CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 20180/S16

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-180/S-015
NDA 20-180/S-016

MAR 20 1998

Merck Research Laboratories
Attention: Robert Silverman, M.D., Ph.D.
Senior Director, Regulatory Affairs
P.O. Box 4
West Point, PA 19486

Dear: Dr. Silverman:

Please refer to your supplemental new drug applications dated May 16, 1997 (S-015) and September 19, 1997 (S-016), received May 19, 1997 (S-015) and September 22, 1997 (S-016), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Proscar® (finasteride) .

We acknowledge receipt of your submissions for Supplement 015 dated August 19, September 8, and October 7, 1997, and March 19, 1998.

We also acknowledge receipt of your submissions for Supplement 016 dated January 13, 21, February 2, 13, and 25, and March 19, 1998.

The User Fee goal date for these applications is May 19, 1998 (S-015) and March 22, 1998 (S-016).

These supplemental applications provide for the treatment of benign prostatic hyperplasia (BPH) in men with an enlarged prostate to improve symptoms, reduce the risk of acute urinary retention and reduce the risk of the need for surgery.

We have completed the review of these supplemental applications, including the submitted draft labeling, 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 draft labeling in the submission dated March 19, 1998. Accordingly, these supplemental applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling submitted on March 19, 1998.

Please submit 20 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. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved supplemental NDAs 20-180/S-015 and 20-180/S-016. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

In addition, please submit three copies of the introductory promotional material 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 material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications,
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Should a letter communicating important information about this drug product (i.e., a Dear Doctor letter) be issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to these NDAs and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20852-9787

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, please contact Randy Olmstead, Project Manager, at 301-827-4260.

Sincerely,

/S/

Lisa D. Rarick, M.D.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20180/S16

MEDICAL REVIEW(S)

MAR 13 1998

NDA 20-180 **Reference No.** 016
Reference No. 015

016 Received: September 19, 1997
015 Received: May 16, 1997
MOR complete: February 19, 1998

Medical Officer's Review
(Supplemental New Drug Application)

Study Reports Submitted:

1. The PROSCAR™ Long Term Efficacy and Safety Study (PLESS).
2. "Prostate Volume as a Predictor of Therapeutic Response" (Meta-Analysis) encompassing the following studies:
   - The Veteran Affairs Cooperative Benign Hyperplasia Study Group Trial (VA).
   - The PROSCAR™ Worldwide Efficacy and Safety Study (PROWESS).
   - The Scandinavian Study for the Reduction of the Prostate (SCARP).
   - A Pilot Double-Blind, Placebo-Controlled, Multicenter Study to Investigate the Effects of Finasteride in Patients with Mild Symptoms Associated with Early Benign Prostatic Hyperplasia (Early Intervention Trial).
   - The PROSCAR™ Safety Plus Efficacy Canadian 2-Year trial (PROSPECT).
   - Finasteride (MK-906) in the Treatment of Benign Prostatic Hyperplasia. The Finasteride Study Group. (International Trial).
   - The Effect of Finasteride in Men with Benign Prostatic Hyperplasia. The Finasteride Study Group (North American Trial).
3. Six-Year Phase III Safety and Efficacy Updates.
4. A Double-Blind, Placebo-Controlled, Multicenter Study to Determine the Effect of Finasteride on Semen Production in Male Volunteers.

Sponsor: Merck Research Laboratories
Sumneytown Pike
West Point, PA 19486
Drug: Proscar™ (finasteride)
Pharmacological Class: 5 α-reductase inhibitor
Route of Administration: oral
Proposed Indication: For the treatment of symptomatic benign prostatic hyperplasia (BPH) and:

1. For the prevention of clinical urologic events, to: reduce the risk of acute urinary retention and reduce the risk of surgery, including transurethral resection of the prostate (TURP) and prostatectomy.
2. Patients with an enlarged prostate are the appropriate candidates for therapy with PROSCAR™.

Regulatory Background: On June 19, 1992, the New Drug Application (NDA) which provides for the use of Proscar™ (finasteride 5 mg) tablets in the treatment of symptomatic benign prostatic hyperplasia (BPH) received Agency approval.

In the summary basis for approval, further studies were recommended by the Agency to identify prospectively those men who would respond best to the compound, to provide long-term follow-up data for those patients treated in the phase III trials and to determine whether long-term treatment with Proscar™ would alter the necessity for prostate surgery or reduce the frequency of complications secondary to BPH "down the line".

In order to resolve these issues, the Agency requested and the sponsor agreed to commit to specific phase IV actions including:

In compliance with these phase IV commitments, in this 36 volume submission, the sponsor has submitted the efficacy and safety results for the following studies:

1. The PROSCAR™ Long Term Efficacy and Safety Study (PLESS) - Protocol 048.

Title: "A Double-Blind, Randomized, Placebo-Controlled Multicenter Study to Investigate the Long-Term Effects of Finasteride (MK-0906) in Patients with Benign Prostatic Hyperplasia."

Principal Investigator: John D. McConnell, MD
University of Texas/Southwestern Medical Center
Division of Urology J8.112
Dallas, TX 75235

Subinvestigators: 95 primary investigators in the United States.

Design and Conduct of the Trial : This was a randomized, double-blind, parallel-arm, placebo-controlled, multicenter study. Following a one month placebo run-in, patients were randomized to finasteride 5 mg or placebo, for a duration of 4 years. All patients were scheduled to be seen every 4 months with Month 48 being the final visit.

The *primary efficacy endpoint* was the change in total symptom score after four years of treatment. The range for the total symptom score was 0 (none) to 52 (severe). The AUA symptom score questionnaire was not available at the time the study started, so the sponsor developed a self-administered and validated symptom questionnaire by modifying the Boyarsky instrument. A "Quasi"-AUA symptom score was also determined based on the modified Boyarsky instrument.

The *secondary efficacy endpoint* was the difference in the rates of patient discontinuation due to "treatment failure". In the original protocol, the definition of "treatment failure" included:

1. Clinical deterioration.
2. Lack of improvement.
3. The need for alternative BPH therapy (medical or invasive).

In a revised data analysis plan submitted with Supplement 016 and dated 07MAR97, "treatment failure" was redefined to include:

1. All "urologic events", including all surgical intervention for BPH and all episodes of acute urinary retention (spontaneous and precipitated) requiring catheterization.
2. Bladder stones that required intervention, UTI resulting in antibiotic treatment in a patient with no prior history of UTI, incontinence , or new-onset renal failure.
3. Discontinuation due to worsening of BPH, lack of improvement, or to receive other medical treatment.
4. Symptom score (Quasi-AUA) ≥ 20 at any two consecutive visits after the Month 4 visit.

Reviewer comment: **It is unclear at what point the data analysis plan was revised and whether the Agency was apprised of the revision prior to the submission of this supplement.**

The *tertiary efficacy endpoints*, measured only in a subset of the study population, were the change in maximum urinary flow rate (Qmax) and change in prostate volume (PV).

Study Population:

Patients were men, aged years of age, ambulatory and in generally good health. All patients had a diminished maximum urinary flow rate, an "enlarged" prostate gland by digital rectal examination and "moderate-to-severe' symptoms of BPH based on the results of a symptom questionnaire.

Three thousand forty (3040) patients were entered into the study and randomized: 1524 patients to the finasteride group and 1516 to the placebo group. The treatment groups were well-matched in regard to the baseline characteristics of age, race, height, weight, presence of co-morbid conditions, total urinary symptom score, maximum urinary flow rate, prostate volume and serum PSA.

Withdrawals:

In the finasteride group, 1000 patients (66%) completed the study. In the placebo group, 883 (58%) patients completed the study. The major reasons for discontinuation were: lack of improvement , clinical adverse event, and use of alternative BPH treatment (invasive or medical) (see Table 1).

Table 1 : Reasons for discontinuation-Protocol 048

	Finasteride 5 mg	placebo
protocol violation	7 (0.5%)	9 (0.6%)
lost to follow-up	52 (3.4%)	36 (2.4%)
relocated	15 (1.0%)	14 (0.9%)
withdrew	27 (1.8%)	29 (1.9%)
death	25 (1.6%)	20 (1.3%)
prostate cancer	24 (1.6%)	36 (2.4%)
lack of improvement	99 (6.5%)	104 (6.9%)
worsening of disease	23 (1.5%)	56 (3.7%)
BPH treatment, invasive	24 (1.6%)	73 (4.8%)
BPH treatment, medical	56 (3.7%)	99 (6.5%)
Clinical AE	127 (8.3%)	109 (7.2%)
Laboratory AE	0	1 (0.1%)
Independent medical advice	14 (0.9%)	11 (0.7%)
other	31 (2.0%)	36 (2.4%)
Total discontinuations	524	633
Total entered	1524	1516

Reviewer comment: It is notable that only 6.9% and 3.7% of patients in the placebo group discontinued treatment due to lack of improvement and worsening of disease, respectively. These results demonstrate an overall lack of symptomatic disease progression in the placebo group.

Efficacy Results:

Urologic Events: The first new indication that the sponsor proposed was "to reduce the risk of acute urinary retention and reduce the risk of surgery". In support of this revision, the sponsor placed particular emphasis on the incidence of "urologic events". A urologic event was defined as a BPH-related invasive procedure or an episode of spontaneous acute urinary retention. Tabulation of the 4-year data is shown in Table 2 below:

Table 2: Number of patients (% of total) with "urologic events".

	FINASTERIDE N (%)	PLACEBO N (%)
Urologic "events"	100 (6.6)	199 (13.2)
BPH-related surgical procedures	69 (4.6)	152 (10.1)
TURP	64 (4.2)	125 (8.3)
Acute urinary retention	42 (2.8)	99 (6.6)
spontaneous	20 (1.3)	56 (3.7)
precipitated	23 (1.5)	49 (3.3)
All treatment failures	397 (26.2)	537 (37.1)

The sponsor believes that these results (decreased incidence of spontaneous acute urinary retention and decreased incidence of BPH-associated prostate surgery) offers substantial new benefit to patients.

Reviewer comment: In terms of "treatment failure" the difference between the placebo group (37.1%) and the finasteride group (26.2%) is actually less marked than the difference in " urologic events". Treatment failure is a clinically relevant endpoint which encompasses "BPH-related surgical procedures", alternative medical treatment and watchful waiting. This endpoint should not be ignored in favor of the sponsor-selected subset "urologic events".

In addition, it is unclear when the secondary endpoint and analysis plan was revised. The original protocol specifically defined the secondary endpoint as "discontinuations secondary to treatment failure". An analysis of the data using the original criteria, is shown in Table 3 below:

Table 3: Discontinuations due to treatment failure as defined in the original protocol

Reason for discontinuation	finasteride 5 mg N (%)	placebo N (%)
lack of improvement	99 (6.5)	104 (6.9)
worsening of disease	23 (1.5)	56 (3.7)
alternative BPH treatment-invasive	24 (1.6)	73 (4.8)
alternative BPH treatment-medical	56 (3.2)	99 (6.5)
All discontinuations due to "treatment failure"	202 (13.3)	332 (21.8)

In terms of "discontinuations secondary to treatment failure" as defined in the original protocol, the differences between finasteride and placebo groups is less marked than the difference in "urologic events". It is unclear if the analysis of "urologic events" thus represents a post-hoc analysis of the PLESS data.

Symptom score: In those subjects completing the full 4 years, Quasi-AUA symptom scores was only mildly reduced from baseline values in both the finasteride and placebo groups (see Table 4). Results using data carried forward are similar with respect to the magnitude of the treatment effect. There appeared to be a small, but persistent advantage in favor of the finasteride group, which increased very slightly over the duration of the treatment period .

Table 4: Analysis of the change in Quasi-AUA symptom score (0 to 34 scale).

	Finasteride 5mg	placebo	mean difference (95% CI)
study completers	-3.3 ± 5.8	-1.3 ± 5.6	-2.1 (-2.6, -1.6)
intent-to-treat pop (LVCF*)	-2.6 ± 6.2	-0.7 ± 6.0	-1.8 (-2.3, -1.4)$^{\Delta}$

*Last value carried forward

$^{\Delta}$adjusted for center

Reviewer comment: It should be noted that the minimally perceptible improvement in the AUA symptom score has been estimated to be approximately 3.0 units. When the baseline AUA score is < 20, the perceptible difference is less (approximately 2.0 units), but when the baseline AUA sore is higher (e.g. ≥ 20) then the perceptible difference is greater (approximately 6.0 units).[1] In PLESS, the overall mean difference between placebo and finasteride groups was 2.1 units for study completers and 1.8 for the intent-to-treat population.

Maximum urinary flow rate: In those subjects completing the full 4 years, maximum urinary flow rate was minimally increased from baseline in both finasteride and placebo groups (see Table 5). Results using data carried forward show even less of an effect. There appeared to be a very small but persistent advantage in favor of the finasteride group.

Table 5: Analysis of change in maximum urinary flow rate. (ml/sec)

	Finasteride 5mg	placebo	mean difference (95% CI)
study completers	1.9 ± 4.0	0.2 ± 4.0	1.7 (1.3, 2.1)
intent-to-treat pop (LVCF*)	1.5 ± 4.4	0.1 ± 4.3	

*Last value carried forward

Reviewer comment: The clinical benefit of this difference in maximum urinary flow rate (1.7 ml/sec) is questionable.

Prostate volume: Mean prostate volume in all subjects completing 4 years was decreased in the finasteride group from 55.9 ± 26.4 cm^3 to 45.8 ± 22.9 cm^3, whereas mean prostate size appeared to increase in the placebo group from 51.3 ± 19.9 cm^3 to 58.5 ± 23.6 cm^3. Analysis using data carried forward and not carried forward are similar.

Safety Analysis: The results of this study support the overall good safety profile of finasteride 5 mg. There were 47 total deaths during the study, 27 in the finasteride group and 20 in the placebo group. The most common cause of death was cardiovascular . The death narratives were consistent with prevailing co-morbid condition in this patient population. There were 912 patients with serious adverse events, 455 (29.9%) in the finasteride group and 457 (30.1%) in the placebo group. Only 2 serious events appear to be likely related to study drug. These were two patients in the finasteride group with *gynecomastia* requiring biopsy (both negative). A third patient in the finasteride group suffered visual disturbances secondary to retinal vein occlusion which may have been drug-related. *Breast enlargement and tenderness* were reported in 47 and 28 patients in

[1] Barry, M.J., Williford, W.O., Chang, Y., Machi, M., Jones, K.M., Walker-Corkery, E. and Lepor, H.: Benign prostatic Hyperplasia Specific Health Status Measures in Clinical Research: How Much Change in the American Urological Association Symptom Index and the Benign Prostatic Hyperplasia Impact Index is Perceptible to Patients? J. Urol., 154: 1770-1774, 1995.

the finasteride group, respectively, compared with 32 and 7 patients in the placebo group. Two patients with documented breast cancer were actually reported in the placebo group and none in the finasteride group. *Sexual adverse events* were reported more frequently in the finasteride group as shown in Table 6 below:

Table 6: Sexual adverse experiences.

adverse event	treatment	n (%)	p-value
libido decreased	finasteride	153 (10.0)	<0.001
	placebo	100 (6.6)	
impotence	finasteride	247 (16.2)	<0.001
	placebo	169 (11.1)	
decreased ejaculate vol.	finasteride	88 (5.8)	<0.001
	placebo	19 (1.3)	

A variety of *urinary tract complaints*, including dysuria, hematuria, renal calculus, prostatitis, renal insufficiency, urinary frequency, urinary incontinence, urinary tract infection, urinary tract obstruction, and urinary urgency were less frequently reported in the finasteride group than in placebo, but not to statistically significant difference.

The new reports of *cataracts* was slightly greater in the finasteride group than the placebo group (66 versus 40). Although this difference was statistically significant ($P \leq 0.05$), when background history was taken into account, no clinically relevant difference was noted for this particular adverse event. Extensive 6 month and 1 year opthalmologic examinations were performed for the original marketing application for finasteride 5 mg and these did not reveal any differences in ocular pathology between active treatment and placebo.

In regard to *screening for prostate cancer* using serum PSA, using the "multiply-by-2" rules appears to maintain a clinically similar level of specificity and sensitivity of the PSA assay. The detection of new prostate cancers was similar between the treatment groups.

Finally, there were no significant differences in laboratory adverse events between the groups.

<u>Reviewer's Assessment of Safety and Efficacy (PLESS):</u>

Although the decreased incidence of "urologic events" lends some support to the efficacy of finasteride 5 mg, the significance of this data must be tempered by the demonstration of a relatively stabile disease process in the placebo group, the repeated demonstration of very little treatment effect (e.g. improvement in the AUA symptom score which may be less than the clinically perceptible and minimal improvement in urinary flow), and the clinically significant overall treatment failure rate seen in the finasteride 5 mg treatment group.

These data do not support the new indication: "to prevent 'urologic events'". First, the term "urologic events" does not encompass all clinically significant paths of treatment failure (including lack of clinical improvement, worsening of symptoms, alternative medical therapy, watchful waiting). In this regard, very little difference was noted in the number of patients who reported lack of clinical improvement between the finasteride and placebo groups. Second, the analysis of "urologic events" appears to be a post-hoc assessment of the PLESS data, rather than a prospective analysis powered to detect a difference in "urologic events". Third, no other study has been submitted to confirm this claim and the actual number of "urologic events" in this study was relatively small. The clinical studies section of the label should describe this new data but a new indication has not been supported. The label should also reflect the percent of overall treatment failures, the relatively benign course of the placebo group, the actual symptom score and maximum flow rate improvements observed in the finasteride group and the sexual adverse events observed in the finasteride group.

2. Prostate Volume as a Predictor of Therapeutic Response (Meta-analysis)

Background: The efficacy of finasteride was questioned in a study sponsored by the Veterans Administration, which compared finasteride with placebo, terazosin and a combination of terazosin and finasteride. The results of this study demonstrated no significant differences between finasteride and placebo in terms of symptom score or maximum urinary flow rate. Since the mechanism of action of finasteride is thought to be reduction of prostate size, and the VA study included men without prostatic enlargement, the sponsor believes that the results of the study did not reflect the true efficacy of finasteride in the intended patient population.

In this portion of Supplement 016, the sponsor submits the results of seven studies (as listed on page 1 of this review) in order to support the claim that men with an enlarged prostate are the appropriate candidates for therapy with Proscar™. These results were previously submitted in Supplement 015 but were updated in this submission to include the results of a seventh trial (PROWESS). The studies represent all of the sponsor's placebo-controlled trials with Proscar™ of at least one year duration.

Design and Conduct of the Trials: These were all double-blind, randomized, placebo-controlled, parallel-arm, multicenter trials. The duration of treatment was either one year (VA, North American, International and Early Intervention) or two years (SCARP, PROSPECT and PROWESS). Overall, the efficacy endpoints were relatively similar for all seven studies. The common elements were change from baseline in symptom score, maximum urinary flow rate, and excluding the VA study, prostate volume.

Study Populations: Overall, the inclusion criteria were relatively similar for all seven studies. The common elements were age and sex (men, aged 40, 45 or 50 years to 75 or

80 years), BPH-related symptoms, diminished maximum urinary flow rates (<15 cc/sec), acceptable post-voiding residual urine volumes, overall good patient health status, and an enlarged prostate gland (excluding the VA and Early Intervention studies).

Withdrawals and Compliance: Table 7 demonstrates the number of patients that entered the finasteride 5 mg and placebo arm of each study and the number of patient that completed the study treatment. Overall, for all seven studies, major protocol violations and loss of patients due to inadequate follow-up appeared relatively minor.

Table 7: Withdrawals: Meta-analysis

		Placebo	finasteride 5mg
VA	entered	305	310
	completed	254	243
PROWESS	entered	1452	1450
	completed	1119	1092
SCARP	entered	354	353
	completed	290	287
Early	entered	97	100
Intervention	completed	91	89
PROSPECT	entered	303	310
	completed	227	248
International	entered	255	246
	completed	205	202
North American	entered	300	297
	completed	266	259

Efficacy Results:

Symptom score: There were improvements seen in the mean symptom score (change-from-baseline) in the finasteride group in every study. The placebo group also demonstrated improvement in mean symptom score in every study, except Early Intervention and SCARP. The actual differences between finasteride and placebo in terms of symptom score improvement were statistically significant in all studies except Early Intervention and VA.

Reviewer comment: The actual numeric improvement in symptom score was uniformly small (see Table 8), and in all cases, was less than the minimally perceptible clinical difference of 2.7 units.

Maximum urinary flow rate: There were improvements seen in the mean maximum urinary flow rate in the finasteride group in every study. Similarly, the placebo group demonstrated improvement in mean maximum urinary flow rate in every study, except SCARP. The differences between finasteride and placebo groups in terms of maximum urinary flow rate improvement were statistically significant in all studies except VA.

Reviewer comment: The actual numeric improvement in maximum urinary flow rate was uniformly small (see Table 9).

Change in symptom score and flow rate stratified by prostate volume:
When these results were stratified by prostate size, there was evidence that the improvement in symptoms and maximum urinary flow rate increased with increasing size of the gland. For symptom score, placebo response seemed to decrease with increasing prostate size, while the treatment effect seemed to remain the same or to improve slightly (see Table 8). For maximum urinary flow, the placebo response did not vary with increasing prostate size, but the finasteride effect appeared to improve (see Table 9).

Table 8: Change from baseline in mean Quasi-AUA symptom score stratified by prostate size: all completers from all 7 studies.

Size	F/P[1] <20 gm	F/P 20-29 gm	F/P 30-39 gm	F/P 40-49 gm	F/P 50-59 gm	F/P ≥60 gm
7 studies	2.13/1.78	2.07/1.53	2.33/1.49	2.24/1.36	2.37/0.93	2.69/0.98
95%CI						
finasteride	(1.42, 2.84)	(1.6, 2.54)	(1.91, 2.75)	(1.74, 2.74)	(1.77, 2.97)	(2.13, 3.25)
placebo	(1.0, 2.57)	(1.09, 1.96)	(1.02, 1.95)	(0.9, 1.82)	(0.33, 1.53)	(0.48, 1.48)

[1]F/P = finasteride/placebo

Table 9: Change from baseline in mean maximum urinary flow rate by prostate size: all completers from all 7 studies.

Size	F/P[1] <20 gm	F/P 20-29 gm	F/P 30-39 gm	F/P 40-49 gm	F/P 50-59 gm	F/P ≥60 gm
7 studies	1.25/0.36	1.48/0.97	1.61/0.80	1.28/0.54	1.37/0.15	1.93/0.32
95%CI						
finasteride	(0.57, 1.94)	(1.04, 1.93)	(1.24, 1.98)	(0.89, 1.67)	(0.81, 1.94)	(1.49, 2.38)
placebo	(-0.21, .92)	(0.57, 1.38)	(0.46, 1.15)	(0.04, 1.05)	(-0.31, .61)	(-0.04, .68)

[1]F/P = finasteride/placebo

Reviewer's assessment of efficacy (Meta-Analysis): **This data supports the claim that finasteride demonstrates statistically greater effects on symptom score and flow rate in men with larger prostates. However, these differences are still modest and are likely to be clinically imperceptible. These results, obtained from all subjects who completed the full duration of each study, do not reflect the intent-to-treat population and must be assumed to represent the best possible treatment effect.**

The label should reflect the actual numeric improvements in symptom score and flow rate in these 7 studies and should describe, in tabular format, the actual numeric improvements in symptom score and flow rate in men with small prostates (< 40 gm) versus men with large prostates (≥ 40 gm).

The sponsor should explain the rationale for choosing 40 gm as a cut-off value for prostate volume for maximal benefit, when the data seems to point to 50 gm as the appropriate break point.

3. Six-Year Phase III Safety and Efficacy Updates - Protocols 008, 507 and 508.

Design and Conduct of the Trial: These studies were five-year, open-label, extensions of the original phase 3 studies. All three original studies were 1 year, multicenter, randomized, placebo-controlled, double-blind studies of finasteride 5 mg (536 subjects) or finasteride 1 mg (537 subjects) versus placebo (547 subjects).

Withdrawals: One thousand six hundred twenty patients (1620) entered the original, 1-year, randomized, double-blind trials. Of these, 1344 participated in the open-label extension. Of these, 739 completed the entire 5-year extension study.

Of the 605 patients that discontinued during the 5-year extension period, 179 did so due to clinical adverse events, 5 did so due to laboratory adverse events and 421 did so for "other" reasons. The most common reasons for discontinuation due to clinical adverse events were sexual (diminished libido, impotence and ejaculation disorder), prostate cancer and urinary retention. The most common reason for discontinuation due to laboratory AE was elevated PSA. The submission does not account for the 421 discontinuations due to "other" reasons.

Efficacy Results:
Data at 72 months was available for 183, 217, 169 subjects from the original finasteride 5 mg treatment group, for prostate volume, Quasi-AUA symptom score and maximum urinary flow rate, respectively.

Prostate volume: There were 183 patients from the original finasteride 5 mg treatment group who had available data at Month 72 for determination of prostate volume. In this group of patients, a decrease in mean prostate volume from 56.1 cc to 43.2 cc (19.5%) was observed at the end of the original 1-year trial. The sponsor believes, that in this group, over the ensuing 5 years, that decrease in prostate volume was maintained.

Quasi-AUA symptom score: There were 217 patients from the original finasteride 5 mg treatment group who had available data at Month 72 for Quasi-AUA symptom score. In this group of patients, a decrease in mean Quasi-AUA symptom score from 12.8 to 9.3 (-3.5 units total) was observed at the end of the original 1-year trial. The sponsor believes that the mean symptom score in this group of patient decreased even further at the end of the first year of the open label period (-4.3 units total) and that that degree of improvement was maintained over the ensuing 4 years.

Maximum urinary flow: There were 169 patients from the original finasteride 5 mg treatment group who had available data at Month 72 for determination of maximum urinary flow rate. In this group of patients, an increase in the mean maximum flow from 11.1 cc/sec to 12.9 cc/sec (+1.7 cc/sec) was observed at the end of the original 1-year

trial. The sponsor believes that the mean flow rate gradually improved over the ensuing 5 years (Month 72 = 14.0 cc/sec).

The sponsor posed an argument to refute the possible claim that these patients represent a self-selected group of responders. The sponsor first argued that the group of patients with Month 72 data was relatively similar to that group without Month 72 data, at baseline. The group with Month 72 data was only slightly less symptomatic, had slightly greater maximum urinary flows and had slightly larger prostates than those without Month 72 data. Secondly, the sponsor argued that the group of patients with Month 72 data were reasonably similar to the group without Month 72 data, with respect to treatment response at the end of the original 1-year trial. The sponsor argues that there were small or no differences between these groups in terms of percent change in prostate volume, total symptom score and maximum urinary flow rate at the end of the original 1-year trial.

Safety Analysis:
Deaths: Of the initial 1620 patients who entered the phase 1 study, 59 died during the 6-year study period. In all cases, these deaths were not drug-related and reflect the general overall co-morbid conditions in the patient population.

Overall clinical adverse events: The actual number of clinical adverse events noted in the 5 year extension study is not defined. However, the percentage of patients in each year reporting clinical adverse events, serious clinical adverse events and drug-related serious clinical adverse events is noted in Table 10 below:

Table 10: Percent of patients reporting clinical AEs per year of study

	Year 2 (N=1344)	Year 3 (N=1218)	Year 4 (N=1085)	Year 5 (N=957)	Year 6 (N=853)
Number (%) of patients with one or more AEs	709 (52.8%)	570 (46.8%)	487 (44.9%)	430 (44.9%)	486 (57.0%)
Number (%) of patients with serious AEs	109 (8.1%)	91 (7.5%)	100 (9.2%)	92 (9.6%)	129 (15.1%)
Number (%) of patients with serious, drug-related AEs	10 (0.7%)	7 (0.6%)	5 (0.5%)	2 (0.2%)	4 (0.5%)

A review of the serious adverse events considered drug-related by the individual investigators reveals 1 adverse event (cataracts) which may be drug-related.

Sexual adverse events: The percent of patients reporting sexual AEs, including impotence, diminished libido and ejaculatory disorder, (7.9% -11.1% yearly) and the actual number of first reports of sexual AEs per year (18-34) remained relatively constant throughout the 5 year period. The sponsor claimed that this data demonstrates that some sexual AEs resolve while on treatment ("low rate of discontinuation due to sexual AE,

coupled with relatively constant reporting of sexual AEs and new reports of sexual AE").
Reviewer comment: The data are insufficient to support the claim that sexual AEs resolve while on treatment.

Breast adverse events: The number of new breast complaints per year (1-7) and percent of patients reporting "breast complaints" (0.6-1.2% yearly) was relatively constant for the 5-year period. However, the sponsor has not provided details concerning these complaints.

Laboratory adverse events: No clinically significant laboratory AEs were observed for the duration of the 5-year study period.

Reviewer's Assessment of Safety and Efficacy - 6-year Phase III Safety and Efficacy Updates: These safety data confirm the acceptable safety profile of finasteride 5 mg in long-term clinical use. The label should reflect the well-known sexual adverse events (impotence, diminished libido and ejaculatory disorder). The sponsor should submit narrative data for the breast "complaints". No claims can be made from the results of PSA testing or the detection of prostate cancer since the PSA assay was performed at differing labs, using differing techniques. The claim that some sexual AEs resolve with time is speculative and unsubstantiated.

In regard to efficacy claims, these data reflect a self-selected group of patients from an open-label extension study. The sponsor has not provided detailed information on the large number of patients (the vast majority, in fact) who did not complete this study. The sponsor's argument that the completers compare favorably to the dropout group at baseline and at the end of the original 1-year trial, does not provide sufficient data to assess the reasons for patient drop-out and to assess the overall efficacy of finasteride 5 mg in this study. No claims for 5-year efficacy have been substantiated by these data.

4. A Double-Blind, Placebo-Controlled, Multicenter study to Determine the Effect of Finasteride on Semen Production in Male Volunteers - Protocol 056.

Background: The Finasteride 12-week Semen Production Study was performed to evaluate the effects of finasteride on semen production and sexual function in men 30 to 50 years of age without BPH. This study was reviewed in NDA 20-788 for Propecia, (finasteride 1 mg). The study demonstrated that subjects treated with finasteride 5 mg per day for 12 weeks did not differ significantly from subjects treated with placebo in terms of sperm concentration, total sperm count, sperm motility or sperm morphology. However, there was a reduction in ejaculate volume that was reversible when treatment was stopped. The object of Protocol 056 was to evaluate the effects of finasteride 5 mg on two spematogenic cycles rather than one, to determine the effects of finasteride 5 mg on sexual function, and to determine when any possible effects reverse.

Design and Conduct of the Study: This was a 60-week, double-blind, randomized, placebo-controlled multicenter study. After a 2-week placebo run-in period, subjects were randomized to either finasteride 5 mg or placebo, daily for 24 weeks. All subjects provided semen samples for analysis at baseline and then at weeks -1, 12, 24, 36, 48 and 60. A total of three semen samples were provided by each subject per collection period (Monday, Wednesday and Friday). Following an interim review of the data, the sponsor decided to collect additional samples at week 84 and 108. A sexual function questionnaire was administered to all subjects at weeks -2, 1, 12, 24, 36, 48 and 60. Full serum lipid profiles were collected at Weeks 12, 24 and 60. Serum levels of testosterone, dihydrotestosterone. LH and FSH were collected at Weeks 12, 24, 36, 48 and 60.

The primary objective of the study was to determine the effect of treatment on semen production and to gauge the reversibility of treatment following a period off drug. The study was powered to detect a mean difference between active treatment and placebo groups of 0.50 ml ejaculate volume and a mean within-group change from baseline of 0.35 ml ejaculate volume.

Study Population: Subjects were healthy males between 18 and 50 years of age, with normal baseline semen analysis parameters.

Withdrawals: Table 11 describes the number of subjects enrolled and number completed.

Table 11: Patient Accounting-Protocol 056

	Finasteride 5 mg	Placebo	Total
entered	70	68	138
completed	59	56	115
discontinued	11	12	23

The reasons for discontinuation are listed in Table 12. All 7 subjects who were discontinued due to laboratory AE demonstrated two consecutive evaluations where their sperm concentration dropped below 20 million per ml. These patients were dropped at Week 12.

Table 12: Reasons for discontinuation-Protocol 056

Reason for discontinuing	Finasteride 5 mg	Placebo
noncompliance	1	0
protocol violation	1	1
pregnancy, mate	1	0
relocating	2	0
withdrew	1	2
Lost to follow-up	2	3
clinical AE	1	1
laboratory AE	2	5
Total	11	12

Safety Results:

Ejaculate volume: No significant decrease in ejaculate volume was noted at any time point in the placebo group. In the finasteride group, however, at Week 12, a mean decrease in ejaculate volume of 0.4 ml (13.8%) was noted, which increased to 0.6 ml (20.7%) at Week 24. After cessation of finasteride 5 mg. treatment, mean ejaculate volume returned to baseline over a period of 72 weeks.

Reviewer comment: Finasteride 5 mg treatment appears to be associated with a reversible decrease in ejaculate volume.

Sperm concentration: At Week 12, similar decreases in mean sperm concentration were noted in both treatment and placebo groups (see Table 13). At Week 24, further slight decreases from baseline were noted in both the finasteride 5 mg group and placebo group. No significant between-group differences were noted for either timepoint. At Week 36 and beyond, both groups appeared to demonstrate no significant difference from baseline.

Reviewer comment: The conclusion that no significant change in sperm concentration is induced by finasteride 5 mg is supported by these data.

Table 13: Change in mean sperm concentration (million/ml) - protocol 056

Week	Treatment	n	pre (mean)	post (mean)	difference
12	finasteride 5mg	68	65.8	59.7	-6.1
	placebo	64	67.2	60.3	-6.9
24	finasteride 5mg	63	66.6	57.8	-8.8
	placebo	57	70.0	61.3	-8.7

Semen pH: Changes in semen pH were insignificant in both groups, for the duration of the study.

Sperm morphology: Changes in percent sperm with normal morphology were insignificant in both groups, for the duration of the study.

Sperm motility: Mean percent motile sperm were diminished at Week 12 and 24 in the finasteride group, but only at Week 12 in the placebo group (see Table 14). Although the change from baseline values were small, and appeared clinically insignificant, significant between-group differences were noted at both 12 and 24 weeks. For the remainder of the study, there were no between group differences.

Table 14: Change in mean percent of motile sperm - protocol 056

Week	Treatment	n	pre (mean)	post (mean)	difference
12	finasteride 5mg	68	59.6	55.2	-4.4*
	placebo	64	58.7	57.2	-1.5
24	finasteride 5mg	63	59.2	55.4	-3.8**
	placebo	57	58.9	59.3	0.4

*p = 0.002, **p = 0.014

Sexual Function: Since the questionnaire was found to be invalid by the sponsor during the conduct of the trial, these results will not be reviewed.

Lipids: At Week 24, there were differences noted between treatment groups in terms of percent change from baseline for total cholesterol and high-density lipoprotein-cholesterol (HDL-C). This was due to a slight increase from baseline in cholesterol and HDL-C in the finasteride 5 mg group. No clinically significant treatment effects were noted on triglycerides, low density lipoproteins and very low density lipoproteins.

Reviewer Assessment of Safety - Protocol 056:

The study supports the claim that finasteride is associated with a small decrease in ejaculate volume which is reversible with cessation of drug treatment. This claim should also reflect the duration of time off-drug that is necessary for complete reversal of this effect, which appears to be 72 weeks. There is a small, clinically insignificant drop in the percent motile sperm at 24 weeks.

Reviewer's Overall Assessment of Safety and Efficacy:

Protocol 048/PLESS: Pursuant to phase IV commitments,

Therefore, the results of PLESS support specific label revisions but do not support sweeping changes to the fundamental indication for Proscar.

5-year extension studies (Protocols 008, 507 and 508): Pursuant to phase IV

Labeling Implications: Based on these study reports, the sponsor has proposed changes to the current label. Reviewer comments are listed below:

Redacted 6

pages of trade

secret and/or

confidential

commercial

information

Recommended regulatory action: I recommend that this efficacy supplement receive approval. The recommended label revisions will be communicated to the sponsor in a regulatory letter.

7/17/98

Mark S. Hirsch, M.D.
Medical Officer
DRUDP
cc: Orig NDA 20-180
HFD-580 Division File
HFD-580/LRarick/DShames/TRumble/ROlmstead

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20180/S16

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

FEB 10 1998

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW
Division of Pharmaceutical Evaluation II

NDA: **20-180**

Compound: Proscar® (Finasteride)

Sponsor: Merck & Co., Inc.

Type of Submission: Supplemental NDA

Date of Submission: 05/16/97 Supplement No. 015
09/19/97 Supplement No. 016

Reviewer: Sam H. Haidar, R.Ph., Ph.D.

Background:

NDA 20-180 for Proscar® (finasteride) 5mg tablets, was approved on June 19,1992. Finasteride is a specific inhibitor of 5 α-reductase isozyme, which metabolizes testosterone to the more potent androgen, dihydrotestosterone. It is currently used in the treatment of benign prostatic hyperplasia (BPH).

Merck submitted efficacy supplement No. 015 to NDA 20-180 on May 16, 1997, which included labeling changes based on the results from a recently published meta-analysis of one-year data from six randomized clinical trails which concluded that baseline prostate size helps predict the outcome from treatment of symptomatic benign prostatic hyperplasia with Proscar®. Efficacy supplement No. 016 to NDA 20-180 was submitted on September 19, 1997, to support the use of Proscar® for reducing the risk of acute urinary retention, and reducing the risk of surgery (i.e., transurethral resection of the prostate and prostatectomy). A new labeling with the proposed changes was included in the submission.

Comments:

1. Efficacy supplement 015, submitted on May 15, 1997, should include the changes recommended by the Agency for Efficacy Supplement 016, submitted on September 19, 1997.

2. Recommended changes for the labeling included in Efficacy Supplement 016 are the following:

Recommendation:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) has reviewed NDA 20-180, Supplements 015 and 016 submitted on 05/16/97 and 09/19/97, respectively. The proposed labeling is acceptable provided that the changes listed in Comment 2 are incorporated as appropriate.

Please convey the Comments and Recommendation as appropriate to the sponsor.

Sam H. Haidar, R.Ph., Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

RD initialed by Angelica Dorantes, Ph.D., Team Leader AD 2/10/98
FT signed by Angelica Dorantes, Ph.D., Team Leader 2/10/98

cc:
NDA 20-180
HFD-870 (M. Chen, A. Dorantes, S. Haidar)
HFD-580 (R. Olmstead, M. Hirsch)
CDR (Barbara Murphy For Drug)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20180/S16

ADMINISTRATIVE DOCUMENTS

ITEM 13
PATENT AND EXCLUSIVITY INFORMATION
MERCK RESEARCH LABORATORIES

1)	Active Ingredient(s)	Finasteride
2)	Strength(s)	5 mg
3)	Trade Name	PROSCAR®
4)	Dosage Form, Route of Administration	Tablets, Oral
5)	Applicant Firm Name	Merck Research Laboratories
6)	NDA Number	20-180
7)	Approval Date	
8)	Exclusivity - Date First ANDA could be approved	Three (3) Years from this NDA approval date or Five (5) Years from June 19, 1992 (June 19, 1997)
9)	Applicable patent numbers and expiration date of each	4,377,584 Expiration Date: 3/22/2000 4,760,071 Expiration Date: 6/19/2006 w/PTR

Patent Department

Merck & Co., Inc.
P.O. Box 2000
Rahway NJ 07065-0907
Fax 908 594 4720
Tel 908 594 4000
Cable MERCKRAH
Telex 138825

May 9, 1997

MERCK

PROSCAR®
NDA 20-180
Finasteride

Item 14

Pursuant to the provisions of Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act 21 U.S.C. § 355 (b)(1) and in accordance with Title 21 C.F.R. 314.70(b), attached hereto please find the patent information for the above-identified application.

The undersigned declares that U.S. Patent Nos. 4,377,584, and 4,760,071, cover the formulation, composition, and/or method of use of PROSCAR® (finasteride 5 mg tablet), the subject of this application for which approval is being sought.

U.S. Patent No. 4,377,584, having an expiration date of March 22, 2000, claims a genus of chemical compounds including finasteride. This patent is owned by Merck & Co., Inc., Rahway, NJ.

The undersigned declares that U.S. Patent No. 4,377,584 covers the composition PROSCAR®. This product is the subject of this application for which approval is being sought.

U.S. Patent 4,760,071 has an expiration date of June 19, 2006 as extended by granted Patent Term Restoration under 35 U.S.C. § 156. This patent claims the chemical compound finasteride 17β-(N-tert-butyl-carbamoyl)-4-aza-5α-androst-1-ene-3-one. It is owned by Merck & Co., Inc., Rahway, NJ.

The undersigned declares that U.S. Patent No. 4,760,071 covers the composition PROSCAR®. This product is the subject of this application for which approval is being sought.

A claim of infringement could be asserted if a person not licensed by the owner of U.S. Patent Nos. 4,377,584 or 4,760,071 engaged in the manufacture, use or sale of PROSCAR®.

Sincerely,

Catherine D. Fitch
Senior Patent Attorney

ITEM 13
PATENT AND EXCLUSIVITY INFORMATION
MERCK RESEARCH LABORATORIES

1)	Active Ingredient(s)	Finasteride
2)	Strength(s)	5 mg
3)	Trade Name	PROSCAR®
4)	Dosage Form, Route of Administration	Tablets, Oral
5)	Applicant Firm Name	Merck Research Laboratories
6)	NDA Number	20-180
7)	Approval Date	
8)	Exclusivity - Date First ANDA could be approved	Three (3) Years from this NDA approval date
9)	Applicable patent numbers and expiration date of each	4,377,584 Expiration Date: 3/22/2000 4,760,071 Expiration Date: 6/19/2006 w/PTR

August 25, 1997

PROSCAR®
NDA 20-180
Finasteride

Item 14

Pursuant to the provisions of Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act 21 U.S.C. § 355 (b)(1) and in accordance with Title 21 C.F.R. 314.70(b), attached hereto please find the patent information for the above-identified application.

The undersigned declares that U.S. Patent Nos. 4,377,584, and 4,760,071, cover the formulation, composition, and/or method of use of PROSCAR® (finasteride 5 mg tablet), the subject of this application for which approval is being sought.

U.S. Patent No. 4,377,584, having an expiration date of March 22, 2000, claims a genus of chemical compounds including finasteride. This patent is owned by Merck & Co., Inc., Rahway NJ.

The undersigned declares that U.S. Patent No. 4,377,584 covers the composition PROSCAR®. This product is the subject of this application for which approval is being sought.

U.S. Patent 4,760,071 has an expiration date of June 19, 2006 as extended by granted Patent Term Restoration under 35 U.S.C. § 156. This patent claims the chemical compound finasteride 17β-(N-tert-butyl-carbamoyl)-4-aza-5α-androst-1-ene-3-one. It is owned by Merck & Co., Inc., Rahway, NJ.

The undersigned declares that U.S. Patent No. 4,760,071 covers the composition PROSCAR®. This product is the subject of this application for which approval is being sought.

A claim of infringement could be asserted if a person not licensed by the owner of U.S. Patent Nos. 4,377,584 or 4,760,071 engaged in the manufacture, use or sale of PROSCAR®.

Sincerely,

Melvin Winokur
Patent Counsel

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

NDA/BLA # 20-180 Supplement # 015 Circle one: SE1 SE2 SE3 SE4 **SE5** SE6

HF- 580 Trade and generic names/dosage form: Proscar® (finasteride) 5 mg orally Action: **AP** AE NA

Applicant: Merck Research Laboratories Therapeutic Class: 6S

Indication(s) previously approved: Benign Prostatic Hyperplasia (BPH)
Pediatric information in labeling of approved indication(s) is adequate X inadequate ____ ____
Proposed indication in this application: BPH in men with enlarged prostate

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.
IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? ___Yes (Continue with questions) _X_No (Sign and return the form)
WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)
__Neonates (Birth-1month) __Infants (1month-2yrs) __Children (2-12yrs) __Adolescents(12-16yrs)

1. PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

2. PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

3. PEDIATRIC STUDIES ARE NEEDED. There is potential for use in children, and further information is required to permit adequate labeling for this use.

a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

c. The applicant has committed to doing such studies as will be required.
(1) Studies are ongoing,
(2) Protocols were submitted and approved.
(3) Protocols were submitted and are under review.
(4) If no protocol has been submitted, attach memo describing status of discussions.

d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

4. PEDIATRIC STUDIES ARE NOT NEEDED. The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

5. If none of the above apply, attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? ___ Yes ___No
ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from Medical Review (e.g., medical review, medical officer, team leader)

/S/ Project Manager 3/20/98

Signature of Preparer and Title Date

cc: Orig NDA/BLA # 20-180/S-015
HFD-580 /Div File
NDA/BLA Action Package
HFD-006/ KRoberts(revised 10/20/97)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK)

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

NDA/BLA # 20-180 Supplement # 016 Circle one: **SE1** SE2 SE3 SE4 SE5 SE6

HF- 580 Trade and generic names/dosage form: Proscar® (finasteride) 5 mg orally Action: **AP** AE NA

Applicant: Merck Research Laboratories Therapeutic Class: 6P

Indication(s) previously approved: Benign Prostatic Hyperplasia (BPH)
Pediatric information in labeling of approved indication(s) is adequate X inadequate ____ ___
Proposed indication in this application: BPH in men with enlarged prostate to improve symptoms, reduce risk of acute urinary retention, reduce risk of surgery

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.
IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? ___Yes (Continue with questions) _X_No (Sign and return the form)
WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)
__Neonates (Birth-1month) __Infants (1month-2yrs) __Children (2-12yrs) __Adolescents(12-16yrs)

1. PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

2. PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

3. PEDIATRIC STUDIES ARE NEEDED. There is potential for use in children, and further information is required to permit adequate labeling for this use.

a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

c. The applicant has committed to doing such studies as will be required.
(1) Studies are ongoing,
(2) Protocols were submitted and approved.
(3) Protocols were submitted and are under review.
(4) If no protocol has been submitted, attach memo describing status of discussions.

d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

4. PEDIATRIC STUDIES ARE NOT NEEDED. The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

5. If none of the above apply, attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? ___ Yes ___No
ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from Medical Review (e.g., medical review, medical officer, team leader)

/S/ Project manager 3/20/98
Signature of Preparer and Title Date

cc: Orig NDA/BLA # 20-180/S-016
HFD-580 /Div File
NDA/BLA Action Package
HFD-006/ KRoberts(revised 10/20/97)

NDA 20-180/S-015
NDA 20-180/S-016
Proscar® (finasteride)
Merck Research Laboratories

DSI Audit of Clinical Studies

No clinical studies were audited.

NDA 20-180/S-015
NDA 20-180/S-016
Proscar® (finasteride)
Merck Research Laboratories

Division Director's Memo

The application will be signed off at the Division level. No memo is necessary.

NDA 20-180/S-015
NDA 20-180/S-016
Proscar® (finasteride)
Merck Research Laboratories

Group Leader's Memo

No Group Leader's memo will be prepared; the medical review has been done in conjunction with both the Deputy Director and the Division Director; neither of which felt a memo was required.

NDA 20-180/S-015
NDA 20-180/S-016
Proscar® (finasteride)
Merck Research Laboratories

Safety Update Review

Included in Medical Officer review dated February 19, 1998.

NDA 20-180/S-015
NDA 20-180/S-016
Proscar® (finasteride)
Merck Research Laboratories

Pharmacology Review

Review based on original NDA submission, only labeling review required on these submissions. Comments incorporated in the label.

NDA 20-180/S-015
NDA 20-180/S-016
Proscar® (finasteride)
Merck Research Laboratories

Chemistry Review

Review based on original NDA submission, only labeling review required on these submissions. Comments incorporated in the label.

NDA 20-180/S-015
NDA 20-180/S-016
Proscar® (finasteride)
Merck Research Laboratories

EER

There were no manufacturing changes - no EER is required.

NDA 20-180/S-015
NDA 20-180/S-016
Proscar® (finasteride)
Merck Research Laboratories

Microbiology Review

Oral dose, no microbiology review is required.

NDA 20-180/S-015
NDA 20-180/S-016
Proscar® (finasteride)
Merck Research Laboratories

Advisory Committee Meeting Minutes

This application was not the subject of an Advisory Committee Meeting.

NDA 20-180/S-015
NDA 20-180/S-016
Proscar® (finasteride)
Merck Research Laboratories

Federal Register Notices

This application was not the subject of any Federal Register Notices.

NDA 20-180/S-015
NDA 20-180/S-016
Proscar® (finasteride)
Merck Research Laboratories

Advertising Material

No advertising material has been submitted.

NDA 20-180/S-015
Proscar® (finasteride)
Merck Research Laboratories

Efficacy Summary

The effieacy summary is based on the information submitted to NDA 20-180.

NDA 20-180/S-015
Proscar® (finasteride)
Merck Research Laboratories

Safety Summary

The safety summary is based on the information submitted to NDA 20-180.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20180/S16

CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

DF

Food and Drug Administration
Rockville MD 20857

NDA 20-180

Merck Research Laboratories
Attention: Robert Silverman, M.D., Ph.D.
Senior Director, Regulatory Affairs
P.O. Box 4
West Point, PA 19486

AUG 25 1997

Dear Dr. Silverman:

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

Reference is also made to your letter of July 30, 1997, requesting a waiver of the requirements for the submission of paper case report forms and/or case report tabulations in conjunction with your forthcoming supplemental new drug application and requesting consideration of priority review status for this forthcoming application.

You have represented in your letter that the electronic case report forms and case report tabulations have been prepared in a manner that is substantially consistent with the FDA's proposed rules regarding electronic signatures and electronic records, proposed 21 CFR Part 11 [59 FR 45160 (August 31, 1994)].

Therefore, we have concluded that, under 21 CFR 314.90(b)(2), your alternative electronic submission justifies a waiver of the "hard copy" requirements of 21 CFR 314.50(f). Consequently, your waiver request is granted.

It is important that, before preparing or submitting your electronic submission, you contact our Division of Information Systems Design, phone 301-827-3276, to discuss CDER's archiving policy.

Should future retrieval be deemed necessary, and as a condition of granting this waiver, you are required to maintain paper copies of the case report forms and tabulations as required under 21 CFR 312.57(b).

Regarding your request for a priority review, we have concluded that this drug product would be considered for a standard review status. This conclusion was reached based on the facts that your product is currently available on the market and the disease being treated is not life-threatening. Consequently, your request for consideration for priority review status is denied.

If you have any questions, please contact Terri F.Rumble, B.S.N., Regulatory Health Project Manager, at (301) 827-4260.

Sincerely,

/S/

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

cc:
Original NDA 20-180
HFD-580/Div. Files
HFD-001/CDER (Center Director)
HFD-005/CDER (Assistant Center Director for Policy)
HFD-070/DISD
HFD-102 /Office Director
HFD-580/CSO/T.Rumble/Pauls
HFD-580/Rarick/Jolson/Shames/Fourcroy/Hirsch

Drafted by: Rumble/August 18, 1997/20180wav.std
Initialed by: Rarick,8.18.97/Pauls,8.18.97
final: Rumble,8.19.97

GENERAL CORRESPONDENCE (waiver granted for CRFs)

Rumble

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-180/S-015

JUL 29 1997

Merck Research Laboratories
Attention: Robert E. Silverman, M.D., Ph.D.
Senior Director, Regulatory Affairs
P.O. Box 4
West Point, PA 19486

Dear Dr. Silverman:

Please refer to your pending May 16, 1997, supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Proscar™ (finasteride).

To complete our review of the Statistical section of your submission, we request the following:

1. Protocols 024-01 and 024-10, 901-OA, and 901-OE were located for only three studies. Please provide the other three protocols or the locations of where to locate these protocols in the submission.

2. A detailed explanation should be provided of why the maximum likelihood Empirical Bayes' approach to meta-analysis is applicable to the six studies considered in this submission.

3. A detailed description should be provided of how the data were prepared and analyzed using the maximum likelihood Empirical Bayes' approach to meta-analysis.

4. A detailed description of the computer programs utilized to conduct this analysis should be provided.

5. Please provide a copy of the computer code (ready to load onto a PC) and the necessary data so that the statistical reviewer can reproduce and verify the accuracy of the results.

We would appreciate your prompt written response so we can continue our evaluation of your supplemental application.

If you have any questions, please contact Terri F.Rumble, B.S.N., Regulatory Health Project Manager, at (301) 827-4260.

Sincerely,

/S/ 7-25-97

Lisa D. Rarick, M.D.
Director
Division of Reproductive and Urologic
Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 20-180
HFD-580/Div. Files
HFD-580/Rarick/Jolson/Fourcroy/Rumble
HFD-715/Nevius/Kammerman/Taneja

Drafted by: Rumble/July 25, 1997/20180ir.015
Initialed by: Jolson,7.25.97 /Taneja,7.25.97 /Kammerman,7.25.97
final: Rumble, 7.25.97

INFORMATION REQUEST (IR)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-180/S-015

JUN - 3 1997

Merck Research Laboratories
Sumneytown Pike, P.O. Box 4 BLA-20
West Point, PA 19486

Attention: Robert E. Silverman, M.D., Ph.D.

Dear Dr. Silverman:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: PROSCAR (Finasteride)

NDA Number: 20-180

Supplement Number: S-015

Date of Supplement: May 16, 1997

Date of Receipt: May 19, 1997

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on July 18, 1997 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Office of Drug Evaluation II
Attention: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

/S/

Lana L. Pauls, M.P.H.
Chief, Project Management Staff
Division of Reproductive and Urologic
Drug Products, HFD-580
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 20-180/S-015
HFD-580/Div. Files
HFD-580/CSO/

SUPPLEMENT ACKNOWLEDGEMENT

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-180

Merck Research Laboratories
Attention: Robert E. Silverman, M.D., Ph.D.
Director, Regulatory Affairs
P.O. Box 4
West Point, PA 19486

APR 18 1997

Dear Dr. Silverman:

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

Reference is also made to your letter of March 6, 1997, requesting a waiver of the requirements for the submission of paper case report forms and/or case report tabulations in conjunction with your forthcoming supplemental new drug application.

You have represented in your letter that the electronic case report forms and case report tabulations have been prepared in a manner that is substantially consistent with the FDA's proposed rules regarding electronic signatures and electronic records, proposed 21 CFR Part 11 [59 FR 45160 (August 31, 1994)].

Therefore, we have concluded that, under 21 CFR 314.90(b)(2), your alternative electronic submission justifies a waiver of the "hard copy" requirements of 21 CFR 314.50(f). Consequently, your waiver request is granted.

It is important that, before preparing or submitting your electronic submission, you contact our Division of Information Systems Design, phone 301-827-3276, to discuss CDER's archiving policy.

Should future retrieval be deemed necessary, and as a condition of granting this waiver, you are required to maintain paper copies of the case report forms and tabulations as required under 21 CFR 312.57(b).

If you have any questions, please contact Terri F. Rumble, B.S.N., Regulatory Health Project Manager, at (301) 827-4260.

Sincerely,

/S/

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

cc:
Original NDA 20-180
HFD-580/Div. Files
HFD-001/CDER (Center Director)
HFD-005/CDER (Assistant Center Director for Policy)
HFD-070/DISD
HFD-102 /Office Director
HFD-580/CSO/T.Rumble
HFD-580/Rarick/Jolson/Fourcroy/Kammerman

Drafted by: Rumble/April 1, 1997/20180.wvr
Initialed by: Rarick,4.4.97/Jolson,4.2.97/Fourcroy,4.1.97/Kammerman,4.1.97/Pauls,4.1.97
final: Rumble, 4.4.97

GENERAL CORRESPONDENCE (waiver granted)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Olmstead

Food and Drug Administration
Rockville MD 20857

FEB 24 1998

NDA 20-180/S-016

Merck Research Laboratories
Attention: Robert E. Silverman, M.D., Ph.D.
Senior Director, Regulatory Affairs
P.O. Box 4, BLA-20
West Point, PA 19486-0004

Dear Dr. Silverman:

Please refer to your pending September 19, 1997, supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Proscar® (finasteride).

We have completed our review of the physician package insert and have several comments. Additions have been noted in double underline, deletions have been noted as ~~strikeouts~~. Additional comments requiring response are in boxes marked

FDA Comment:

Please submit your revised package insert as soon as available so that we may continue the evaluation of your Supplemental NDA.

If you have any questions, please contact Randy Olmstead, Project Manager at (301) 827-4260.

Sincerely,

/S/ 2/20/98

Lisa D. Rarick, M.D.
Director
Division of Reproductive and
Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Revised physician package insert

cc:
Original NDA 20-180
HFD-580/Div. Files
HFD-580/CSO/Olmstead
HFD-580/Rarick/Pauls/Rumble/Shames/Hirsch/Haidar/Kammerman/El-Hage

Drafted by: Olmstead/February 11, 1998/irlabel.doc

Concurrence: Pauls 2.12.98/Rarick 2.16.98/Rumble 2.18.98/Shames 2.13.98/Hirsch 2.18.98/
Kammerman 2.19.98/Haidar 2.19.98/El-Hage 2.18.98

INFORMATION REQUEST (IR)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-180/S-016

SEP 25 1997

Merck Research Laboratories
Sumneytown Pike
West Point, PA 19486

Attention: Robert E. Silverman, M.D., Ph.D.
Senior Director, Regulatory Affairs

Dear Dr. Silverman:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: PROSCAR (Finasteride)

NDA Number: 20-180

Supplement Number: S-016

Date of Supplement: September 19, 1997

Date of Receipt: September 22, 1997

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on November 21, 1997 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Office of Drug Evaluation II
Attention: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

/S/

Lanau Pauls, M.P.H.
Chief, Project Management Staff
Division of Reproductive and Urologic
Drug Products, HFD-580
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 20-180/S-016
HFD-580/Div. Files
HFD-580/CSO/

SUPPLEMENT ACKNOWLEDGEMENT

Robert E. Silverman, M.D., Ph.D.
Senior Director
Regulatory Affairs

Merck & Co., Inc.
P.O. Box 4
West Point PA 19486
Fax 610 397 2516
Tel 610 397 2944
215 652 5000

May 16, 1997

Lisa D. Rarick, M.D. - Division Director
Division of Reproductive and Urologic
Drug Products HFD-580
Office of Drug Evaluation II (CDER)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

MERCK
Research Laboratories

Dear Dr. Rarick:

NDA 20-180: PROSCAR™
(Finasteride)

Supplemental New Drug Application

Pursuant to Section 505(b) of the Food Drug and Cosmetic Act and in accordance with 21 CFR 314.70(b), we submit, for your approval, a supplement to NDA 20-180.

As indicated on the attached Form FDA 356h, this supplemental application provides for changes in Item 4(c)(i), 8, 11, 12, 13 and 14 of the approved New Drug Application for PROSCAR™.

MRL proposes, herein, to modify current product labeling with additional information to help prescribers identify the best candidates for treatment with PROSCAR™. This submission centers upon the results from a recently published meta-analysis of one-year data from six randomized clinical trials which concludes that baseline prostate size helps predict the outcome from treatment of symptomatic benign prostatic hyperplasia with PROSCAR™. The six studies in the meta-analysis include the two Phase III clinical trials from the original NDA, the VA Cooperative Study, the Early Intervention Trial, the Scandinavian Study for the Reduction of the Prostrate (SCARP), and the PROSCAR™ Safety Plus Efficacy Canadian Two-Year Trial (PROSPECT).

Supporting documentation provided for these studies includes references to the previously submitted clinical study reports (CSRs) from the NDA for the Phase III studies; the published manuscript for the VA study; and new CSR's for the Early Intervention, SCARP and PROSPECT studies. The established safety profile for PROSCAR™ is corroborated in each of the new CSR's provided with this submission and, therefore, is not further summarized.

It is noteworthy that an additional large clinical trial with a parallel design to SCARP and PROSPECT, the PROSCAR™ Worldwide Efficacy and Safety Study (PROWESS), has been recently completed. The results of this study are consistent with the published meta-analysis contained in this submission. A complete CSR for PROWESS will be included in a subsequent submission to this NDA.

The format of this submission is presented in the Index To Contents Of Application (Item 1). As previously discussed with the Agency on May 8, 1997, this submission is being provided in both hard copy and, subsequently, in electronic medium. As per prior agreement, Item 11 (Case Report Tabulations) and Item 12 (Case Report Forms) will be provided only in electronic medium.

In accordance with the Prescription Drug User Fee Act of 1992, a check (Check No. in the amount of was sent to the Mellon Bank, Three Mellon Bank, 27th Floor (FDA 360909), Pittsburgh, PA on May 9, 1997. The User Fee I.D. number is

As required by Section 306(k)(1) of the Generic Drug Enforcement Act [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.

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

If you have any questions or need additional information please contact Robert E. Silverman, M.D., Ph.D. (610) 397-2944 or, in my absence, Bonnie J. Goldmann, M.D. (610) 397-2383.

Sincerely,

Robert E. Silverman, M.D., Ph.D.
Senior Director, Regulatory Affairs

mcs/q/ltr/443

Attachment

Federal Express #1

Desk Copies:
Dr. Jean Fourcroy (w/Attachment): HFD-580, Rm. 17B-31 - Federal Express #1
Ms. Terri Rumble (Cover Letter Only): HFD-580, Rm. 17B-45 - Federal Express #1

Desk Copy (Letter and Patent Information Only): - Federal Express #2
Mr. George Scott
Room 218 Chapman Building
1901 Chapman Avenue
Rockville, MD 20852

Robert E. Silverman, M.D., Ph.D.
Senior Director
Regulatory Affairs

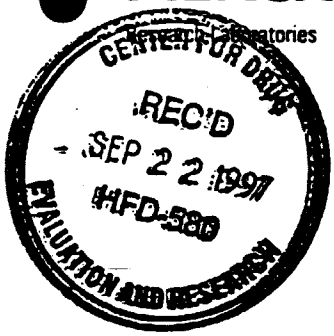
ORIGINAL

Merck & Co., Inc.
P.O. Box 4
West Point PA 19486
Fax 610 397 2516
Tel 610 397 2944
215 652 5000

September 19, 1997

NDA NO. 20-180 REF. NO. 016 Nov 21
NDA SUPPL FOR SE1

MERCK
Research Laboratories



Lisa D. Rarick, M.D.
Division of Reproductive and Urologic
Drug Products HFD-580,
Office of Drug Evaluation II (CDER)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

REVIEWS COMPLETED	
CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO	
CSO INITIALS	DATE

Dear Dr. Rarick:

Supplemental New Drug Application
NDA 20-180: Tablets PROSCAR™ (Finasteride)
User Fee No.

Pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act and in accordance with Title 21 of the Code of Federal Regulations, Merck Research Laboratories (MRL) is submitting a Supplemental New Drug Application (SNDA) for PROSCAR™ (Finasteride).

As indicated on the attached Form FDA 356h, this supplemental application provides for changes in Items 4(c)(i), 6, 8, 10, 11, 12, and 13 of the approved New Drug Application (NDA) for Tablets PROSCAR™.

NDA 20-180 for Tablets PROSCAR™, 5 mg was approved on June 19, 1992. PROSCAR™, also referred to as finasteride, MK-0906 and L 652,931 is a specific inhibitor of steroid 5 α-reductase, and is currently used for the treatment of symptomatic benign prostatic hyperplasia (BPH).

This application supports the use of PROSCAR™ for the prevention of clinical urologic events, to: reduce the risk of acute urinary retention; reduce the risk of surgery including transurethral resection of the prostate (TURP) and prostatectomy. The application also corroborates the statement that patients with an enlarged prostate are the appropriate candidates for therapy with PROSCAR™ which is the subject of a previous submission, SNDA 20-180/S-015 (May 16, 1997). In addition, an update from the ongoing open extensions of the original Phase III clinical studies (total exposure to 6 years) is included in this submission.

At the time of the original NDA approval, MRL agreed to a Phase IV commitment to conduct a large, long-term, placebo controlled clinical trial with PROSCAR™ to extend the efficacy and safety experience with this drug in men with symptomatic benign prostatic hyperplasia (BPH) and to address additional issues related to the impact of therapy on the risk for clinical urologic events (e.g., acute urinary retention, TURP, etc.) and on the ability to detect prostate cancer.

The PROSCAR™ Long Term Efficacy and Safety Study (PLESS, Protocol No. 048) was conducted to meet the Phase IV commitment cited above. In this study, 3040 men with moderate to severe symptoms of BPH and enlarged prostates were enrolled into a 4-year double blind trial and received either PROSCAR™ or placebo. BPH related clinical outcomes, symptom scores, urinary flow rates and prostate volume were assessed over 4 years of follow-up.

In addition, this SNDA contains reports on three placebo-controlled 2-year studies, referred to as SCARP (Scandinavian Study for the Reduction of the Prostate, Protocol No. 901-0A), PROSPECT (PROSCAR™ Safety Plus Efficacy Canadian 2-Year Trial, Protocol No. 901-0E) and PROWESS (PROSCAR™ Worldwide Efficacy and Safety Study, Protocol Nos. 901-0B, -0C, -0E), that have demonstrated effects on BPH related clinical outcomes, symptom scores, urinary flow rates and prostate volume that are very consistent with the results of PLESS.

The previously submitted SNDA 20-180/S-015 provided the results of a meta-analysis from six clinical trials, including SCARP and PROSPECT, that demonstrated the correlation between baseline prostate size and symptom response to treatment with finasteride. In this submission, the results of PROWESS have been incorporated into the meta-analysis. This seven study meta-analysis confirms the previous analysis. In addition, the results of a recently completed semen production study (Protocol 056) are included, in fulfillment of Phase IV commitments made to the Agency, that disclose no clinically meaningful effects on sperm concentration, mobility, morphology or pH and no adverse effects on serum cholesterol.

This SNDA also includes open extension follow-up efficacy and safety data from the original Phase III clinical studies (Protocol Nos. 008, 507 and 508; total exposure to 6 years).

The Agency has previously requested that the information in the Pharmacokinetics portion of the CLINICAL PHARMACOLOGY section of the package insert for PROSCAR™ be reorganized in any forthcoming labeling supplement to conform with the Agency's draft "Guidelines for the Preparation of the Pharmacokinetic Section of the Labeling" (received by MRL in August, 1996). The product labeling proposal in this supplemental application fulfills that request.

This application is formatted as required in Title 21, paragraph 314.50 of the Code of Federal Regulations. It consists of a complete "archival" copy (Blue Binders), comprising 36 volumes and three "review" copies as described in the Statement of Organization which is attached to this letter.

This SNDA is being provided in electronic format and hard copy with the exception of Items 11 and 12 (case report tabulation and forms). Items 11 and 12 are being provided in electronic format only, for which a formal waiver from the requirements of 21 CFR 314.50(f) has been approved (FDA approval letter dated August 25, 1997) in accordance with current CDER policy.

The electronic format of this submission will be submitted on or about October 3, 1997 to the FDA Technology Support Service Staff (TSSS). MRL will contact the FDA to arrange an orientation to the electronic submission for all relevant Agency reviewers. Any differences between the hard copy and the electronic version will be noted in the documentation accompanying the electronic version.

Copies of the documentation provided with the electronic submission will also be submitted to the NDA.

As noted in a letter to this NDA on September 15, 1997, the Agency has agreed to provide priority review status to this SNDA.

In accordance with the Prescription Drug User Fee Act of 1992, a check for this SNDA in the amount of (Check No. ; User Fee I.D. No. was sent to the Mellon Bank, Three Mellon Bank Center, 27th Floor (FDA 360909), Pittsburgh, PA 15259-0001, on September 12, 1997.

As required by Section 306(k)(1) of the Generic Enforcement Act [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.

We consider the filing of this New Drug Application to be a confidential matter and request that the Food and Drug Administration not make its existence public without first obtaining written permission from Merck & Co., Inc.

Questions concerning this information should be directed to Robert E. Silverman, M.D., Ph.D. (610/397-2944) or, in my absence, Bonnie J. Goldman, M.D. (610/397-2383).

Sincerely,

Robert E. Silverman, M.D., Ph.D.
Senior Director, Regulatory Affairs

q/mcs/ltr/481

Attachment
Federal Express #1

Desk Copy (Letter and Patent Information Only):
Mr. George Scott, HFD-984
5516 Nicholson Lane, Rm. 238
Rockville, MD 20857
Federal Express #2

Robert E. Silverman, M.D., Ph.D.
Senior Director
Regulatory Affairs

DESK COPY

Merck & Co., Inc.
P.O. Box 4
West Point PA 19486
Fax 610 397 2516
Tel 610 397 2944
215 652 5000

October 7, 1997

Lisa D. Rarick, M.D. - Division Director
Division of Reproductive and Urologic
Drug Products HFD-580
Office of Drug Evaluation II (CDER)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Rarick:

NDA 20-180/S-015: PROSCAR™
(Finasteride)

Reference is made to the above noted Supplemental New Drug Application (SNDA); submissions of additional information on August 19 and September 8, 1997, and a follow-up telephone conversation between Dr. Silverman and Ms. Rumble on September 22, 1997.

By enclosure, Merck Research Laboratories (MRL) is, herein, providing to Dr. Taneja a diskette that contains electronic files sufficient to duplicate the meta-analysis contained in S-015. These files include the necessary data sets and analytic programming derived from software. A hard copy of the instructions to allow Dr. Taneja to load and run these files is also attached.

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

If you have any questions or need additional information please contact Robert E. Silverman, M.D., Ph.D. (610) 397-2944 or, in my absence, Bonnie J. Goldmann, M.D. (610) 397-2383.

Sincerely,

Robert E. Silverman, M.D., Ph.D.
Senior Director, Regulatory Affairs

mcs/q/ltr/537

Attachment
Federal Express #1
Desk Copy: Ms. Terri Rumble, HFD-580, PKLN 17B-45, Federal Express #1 (w/att.)
Dr. Baldeo Taneja, HFD-715, PKLN 18B-45, Federal Express 2
(w/att. and diskette)

Robert E. Silverman, M.D., Ph.D.
Senior Director
Regulatory Affairs

DESK COPY

Merck & Co., Inc.
P.O. Box 4
West Point PA 19486
Fax 610 397 2516
Tel 610 397 2944
215 652 5000

September 8, 1997

MERCK
Research Laboratories

Lisa D. Rarick, M.D. - Division Director
Division of Reproductive and Urologic
Drug Products HFD-580
Office of Drug Evaluation II (CDER)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Rarick:

NDA 20-180/S-015: PROSCAR™
(Finasteride)

Reference is made to the above noted Supplemental New Drug Application (SNDA); a submission of additional information on August 19, 1997; and a teleconference on August 26, 1997 between Dr. Silverman and Dr. Gould from Merck Research Laboratories (MRL) and Ms. Rumble and Dr. Taneja from FDA.

During the August 26 teleconference, the Agency clarified their request for the data sets and relevant programming to allow reproduction of the published meta-analysis that supports the labeling request in the SNDA. Dr. Gould explained that the analysis utilized a non-SAS commercial software package, which the Agency, apparently, did not have and with which Dr. Taneja was not familiar. It was agreed that MRL would provide additional hard copy documentation from the analysis while continuing to develop a mutually satisfactory plan to provide the Agency with access to the necessary software and electronic data sets.

By attachment, MRL is, herein, providing the following documents in hard copy.

1. Documentation of the statistical analysis program including: a description of the input data format and parameters; input data sets from each of the six clinical studies; and the output for the six cases analyzed (changes in maximum urine flow rate, total symptom score and quasi-IPSS score, each alone and versus baseline prostate volume).

2. Manuscript that compares several analytic approaches, including the Empirical Bayes approach used for the analysis in this SNDA, for a similar, but unrelated, statistical question (Statistics in Medicine, in press).

MRL is pursuing the acquisition of the relevant software for the Agency's use while suggesting that the attached material may be sufficient to satisfy the Agency's needs for completion of their review of the SNDA. Dr. Silverman will follow-up with Ms. Rumble on the outstanding aspects of this issue in the near future.

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

If you have any questions or need additional information please contact Robert E. Silverman, M.D., Ph.D. (610) 397-2944 or, in my absence, Bonnie J. Goldmann, M.D. (610) 397-2383.

Sincerely,

Robert E. Silverman, M.D., Ph.D.
Senior Director, Regulatory Affairs

mcs/q/ltr/476

Attachment

Federal Express #1

Desk Copy: Ms. Terri Rumble, HFD-580, Rm. 17B-45, Federal Express #1
Dr. Baldeo Taneja, HFD-715, Rm. 17B-31, Federal Express #2

Larry P. Bell, M.D.
Senior Director
Regulatory Affairs

Merck & Co., Inc.
P.O. Box 4, BLA-20
West Point PA 19486
Fax 610 397 2516
Tel 610 397 2310
215 652 5000

August 21, 1997

These copies are OFFICIAL FDA Copies not desk copies.

ORIGINAL

SUPPL NEW CORRESP

MERCK Research Laboratories

Mr. David M. Moss
Director, Technology Support Service Staff
Center for Drug Evaluation & Research
Food & Drug Administration
5600 Fishers Lane, 8B-11
Rockville, Maryland 20857

CENTER FOR DRUG REC'D AUG 22 1997 HFD-510 EVALUATION AND RESEARCH

Supplemental New Drug Application
NDA 20-180 PROSCAR™ (Finasteride)

Dear Mr. Moss:

Reference is made to the correspondence dated January 16, 1997 regarding Merck Research Laboratories (MRL) proposed electronic submissions during 1997.

The purpose of this letter is to confirm delivery of the NDA 20-180 PROSCAR™ (Finasteride) - PLESS electronic submission on or about September 25, 1997.

Attachment 1 details the environment under which the electronic submission will be created. We will assume this configuration will be acceptable to the Agency, unless notified.

Any questions relating to the PROSCAR™ (Finasteride) - PLESS submission or to the electronic submissions schedule for 1997 should be addressed to me (610/397-2310) or, in my absence, Marie A. Dray (301/881-9000).

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☒ N.A.I. ☐ MEMO

CSO INITIALS DATE 9/8/97

Sincerely,

Larry Bell

Larry Bell, M.D.
Senior Director, Regulatory Affairs

cc: Mr. G. Brolund, HFD-72
Mr. M. Buster, HFD-72
Mr. K. Edmunds, HFD-70

FDA File: NDA 20-180 PROSCAR™ (Finasteride), HFD-580 (2 copies)

Federal Express
Attachment (1)

CENTER FOR DRUG REC'D SEP 02 1997 HFD-580 EVALUATION AND RESEARCH

Robert E. Silverman, M.D., Ph.D.
Senior Director
Regulatory Affairs

Merck & Co., Inc.
P.O. Box 4
West Point PA 19486
Fax 610 397 2516
Tel 610 397 2944
215 652 5000

June 9, 1997

Lisa D. Rarick, M.D. - Division Director
Division of Reproductive and Urologic
Drug Products HFD-580
Office of Drug Evaluation II (CDER)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

MERCK
Research Laboratories

Dear Dr. Rarick:

Supplemental New Drug Application
NDA 20-180/S-015: PROSCAR™
(Finasteride)

Reference is made to the above Supplemental New Drug Application (SNDA) submitted on May 16, 1997 and a telephone conversation between Ms. Terri Rumble and Dr. Robert Silverman on June 2, 1997. Ms. Rumble requested an additional hard copy of this SNDA be sent to Dr. Lisa Kammerman.

By copy of this letter and attachment, Merck Research Laboratories is providing the requested information.

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

If you have any questions or need additional information please contact Robert E. Silverman, M.D., Ph.D. (610) 397-2944 or, in my absence, Bonnie J. Goldmann, M.D. (610) 397-2383.

Sincerely,

Robert E. Silverman, M.D., Ph.D.

q/mcs/ltr/453

Federal Express #1
Desk Copy: Dr. Lisa Kammerman, HFD-580, Room 17B-45, Federal Express #1
(Cover letter w/att.)
Ms. Terri Rumble HFD-580, Room 17B-45, Federal Express #1
(Cover letter only)

Larry P. Bell, M.D.
Senior Director
Regulatory Affairs

SUPPL NEW CORRESP
These copies are
OFFICIAL FDA COPIES
not desk copies.

Merck & Co., Inc.
P.O. Box 4, BLA-20
West Point PA 19486
Fax 610 397 2516
Tel 610 397 2310
215 652 5000

ORIGINAL

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☒ N.A.I. ☐ MEMO

CSO INITIALS Terri Rumble 6/18/97 DATE

June 2, 1997

MERCK
Research Laboratories

Mr. David M. Moss
Director, Division of Information Systems Design
Center for Drug Evaluation & Research
Food & Drug Administration
5600 Fishers Lane, 8B-11
Rockville, Maryland 20857

6/17/97

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUN - 6 1997
HFD-580

Noted 6/18/97 JE

NDA 20-180: PROSCAR™ (Finasteride)
Supplemental New Drug Application

Noted 6-12-97

Dear Mr. Moss:

By copy of this letter, Merck Research Laboratories (MRL) is providing to the Division of Information Systems Design (DISD) one (1) CD which contains the above-referenced supplemental New Drug Application (sNDA) for PROSCAR™ (Finasteride) submitted to the Agency in hardcopy on May 16, 1997.

The information on this CD (Serial Number 6104 2036 0627) is to be copied to the *StorageWorks* Building Block (SBB) (Serial Number NI65025526) currently installed on the MRL-dedicated network server at the Agency.

The reviewers from the Division of Reproductive and Urological Drug Products (DRUDP) who should be provided access to the electronic submission from their desktops are as follows:

Dr. Jean Fourcroy	Medical Reviewer	DRUDP	HFD-580 PKLN 17B-31	301-827-4260
Dr. Lisa Kammerman	Biostatistics	DRUDP	HFD-580 PKLN 17B-45	301-827-4260
Ms. Terri Rumble	Project Manager	DRUDP	HFD-580 PKLN 17B-45	301-827-4260

Please notify MRL's Regulatory Agency Relations (RAR) Office (301/881-9000) when the copy is successfully completed and access from the reviewers' desktops is functional.

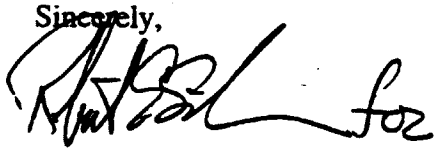
The information submitted in electronic form on this CD may be retained indefinitely by the Agency as an archival copy.

There are five attachments to this letter:

Attachment 1	A Table of Organization of the contents of the accompanying electronic submission.
Attachment 2	A Difference Report of differences between the electronic version of this submission and the hard copy submission identified.
Attachment 3	Installation Instructions detailing how to copy the information on the CD to the SWBB on the server.
Attachment 4	Documentation regarding the development procedures performed at MRL for this electronic submission.
Attachment 5	A complete list of file names.

During the time that the hard disk is actively being used, MRL will provide technical support. Any questions relating to this hard disk should be addressed to me (610/397-2310) or, in my absence, Marie A. Dray (301/881-9000).

Sincerely,



Larry Bell, M.D.
Director, Regulatory Affairs

Attachments (5)
CD (1)
Federal Express #1

cc (cover letter only):

Mr. D. Isom, Office of Information Technology HFD-1
Federal Express #2
Mr. G. Brolund, Information Systems Branch One, HFD-72
Federal Express #3
Mr. M. Buster, Systems and Network Section, HFD-72
Federal Express #3
Mr. K. Edmunds, Division of Information Systems Design (DISD), HFD-70
Federal Express #4

cc (cover letter only):

LIST OF REVIEWERS

Dr. Jean Fourcroy, HFD-580, PKLN 17B-31, Federal Express #1
Dr. Lisa Kammerman, HFD-580, PKLN 17B-45, Federal Express #1
Ms. Terri Rumble, HFD 580, PKLN 17B-45, Federal Express #1

cc (cover letter with attachments):

NDA 20-180, HFD-580 (2 copies), Federal Express #1 (as above)

q/mcs/ltr/449

Robert E. Silverman, M.D., Ph.D.
Senior Director
Regulatory Affairs

ORIGINAL

Merck & Co., Inc.
P.O. Box 4
West Point PA 19486
Fax 610 397 2516
Tel 610 397 2944
215 652 5000

May 16, 1997

NDA NO. 20-180 REF. NO. 015
NDA SUPPL FOR SE5

MERCK
Research Laboratories

Lisa D. Rarick, M.D. - Division Director
Division of Reproductive and Urologic
Drug Products HFD-580
Office of Drug Evaluation II (CDER)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Rarick:

NDA 20-180: PROSCAR™
(Finasteride)

Supplemental New Drug Application

Pursuant to Section 505(b) of the Food Drug and Cosmetic Act and in accordance with 21 CFR 314.70(b), we submit, for your approval, a supplement to NDA 20-180.

As indicated on the attached Form FDA 356h, this supplemental application provides for changes in Item 4(c)(i), 8, 11, 12, 13 and 14 of the approved New Drug Application for PROSCAR™.

MRL proposes, herein, to modify current product labeling with additional information to help prescribers identify the best candidates for treatment with PROSCAR™. This submission centers upon the results from a recently published meta-analysis of one-year data from six randomized clinical trials which concludes that baseline prostate size helps predict the outcome from treatment of symptomatic benign prostatic hyperplasia with PROSCAR™. The six studies in the meta-analysis include the two Phase III clinical trials from the original NDA, the VA Cooperative Study, the Early Intervention Trial, the Scandinavian Study for the Reduction of the Prostrate (SCARP), and the PROSCAR™ Safety Plus Efficacy Canadian Two-Year Trial (PROSPECT).

Supporting documentation provided for these studies includes references to the previously submitted clinical study reports (CSRs) from the NDA for the Phase III studies; the published manuscript for the VA study; and new CSR's for the Early Intervention, SCARP and PROSPECT studies. The established safety profile for PROSCAR™ is corroborated in each of the new CSR's provided with this submission and, therefore, is not further summarized.

It is noteworthy that an additional large clinical trial with a parallel design to SCARP and PROSPECT, the PROSCAR™ Worldwide Efficacy and Safety Study (PROWESS), has been recently completed. The results of this study are consistent with the published meta-analysis contained in this submission. A complete CSR for PROWESS will be included in a subsequent submission to this NDA.

The format of this submission is presented in the Index To Contents Of Application (Item 1). As previously discussed with the Agency on May 8, 1997, this submission is being provided in both hard copy and, subsequently, in electronic medium. As per prior agreement, Item 11 (Case Report Tabulations) and Item 12 (Case Report Forms) will be provided only in electronic medium.

In accordance with the Prescription Drug User Fee Act of 1992, a check (Check No. , in the amount of , was sent to the Mellon Bank, Three Mellon Bank, 27th Floor (FDA 360909), Pittsburgh, PA on May 9, 1997. The User Fee I.D. number is

As required by Section 306(k)(1) of the Generic Drug Enforcement Act [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.

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

If you have any questions or need additional information please contact Robert E. Silverman, M.D., Ph.D. (610) 397-2944 or, in my absence, Bonnie J. Goldmann, M.D. (610) 397-2383.

Sincerely,

Robert E. Silverman, M.D., Ph.D.
Senior Director, Regulatory Affairs

mcs/q/ltr/443

Attachment

Federal Express #1

Desk Copies:
Dr. Jean Fourcroy (w/Attachment): HFD-580, Rm. 17B-31 - Federal Express #1
Ms. Terri Rumble (Cover Letter Only): HFD-580, Rm. 17B-45 - Federal Express #1

Desk Copy (Letter and Patent Information Only): - Federal Express #2
Mr. George Scott
Room 218 Chapman Building
1901 Chapman Avenue
Rockville, MD 20852

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Robert E. Silverman, M.D., Ph.D.
Director
Regulatory Affairs

These copies are
OFFICIAL FDA Copies
not desk copies.

Merck & Co., Inc.
P.O. Box 4
West Point PA 19486
Fax 610 397 2516
Tel 610 397 2944
215 652 5000

March 6, 1997

ORIGINAL

SUPPL NEW CORRESP

MERCK
Research Laboratories

Lisa D. Rarick, M.D. - Division Director
Division of Reproductive and Urologic
Drug Products HFD-580
Office of Drug Evaluation II (CDER)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Noted 3/26/97 QJ Noted 3/25/97

Dear Dr. Rarick:

NDA 20-180: PROSCAR™
(Finasteride)
GENERAL CORRESPONDENCE

Noted 3-12 AT

Merck Research Laboratories (MRL) anticipates the submission of a supplemental New Drug Application (NDA) to the above noted NDA in April/May, 1997 that will propose changes to the product labeling which will be supported by clinical study reports of several large clinical trials including the Scandinavian Study for the Reduction of the Prostate (SCARP), PROSCAR Safety Plus Efficacy Canadian Two-Year Study (PROSPECT), and the PROSCAR Worldwide Efficacy and Safety Study (PROWESS). MRL plans to provide this supplemental NDA in both hard copy and electronic format.

Pursuant to Section 505(b) of the Food, Drug and Cosmetic Act and in accordance with 21 CFR 314.50(f)(4) and 21 CFR 314.90, we submit, for your approval, a request for a waiver allowing for the submission of only electronic case report tabulations (CRTs) for Item 11 and case report forms (CRFs) for Item 12 in this supplemental NDA in lieu of hard copy CRTs and CRFs.

The electronic CRTs and CRFs have been prepared in a manner that is substantially consistent with the FDA's proposed rules regarding electronic signatures and electronic records, proposed 21 CFR Part 11, 59 FR 45160 (August 31, 1994). Paper copies of the CRFs and CRTs will be maintained as required under 21 CFR 312.57(b).

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

If you have any questions or need additional information, please contact Robert E. Silverman, M.D., Ph.D. (610-397-7052) or, in my absence, Bonnie J. Goldmann, M.D. (610-397-2383).

Sincerely,

Robert E. Silverman, M.D., Ph.D.
Director
Regulatory Affairs

q/mcs/ltr/416

Federal Express #1

Desk Copy: Dr. Jean Fourcroy, HFD-580, Rm. 17B-31, Federal Express #1
Ms. Terri Rumble, HFD-580, Rm. 17B-45, Federal Express #1

Robert E. Silverman, M.D., Ph.D.
Senior Director
Regulatory Affairs

Merck & Co. Inc
P.O. Box 4
West Point PA 19486
Fax 610 397 2516
Tel 610 397 2944
215 652 5000

March 19, 1998

Lisa D. Rarick, M.D. - Division Director
Division of Reproductive and Urologic
Drug Products HFD-580
Office of Drug Evaluation II (CDER)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

MERCK
Research Laboratories

Dear Dr. Rarick:

SNDA 20-180/S-016: PROSCAR™
(Finasteride)

Reference is made to the above Supplemental New Drug Application (SNDA); several labeling discussions by telephone between Merck Research Laboratories (MRL) and the Agency on March 13, 17, 18 and 19, 1998; and submission by MRL of a labeling proposal on March 17. Based on the discussion of March 19, MRL is providing, as an attachment, a revised product circular that incorporates all the agreed upon changes which supersedes the March 17 proposal. This proposal is provided in an annotated and clean text version. The proposed patient package circular (PPI) provided on March 17 was not changed in subsequent discussions, so MRL has not included a repeat copy of the PPI with the attachment provided herein.

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

If you have any questions or need additional information please contact Robert E. Silverman, M.D., Ph.D. (610) 397-2944 or, in my absence, Bonnie J. Goldmann, M.D. (610) 397-2383.

Sincerely,

Robert E. Silverman, M.D., Ph.D.
Senior Director, Regulatory Affairs

wcs/q/ltr/555
Attachment
Federal Express #1
Desk Copy: Via fax (301-827-4267): Mr. Randy Olmstead, HFD-580, Room 17B-45
Federal Express #1

Robert E. Silverman, M.D., Ph.D.
Senior Director
Regulatory Affairs

Merck & Co., Inc.
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DESK COPY

March 17, 1998

MERCK
Research Laboratories

Lisa D. Rarick, M.D. - Division Director
Division of Reproductive and Urologic
Drug Products HFD-580
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Rarick:

SNDA 20-180/S-016: PROSCAR™
(Finasteride)

Reference is made to the above Supplemental New Drug Application (SNDA) and labeling discussions by telephone between Merck Research Laboratories (MRL) and Agency personnel on March 13 and 17, 1998. At the conclusion of the March 17 teleconference, outstanding issues remained concerning the description of treatment failure (including urologic endpoint) results in the CLINICAL PHARMACOLOGY section of the proposed circular. An updated labeling proposal, including the changes agreed to on March 13 and 17 and MRL's current proposal for the section still under discussion, is attached. The product circular and patient package insert are each provided in an annotated version and clean running text.

MRL continues to believe that the most informative product labeling for the prescriber should incorporate an expression of the ratios (i.e., relative risks) of the urologic event outcomes between treatment groups in PLESS. This position is based, briefly, on the following rationales:

- The use of ratios was specified in the Data Analysis Plan for PLESS.

- The use of ratios is essential to conveying the totality of the data because the ratios are consistent over time and between subgroups with different placebo rates of events (e.g., age, baseline symptom severity, etc.).

- The use of ratios is an accepted standard for the presentation of endpoint data from long-term clinical trials across therapeutic areas including studies where the underlying endpoint rates are comparable to those seen in PLESS.

MRL recognizes the Agency's expressed concerns about the potential interpretation of ratios in isolation. Therefore, we are making the following proposals which are incorporated into the attached draft.

- The actual event rates are provided with equivalent prominence to the ratios in the tabular and textual presentation of this data. Further, MRL commits to the appropriate presentation of the underlying event rates along with ratio data in promotional materials.

- The attached proposal incorporates the 95% confidence intervals around the ratios.

- The attached proposal presents the ratios as "Relative Risks", a terminology that is familiar to practitioners. However, MRL is willing to consider referring to these ratios as "Hazard Ratios", a less well understood term.

MRL looks forward to the Agency's consideration of the attached proposal and are prepared to continue our discussions with the Agency toward a mutually satisfactory and timely conclusion of the Agency's review of this SNDA.

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

If you have any questions or need additional information please contact Robert E. Silverman, M.D., Ph.D. (610) 397-2944 or, in my absence, Bonnie J. Goldmann, M.D. (610) 397-2383.

Sincerely,

Robert E. Silverman, M.D., Ph.D.
Senior Director, Regulatory Affairs

mcs/q/ltr/552A

Attachment
Federal Express #1
Desk Copy: Via Fax (301-827-4267): Mr. Randy Olmstead, HFD-580, Room 17B-45
Federal Express #1

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code Of Federal Regulations, 314)

Form Approved OMB No. 0910-0338.
Expiration Date: April 30, 2000
See OMB Statement on last page.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Merck Research Laboratories	3/17/98
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE (FAX) Number** *(Include Area Code)*
(610) 397-2944	(610) 397-2516

APPLICANT ADDRESS *(Number, Street, City, State, Country, Zip Code or Mail Code, and U.S. License number if previously issued):*
Sumneytown Pike, P.O. Box 4
BLA-20
West Point, PA 19486

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 20-180

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Finasteride	Tablets PROSCAR

CHEMICAL/ BIOCHEMICAL/BLOOD PRODUCT NAME *(if any)*
N-(1,1-dimethylethyl)-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide

CODE NAME *(if any)*

DOSAGE FORM	STRENGTHS:	ROUTE OF ADMINISTRATION
Tablet	5 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:
Treatment and control of symptomatic benign prostatic hyperplasia (BPH), PROSCAR, causes regression of the enlarged prostate gland, an increase in urinary flow, and improvement in the sympytoms associated with BPH.

APPLICATION INFORMATION

APPLICATION TYPE *(Check one)*
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCED LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one)
☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

REASON FOR SUBMISSION General Correspondence

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for the drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)