval, S-020

**Review:**

In Section 1, the proposed changes for each of the sections mentioned in the preceding paragraph are compared to the most recently approved Proscar labeling (S-018, August 2, 1999). For each section, the proposed wording is listed first and it is highlighted. The approved labeling is included in the following paragraph. Additional discrepancies that were noted between the proposed label and the approved label are listed in Section 2.

Section 1

**CLINICAL PHARMACOLOGY**, Pharmacokinetics section, Special Populations subsection:  
Geriatric heading:

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**.

No dosage adjustment is necessary in the elderly. Although the elimination rate of finasteride is decreased in the elderly, these findings are of no clinical significance. See also Pharmacokinetics, Excretion and DOSAGE AND ADMINISTRATION.

Sponsor's comments: Editorial revision to add cross-reference to new Geriatric Use subsection.

RPM's comments: The introduction of the words "PRECAUTIONS, Geriatric Use" to the Special Populations under the Geriatric heading serve as cross-reference to the PRECAUTIONS section as indicated by the sponsor.

**PRECAUTIONS, Geriatric Use subsection:**

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).

Most recently approved label does not contain a Geriatric heading under the **PRECAUTIONS** section.

Sponsor's comments: Added subsection for compliance with the Geriatric Use ruling (21 CFR 201.57(f)(10)(ii)). The new text states that there are no overall differences in safety or effectiveness between subjects 65 and over and 75 and over and younger subjects and was based on searches of the Merck clinical and adverse experience databases and of published literature databases.

RPM's comments: Sponsor submitted a list of publications in support of the proposed changes. This list was obtained from the Published Information Resources, which retrieved all articles up to July 15, 1999.

Section 2:

**PRECAUTIONS** section, General subsection, *Effects on PSA and Prostate Cancer Detection:*

The proposed label (in S-022) is missing the following paragraph, already included in the approved label:

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.

RPM's comments: Sponsor submitted an amendment to a pending supplemental new drug application, dated April 14, 2000, to reflect that the approved Package Circular #9132102 (approved August 2, 1999) should be used as the basis for the proposed new geriatric labeling text instead of the text submitted on August 24, 1999. The approved circular includes the three sentences which address percent free PSA, and are mentioned in the previous paragraph.

HOW SUPPLIED section:

NDC 0006-0072-31 unit of use bottles of 30  
(6505-01-362-5331, 5 mg 30's)  
NDC 0006-0072-58 unit of use bottles of 100  
(6505-01-362-74 / 5 mg 100's)  
NDC 0006-0072-28 unit dose packages of 100  
(6505-01-362-533 / 5 mg individually sealed 100's)

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

RPM's comments: Sponsor submitted an amendment to a pending supplemental new drug application, dated April 14, 2000, indicating that the HOW SUPPLIED section of the proposed label should be identical to that of the last approved label (S-018, August 2, 1999).

Logo, last page of label:

Dist. by:  
MERCK & CO. INC., West Point, PA 19486, USA

Dist. by:  
MERCK & CO., INC., Whitehouse Station, NJ 08880, USA

RPM's comments: Sponsor submitted an amendment to a pending supplemental new drug application, dated April 14, 2000, indicating that the proposed label in the Logo should be identical to that of the last approved label (S-018, August 2, 1999).

**Conclusion:**

Addition of the proposed language complies with the Geriatric Use Ruling. Exclusion for the requirements to prepare an Environmental Assessment under 21 CFR 25.31(a) is acceptable.

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Evelyn R. Farinas, R.Ph., MGA  
Regulatory Project Manager

Concurrences:

Comments:

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Cc:  
Original NDA (20-180 S022)  
HFD-580  
HFD-580/Allen/Mann/Shames/Hirsch/Rumble/Farinas

Drafted: erf/4.21.00  
Final: erf/

/s/

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pm label review Proscar S022

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