

mL with 5 mg/d vs -0.3 mL with 1 mg/d).

4. In this clinical study, finasteride 1 mg/day was given for 48 weeks such that any effect over 4 spermatogenic cycles could be evaluated, which increased the probability that any effect of study drug would be observed. The Applicant concludes that the negative findings on **semen parameters** (apart from ejaculatory volume) suggested that treatment with finasteride 1 mg/day had little detectable effect on spermatogenesis. This conclusion is premature, as (a) current methodology may not be able to evaluate all aspects of spermatogenesis and (b) **long-term effects beyond 48 weeks are unknown**.

5. Although a previous study showed that older men with BPH treated with finasteride 1 or 5 mg/day had little change in **BMD** after 12 months (measured by ^{45}Ca , serum osteocalcin in another study of men with BPH showed a small but significant decrease in the patients treated with finasteride 5 mg compared with placebo. This effect on osteocalcin was more consistent with an increase than a decrease in androgen effects on bone. In 094, finasteride 1 mg/d for 48 weeks yielded no treatment group differences for lumbar BMD, although there was a trend for finasteride patients to have a small increase of 0.7% ($p=0.08$ vs placebo). For the **marker of bone resorption (NTX)**, finasteride subjects showed a significant reduction from baseline with the Week 48 result reaching statistical significance compared with placebo. For the **marker of bone formation (BSAP)**, a treatment group difference was detected at Week 48, but this was due to a rise of 14% in the placebo subjects. The 4.4% increase in finasteride subjects was not significantly different from baseline.

6. No effect of finasteride 1 mg/d was observed on the fasting lipid profile.

7. No effect on the patient's overall satisfaction with his sex life as measured by a Sexual Function Questionnaire was observed with finasteride 1 mg/d for 48 weeks.

8. Reversibility of finasteride effect was demonstrated for NTX, BSAP and PSA by Week 60. However, if finasteride 1 mg/d is to be approved for chronic use, reversibility of effect will *not* be the issue; rather, **the long-term maintenance of a pharmacologic effect on bones** will require careful consideration, even though this may be exerted secondarily through hormonal action.

10.1.10 Withdrawal Phenomena/Abuse Potential not applicable

10.1.11 Human Reproduction Data Finasteride is not indicated in women. The current marketed product, PROSCAR™ is for use in symptomatic benign prostatic hypertrophy. Because of the ability of 5α -reductase inhibitors to inhibit the conversion of testosterone to DHT, finasteride may cause abnormalities of the external genitalia of a male fetus of a pregnant woman who receives finasteride. In rats, low doses of finasteride administered during pregnancy have produced abnormalities of the external genitalia in male offspring. In humans, two cases of hypospadias have been reported following exposure to crushed tablets of finasteride in pregnancy. One was unlikely to be related to finasteride because of the timing of exposure (last 2 months of pregnancy). The other case involved chronic handling without gloves daily throughout pregnancy. No case of birth defect have been reported for oral or semen exposure.

In the approved marketing application for finasteride 5 mg, potential reproductive toxicity was extensively evaluated in preclinical studies. Finasteride in semen has also been measured in 35 men taking finasteride 1 mg/d for 6 weeks (Study 065). In 60% (21 of 35) of the samples, finasteride levels were undetectable. The mean finasteride level was 0.26 ng/mL and the highest level measured was 1.52 ng/mL. Using this highest semen level measured and assuming 100% vaginal absorption from a 5-mL per

day, human exposure would be up to 7.6 ng/d, which is >650 times lower than the no-effect level for serum DHT suppression (5 mg/day) and 750 times lower than the no-effect dose for developmental abnormalities in Rhesus monkeys (800 ng/d i.v). Thus, exposure of a pregnant women to the semen of a man taking finasteride 1 mg/d leading to birth defect in the male human fetus appears to be unlikely.

For effects on male fertility, see Section 10.2.2.2.

10.1.12 Overdose Experience

Based on animal studies and clinical experience, it is not likely that an overdose would create any organ-specific toxicity and, therefore, any risk of clinical importance. Since subjects have received doses of up to 400 mg, it is unlikely that a single episode of overdosing would cause organ damage. There is also no evidence of toxicity associated with supratherapeutic doses (up to 80 mg/day for 3 months).

10.2 Review of Systems

10.2.1 Endocrine/Metabolism

Hypothalamic-Pituitary-Testicular Axis

- Serum Testosterone The marked and persistent decrease in serum DHT at Month 12 in finasteride subjects was associated with a small increase in serum T (13.1% from baseline) statistically different from placebo but within normal range.
- Serum LH and FSH No clinically significant changes from baseline in serum LH or FSH.
- Serum Estradiol and Prolactin On 9/30/97, the Applicant submitted data from subjects who took study drug for 48 weeks (finasteride 1 mg or placebo) in study 094, showing a significant increase of 14.8% in serum estradiol in subjects treated with finasteride 1 mg (despite levels remaining within normal range for men, i.e., 0.8 to 3.5 ng/dL), which correlated with the increase in serum-testosterone ($r=0.50$). This was interpreted as increase due to more testosterone for aromatization. There was no significant change in prolactin levels in the finasteride group, but an increase of 15% was observed with subjects who took placebo.

Table 10.2.1 Effects of Finasteride on Estradiol and prolactin at Week 48 in Study 094

	Finasteride 1 mg				Placebo				p-Value
	N	Baseline	Week 48	%Change	N	Baseline	Week 48	%Change	
Estradiol (mean, ng/dL)	82	2.5	2.7	14.8*	69	2.5	2.5	2.1	0.0170
Prolactin (mean, ng/mL)	82	10.2	9.9	5.1	72	9.5	11.2	25.3**	0.0281

*,**: Significant change from baseline at the $p \leq 0.050$ and ≤ 0.01 levels respectively.

Comments

1. Reversibility of the estradiol increase would be expected if this is derived from

increased aromatization of testosterone. This has not been demonstrated.

2. Material submitted in the Advisory Committee Briefing Package on 10/10/97 gave patient numbers and hormone levels different from those in Table 10.2.1. The differences remain to be explained.

Plasma Lipids No significant changes in lipid profile as compared with placebo.

Bone Density and Indices of Bone Metabolism See under 10.1.9.3, Study 094.

10.2.2 Urogenital

10.2.2.1 Effects of Finasteride on the Prostate See under 10.1.9.3, Study 094, for effect on prostate size and PSA levels. The long-term consequences of changes in the prostate have been evaluated in clinical trials in men with BPH who have received finasteride for up to 6 years with no significant adverse effects. In men with genetic 5 α -reductase deficiency, there does not appear to be deleterious consequences. However, finasteride has been found to stimulate the growth of human prostate cancer cells in athymic mice (PNAS 93: 11802-7, 1996). Although this was an artificial system quite different from the actual clinical situation, caution should be exercised in the long-term use of finasteride, especially in younger men for a cosmetic indication.

The effect of finasteride 1 mg/d on PSA levels may be of concern with respect to screening for prostate cancer. The PROSCAR label proposes a "multiplication by 2" rule for patients using finasteride 5 mg/d when PSA levels are measured, because PSA levels are suppressed by approximately 50% in older men using that dose in the treatment of BPH. The studies on finasteride 1 mg/d consistently show that mean PSA levels decrease from _____ ng/mL with this dose. The Applicant suggested at the Advisory Committee meeting of 11/13/97 that the most conservative way to interpret PSA levels in patients using finasteride 1 mg/d would still be the "multiplication by 2" rule. However, this may overestimate the incidence of prostate cancer and yield more false positives which cost resources and create human anguish.

10.2.2.2 Effects of Finasteride on Male fertility In male rats, finasteride may decrease fertility as the result of disruption of seminal plug, which is necessary for reproduction. This phenomenon is species-specific. In the clinical studies submitted in this NDA, although a reversible reduction in ejaculatory volume was seen with finasteride 5 mg/d treatment (Studies 012 and 056), the long-term reversibility study using 1 mg/d in male volunteers (Study 094) showed little difference between finasteride and placebo groups in terms of semen parameters. Study 094 was designed to provide finasteride dosing for four spermatogenesis cycles (48 weeks). Absence of apparently significant effect in the short term and the fact that patients with homozygous type 2 5 α -reductase deficiency have successfully fathered children suggest that dosing for up to 48 weeks is probably safe with respect to male fertility. In

the submission of 10/10/97, the Applicant also attempted to support this by giving the pregnancy rates in sexual partners of the clinical trial subjects:

Table 10.2.2.2 Pregnancies Reported in Sexual Partners of Phase 3 Trial Subjects

<u>Initial Controlled Study Period (Year 1)</u>		<u>Controlled Extension Period (Year 2)</u>	
<u>Finasteride 1 mg</u>	<u>Placebo</u>	<u>Fin 1 mg/Fin 1 mg</u>	<u>Pbo/Fin 1 mg</u>
12/945	4/934	2/547	8/543

Comment The semen parameters in patients treated with finasteride 1 mg/d for 48 weeks appear not to be affected. The pregnancy data of sexual partners of clinical trial subjects are difficult to interpret. Although patients with type 2 5 α -reductase deficiency are fertile, little is known of a comparison of their fertility with that of the general male population. Study 094 did provide evidence of a significant reduction of prostate size with finasteride 1 mg/d treatment for 48 weeks, although this is regarded by the Applicant as being not clinically meaningful. It is reasonable to conclude that despite short-term safety, the long-term effect of finasteride on male fertility remains unknown.

10.2.3 Breast

A low incidence of breast-related clinical AE (breast tenderness or enlargement) has been associated with use of finasteride 5 mg in older men with BPH. In the studies for male pattern baldness, the incidence is shown in Table 10.2.4.

Table 10.2.3A Breast-Related Clinical Adverse Experiences by Study Category--Patient Count (%)# Phase 3 Controlled, Phase 2 Controlled and Uncontrolled Studies

<u>Study Category</u>	<u>Original Submission</u>		<u>Updated Figures (10/10/97)</u>	
	<u>Finasteride</u>	<u>Placebo</u>	<u>Finasteride</u>	<u>Placebo</u>
Phase 3 Controlled	4/945 (0.4%)	4/934 (0.4%)	4/945 (0.4%)	4/934 (0.4%)
Phase 3 Controlled Extension	---	---	2/1090 (0.2%)	0/125
Phase 2 Controlled	3/836 (0.4%)	0/490	3/836 (0.4%)	0/490
Phase 3 Uncontrolled Extension	---	---	0/256	N/A
Phase 2 Uncontrolled Extensions	2/502 (0.4%)	N/A	2/502 (0.4%)	N/A

N/A = Not applicable # Patients with AE/patients in a category.

All 4 finasteride patients in the phase 3 trials who developed breast symptoms reported that this AE resolved while continuing on treatment. For the phase 2 controlled studies, 2 of the 3 finasteride patients reported the AE resolved while on treatment with finasteride. One patient, who participated in a 6-week Clinical Pharmacology study, had a previous history of gynecomastia and reported increase in breast size after 21 days of treatment. The AE was present at the end of the 6-week study. Two patients in the phase 2 uncontrolled studies reported breast-related AE, 1 with breast tenderness on 0.2 mg at Day 185 and 1 with a breast lump on 5 mg at Day 404, which lasted 60 days and resolved on finasteride therapy.

Table 10.2.3B Breast-Related Clinical Adverse Experiences--Listing of Patients Phase 3 Controlled, Phase 2 Controlled and Uncontrolled Studies

<u>Study and Patient Number</u>	<u>Dosage (mg)</u>	<u>Day of Onset</u>	<u>AE Specific Term</u>	<u>Duration</u>	
				<u>(Days)</u>	<u>Outcome</u>
Phase 3 Controlled					
087	1	31	Soreness, breast	93	Recovered on drug
087	1	48	Breast tenderness	53	Recovered on drug

087	1	196	Breast fullness	155	Recovered on drug
087	1	206	Breast tenderness	76	Recovered on drug
087	Placebo	27	Breast tenderness, nipple	134	Recovered off drug
087	Placebo	1	Breast pain	71	Still present off drug
087	Placebo	120	Sensitivity nipple	231	Resolved in blinded extension*
087	Placebo	346	Increased gynecomastia	348	Still present in controlled extension*
Phase 2 Controlled					
094	1	54	Breast tenderness, enlargement	146	Recovered on drug
094	1	150	Nipple indurations	38	Recovered on drug
		249	Itching, nipple	46	Recovered on drug
031	0.05	21	Increased gynecomastia	51	Still present on drug*
Phase 3 Controlled Extension					
087	1	438	Unilateral gynecomastia	108	Recovered off drug
089	1	580	Breast tenderness, bilateral	139	Still present on drug*
Phase 2 Uncontrolled					
047	5	404	Breast lump	60	Recovered on drug
081	0.2	185	Breast tenderness, nipple tenderness	91	Recovered on drug

* Outcome based on follow-up obtained after the cutoff date for respective CSRs.

Comment In the experience with PROSCAR™ (finasteride 5 mg/d) for the treatment of BPH, the Applicant noted (1) 4 reports of breast cancer in controlled trials (2 finasteride and 2 placebo), (2) 1 report in an open extension trial using finasteride and (3) 14 reports from marketed use. In addition, gynecomastia appeared to be the most common reported AE for PROSCAR™. The Applicant assumes that over men have used finasteride 5 mg for 2.5 years so that the reported incidence is well below the background male breast cancer rate adjusted for age per person-years or per person-years). However, it is unclear whether the person-year assumption is valid and how much under-reporting is present. Continued surveillance is warranted.

10.2.5 Other

10.2.5.1 Drug-Drug Interactions

Because finasteride is principally metabolized by cytochrome P450 3A4 family of enzymes within the liver, several studies were included in the approved marketing application for finasteride 5 mg to evaluate potential interactions. These included an antipyrine metabolism study to evaluate a specific hepatic cytochrome P450 oxidative metabolic pathway. No interaction was found. Several commonly used drugs, where small changes in drug levels can affect efficacy or safety, were also evaluated including digoxin, glyburide, propranolol, theophylline, and warfarin with negative results. This absence of drug-drug interactions is also supported by postmarketing experience.

10.2.5.2 Drug-Demographic Interactions

10.2.5.2.1 Age

Analysis of two subsets based on age showed no difference in the incidence of drug-related adverse events (7.5% and 7.8% respectively) in the finasteride group and in the placebo group (7.2% and 6.8% respectively).

10.2.5.2.2 Race

In phase 3 controlled studies, 88% of the patients were Caucasian, 6% were Black, and 6% were categorized as "Other" (Hispanic, Asian, and others). The majority of Black patients were recruited in the U.S., where the proportion enrolled (10.5%) is consistent with the general population in the U.S.

Table 10.2.5.2.2 Clinical Adverse Experience Summary by Race—Patient Count (%)# Phase 3 Controlled Studies

	Finasteride (N = 945)	Placebo (N = 934)
Patients With One or More AE		
Caucasian	530/840 (63)	488/817 (60)
Black	24/44 (55)	39/63 (61)
Other	42/61 (69)	33/54 (61)
Drug-Related AE		
Caucasian	57/840 (6.8)	56/817 (6.9)
Black	8/44 (18.2)	4/63 (6.3)
Other	8/61 (13.1)	5/54 (9.3)
Serious AE		
Caucasian	14/840 (1.7)	20/817 (2.4)
Black	1/44 (2.3)	0/63
Other	2/61 (3.3)	0/54
Drug-Related Sexual AE		
Caucasian	30/840 (3.6)	16/817 (2.0)
Black	3/44 (6.8)	3/63 (4.8)
Other	3/61 (4.9)	1/54 (1.9)

Patients with AE/patients per race

Comment There were more drug-related AE on finasteride in the "Black" and "Other" groups. The Applicant noted that differences (race by treatment group interaction) were not significant. As the numbers of patients with serious AE and drug-related sexual AE in the "Black" and "Other" groups was small (3 or fewer in each treatment group), these data should be interpreted with caution. However, there is evidence of clinical and biochemical differences in androgen action between normal healthy individuals from different ethnic backgrounds (J Clin Endocrinol Metab 72:1242-8, 1991), this issue of racial difference in safety cannot be ignored. The Applicant should provide an analysis of the significance levels of these data.

10.3 Summary of Key Safety Findings

1. The use of finasteride 1 mg/d appears to be well tolerated.
2. The most common drug-related AE relate to sexual function (decreased libido, erectile or ejaculatory dysfunction) and breast symptoms. Nevertheless, in many subjects, the AE might resolve off therapy or even when drug is maintained.
3. The sexual function questionnaire seems to have given a sensitive reflection of the disturbance in sexual function.
4. The short-term effects of finasteride 1 mg/d (on prostate, semen and bone parameters) appear to be reversible.
5. The long-term effects of finasteride 1 mg/d on male fertility and in the possible promotion of prostate cancer, especially if given as chronic therapy, remain unknown.
6. Use of finasteride 1 mg/d suppresses serum PSA level which may affect screening for prostate cancer.
7. Finasteride is a teratogen, but the level attained in semen of men taking finasteride 1 mg/d appears to be inadequate to pose a risk to the developing male fetus.

11 Labeling Review A labeling amendment was submitted on 9/25/97 in which changes to the original proposed label were made by incorporation of information provided in the 120 safety update and in the 8/11/97 amendment. Review of this proposed label (of 9/25/97) and the related patient package insert resulted in a revised version, which was presented to the Applicant on 11/21/97 by facsimile (Appendix XI). The Applicant responded with a new version on 12/2/97. Comments on this version are given in a second Medical Officer's Review on 12/4/97.

12 Conclusions

(1) Finasteride 1mg/d for 12 months in the treatment of MPB resulted in significant net increase in hair count as evaluated by dotmapping. Findings from patient hair growth questionnaire supported the clinical relevance and cosmetic significance of the quantitative improvement seen in scalp hair count as perceptible benefit to the patient. There was little additional objective beneficial effect other than maintenance of hair count beyond 12 months, although subjective assessments appeared to show continued improvement up to 24 months.

(2) Placebo treatment resulted in progressive loss of hair.

(3) The treatment effect of finasteride 1 mg/d has been demonstrated in males aged 18 to 41, with mild to moderate degrees of MPB (specific patterns in the modified Norwood-Hamilton scale) and with concomitant use of Neutrogena T-Gel Shampoo.

(4) Results in the pivotal trials and in the "frontal baldness study" (092) have demonstrated efficacy in vertex baldness and hair loss in the "frontal" area, which includes mid-scalp. Efficacy in the anterior hairline and temporal recession has not been established.

(3) Finasteride 1mg/d in the treatment of MPB has been well tolerated, with a low incidence of drug-related adverse events, chiefly in the area of sexual adverse events. Its concomitant effects on indices of bone resorption and bone formation appear to be reversible within 12 weeks of cessation of therapy.

(4) Finasteride 1 mg/d for 12 months appears to be safe and effective over the duration of treatment.

(5) The long-term benefits of finasteride 1 mg/d in MPB is uncertain. Although finasteride at a 5 mg/d use has been used for 6 or more years in older patients with BPH, the long-term risks in **younger men** is unknown, especially in terms of its effects on male fertility and on prostate neoplasia. Therefore, a risk-benefit analysis for the long-term therapy with finasteride 1 mg/d in MPB cannot be made at this time.

13 Recommendations

13.1 Approval, Approvable, Non-Approval

Medical Officer's Review of NDA 20-788

DEC 19 1997

NDA #20-788

Amendments to Pending Application Submitted: December 19, 1997

Received: December 19, 1997

Review Completed: December 19, 1997

Drug name: finasteride 1 mg tablets

Generic name: finasteride

Proposed trade name: PROPECIA™

Chemical name : *N*-(1,1-Dimethylethyl)-3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide

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

Pharmacologic category: 5 α -reductase inhibitor

Proposed Indication: male pattern baldness (MPB) in men

Dosage Form(s) and Route(s) of Administration: tablet, oral

NDA Drug Classification: 3 S

Related NDAs and INDs:

NDA 20-180 PROSCAR™ for the treatment of symptomatic benign prostatic hyperplasia (BPH)

IND

Studies done by the Applicant for NDA 20-788 were conducted under IND

Background:

The Applicant had a teleconference with the Agency on labeling on 12/18/97. This submission is to provide a new revised draft for the Agency's consideration.

Review of Label:

Areas commented on are double-underlined and numbered in the text, which is attached in Appendix I.

Recommendation:

This NDA may be approved upon revision of this label and if the Applicant would commit to the recommendations for phase 4 as follows:

12-19-97

Hon-Sum Ko, M.D.

c.c. NDA 20-788
HFD-540 Files
HFD-540/Chem/Hathaway
HFD-540/Pharm/Avalos
HFD-880/Biopharm/Kumi
HFD-725/Biometrics/Freidlin
HFD-540/CSO/Kummerer
HFD-540/MO/Ko

Medical Officer's Review of NDA 20-788

DEC 18 1997

NDA #20-788

Amendments to Pending Application Submitted: December 15, 1997
Received (by FAX): December 15, 1997
Review Completed: December 15, 1997

Drug name: finasteride 1 mg tablets

Generic name: finasteride

Proposed trade name: PROPECIA™

Chemical name : *N*-(1,1-Dimethylethyl)-3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide

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NDA Drug Classification: 3 S

Related NDAs and INDs:

NDA 20-180 PROSCAR™ for the treatment of symptomatic benign prostatic hyperplasia (BPH)

IND

Studies done by the Applicant for NDA 20-788 were conducted under IND

Background:

The Applicant is responding to a question from the Agency concerning sensitivity of the PSA test in prostate cancer detection.

Question:

The answers to question 5 and 7 (from Merck's submission on 12/10/97) indicate that Merck interprets the multiplication by 2 rule as giving better sensitivity in the "discrimination" of cancer vs no cancer. Do they mean "detection" rather than "discrimination"? Greater sensitivity with this x2 rule will detect more false positives, which will cost resources for further investigations and human anguish. Are they going to put something in the label to address this possibility?

Merck's Response:

Merck gave an example using community-dwelling men aged 40-49 (n=309) in randomly sampled from the population regardless of prostate size.

Although these men had not taken finasteride, applying the multiplication by 2 rule to their real PSA values would result in a false positive rate of 2 to 3 % (1% if not multiplied), assuming the upper limit of normal as 4 ng/mL. If the upper limit is taken as 2.5 ng/mL (favored by some urologist for this age group), then the false positive rate would be 10% (4% if not multiplied). The Applicant concludes that in men less than 40 years of age, the false positive rates would be expected to be lower.

The Applicant states that these estimates are worst case scenarios and must be considered in the context of a false positive rate of about 40% in older men with BPH not taking finasteride.

Comments

1. The Applicant appears to have addressed this issue of false positivity in PSA testing, since (1) with a "worst case scenario", the false positive rate has increased from 3% in men aged 40-49 (2) the false positive rate in older men with BPH not taking finasteride is about 40% and (3) PSA testing for men less than 40 years of age is generally not recommended. However, there is still some concern because of the possibility of off-label use in older men.

2. Opinion from the Division of Urologic and Reproductive Drug Products has been sought. Drs. M. Hirsch and D. Shames have suggested modifying the third sentence in the subsection on Drug/Laboratory Test Interactions under PRECAUTIONS to the following:

Recommendation:

The Applicant should modify the label to inform the prescriber on the relative lack of information on interpreting PSA data in younger men using PROPECIA.

12-16-97
Hon-Sum Ko, M.D.

c.c. NDA 20-788
HFD-540 Files
HFD-540/Chem/Hathaway
HFD-540/Pharm/Avalos
HFD-880/Biopharm/Kumi
HFD-725/Biometrics/Freidlin
HFD-540/CSO/Kummerer
HFD-540/MO/Ko

12/18/97

Medical Officer's Review of NDA 20-788

DEC 18 1997

NDA #20-788

Amendments to Pending Application Submitted: November 11 & 19, 1997

Received: November 12 & 20, 1997

Review Completed: December 9, 1997

Drug name: finasteride 1 mg tablets

Generic name: finasteride

Proposed trade name: PROPECIA™

Chemical name : *N*-(1,1-Dimethylethyl)-3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide

Applicant: Merck Research Laboratories
Sumneytown Pike
P.O. Box 4, BLA-20
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Pharmacologic category: 5 α -reductase inhibitor

Proposed Indication: male pattern baldness (MPB) in men

Dosage Form(s) and Route(s) of Administration: tablet, oral

NDA Drug Classification: 3 S

Related NDAs and INDs:

NDA 20-180 PROSCAR™ for the treatment of symptomatic benign prostatic hyperplasia (BPH)

IND

Studies done by the Applicant for NDA 20-788 were conducted under IND

Background:

1. In the 90-day meeting for this NDA dated 3/19/97, a discussion was made as to whether the use of tar-based shampoo might have had an effect on hair count. The Applicant subsequently submitted Protocol 110, which was intended to examine this issue. The study has been completed and this submission with preliminary, unaudited data was made on November 11, 1997, because the Applicant anticipated discussions on this issue by the Advisory Committee at the

DODAC meeting on 11/13/97. One of the questions to the Committee concerned the entry requirement of Neutrogena T-Gel Shampoo use.

2. The submission of 11/19/97 (1) addresses the Applicant's perspectives on a number of issues discussed at the Advisory Committee meeting of 11/13/97 and (2) supplied the following data which were requested as the issues arose during the discussions at the Advisory Committee meeting: (a) photographic global assessments of three other views apart from the vertex in the pivotal trials 087 and 089; and (b) excerpts of the safety summary of the PLESS study, which was a long-term placebo-controlled study involving PROSCAR™ (finasteride 5 mg) in the treatment of benign prostatic hyperplasia.

Review of Preliminary Data of Study 110

Study 110 was a crossover experiment with 44 subjects randomized to one of two sequences: (1) tar-based shampoo for 7 days followed by non tar-based shampoo for another 7 days or (2) non tar-based shampoo for 7 days followed by tar-based shampoo for 7 days. No washout was undertaken between the two periods. Hair counts were obtained from dot maps of macrophotographs on a 1-inch diameter circular area of clipped hair, centered at the anterior edge of the vertex bald spot. A memorandum with comments of this protocol is attached in Appendix I.

Results:

Sequence	Hair Count Data for Two Treatment Sequences							
	Non-Tar-Based/Tar-Based				Tar-Based/Non-Tar-Based			
	N	Mean	SD	Median	N	Mean	SD	Median
Baseline	22	920	207	932	22	870	230	851
Week 1	22	922	218	945	22	884	259	841
Week 2	22	941	216	966	22	887	255	840

	N	Mean Hair Count Changes from Baseline		Difference	p
		Non-Tar-Based	Tar-Based		
Overall	44	9.8	17.5	-7.7 (90% C.I.=-16.2, 0.8)	0.143
End of Week 1	22	2.6	13.5	-10.9 (90% C.I.=-33.8, 12.0)	

The Applicant noted that there was no significant effect for shampoo ($p=0.143$) or sequence ($p=0.809$) but there was a significant effect for period ($p<0.036$), i.e., the small increase in favor of a tar-based shampoo was greater in period 1 than in period 2.

Comments

1. There is a definite, although small, effect given by the tar-based shampoo. It increased the hair count by %. The mean changes in hair count between the two shampoos did not reach significance because (1) the sample size was small: this study enrolled 44 subjects, with 22 per group, as compared to the pivotal trials, which had 308 to 471 per treatment group; and (2) the variability of the mean changes were big (mean±SD=2.6±45.9 and 13.5±46.3 for non-tar-based and tar-based shampoos, respectively, in hair count changes at the end of Week 1).

2. The conclusion that the increase in favor of tar-based shampoo was greater in period 1 is not apparently supported by the above data, as the mean changes from the end of week 1 to that of week 2 has not been provided. In fact the above data show that the increase in favor of tar-based shampoo was greater in period 2 [(941-922)-(887-884)=16] than in period 1 [(884-870)-(992-990)=12].
3. The effect of having no washout has not been determined.
4. These data have not been audited.

Merck's Perspectives on Issues Discussed at Advisory Committee Meeting of 11/13/97

Efficacy Issues

1. Treatment of "frontal" baldness. Merck maintains that finasteride is a systemic therapy which should provide efficacy for scalp hair growth regardless of regionality and that their studies have sufficient data from the four endpoints in study 092 to establish efficacy on frontal baldness. At the meeting, the Applicant showed a slide intended to demonstrate that improvement in patient self-assessment for the vertex studies and the frontal baldness study was comparable (submitted later on 11/19/97):

	Patient Self-Assessment Questionnaire at Month 12: Percent Positive Scores			
	Finasteride 1 mg		Placebo	
	Vertex	"Frontal"	Vertex	"Frontal"
Q.2 Appearance	57	53	35	30
Q.3 Hair growth	56	49	33	34
Q.4 Hair loss	68	65	45	45
Q.5 Satisfaction on anterior hairline	29	33	17	16
Q.5b Satisfaction on top of scalp	36	42	20	27
Q.5c Satisfaction overall	39	41	22	25

In addition, Merck will provide data from photographic global assessment in three different views in the pivotal studies (see below) that may further support this opinion.

2. Merck reiterates its strong opinion that finasteride alters the underlying process of androgenetic alopecia and anticipates appropriate language in the INDICATIONS section of the label to be reached with the Agency with respect to the issue of "prevention of further hair loss".

Safety Issues

1. General comments. Merck believes that the safety issues have largely been addressed in NDA 20-180 (PROSCAR™) and that the only significant toxicity is teratogenicity to a male fetus. The syndrome of 5α-reductase deficiency attests to the long-term safety of finasteride treatment.

2. Hormonal specificity. Merck argues that the case report of "glucocorticoid-like" myopathy (*Muscle Nerve* 20:502, 1997) discussed at the Advisory Committee meeting is not supported by the accumulated safety database with PROSCAR or in the clinical studies for PROPECIA. Finasteride has not been found to show any other effects on

steroid hormone action or metabolism.

3. Bone changes. Merck summarized the monitoring of bone mineral density data from the PLESS study, which has been submitted to NDA 20-180 recently. Treatment of older men with finasteride 5 mg did not adversely affect BMD. Relevant portions from that submission to NDA are provided (see below).

4. Prostate cancer. Merck argues that the report on finasteride stimulating growth of prostate cancer cell line in the Proceedings of the National Academy of Science is of no clinical relevance (*PNAS 93:11806, 1996*).

5. Fertility. Merck maintains the position that finasteride 1 mg should not affect male fertility. However, at the meeting, they had presented a slide showing reductions in ejaculatory volume among study subjects in Study 056 stratified by baseline ejaculatory volumes, which showed approximately similar degrees of drop among them:

Reduction in Ejaculatory Volume in Subjects Treated with Finasteride 5 mg (Study 056)		
High Tertile	Medium Tertile	Low Tertile
BL --->Week 24	BL --->Week 24	BL --->Week 24
3.6 mL--->2.7 mL	2.9 mL--->2.4 mL	2.0 mL--->1.5 mL
(-25%)	(-17%)	(-25%)

Comment Assuming the decrease in ejaculatory volume to be 25% with finasteride 5 mg treatment, men with an initial volume of 1.3 mL will develop an ejaculatory volume of less than 1.0 mL, "a value below which, experts agree, male fertility may be impaired".

Merck concedes that since they did not meet the predefined criteria in Study 094 to conclude that there was no change in ejaculatory volume, they will work with the Agency to develop label language that accurately reflects the results of this study.

6. PSA. Merck suggested that the "multiplication by 2 rule" as used in the case of PROSCAR would be the most conservative approach when PSA is tested for the screening of prostate cancer in men taking PROPECIA™.

Analysis of Four Position Global Photography

In Studies 087 and 089, global photographs included:

1. Anterior Hairline: Hair is pulled back with the supplied headband to expose the entire anterior hairline. This documents the advancing or receding of the anterior hairline.
2. Superior/frontal: Hair is center-parted and combed away from the part. This will document closing or widening of the entire center part from the vertex to the anterior hairline.
3. Temporal hairline: Hair is pulled back with the supplied headband to expose the entire temporal hairline. This photograph will document the advancing or receding of the temporal hairline.
4. Vertex: Hair is combed away from the vertex (like spokes of a wheel). This photograph will document hair growth or loss of the vertex balding area.

The results are shown as follows:

I. Global Photographic Assessment at the End of First 12 months.

Median Scores for Global Photographic Assessment at Month 12

	Pooled Data				087				089			
	Finasteride		Placebo		Finasteride		Placebo		Finasteride		Placebo	
	N	Median	N	Median	N	Median	N	Median	N	Median	N	Median
Anterior Hairline	652	0.2	645	0	396	0.2	380	0	256	0.2	265	-0.1
Superior/Frontal	654	0.6	643	0	394	0.8	376	0	260	0.5	267	-0.1
Temporal Hairline	655	0.2	645	0	397	0.2	379	0	258	0.1	266	0
Vertex	720	0.7	709	0	435	0.7	417	0	285	0.6	292	0

All between group comparisons gave p values of <0.001.

Percent of Patients in Scoring for Global Photographic Assessment at Month 12

Scores		-3	-2	-1	0	1	2	3
Meaning		<-----Decreased-----			No Change	-----Increased----->		
Combined Data								
<u>Anterior Hairline</u>	Finasteride 1 mg N=652	0	0	0	82	15	2	0
	Placebo N=645	0	0	5	94	1	0	0
<u>Superior/Frontal</u>	Finasteride 1 mg N=654	0	0	1	51	33	13	2
	Placebo N=643	0	1	10	81	7	1	0
<u>Temporal Hairline</u>	Finasteride 1 mg N=655	0	0	1	85	12	2	0
	Placebo N=645	0	0	3	95	2	0	0
<u>Vertex</u>	-----Data Provided Previously in Original NDA-----							
Study 087								
<u>Anterior Hairline</u>	Finasteride 1 mg N=396	0	0	0	81	15	3	0
	Placebo N=380	0	0	4	94	1	0	0
<u>Superior/Frontal</u>	Finasteride 1 mg N=394	0	0	1	48	32	17	3
	Placebo N=376	0	1	9	82	8	1	0
<u>Temporal Hairline</u>	Finasteride 1 mg N=397	0	0	1	83	13	2	1
	Placebo N=379	0	0	3	94	2	0	0
<u>Vertex</u>	-----Data Provided Previously in Original NDA-----							
Study 089								
<u>Anterior Hairline</u>	Finasteride 1 mg N=256	0	0	0	83	14	2	0
	Placebo N=265	0	0	5	94	0	0	0
<u>Superior/Frontal</u>	Finasteride 1 mg N=260	0	0	2	57	35	7	1
	Placebo N=267	0	1	13	79	6	0	0
<u>Temporal Hairline</u>	Finasteride 1 mg N=258	0	0	0	88	10	2	0
	Placebo N=266	0	0	3	95	1	0	0
<u>Vertex</u>	-----Data Provided Previously in Original NDA-----							

II. Global Photographic Assessment at the End of 24 Months.

Median Scores for Global Photographic Assessment at Month 24

		F/F*		F/P		P/F		P/P	
		N	Median	N	Median	N	Median	N	Median
Combined Data	Anterior Hairline	453	0.3	49	-0.1	444	0.1	43	-0.2
	Superior/Frontal	453	0.7	49	0	443	0.4	44	0.3
	Temporal Hairline	459	0.2	49	0	453	0.1	45	0
	Vertex	508	1.0	54	-0.1	499	0.5	55	-0.4
Study 087	Anterior Hairline	275	0.3	31	0	258	0.1	25	-0.2
	Superior/Frontal	274	0.8	31	0.1	258	0.4	26	-0.3
	Temporal Hairline	277	0.2	31	0	260	0.1	27	-0.1
	Vertex	308	1.1	34	0.1	290	0.7	33	-0.1
Study 089	Anterior Hairline	178	0.2	18	-0.2	186	0	18	-0.2
	Superior/Frontal	179	0.6	18	0	185	0.3	18	-0.4
	Temporal Hairline	182	0.2	18	0	193	0.1	18	0
	Vertex	200	0.9	20	-0.2	209	0.4	22	-0.8

Data carried forward. Between-group comparison for F/F vs P/P <0.001 for all 3 sets of data. *F/F=Finasteride 1 mg throughout 24 months. F/P=Finasteride in first 12 months and placebo in second 12 months, P/F=Placebo in first 12 months and finasteride in second 12 months, and P/P=placebo throughout 24 months.

Median Scores for Global Photographic Assessment at Month 24 vs Month 12

		F/F*		F/P		P/F		P/P	
		Median		Median		Median		Median	
		N	M12 M24	N	M12 M24	N	M12 M24	N	M12 M24
Combined Data	Anterior Hairline	453	0.2 0.3	48	0.1 -0.1	426	0 0.1	42	0 -0.2
	Difference		0.0		-0.1¶		0.1¶¶¶		-0.1
	Superior/Frontal	447	0.7 0.7	48	0.5 0	428	0 0.4	42	-0.2 -0.3
	Difference		0.0		-0.5¶¶¶		0.4¶¶¶		-0.2
	Temporal Hairline	450	0.2 0.2	48	0.1 0	435	0 0.1	42	0 0
Difference		0.0		-0.1		0.1¶¶¶		0.0	
Vertex	459	0.7 1.1	48	0.7 0	442	0 0.6	42	-0.1 -0.4	
Difference		0.3¶¶¶		-0.8¶¶¶		0.6¶¶¶		-0.4¶¶	
Study 087	Anterior Hairline	271	0.3 0.3	30	0 0	252	0 0.1	24	0 -0.2
	Difference		0.0		0.0		0.1¶¶¶		-0.1
	Superior/Frontal	270	0.8 0.8	31	0.5 0.1	253	0 0.5	25	-0.2 -0.3
	Difference		0.0		-0.4¶¶		0.4¶¶¶		-0.1
	Temporal Hairline	272	0.2 0.2	31	0 0	254	0 0	27	0 -0.1
Difference		0.0		0.0		0.1¶		0.0	
Vertex	279	0.8 1.1	32	0.8 0.1	257	0 0.7	27	0 -0.1	
Difference		0.3¶¶		-0.7¶¶¶		0.7¶¶¶		-0.1	
Study 089	Anterior Hairline	172	0.2 0.2	18	0.2 -0.2	174	0 0	1	-0.1 -0.2
	Difference		0.0		-0.4¶¶		0.1¶		-0.1
	Superior/Frontal	177	0.6 0.6	18	0.6 0	175	-0.1 0.3	17	-0.1 -0.4
	Difference		0.1		-0.6¶¶		0.3¶¶¶		-0.3
	Temporal Hairline	178	0.1 0.2	18	0.1 0	181	0 0.1	18	0 0
Difference		0.0		-0.1		0.1¶¶		0.0	
Vertex	180	0.7 1.0	18	0.7 -0.2	185	0 0.4	19	-0.1 -0.8	
Difference		0.3¶¶		-0.9¶¶¶		0.5¶¶¶		-0.7¶¶¶	

Data not carried forward. *F/F=Finasteride 1 mg throughout 24 months. F/P=Finasteride in first 12 months and placebo in second 12 months, P/F=Placebo in first 12 months and finasteride in second 12 months, and P/P=placebo throughout 24 months; M12=Month 12 and M24=Month 24. Significant differences (p<0.05) between Months 12 and 24 are shaded: ¶, ¶¶ and ¶¶¶ = p<0.05, 0.01 and 0.001 respectively.

Percent of Patients in Scoring for Global Photographic Assessment at Month 24

Scores			-3	-2	-1	0	1	2	3
Meaning			←-----Decreased-----			No Change-----		-----Increased----->	
Combined Data (087 PLUS 089)									
Anterior Hairline	F/F	N=453	0	0	1	77	17	4	0
	F/P	N=49	0	2	4	92	2	0	0
	P/F	N=444	0	1	4	83	11	1	0
	P/P	N=43	0	0	16	84	0	0	0
Superior/Frontal	F/F	N=453	0	0	3	44	32	19	3
	F/P	N=49	0	0	12	71	16	0	0
	P/F	N=443	0	1	5	60	23	9	2
	P/P	N=44	0	7	23	66	5	2	0
Temporal Hairline	F/F	N=459	0	0	0	85	12	3	0
	F/P	N=49	0	0	0	100	0	0	0
	P/F	N=453	0	0	2	91	6	1	0
	P/P	N=45	0	0	4	96	0	0	0

*F/F=Finasteride 1 mg throughout 24 months. F/P=Finasteride in first 12 months and placebo in second 12 months, P/F=Placebo in first 12 months and finasteride in second 12 months, and P/P=placebo throughout 24 months.

Comments

1. It is noted that patients entering into the extension phase had better responses to treatment than those who did not enter. The data on changes in hair count showed:

	Finasteride 1 mg		Placebo	
	N	Mean Change in Hair Count	N	Mean Change in Hair Count
All Eligible	679	86	672	-21
Entered Extension	602	92	593	-20
Not Entered	79	30	79	-36

Data from Merck's slide shown at Advisory Committee meeting and submitted 11/19/97.

- The placebo/placebo groups in 087 and 089 had very contrasting results at the end of Month 24, with a photographic global change of -0.1 for 087 and -0.8 for 089.
- It is not clear why the photographic global data of the four views presented in this submission uses a nonparametric analysis (using median instead of mean) although in the original submission, analysis of such data for the vertex view was parametric.
- These data show that systemic therapy with finasteride 1 mg gives beneficial effect mostly to the vertex and "superior/frontal" areas, and, to a substantially lesser extent, to the anterior hairline and temporal areas.

Excerpts from NDA 20-180 on PLESS Study: Safety Data

This supplement for NDA 20-180 has been submitted to DURDP and is under review. Merck has provided sections on: breast-related adverse events, bone mineral density and prostate cancer/PSA. PLESS is a 4-year study of 3040 men taking finasteride 5 mg (PROSCAR™) (1524) or placebo (1516) in the treatment of BPH.

Breast-Related Adverse Events

The following Table shows the incidence of breast-related adverse events in this study.

	Finasteride 5 mg	Placebo	p-value
No. & (%) with Breast AE	66 (4.3%)	42 (2.8%)	0.024
No. & (%) with Drug-Related Breast AE	45 (3.0%)	23 (1.6%)	0.014
Asymmetry, breast	0	1 (0.1%)	
Breast disorder	2 (0.1%)	0	
Fibrocystic disease	1 (0.1%)	0	
Breast enlargement	35 (2.3%)	18 (1.2%)	0.026
Year 1	0.5%	0.1%	
Cumulative Years 2,3,4	1.8%	1.1%	
Breast mass	5 (0.3%)	2 (0.1%)	
Breast tenderness	17 (1.1%)	6 (0.4%)	0.034
Year 1	0.4%	0.1%	
Cumulative Years 2,3,4	0.7%	0.3%	

Two placebo patients had intraductal breast cancer detected.

Bone Mineral Density

No significant differences between treatment groups were found at the end of 48 months of treatment.

Prostate Cancer/PSA

Incidence of prostate cancer diagnosed over the 4-year study period is shown in the following Table:

		Finasteride 5 mg	Placebo
All Patients	Randomized	1523	1511
	Patients biopsied	325	319
	Number of biopsies	385	395
	N (%) of patients biopsied with cancer detected	68 (21%)	67 (21%)
	N (%) of biopsies with cancer detected	68 (18%)	67 (17%)
PSA <4 ng/mL	Randomized	1149	1154
	Patients biopsied	110	118
	Number of biopsies	126	137
	N (%) of patients biopsied with cancer detected	25 (23%)	25 (21%)
	N (%) of biopsies with cancer detected	25 (20%)	25 (18%)
PSA ≥4 ng/mL	Randomized	374	357
	Patients biopsied	215	201
	Number of biopsies	259	258
	N (%) of patients biopsied with cancer detected	43 (20%)	42 (21%)
	N (%) of biopsies with cancer detected	43 (17%)	42 (17%)

Effect of Finasteride 5 mg on PSA Test

Previous studies have shown that treatment with finasteride 5 mg might reduce PSA level by approximately 50%. In PLESS, the median percent changes from baseline in PSA showed that at the end of 48 months, there was an increase of approximately 10% in the placebo group and a decrease of approximately 54% in the finasteride group. Using the multiplication by 2 rule in the finasteride group, the specificity and sensitivity of the test were compared between the two treatment groups. The Applicant concluded that specificity of the PSA assay was significantly improved ($p < 0.001$) in finasteride-treated patients, while for any given level of specificity, the sensitivity of PSA in the finasteride group was higher, although not significantly, than that in the placebo group ($p = 0.066$).

Comments

1. There is a higher incidence of breast-related adverse events in patients treated with finasteride 5 mg, especially with respect to breast enlargement and breast tenderness.
2. No adverse effect on bone mineral density was demonstrated in this four-year study.
3. Incidence of prostate cancer detected, whether among all randomized subjects or among those who had biopsies, was similar between treatment groups. This was true regardless of whether PSA level was above or below 4 ng/mL. However, the 4 ng/mL level did distinguish the risks of prostate cancer detection: approximately 2% if PSA was below 4 ng/mL and 12% if 4 ng/mL or higher, although comparison between treatment groups again showed no difference.
4. The assertion that finasteride 5 mg improves specificity and sensitivity of PSA in the detection of prostate cancer is based on a number of assumptions, including a clinical trial setting where both physician and patient are aware of the use of finasteride and its effect on the assay, the rule of multiplication by 2 and modeling with ROC receiver operating characteristic curves. Its relevance in a real clinical practice setting remains to be determined.

Conclusions:

1. Results of Study 110 on Tar-Based Shampoo Effect

There is a definite, although small, effect given by the tar-based shampoo. However,

the effect of having no washout in this study has not been determined. Furthermore, these data have not been audited.

2. Merck's Perspectives on Issues Discussed at Advisory Committee Meeting

Efficacy Issues

- Treatment of "frontal" baldness. The area studied in Study 092 was in fact including frontal and mid-area. Since "frontal" carries a number of meanings, it may be necessary to use language that can clearly convey to the prescriber the region for which efficacy has been demonstrated.
- Although Merck reiterates that finasteride alters the underlying process of androgenetic alopecia, appropriate language in the INDICATIONS section of the label cannot include the unsubstantiated claim of
Rather, the data may be appropriately presented in the Clinical Studies section for the prescriber's information.

Safety Issues

- Merck's position on hormone specificity, risk of prostate cancer and bone changes have been supported by data involving preclinical studies and long-term human studies in the treatment of BPH.
- Fertility. No new data have been presented. The reduction in ejaculatory volume is still of concern, especially in men who may have a low volume before initiating treatment.
- PSA. Although there is a lack of evidence that the relatively low PSA levels in younger men provide any effective means for prostate cancer detection, Merck suggested that the "multiplication by 2 rule" as used in the case of PROSCAR would be the most conservative approach when PSA is tested for the screening of prostate cancer in men taking PROPECIA™. The risk and benefit of false positives have not been determined. However, this issue does deserve physician awareness and education. The labeling should prominently address this effect of finasteride.

Analysis of Four Position Global Photography

The data show that systemic therapy with finasteride 1 mg gives beneficial effect mostly to the vertex and "superior/frontal" areas, and, to a substantially lesser extent, to the anterior hairline and temporal areas.

Excerpts from NDA 20-180 on PLESS Study: Safety Data

No significant new information that impacts on the use of finasteride 1 mg has been presented. The assertion that finasteride 5 mg improves specificity and sensitivity of PSA in the detection of prostate cancer is based on a number of assumptions, including

a clinical trial setting where both physician and patient are aware of the use of finasteride and its effect on the assay, the rule of multiplication by 2 and modelling with ROC receiver operating characteristic) curves. Its relevance in a real clinical practice setting remains to be determined.

Recommendations:

It is recommended that the above conclusions be conveyed to the Applicant.

Hon-Sum Ko, M.D. *12-9-97*

c.c. NDA 20-788
HFD-540 Files
HFD-540/Chem/Hathaway
HFD-540/Pharm/Avalos
HFD-880/Biopharm/Kumi
HFD-725/Biometrics/Freidlin
HFD-540/CSO/Kummerer
HFD-540/MO/Ko

NDA #20-788

Amendments to Pending Application Submitted: December 10 & 12, 1997

Received: December 11 & 12, 1997

Review Completed: December 13, 1997

Drug name: finasteride 1 mg tablets

Generic name: finasteride

Proposed trade name: PROPECIA™

Chemical name : *N*-(1,1-Dimethylethyl)-3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide

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

Pharmacologic category: 5 α -reductase inhibitor

Proposed Indication: male pattern baldness (MPB) in men

Dosage Form(s) and Route(s) of Administration: tablet, oral

NDA Drug Classification: 3 S

Related NDAs and INDs:

NDA 20-180 PROSCAR™ for the treatment of symptomatic benign prostatic hyperplasia (BPH)

IND

Studies done by the Applicant for NDA 20-788 were conducted under IND

Background:

The Applicant is responding to questions and comments from the Agency. The submission on 12/10/97 responds to request of information and that on 12/12/97 contains, in addition, a revised label and patient package insert modified as a result of labeling comments conveyed by phone by this Reviewer and Dr. M. Weintraub, Director of ODE V.

Responses to Questions:

1. Recovery from Sexual Adverse Events

The Applicant provided documentation on the figures given in the proposed label of 12/2/97: all patients who discontinued finasteride and 58% of those who continued treatment recovered. A listing was provided for each group.

Comment Among those who continued drug with recovery, four are problematic:
Patient [redacted] Libido decrease and erectile dysfunction both started on day 1 and lasted 28 days. However, the listing says drug was discontinued for libido decrease and not for erectile dysfunction. It is unclear whether the drug was continued.
Patient [redacted] Erectile dysfunction started on day 1 and lasted for one day. Drug was discontinued and yet patient listed as "recovered on drug".
Patient [redacted] Libido decrease started on day 1 and lasted for 57 days, with patient recovering on drug; but this AE recurred on day 92 and lasted for 243 days, with recovery off drug. Thus, this patient should not be classified as "recovery on drug".
Patient [redacted] Erectile dysfunction, said to be recovered off drug. The patient, however, was listed as "discontinued"
 The Applicant should substantiate these cases of recovery on drug.

2. Neutrogena T-Gel conditioner

This conditioner, although mentioned on the carton of Neutrogena T-Gel Shampoo to be used after shampooing, was not dispensed with the shampoo.

3. Correlation Between Decrease in Prostate Volume and PSA Decrease in Study 094

The Applicant states that there was no correlation between prostate volume decrease and PSA changes. However, although these changes did not show significant correlation, the correlation coefficients in the finasteride group were quite different from those in the placebo group:

Method	Finasteride		Placebo		Total	
	Y	p-value	Y	p-value	Y	p-value
Pearson	-0.086	0.452	-0.016	0.900	0.004	0.957
Spearman	-0.050	0.664	-0.003	0.983	0.034	0.680
Kendall's T	-0.037	0.635	-0.002	0.983	0.026	0.654

Comment The data should be reviewed by Biometrics.

The Applicant also states that the reversibility phase of this study is now complete. Data on prostate volume and PSA at the 60th week of follow up off drug (108 weeks from beginning of study) were presented. No significant within or between group differences in prostate volume were noted. For serum PSA, the between group differences at or after week 60 (12 weeks off drug) were not significant.

4. Subjects with Undetectable PSA Levels at the End of Treatment

Percent of Subjects Tested with Undetectable Levels (0.2 ng/mL) in Four Studies on Finasteride 1 mg

	Finasteride		Placebo	
	Baseline	Month 12	Baseline	Month 12
087	1.6%	11.6%	1.9%	2.5%
089	3.1%	17.0%	2.1%	2.5%
092	3.9%	11.6%	2.3%	0.8%
094	3.8%	13.8%*	2.9%	1.4%

*Week 48 for Study 094

Comment A substantial increase in the occurrence of undetectable PSA levels at the end of 12 months of treatment with finasteride 1 mg is noted in men aged 18-41 in the clinical trials.

5. Onset of PSA Level Decrease and the "Multiplication by 2 Rule"

The Applicant has no information before Month 3 of finasteride 1 mg therapy on PSA levels. Merck reiterates its position at the Advisory Committee meeting of 11/13/97 that multiplying by 2 "insures that the sensitivity of PSA as a screening tool for prostate cancer is not compromised nor is the use of PSA complicated for the practitioner by the introduction of multiple adjustment factors applicable in varying clinical situations."

Comment In all the clinical studies for the finasteride 1 mg/d dose in younger men, a very consistent finding is the decrease of serum PSA from ng/mL. The "multiplication by 2 rule" may result in overestimation of the real level by approximately 0.3 ng/mL (or 0.3/0.7=43%). The significance of this is unknown in men of this age group who do not have enlarged prostates, but the possibility of false detection of prostate cancer with unnecessary additional investigations and human anguish may be a very real cost to the insuring of the test's sensitivity.

6. Data Listing for Location of Scalp Tattoo in the "Frontal" Baldness Study, 092

This data listing has not been submitted in the original NDA. The Applicant now supplies the listing.

On analyzing this listing, the distance of the tattoo from the tip of the nose was used as a guide as to how far to the front the hair count data were collected. Although it is recognized that the tattoo may not be in the midline, an arbitrary cutoff of 200 mm was used to distinguish the frontal and mid-area by this Reviewer, since the figure of 200 mm is quite conservative and extends some distance into the mid-scalp. Another cutoff between 200 and 225 mm was also used to examine those who might have had hair counts further back but not beyond 225 mm from the tip of the nose.

Distribution of Patients by Investigator for Tattoo Distance from Tip of Nose

Tattoo Distance (mm)	Patient Numbers with Tattoo Distance from Tip of Nose								
	Finasteride 1 mg			Placebo			Total		
	<200	221-225	≥225	<200	221-225	≥225	<200	221-225	≥225
092001 Baldwin, H.	0 +	6 +	5 -->11	0 +	3 +	7 -->10	0 +	9 +	12 -->21
092002 Draelos, Z.	1 +	2 +	7 -->10	1 +	4 +	5 -->10	2 +	6 +	12 -->20
092003 Dunlap, F.	0 +	2 +	19 -->21	0 +	6 +	13 -->19	0 +	8 +	32 -->40
092004 Kang, S.	9 +	0 +	0 -->9	9 +	0 +	0 -->9	18 +	0 +	0 -->18
092005 Kraus, S.	0 +	4 +	7 -->11	2 +	2 +	7 -->11	2 +	6 +	14 -->22
092006 Lebwohl, M.	1 +	9 +	3 -->13	1 +	7 +	4 -->12	2 +	16 +	7 -->25
092007 Leyden, J.	1 +	2 +	3 -->6	0 +	2 +	3 -->5	1 +	4 +	6 -->11
092008 Winters, P.	0 +	4 +	10 -->14	1 +	7 +	6 -->14	1 +	11 +	16 -->28
092009 Miller, B.	1 +	11 +	8 -->20	0 +	7 +	12 -->19	1 +	18 +	20 -->39
092010 Pariser, D.	2 +	4 +	2 -->8	2 +	3 +	4 -->9	4 +	7 +	6 -->17
092011 Rapaport, M.	0 +	2 +	8 -->10	1 +	1 +	8 -->10	1 +	3 +	16 -->20
092012 Thiboutot, D.	0 +	5 +	5 -->10	1 +	6 +	3 -->10	1 +	11 +	8 -->20
092014 Webster, G.	1 +	3 +	0 -->4	1 +	2 +	0 -->3	2 +	5 +	0 -->7
092015 Markou, M.	6 +	3 +	1 -->10	10 +	0 +	0 -->10	16 +	3 +	1 -->20
092016 Kelly, T.	6 +	3 +	0 -->9	7 +	2 +	0 -->9	13 +	5 +	0 -->18
Total	28 +	60 +	78 -->166	36 +	52 +	72 -->160	64 +	112 +	150 -->326
	(17%)	(36%)	(47%)	(23%)	(33%)	(45%)	(20%)	(34%)	(46%)

Centers with all patients <200 = 1 (004)

Centers with all patients <225 = 3 (004, 014, 016)
Centers having more patients with <225 than >225 = 7 (004, 006, 010, 012, 014, 015, 016)
Centers having more patients with >225 than <225 = 8 (001, 002, 003, 005, 007, 008, 009, 011): distribution of (<225) : (>225) was between 1:2 & 1:1, except in two centers (003, 011) in which this ratio was 1:4
Centers having most patients with distance between 225-250 =4:

006	16/25 patients
010	7/17 patients (<50% but more than in <200 or >225 groups)
012	11/20 patients
014	5/7 patients

Comment In Study 092, only 28/166 patients (17%) in the finasteride group and 36/160 patients (23%) in the placebo group had hair counts taken anterior to a cutoff 200 mm from the tip of the nose. Therefore, most of the data have been collected in the anterior mid-scalp area. Labeling should avoid the term "frontal" to prevent confusion.

7. Explanation on the ROC Curve shown at the Advisory Committee meeting on 11/13/97

This is a receiver operating characteristic (ROC) curve generated from the PLESS trial database of men with BPH, submitted in NDA 20-180 to the DURDP. These data have also been submitted as an amendment to NDA 20-788 on 11/19/97. The Applicant reiterates that this curve illustrates that using the "multiplication by 2 rule", PSA levels show greater sensitivity in prostate cancer detection in the finasteride group as compared to the placebo group. For comments, see above (item 5) and Medical Officer's Review of 12/9/97.

8. And 9. Comments by the Biopharm Reviewer

These will be reviewed by Biopharm.

Precedents of Not Mentioning Ancillary Treatment in Label and the Issue on the Name PROPECIA:

The Applicant has been asked by the Agency to provide (1) precedents of not mentioning ancillary treatment in the label and (2) reasoning for having a tradename different from the currently marketed product for finasteride (PROSCAR).

Precedents of Not Mentioning Ancillary Treatment in Label

The following four examples were cited in which concomitant modalities were used in clinical trials but reference was not required in product label:

1. FOSAMAX for osteoporosis and supplementary calcium
2. ZOCOR for reducing the risk of serious cardiovascular events where low dose aspirin was used in a majority of patients
3. H2 blockers for treatment of ulcers, GERD, etc., where low potency antacids were used and
4. Antidepressants where concomitant psychotherapy was included in trials.

The Applicant argues that in cases where Merck has specific knowledge, documentation of the equivalent use of concomitant treatments by the placebo group was the foundation for the labeling decisions.

Comments

1. The Applicant has not clarified whether the ancillary treatment in the examples were mandated in the clinical trials, For example, in Zocor, it is stated that aspirin was used in a majority of patients but it is not clear if all patients were required to use it. In addition, in the examples of antacids with H2 blockers and psychotherapy with antidepressants, the Applicant does not indicate whether one brand of antacid was required or if only one form of psychotherapy was allowed in the protocol.
2. In the trials for finasteride in the treatment of MPB, use of Neutrogena T-Gel Shampoo was required for participation.
3. There are also other examples where the label stresses the need of ancillary treatment. The Applicant should review the label for RENOVA in the treatment of the clinical signs of photoaging.

Issue on Changing the Name PROPECIA to PROSCAR

The Applicant has been told on 12/10/97 by teleconference that there is a possibility of not allowing the name PROPECIA, since there is a new policy in CDER that drug products from the same firm having the same active ingredient should have the same tradename.

In the cover letter to the submission of 12/12/97, besides the premise of timeliness, the Applicant gave one reason: "that using the established trademark of PROSCAR would engender confusion in patients and prescribers that might result in overdosing in men with androgenetic alopecia and splitting of the higher dose pills, which is a particular issue for **cutaneous exposure to the active ingredient for women.**"

Comment

The new initiative in a Memorandum from the Center Director dated 11/3/97 states:

"The Center will not ordinarily approve different proprietary names for such similar products, regardless of differences in strength, dosage form, release mechanism, or indication. The draft guidance, "Proprietary and Established Drug Names", will state this policy and will specifically request public comment on its application."

It is unclear whether this Draft Guidance has been published for comment and whether this policy is already in effect at this stage. There are reasons for both PROSCAR and for PROPECIA as tradenames. It is not likely that patients with BPH using PROSCAR can be overdosed with an additional 1 mg of finasteride. In contrast, there is a possibility that patients with BPH using a "PROSCAR 1-mg tablet" may develop acute urinary retention. Overdosing of patients with androgenetic alopecia with PROSCAR 5 mg is also unlikely, as in Study 047, safety and efficacy were also demonstrated in the treatment of patients with MPB using finasteride 5 mg/d.

New Revised Labeling:

Comments of the label submitted on 12/2/97 were conveyed to the Applicant according to the issues in the cover letter of that submission. The Applicant provided a new label with the following changes:

Comment The Applicant has been responsive to the Agency's comments. However, the information provided for ejaculatory volume, ethnic analysis, sexual function questionnaire and adverse events from PROSCAR use is still inadequate and further work will be required to come to an agreement.

Recommendation:

The Applicant should further modify the label to meet the comments conveyed.

12-13-97

Hon-Sum Ko, M.D.

c.c. NDA 20-788
HFD-540 Files
HFD-540/Chem/Hathaway
HFD-540/Pharm/Avalos
HFD-880/Biopharm/Kumi
HFD-725/Biometrics/Freidlin
HFD-540/CSO/Kummerer
HFD-540/MO/Ko

12/12/97

DEC 17 1997

Medical Officer's Review of NDA 20-788

NDA #20-788

Amendments to Pending Application Submitted: December 16, 1997

Received (by FAX): December 16, 1997

Review Completed: December 16, 1997

Drug name: finasteride 1 mg tablets

Generic name: finasteride

Proposed trade name: PROPECIA™

Chemical name : *N*-(1,1-Dimethylethyl)-3-oxo-4-aza-5 α -androst-1-ene-17 β -carboxamide

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

Pharmacologic category: 5 α -reductase inhibitor

Proposed Indication: male pattern baldness (MPB) in men

Dosage Form(s) and Route(s) of Administration: tablet, oral

NDA Drug Classification: 3 S

Related NDAs and INDs:

NDA 20-180 PROSCAR™ for the treatment of symptomatic benign prostatic hyperplasia (BPH)

IND

Studies done by the Applicant for NDA 20-788 were conducted under IND

Background:

The Applicant is responding to labeling questions from the Agency.

Response of the Applicant to Labeling Questions:

Comment "MEN ONLY" may be insufficient. It is preferable to retain the reasoning for not using PROPECIA in women and children.

Comment Not acceptable. The anecdotal information on lack of drug-drug interaction was not based on actual studies and may be misleading to the prescriber.

agrees.

Merck

Merck agrees.

Merck agrees.

Merck believes that the information is already contained in other sections of the patient package insert.

Comment The answer to this question contains information not present elsewhere, including (a) finasteride being a steroid-like molecule and (b) blocking of 5 alpha-reductase.

7. Use of PK Parameters to Calculate Exposure in Animal Studies: Merck believes that calculation on the basis of dose provides consistency with the PROSCAR label. Merck further proposes to have initial approval with language similar to that in the PROSCAR label and have the differences addressed subsequently.

Comment Not acceptable. The Agency is moving towards calculations based on PK parameters for drug exposure.

8. Question on Baseline Scores for Body Hair Questionnaire: Merck confirms that the baseline scores were assumed to be zero.

Comment The Body Hair Questionnaire had baseline data collection with questions

identical to those in later visits, i.e., questions asking hair growth since the start of study. The Applicant has not explained the meaning of such data collected at baseline. Rather, the value zero was assumed in analysis. However, statistical significance levels for comparison to an assumed zero baseline score is meaningless, since the scores themselves already represent a comparison with baseline because of the nature of the questions ("Since the start of the study, how would you describe the growth of your hair on chest, face or extremities?"). In effect such analysis amounted to comparison with baseline twice.

9. Clarification of Patients Who Recovered from Sexual Adverse Events: Merck has given details on the 4 problematic cases: 2223, 2417, 1035 and 1376. These appear to be adequate to support them as being patients with "recovery on drug" for the calculation of the figure 58% in the ADVERSE REACTIONS section of the label.

10. Ancillary Treatments Not in Label: The Applicant is unable to confirm that the ancillary treatments in the examples they cited were mandated in the clinical trial protocols - calcium (FOSAMAX), aspirin (ZOCOR), antacid (famotidine) and psychotherapy (antidepressants).

Comment Merck does not have detailed knowledge on the form of psychotherapy used in clinical protocols with antidepressants. It is, however, confirmed that aspirin was given on an individual basis in ZOCOR studies. It is also possible that antacids were given as escape medications in trials on ulcers. There is no adequate support for the Applicant's contention that ancillary treatments should not be mentioned in the label. In the case of Neutrogena T-Gel Shampoo in the PROPECIA studies, there is no way to distinguish the real effect of finasteride from possible enhancement exerted on the scalp by the tar-based medicated shampoo, even though at this point, the effect of tar on hair follicles has not been fully determined.

Recommendation:

The Applicant should modify the label and patient package insert as shown in Appendix I.

12-17-97

Hon-Sum Ko, M.D.

c.c. NDA 20-788
HFD-540 Files
HFD-540/Chem/Hathaway
HFD-540/Pharm/Avalos
HFD-880/Biopharm/Kumi
HFD-725/Biometrics/Freidlin
HFD-540/CSO/Kummerer
HFD-540/MO/Ko

12/17/97