CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-834

MEDICAL REVIEW(S)

M E M O R A N D U M

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

DATE: October 1, 1997

FROM: Debra Bowen, M.D. Debra Bowen 10/01/97
Director, Division of OTC Drug Products (HFD-560)

TO: Jonathan Wilkin, M.D.
Director, Division of Dermatologic and
Dental Drug Products (HFD-540) 10/9/97

SUBJECT: Labeling Review
Rogaine Extra Strength for Men
NDA 20-834

Please find our division's labeling review attached. Since, as you recall, much of the 2% label was tested in iterative label consumer comprehension tests, the 5% Rogaine Extra Strength for Men differs from 2% labeling in specific respects only. The differences are based on data derived from the 5% studies, reflect the uniqueness of the marketing situation (the need to reinforce the differences between the product concentrations for men and the gender-specific 5% product for men), and incorporate specific suggestions made by our advisory members at the recent joint advisory committee meeting.

LABELING REVIEW OF NDA

NDA 20-834

Submission Date:	2/28/97	**Review Date:**	6/3/97
Amendment Date:	4/9/97		8/12/97
	7/23/97		9/11/97
	8/4/97		9/18/97
			9/29/98

Applicant: Pharmacia & Upjohn Company

Applicant's Representative: Raymond E. Dann, Ph.D.
(616) 833-0438

Drug: Rogaine Extra Strength For Men
(5% Minoxidil Topical Solution)

Pharmacologic Category: Hair regrowth product

Reviewed:
1. The revised draft carton label submitted 7/23/97 in response to NDAC meeting held on 7/16/97
2. The revised draft bottle label submitted 8/4/97 to match the proposed carton label of 7/23/97
3. A revised draft consumer booklet submitted 8/4/97 to match the revised carton label

Reviewer's Comments:

1. Extra Strength - Phamacia & Upjohn, Inc., has developed Rogaine 5% topical Minoxidil solution (TMS) to be labeled "Rogaine Extra Strength For Men," as a nonprescription (OTC) product. When Rogaine Extra Strength For Men is approved, the approved 2% Rogaine For Men will be changed to read "Rogaine Regular Strength For Men." Women will continue to have only the current Rogaine for Women, which is 2% TMS.

2. Labeling - The sponsor has made several labeling changes regarding further cautioning and directing women not to use the product. The "EXTRA STRENGTH" and "FOR MEN"

designation on the front panel is enlarged considerably (equalized in type size) compared to submission of 4/9/97. Additionally, the carton label has been revised, i.e., the front warning box, "NOT FOR USE BY WOMEN" was enlarged. Moreover, a prominent yellow-color offset warning box reiterating "NOT FOR USE BY WOMEN" was placed on the back panel. It includes the language "does not work better in women than Rogaine for Women."

3. Labeling review: The following revised drafts of the carton label, the bottle label, and the consumer leaflet have been submitted by the sponsor in response to the suggestions made by members of the Nonprescription Drug Advisory Committee (NDAC) which was held on July 16, 1997. This review is based on comparison of final printed labeling of Rogaine Regular Strength For Men, NDAC comments, and the proposal rule for the labeling requirements for OTC drug products published in the Federal Register of February 27, 1997 (62FR9024). Our concern is (1) whether women will not select Rogaine Extra Strength For Men, and (2) whether men will be able to appropriately choose between Rogaine Extra Strength For Men and Rogaine Regular Strength.

The background text is identical to sponsor's submission of August 4, 1997. Reviewer recommended additions are identified by redline. Reviewer recommended deletions are identified by a ~~single strike out line~~. The draft information consumer booklet has also been reorganized. Usage, directions, and warnings appear in the same sequence as on the carton and segments have been consolidated under the appropriate topics.

I. CARTON LABEL FOR ROGAINE® EXTRA STRENGTH FOR MEN

Front Panel

Reviewer' s Comments:

1. Do not use reverse type on the labeling. The black background should be changed to improve readability.
2. Upper and lower case should be used to enhance readability
   Extra Strength For Men Hair Regrowth Treatment).
3. Replace the box with
4. We suggest that the box be highlighted or be placed in a prominent yellow-color offset, the same as the warning box on the back panel and moved to the top of the label. The warning should be case specific.
5. The applicant should be reminded that the word may only be used for six months.

Back Panel

Reviewer's Comments:

1. It is recommended that information on the back panel be presented in the following order: **Active Ingredient, Purpose, Use, Warnings,** and **Directions**. Note that these headings are in bold print and only the first letter of the word is capitalized.

Reviewer's Comments:

1. Please bold and change to
2. It is recommended that be added to the Warnings section before as well as here.
4. It is recommended that be added to Warning section as well as here.

Reviewer's Comments:

1. Use bold for the heading Warnings, and all the subheading:
   and
2. It is recommended that two new subheadings be created for Do not use if
   and
3. Delete
   warning
   Add the pregnancy
4. Delete , and add on the scalp.
5. The statement can be deleted.
6. Add to

Top panel

Rogaine®

Side Panel

Side Panel

II. BOTTLE LABEL FOR ROGAINE® EXTRA STRENGTH FOR MEN

Reviewer' s Comments:

1. Delete the statement Add
2. The warning statement should match the carton.
3. The storage temperature appears on the left panel which allows for font size to be larger.

Redacted 9

pages of trade

secret and/or

confidential

commercial

information

Recommendation:
Revisions may be transmitted to the sponsor.

Nahid Mokhtari-Rejali, Ph. D.

Steven Aurecchia, M.D. 10/22/97

cc:
Orig NDA 20-834
HFD-540
HFD-560/Internal Files
HFD-560/Bowen/Katz
HFD-560/Aurecchia/10/1/97
HFD-560/Rejali/10/1/97
HFD-560/Wright
HFD-560/Martin
HFD-540/Wilkin/Huene/Kozma-Fornaro
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DB 10/22/97

JUN 30 1997

~~JUL 17 1997~~

Medical Officer's Comments/OTC Division
NDA NO: 20-834
Sponsor: Pharmacia & Upjohn
Product: Minoxidil 5% topical solution
Indication: Androgenetic Alopecia in Adult Males

NOTE: Reference is made to the primary medical review (Phyllis Huene, M.D., September 20, 1996) and the clinical/statistical review of the initial submission of this NDA (Shahla Farr, M.S., August 23, 1996) as well as the consultative safety review provided by the Division of Cardio-Renal Drug Products (Raymond Lipicki, M.D. and James Hung, Ph.D., August 5, 1996).

NDA for minoxidil 5% topical solution as a prescription product for the treatment of men and women with androgenetic alopecia was first submitted in December 1995. On the basis of efficacy and safety data (see below), it was considered approvable for males only. This NDA (#20-834), submitted in February 1997, is a resubmission of NDA It differs from initial submission in the following principal ways:

1) the intended use of the product has been changed to reflect males only in an OTC setting
2) a summary statement has been added on time to response in men
3) data has been added on study terminations by treatment group and sex for the controlled trials and on terminations by treatment group for the placebo-controlled trials with a 5% minoxidil arm
4) safety information from sources other than clinical trials has been added
5) patient exposure data to 5% topical minoxidil has been updated
6) three label comprehension studies have been added and consumer packaging and labeling has been revised.

EFFICACY

Four definitive studies were conducted in support of the superiority of 5% minoxidil to the 2% topical solution and to placebo—two in men (numbers -0001 and -0285) and two in women (numbers -0009 and -0286). Each was a double-blind, placebo-controlled, randomized, parallel design trial conducted in patients with androgenetic alopecia. Patients were randomized to either 5% topical minoxidil solution, 2% solution, or placebo. Study subjects were instructed to apply 1.0 ml of the test solution twice daily to the affected area.

Study -0001 was a single-center trial in which male patients were randomized in approximately a 2:1:1 ratio. A total of 321 subjects completed the 32-week study period. Study -0285 was a six-center trial in which male patients were randomized in approximately a 2:2:1 fashion. A total of 346 individuals completed the 48-week study period for this trial. Study -0009 was a four-center trial which employed a similar

randomization scheme; a total of 225 female patients completed 32 weeks of treatment and 179 completed the entire 48 week treatment period. Study -0286 was a nine-center trial; the randomization scheme was similar to the preceding two trials. A total of 253 females completed the entire 48 week study cycle.

The primary endpoint parameter in each of these trials was change in non-vellus hair count in a target area. In both trials in men, statistical superiority was demonstrable for the 5% solution over both placebo and the 2% solution, i.e., there was a clear dose-response relationship.[1] For both the pivotal trials in women, the 5% solution was statistically indistinguishable from the 2% solution with respect to non-vellus hair count.

In studies -0285 (men) and -0286 (women), patient questionnaires were also used as co-primary subjective endpoints to asses change in scalp coverage (rated by the patient on a scale of 0 to 100) and to assess whether drug treatment was beneficial. The latter question was asked at the study endpoint and evaluated on a visual analog scale in which 0 corresponded to no benefit, 50 to moderate benefit, and 100 to great benefit. In the male trial, a statistically significant dose-response relationship was demonstrable for both subjective endpoints for the 5% minoxidil solution over the 2% solution and placebo. This was not true of the female study, although a trend was evident for both these subjective endpoint parameters.

SAFETY

There was no evidence of photosensitization, phototoxicity, or contact sensitization in the initial safety studies with 5% minoxidil solution.

A total of 1562 patients (827 males; 735 females) were randomized in the controlled, 32-48 week androgenetic alopecia studies. The majority of males (91.6%) were exposed for at least 8 months, whereas only 72.1% of women achieved this duration of exposure.[2] Terminations from these studies for all treatment groups by sex is summarized in the table below.[3]

	PERCENT (%) OF PATIENTS TERMINATED BY REASON					
	5% Minoxidil		2% Minoxidil		Placebo	
REASON	Males (N=371)	Females (N=301)	Males (N=252)	Females (N=273)	Males (N=204)	Females (N=161)
End of Planned Tx	90.6	62.1	90.1	67.8	90.6	72.7
Medical Events	3.2	13.0	1.6	8.8	1.0	4.3
Serious	0.3	1.0	0.4	1.5	0.5	0.0
Non-Serious	3.0	12.0	1.2	7.3	0.5	4.3
Administrative Reasons	5.9	24.9	8.3	23.4	8.3	21.1
Lack of Efficacy	0.3	0.0	0.0	0.0	0.0	1.9

[1] The statement (and labeling claim) is also made that hair count data from both these studies indicate that the response to 5% minoxidil occurs at an earlier time point than with 2% minoxidil. However, this claim is not supported by an appropriate study or prospective analysis (i.e., time-to-response).

[2] From Table H.4.b.3., page 2/1/186.

[3] From Table H.4.b.8a, page 2/1/189.

A dose-dependent trend for terminations due to medical events was apparent in all study groupings and was confirmed by assessments of relative risk for both the 5% solution versus placebo and the 5% solution versus the 2% solution. The relationship was disproportionate by gender: the proportion of men who discontinued from a study because of medical reasons was four times less than that for women. Of the 1562 randomized patients, 5.6% or 88 (18 males; 70 females) discontinued treatment with study medication due to treatment-emergent adverse medical events, with dermatological events the primary cause. This finding was dose-dependent, relative to the concentration of minoxidil in the formulation, and again driven primarily by the female contribution to the rate (the relative risk estimates showed a significant result for female patients). Dermatological events were of two general types: dermatitis-like and hypertrichosis. Dermatitis-like events occurred in 10.4% (70/672) of patients in the 5% minoxidil group, 7.0% (37/525) in the 2% minoxidil group and 5.2% (19/365) of the placebo cohort. Hypertrichosis was reported in 3.1% (21/672), 0.2% (1/525), and 0.3% (1/365) of these treatment groups, respectively. All the cases of hypertrichosis occurred in women, 8 of whom terminated study participation prematurely. By treatment group, the percentages of women in the controlled androgenetic alopecia studies who discontinued due to hypertrichosis were 1.0% (7/672), 0.2% (1/525), and 0.0% (0/365) in the 5% minoxidil, 2% minoxidil, and placebo groups, respectively. Discontinuations in each treatment group due to dermatitis-like events (pruritus, dermatitis not otherwise specified, scaling, skin problem, skin disorder, contact dermatitis, dermatitis localized, erythema, skin inflammation-topical agent) were as follows: 2.8% (19/672), 1.1% (6/525), and 1.1% (4/465), respectively, in the 5% minoxidil, 2% minoxidil, and placebo groups. Pooled data on the 738 male patients randomized to the two pivotal trials was analyzed specifically for the cutaneous parameters dryness, erythema, folliculitis, itching, and stinging.[4] The numbers of individuals in the 5% arm experiencing either dryness or itching were greater, by a statistically significant margin, in the 5% arm relative to both the 2% and the vehicle arms (values for erythema and folliculitis were not collected for study -0285):

				P-VALUES			
ADVERSE EVENTS	5% Minoxidil N	2% Minoxidil N	Placebo N	All Tx's	5% vs. 2%	5% vs. Pl	2% vs. Pl
Dryness	**331**	**244**	**163**	**0.001**	**0.001**	**0.05**	**0.003**
Erythema	174	86	85	0.08	0.05	0.37	0.05
Folliculitis	174	86	85	0.89	0.78	0.74	0.77
Itching	**331**	**244**	**163**	**0.001**	**0.001**	**0.02**	**0.66**
Stinging	331	244	163	0.43	0.64	0.22	0.35

When administered systemically, minoxidil is a potent peripheral vasodilator and anti-hypertensive. In the pivotal male studies, the available data is reassuring in that there were no differential effects between treatment cohorts on blood pressure, pulse, body weight electrocardiograms, chest-X-rays, or hematologic or renal laboratory parameters.

[4] Shahla Farr, M.S., Addendum to Clinical/Statistical Review, October 21, 1996.

Some post-marketing safety data with 5% minoxidil is available from outside the United States. REGAINE 5% topical solution has been commercially available by prescription in the following countries which collaborate with the WHO Adverse Reaction Monitoring Program: Belgium, Denmark, Finland, France, Greece, Ireland, Italy, New Zealand, Portugal, Switzerland, and the United Kingdom. REGAINE 5% was approved as a nonprescription product in Denmark in January 1994 (pharmacy-only) and in New Zealand in August 1993 (pharmacy-only). The sponsor estimates that some individuals have been exposed to this product. As of December 31, 1996, a total of 68 medical events were reported for 38 patients. Nearly all of these spontaneous adverse reaction reports (29 patients—16 males, 10 females, 3 gender unknown) were received from New Zealand. The most frequently reported events were dermatologic in nature, including 8 reports of itching; 4 each of hypertrichosis, rash, and skin irritation; 3 reports of exacerbation of hair loss and scalp burning; 2 reports each of flaking scalp, hair loss, and papular-like rash; and 1 report each of allergic rash, blisters, dry scalp, eczema, erythema, erythematous rash, scaling, skin reaction, skin ulceration, and sore scalp. None of these events were considered serious in nature. This post-marketing experience is consistent with the safety profile of 5% topical minoxidil solution observed in the NDA database.

In considering the safety of 5% topical minoxidil as a candidate OTC product, a key element is the extent of percutaneous absorption of minoxidil with repeated cutaneous application and thus the potential for cardiovascular adverse events. From previous kinetic studies with 2% topical minoxidil (considered relevant to the 5% solution because of the constant minoxidl:propylene glycol ratio), gender, UVB irradiation resulting in mild sunburn, concomitant use of either a skin moisturizer or Vaseline, occlusive covering, rapid evaporation of the applied dose using a hot air blow dryer, and surface area application ranging from 100 to 200 cm^2 each produced minimal or no effect on absorption. Age has not been specifically studied. Serum minoxidil concentrations were measured in both the pivotal efficacy trials with 5% minoxidil (page 5). In Study -0285 in the 5% minoxidil cohort, parent drug levels did not accumulate in the serum over the course of the trial, with a mean level of 1.7 ng/dl recorded at week 40. This was about the 2.5 times the corresponding level for the 2% minoxidil treatment group. Data on the distribution of serum minoxidil levels is reproduced below for Study -0001. Of the 173 specimens assayable at the final study visit in the 5% minoxidil cohort, serum levels in 157 or of these (91%) were 3.0 ng/ml or less. Three values were in the range. The maximum drug levels recorded in Study -0285 were somewhat higher in the 5% topical minoxidil group. Of 441 post-screening serum specimens analyzed, 25 or 5.7% from 16 patients had minoxidil concentrations exceeding 5.0 ng/mL, and of these, 7 samples from 5 patients exceeded 10.0 ng/mL the highest level detected was 16.5 ng/mL). In reviewing the summaries of these 5 patients, none exhibited clinically meaningful cardiovascular symptoms in association with these serum minoxidil levels. These findings appear consistent with the serum concentration of approximately 20 ng/mL suggested as the threshold for minimally

Serum Minoxidil Concentrations: Male Study -0285

	TREATMENT GROUP		
TIMEPOINT	5% MINOXIDIL mean ± SD range (No. Specimens)	2% MINOXIDIL mean ± SD range (No. Specimens)	PLACEBO mean ± SD range (No. Specimens)
Screening	0.0 ± 0.1 (157)	0.0 ± 0.1 (158)	0.0 ± 0.0 (79)
Week 12	2.2 ± 2.1 (148)	0.7 ± 0.8 (151)	0.0 ± 0.1 (73)
Week 28	1.7 ± 1.6 (144)	0.7 ± 0.8 (145)	0.0 ± 0.0 (71)
Week 40	1.7 ± 2.3 (138)	0.7 ± 0.8 (141)	0.1 ± 0.3 (71)

SOURCE: Clinical Study Report, Table 45, pg. 55.

Distribution of Serum Minoxidil Concentrations: Male Study -0001

		TREATMENT GROUP					
		5% MINOXIDIL		2% MINOXIDIL		PLACEBO	
		Screening	Final Visit	Screening	Final Visit	Screening	Final Visit
CONCENTRATION (NG/ML)							
		172	27	84	19	83	75
		2	55	2	57	1	6
			17				1
			37		4	1	
			21		3		
			7				
			6				
			3				
MISSING			1		2		3
UNASSAYABLE					1		
TOTAL		174	174	86	86	85	85
	N	174	173	86	83	85	82
	MEAN	0.00	1.24	0.01	0.39	0.02	0.02
	STD. DEV.	0.02	1.34	0.05	0.54	0.17	0.12
	MIN.						
	MAX.						

SOURCE: Clinical Study Report, pg. 55.
NOTE: Detection limit of the assay is 0.1 ng/ml; precision increases as levels approach 0.8 ng/ml.

detectable hemodynamic changes.[5]

5% TOPICAL MINOXIDIL: OTC CONSIDERATIONS

Several criteria determine whether a drug product is both safe and effective and appropriate for OTC status for a particular indication at given dosage:[6]

a) The drug should have a favorable safety profile—in this case as demonstrated in the controlled and uncontrolled trials and applicable foreign marketing data comprising the NDA database.
b) It should be relatively free of important food, drug, or disease interactions.
c) Significant intervention by a physician or health care provider should not be required for its safe and effective use by the consumer, e.g., for diagnosis or therapeutic monitoring.
d) Product labeling, consisting of directions for use, warnings, and side effects must be able to be written in such a manner as to be understood by ordinary consumers, including individuals of low comprehension, as assessed under customary conditions of purchase and use.

A number of considerations favor OTC marketing status for 5% topical minoxidil for men. First, androgenetic alopecia is a condition that is readily discerned by the patient and one that does not raise differential diagnostic concerns. Second, the consequences of self-medication are obvious. Third, a dose-dependent drug effect with respect to the amount of hair growth has been convincingly established in the NDA trials. And fourth, available data suggest that the safety profile of the 5% solution is acceptable[7]—adverse effects are predominantly dermatologic and reversible in nature. Some care needs to be exercised in extrapolating these data, however. Kinetic studies suggest a reasonable margin of safety with respect to percutaneous drug absorption, but the variance in these measures is quite large. It is conceivable that in rare cases, serum minoxidil levels could be reached with the 5% solution that begin to produce measurable hemodynamic effects. This could be clinically relevant in an individual with underlying cardiovascular disease or in someone taking concomitant medications which impair his ability to mount a physiologic counterregulatory response. In addition, the NDA safety database is too small to detect rare adverse events of potential clinical significance, if in fact they do occur.

The final issue of concern is consumer labeling. Minoxidil 2% solution is currently marketed as an OTC product for both men and women. If this NDA is approved, it will set a precedent in that the currently marketed 2% ROGAINE products will then coexist with a new 5% product specifically indicated for men and contraindicated for women.

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[5] Ferry, JJ., et. al. Hemodynamic Effects of Minoxidil Following Steady-State Intravenous Infusions in Untreated Hypertensive Patients (protocol P/7400/064). Upjohn Techinical Report 7215-92-022, January 6, 1993. [Submitted to IND

[6] 21 CRF § 330.10.

[7] Oral ingestion a topical minoxidil product can be fatal. The container is not child-resistant once the cap has been replaced by an applicator or dropper. This needs to be addressed as a packaging issue.

Three label testing studies have been submitted which address the questions this situation raises, namely, 1) will women appropriately avoid Rogaine Extra Strength for Men; and 2) will men be able to appropriately choose between Rogaine Extra Strength for Men and Rogaine Regular Strength for Men?[8]

The first study in women was a label comprehension and intention-to-heed study completed in December, 1996 in 206 women with hair loss or thinning hair who had never used any minoxidil product and 99 current or past users of OTC ROGAINE or a generic 2% minoxidil preparation. Participants were asked which product they would select from a simulated shelf array of five actual minoxidil products. They then read a test "ROGAINE Maximum Strength for Men" label and were asked whether the product would be appropriate for their personal use. Overall, few women (13 or 4.3%) incorrectly chose one of the products intended for men. A somewhat greater percentage (12.5%) inappropriately chose the 5% product for men after being afforded the opportunity to carefully read the package (17.2 % among users; 10.2% among non-users).

Results from a second intention-to-heed study among women completed in April, 1997 differed substantially. This study, using a different testing method, was undertaken after several labeling changes and a change in the name of the product. Two-hundred seventeen (217) women with hair loss or thinning hair who were not users of a 2% minoxidil product and 99 women purchasers of OTC ROGAINE and/or other minoxidil products were asked to read the "ROGAINE Extra Strength for Men" carton as if in a store, and then were asked if they would buy this product for their personal use. They were subsequently asked to read the label completely and respond as to whether the product was for men only, women only, or both. Thirty-four percent (34%) of female non-users and 37% of female users indicated they would use "ROGAINE Extra Strength for Men" (3% in each group did not know). Results differed after these women participants read the entire package labeling: 81% of non-users and 75% of users indicated that they understood the product is intended for men only.

A label comprehension study was also undertaken in men to test their understanding of the differences between "ROGAINE Extra Strength for Men" (the 5% product) and ROGAINE Regular Strength for Men" (the 2% product) with respect to efficacy and the likelihood of scalp irritation. Two-hundred nine (209) men with hair loss or thinning hair who were not users of a 2% minoxidil product and 97 current users were told about the new OTC category and show pictures of the proposed ROGAINE Extra Strength for Men and ROGAINE Regular Strength for Men products. They were then given a ROGAINE Extra Strength for Men package and asked to read it as if in a store. After completing a self-administered questionnaire, they were then specifically instructed to read the label completely and complete the same questionnaire again. Among non-users, 74% correctly understood the enhanced efficacy of the 5% product on the initial reading; this improved to 80% after the complete reading. Among current users, the

corresponding figures were 77% and 83%. Among non-users, fewer (52%) initially understood that the 5% product was more likely to cause scalp irritation; there was a significant improvement (to 68%) after the compete reading. The pattern was similar among users—the corresponding percentages were 53% and 71%. The majority of respondents understood that they should switch to the ROGAINE Regular Strength product in the event of scalp irritation: the figures among non-users were 63% on the initial reading and 67% after the complete reading and among users 69% and 74%, respectively.

It is difficult to extrapolate the data from these label testing studies. They were conducted under circumstances which at best only approximate a normal purchase setting. There are also a number of variables in the design and conduct of these studies which may serve as sources of bias or otherwise make interpretation of the study findings problematic. For example, the population in the April, 1997 women's study was geographically diverse, but individuals of lower comprehension (as determined by last grade of school completed) were not well represented. Those without high school diplomas comprised only 12% of the sample in both the non-users and users categories. The same was true of the April, 1997 male study. Non-users and users who did not complete high school made up only 10% and 11% of the study sample, respectively. The percentage of participants whose income was less than annually was also small in this study—12% and 13%, respectively, in the non-user and user groups. The same was true for the proportion of individuals over age 55—19% and 16%, respectively. Study size is also a consideration. In controlled clinical trials, sample size is based on a set of pre-specified statistical assumptions. This is not true of label testing trials. Are the label testing studies herein of sufficient size to be predictive of consumer comprehension and behavior in the marketplace? And finally, methodological issues, some of which may not be apparent until the study is completed and data analyzed, may also influence study results. For example, were the questions in the survey leading in nature, or were there demand characteristics of the test situation (as the sponsor has maintained with respect to the April, 1997 women's label study)?

These issues, as well as the risk-benefit assessment of 5% topical minoxidil as an OTC product for men, warrant further discussion with members of the Nonprescription Drug and Dermatolgic Drugs Advisory Committees.

6/30/97

Steven Aurecchia, M.D.

Linda M. Katz, M.D., M.P.H.
Deputy Director, DODP 6/30/97

CC: HFD-560
HFD-560/Katz/Bowen/Wright
HFD-560 5540 6/30/97
HFD-560/Huene/Wilkin/Avalos/Jacobs/Higgins/Anderson
HFD-40/Lechter 7/2/97

JUN 09 1997

MEDICAL OFFICER'S REVIEW OF NDA 20-834
ORIGINAL SUBMISSION

June 3, 1997

SPONSOR: The Upjohn Co.
Kalamazoo, Michigan

PRODUCT: ROGAINE Extra Strength For Men (5% minoxidil topical solution)

FORMULATION:

Minoxidil	5%
Propylene glycol	%
Alcohol USP	%
Purified water qs ad	%

CLINICAL INDICATION: Baldness in males (OTC use)

DOSAGE: Topical administration of 1 ml BID for an indefinite period.

DATE OF SUBMISSION: February 28, 1997

RELATED SUBMISSIONS: IND NDA 18-154 for Loniten tablets; NDA 19-501 for 2% Rogaine solution.

PHARMACOLOGY REVIEW: This is currently pending.

CONTROLS REVIEW: This is currently pending.

Background

NDA for 5% Rogaine was submitted in December 1995 for the Rx treatment of male and female androgenetic alopecia. The clinical effectiveness data and the topical safety data were reviewed by this medical officer, and the systemic safety data were reviewed by Raymond Lapicky, M.D.

In the review of NDA by this medical officer, it was recommended that the application not be approved for the treatment of male and female androgenetic alopecia. In regard to female androgenetic alopecia, both of the two pivotal studies showed that 5% Rogaine was superior to the vehicle, but neither study showed a superiority to 2% Rogaine in the change in hair counts. 5% Rogaine was also not superior to 2% Rogaine in the patient or investigator evaluation of new hair growth in one study, and was not superior to 2% Rogaine in the patient or investigator evaluation of the change in scalp coverage in the other study.

In regard to male androgenetic alopecia, in both of the two pivotal studies 5% Rogaine was superior to 2% Rogaine and to the vehicle in the change in mean hair counts. In one study 5% Rogaine was also significantly superior to 2% Rogaine and to the vehicle in the patient and investigator evaluation of the change in scalp coverage. In the other study 5% Rogaine was not superior to 2% Rogaine or the vehicle in either the patient or investigator evaluation of new hair growth. In view of the position of the Agency that the evaluation of the studies on 5% Rogaine should place greater emphasis on the patient and investigator evaluation of hair growth than did the studies on 2% Rogaine, it was felt by this reviewer that both studies should demonstrate superiority in these parameters, and so the product was felt to be not approvable for male androgenetic alopecia.

Agreement was later reached at the Division level that the application was approvable for androgenetic alopecia in males only, based on the changes in hair counts.

Summary of Phase I studies

The Phase I studies included phototoxicity. contact sensitization, and photosenitization studies, using standard methodology. There was no evidence of phototoxicity, contact sensitization, or photosensitization with 5% Rogaine solution.

Summary of clinical effectiveness studies

The clinical studies submitted in this NDA in support of the OTC use of 5% Rogaine solution in male androgenetic alopecia are the same studies that were submitted in NDA in support of the Rx use of 5% Rogaine solution in male androgenetic alopecia. The two pivotal studies are summarized as follows.

Study M/7415/0001

This was a double blind, single center comparison of 5% Rogaine, 2% Rogaine, and the vehicle in 321 evaluable male patients with androgenetic alopecia; this included 163 patients on 5% Rogaine, 79 on 2% Rogaine, and 79 on the vehicle. Applications were made BID for 32 weeks. The efficacy parameters were 1) nonvellus hair counts within a 1 cm^2 area of the vertex of the scalp, and 2) an investigator and patient assessment of hair growth as none, minimal, moderate, or dense.

1) Hair counts. The mean hair counts and the mean changes from baseline were as follows.

Mean nonvellus hair counts			
	5% Rogaine (n=163)	2% Rogaine (n=79)	Placebo (n=79)
Baseline	106	103	105
Week 16	142	128	109
Week 32	145	133	110

Mean change from baseline Nonvellus hair counts			
	5% Rogaine (n=163)	2% Rogaine (n=79)	Placebo (n=79)
Week 16	+ 36	+ 25	+ 4
Week 32	+ 39	+ 30	+ 5

Statistical analysis showed that 5% Rogaine was significantly superior to 2% Rogaine and to the vehicle at weeks 16 and 32 in the mean change in hair counts from baseline.

2) Investigator evaluation. The investigator's evaluation of new hair growth was as follows.

Investigator evaluation of new hair growth			
	5% Rogaine (n=163)	2% Rogaine (n=79)	Placebo (n=79)
WEEK 16			
No growth	72 (44%)	42 (53%)	33 (42%)
Minimal growth	80 (49%)	36 (46%)	36 (46%)
Moderate growth	7 (4%)	1 (1%)	10 (13%)
Dense growth	4 (3%)	0	0
WEEK 32			
No growth	23 (14%)	11 (14%)	7 (9%)
Minimal growth	75 (46%)	40 (51%)	27 (34%)
Moderate growth	62 (38%)	28 (35%)	45 (57%)
Dense growth	3 (2%)	0	0

There were no significant differences between the treatment groups in the investigator's evaluation of new hair growth.

3) Patient evaluation. The patient's evaluation of new hair growth was as follows.

Patient evaluation of new hair growth			
	5% Rogaine (n=163)	2% Rogaine (n=79)	Placebo (n=79)
WEEK 16			
No growth	63 (39%)	37 (47%)	49 (62%)
Minimal growth	72 (44%)	27 (34%)	25 (32%)
Moderate growth	26 (16%)	15 (19%)	5 (6%)
Dense growth	2 (1%)	0	0
WEEK 32			
No growth	51 (31%)	30 (38%)	28 (35%)
Minimal growth	68 (42%)	37 (47%)	32 (41%)
Moderate growth	41 (25%)	11 (14%)	19 (24%)
Dense growth	3 (2%)	1 (1%)	0

There were no significant differences between the treatment groups

in the patient's evaluation of new hair growth.

The number of patients who experienced local intolerance, and the numbers of events experienced, is summarized as follows.

Incidence of local intolerance						
	5% Rogaine (n=174)		2% Rogaine (n=86)		Placebo (n=85)	
	# events	# pts	# events	# pts	# events	# pts
Erythema	20	16 (9%)	1	1 (1%)	8	6 (7%)
Dryness/scaling	250	103 (59%)	54	35 (41%)	77	40 (47%)
Stinging/burning	21	14 (8%)	5	5 (6%)	7	5 (6%)
Folliculitis	19	14 (8%)	7	6 (7%)	7	5 (6%)
Itching	125	53 (30%)	30	16 (19%)	19	13 (15%)

Three patients in the 5% Rogaine group and one patient in the 2% Rogaine group discontinued treatment due to local intolerance. These were as follows.

1. Patient (5% Rogaine): The patient had moderate itching after 12 weeks of treatment, which had progressed at week 16 to erythema, itching, stinging and burning. Treatment was discontinued, and a patch test indicated sensitivity to propylene glycol.

2. Patient (5% Rogaine): The patient reported mild itching at week 8, and at week 16 had mild stinging, burning, itching, and folliculitis. Treatment was discontinued; patch testing indicated a sensitivity to propylene glycol.

3. Patient (5% Rogaine): The patient had mild stinging/burning and moderate erythema and itching at week 16. At week 20 the patient had moderate erythema, drying/scaling, and stinging/burning, and severe itching. Treatment was discontinued, and patch testing showed a sensitivity to propylene glycol.

4. Patient (2% Rogaine): The patient had moderate dryness/scaling and severe itching of the scalp at week 6. He subsequently developed a macular rash on the face and neck, with mild periorbital edema. Treatment was discontinued; patch testing indicated a probable sensitivity to minoxidil.

Study M/7410/0285

This was a double blind, multicenter comparison of 5% Rogaine, 2% Rogaine, and the vehicle in 352 evaluable male patients with androgenetic alopecia; this included 139 patients on 5% Rogaine, 142 on 2% Rogaine, and 71 on the vehicle. Applications were made BID for 48 weeks. The efficacy parameters were 1) nonvellus hair counts within a 1 cm^2 area of the vertex of the scalp, and 2) an investigator questionnaire and a patient questionnaire, both of which concerned an assessment of various aspects of new hair growth.

1) Hair counts. The mean baseline nonvellus hair counts and the mean change from baseline in nonvellus hair counts were as follows.

Mean nonvellus hair count at baseline			
	5% Rogaine	2% Rogaine	Placebo
Baseline	151	144	152

Mean change in nonvellus hair count from baseline			
	5% Rogaine	2% Rogaine	Placebo
Week 16	35.3	29.8	15.3
Week 32	29.0	22.2	7.7
Week 48	18.6	12.7	3.9

Statistical analysis showed that 5% Rogaine was significantly superior to 2% Rogaine and the vehicle at weeks 8, 16, 32, and 48 in the mean change in hair counts from baseline.

2) Investigator and patient questionnaires. The primary efficacy variables chosen by the Division from the investigator and patient questionnaires were the evaluation of the change in scalp coverage by the patient, and the evaluation of the change in scalp coverage by the investigator.

The investigator evaluated the current coverage of the patient's scalp at each time interval on a 100 mm visual analog scale, based on the visual examination of the scalp. The scale used had 'no coverage' at one end, 'medium coverage' in the middle, and 'complete coverage' at the other end. The change in coverage from baseline was then calculated. The mean changes in scalp coverage from baseline were as follows.

Mean change in scalp coverage (Investigator questionnaire)						
	5% Rogaine		2% Rogaine		Placebo	
	# pts	Mean	# pts	Mean	# pts	Mean
Week 16	138	10.9	138	4.2	71	0.1
Week 32	138	8.9	139	4.8	71	1.6
Week 48	138	12.3	140	7.0	71	2.5

In the investigator's evaluation of the change in scalp coverage, 5% Rogaine was significantly superior to 2% Rogaine at weeks 16 and 48, but not at week 32, and was significantly superior to the vehicle at weeks 16, 32, and 48.

The patient assessed the change in scalp coverage from baseline by comparing baseline and current photographs, and recorded his response to this question on a 100 mm visual analog scale. The low end of the scale indicated "much less scalp coverage", the midpoint indicated "the same scalp coverage", and the high end indicated "much more scalp coverage". Therefore a value below 50 represented a worsening, a value above 50 was an improvement, and a value of 50 was no change. The mean values over time were as follows.

Mean change in scalp coverage (Patient questionnaire)						
	5% Rogaine		2% Rogaine		Placebo	
	# pts	Mean	# pts	Mean	# pts	Mean
Week 16	135	63.5	141	58.2	68	51.4
Week 32	135	63.4	141	58.0	71	52.0
Week 48	138	62.0	141	56.9	70	51.0

In the patient's evaluation of the change in scalp coverage, 5% Rogaine was significantly superior to both 2% Rogaine and the vehicle at weeks 16, 32, and 48.

The dermatologic adverse events which occurred in at least 1% of patients were as follows.

Dermatological adverse events In ≥ 1% of patients			
	5% Rogaine (n=157)	2% Rogaine (n=158)	Placebo (n=78)
Pruritus	7 (4.5%)	3 (1.9%)	0
Contact dermatitis	3 (1.9%)	2 (1.3%)	0
Inflammatory skin disorder	3 (1.9%)	1 (0.6%)	0
Acneform dermatitis	2 (1.3%)	2 (1.3%)	1 (1.3%)
Dermatitis	2 (1.3%)	1 (0.6%)	2 (2.6%)
Skin disorders	1 (0.6%)	3 (1.9%)	0
Skin infection	1 (0.6%)	2 (1.3%)	0
Total	23 (14.6%)	19 (12.0%)	6 (7.7%)

The dermatological adverse events which were considered by the investigator to be possibly related to treatment were as follows.

Dermatological adverse events Possibly related to treatment			
	5% Rogaine (n=157)	2% Rogaine (n=158)	Placebo (n=78)
Pruritus	6 (3.8%)	2 (1.3%)	0
Contact dermatitis	1 (0.6%)	0	0
Localized dermatitis	1 (0.6%)	0	0
Eruption	1 (0.6%)	0	1 (1.3%)
Erythema	1 (0.6%)	0	0
Scalp excoriations	1 (0.6%)	0	0
Scaling	1 (0.6%)	0	0
Skin inflammation	1 (0.6%)	1 (0.6%)	1 (1.3%)
Total	9 (5.7%)	3 (1.9%)	2 (2.6%)

Five patients in the 5% Rogaine group and 1 patient in the 2% Rogaine group discontinued treatment due to dermatologic adverse events. These were as follows.

1. Pt (5% Rogaine): Scalp itching. The patient had mild to moderate itching of the scalp during weeks 12 - 20, and discontinued the drug for several days. After resumption of treatment the patient reported severe itching and moderate stinging/burning. Treatment was discontinued at week 22 and patch testing was performed. The results of the patch test were equivocal for the 2% and 5% Rogaine solutions at the 48 hour evaluation.

2. Pt (5% Rogaine): Contact dermatitis. Beginning at week 8, the patient developed pruritus and mild erythema of the scalp, which progressed to severe pruritus and red, scaly areas of the scalp by week 16. Treatment was discontinued at week 16 and the patient was patch tested. The results were positive with propylene glycol, and 2% and 5% Rogaine solutions.

3. Pt (5% Rogaine): Scalp itching. This patient reported moderate scalp itching and mild stinging/burning beginning at week 5. The itching became severe by week 11, and treatment was discontinued.

4. Pt (5% Rogaine): Scalp dermatitis. This patient reported mild itching and dryness/scaling at weeks 4 - 12, and moderate stinging/burning, itching, and dryness/scaling at week 16. This progressed to severe stinging/burning and itching immediately after applications, and at week 18 the patient presented with marked erythema, scaling, and mild infiltration of the scalp. Treatment was discontinued; the patient refused to be patch tested.

5. Pt (5% Rogaine): Contact dermatitis. This patient reported mild to moderate itching of the scalp at weeks 4 - 8. This progressed to marked erythema of the treated area and moderate stinging/burning and itching at week 20. Treatment was discontinued and the patient was patch tested. Results were positive with propylene glycol and 2% and 5% Rogaine solutions.

6. Pt (2% Rogaine): Dermatitis. This patient reported moderate stinging following applications at week 16. The patient discontinued treatment, and on examination three weeks later there was mild erythema and moderate dryness/scaling of the entire scalp. The patient was not patch tested.

b. Signs of contact dermatitis. The highest rating of signs of contact dermatitis obtained for each patient during the course of the study was as follows.

Table 48.
Ratings of signs of contact dermatitis

Ratings	5% Rogaine (n=157)	2% Rogaine (n=158)	Placebo (n=78)
0	64 (40.8%)	105 (66.5%)	38 (48.7%)
1/2	89 (56.7%)	48 (30.4%)	36 (46.2%)
1	2 (1.3%)	5 (3.2%)	4 (5.1%)
2	2 (1.3%)	0	0
3	0	0	0

0 = no reaction.
1/2 = scaling or very weak erythema.
1 = weak erythema, possible slight infiltration.
2 = marked erythema, infiltration, possibly vesicles and crusting.
3 = pronounced erythema, infiltration, possibly vesicular, bullae, pustules and/or pronounced crusting.

The two patients who obtained a score of 2 were patients these are described above under the patient discontinuations. Three patients in the 5% Rogaine group had a patch test performed; these patients (312, 429, and 53) are described above under the patient discontinuations.

c. Local subjective symptoms. The greatest severity for each symptom reported by each patient during the course of the study was as follows.

Table 49.
Greatest severity of contact dermatitis symptoms

	5% Rogaine (n=157)	2% Rogaine (n=158)	Placebo (n=78)
Stinging/burning			
Mild	22 (14.0%)	19 (12.0%)	6 (7.7%)
Moderate	5 (3.2%)	4 (2.5%)	1 (1.3%)
Severe	2 (1.3%)	0	0
None	128 (81.5%)	135 (85.4%)	71 (91.0%)
Itching			
Mild	42 (26.8%)	36 (22.8%)	22 (28.2%)
Moderate	23 (14.6%)	4 (2.5%)	7 (9.0%)
Severe	6 (3.8%)	2 (1.3%)	0
None	86 (54.8%)	116 (73.4%)	49 (62.8%)
Dryness/scaling			
Mild	71 (45.2%)	34 (21.5%)	26 (33.3%)
Moderate	12 (7.6%)	5 (3.2%)	8 (10.3%)
Severe	2 (1.3%)	0	0
None	72 (45.9%)	119 (75.3%)	44 (56.4%)

Reviewer's comments on topical safety data in Studies 0001 and 0285: In Study 0001, the incidence of local intolerance was higher with 5% Rogaine solution than with 2% Rogaine solution, particularly in regard to erythema, dryness/scaling, and itching. Three patients (1.7%) in the 5% Rogaine group and one patient (1.1%) in the 2% Rogaine group discontinued treatment due to local intolerance. These reactions in the 5% Rogaine group developed slowly over the course of weeks of treatment, and included erythema, stinging/burning, dryness/scaling, and pruritus.

In Study 0285 the symptoms of local intolerance were similar to those in Study 0001, but were much less frequent in the 5% Rogaine group than in Study 0001. Five patients (3.1%) in the 5% Rogaine group and one patient (0.6%) in the 2% Rogaine group discontinued treatment because of local intolerance. As in the first study, the reactions in the 5% Rogaine group developed slowly over the course of weeks of treatment and included erythema, stinging/burning, dryness/scaling, and pruritus.

Conclusions: 5% Rogaine has previously been found to be safe and effective for the Rx treatment of male androgenetic alopecia, and has been ~~approved~~ for that indication. The clinical studies showed somewhat more local intolerance with 5% Rogaine solution than with 2% Rogaine solution, but in the opinion of this reviewer the local reactions can be minimized by precautionary statements in the labeling, and should not preclude approval for OTC use.

Recommendations: From the standpoint of cutaneous safety it is recommended that, with appropriate OTC labeling, 5% Rogaine be approved for the ~~OTC~~ treatment of baldness in males.

Phyllis A. Huene, M.D.

cc: Orig NDA
HFD-540
HFD-540/Huene
HFD-540/Anderson
HFD-540/DeCamp
HFD-540/Jacobs

HFD-560/Bowen
HFD-560/Katz
HFD-560/Aurecchia
HFD-560/Merritt

HFD-40/Lechter