

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-834

CHEMISTRY REVIEW(S)

DIVISION OF DERMATOLOGIC AND DENTAL DRUG PRODUCTS

HFD-540

Review of Chemistry, Manufacturing, and Controls

NDA #:	CHEM.REVIEW #:	1	REVIEW DATE:	05-NOV-1997
SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE	
ORIGINAL	28-FEB-1997	28-FEB-1997	05-MAR-1997	
AMENDMENT/BC	22-APR-1997	23-APR-1997	25-APR-1997	
AMENDMENT/BC	22-JUL-1997	24-JUL-1997	29-JUL-1997	
AMENDMENT/BC	23-JUL-1997	24-JUL-1997	29-JUL-1997	
AMENDMENT/BC	04-AUG-1997	05-AUG-1997	08-AUG-1997	
AMENDMENT/BC	04-AUG-1997	05-AUG-1997	08-AUG-1997	
AMENDMENT/BC	29-OCT-1997	30-OCT-1997	30-OCT-1997	
AMENDMENT/BC	03-NOV-1997	04-NOV-1997	05-NOV-1997	
IND 13,267/N-154	26-DEC-1996	27-DEC-1996	07-JAN-1997	

NAME & ADDRESS OF APPLICANT: Pharmacia and Upjohn Company
7031-298-112
7000 Portage Road
Kalamazoo, MI 49001

DRUG PRODUCT NAME

Proprietary:	ROGAINE Extra Strength for Men
Nonproprietary/USAN:	Minoxidil
Code Names/#'s:	U-10,858
Chemical Type/	Triaminopyrimidine N-oxide
Therapeutic Class:	3 S

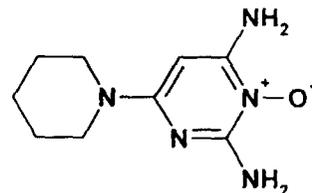
ANDA Suitability Petition/DESI/Patent Status: N/A

PHARMACOLOGICAL CATEGORY/INDICATION: For treatment of androgenic alopecia.

DOSAGE FORM: Solution
STRENGTHS: 5%
ROUTE OF ADMINISTRATION: Topical
DISPENSED: _____ Rx X OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

6-(1-Piperidinyl)-2,4-pyrimidinediamine 3-oxide



Molecular Formula: C₈H₁₁N₃O
Molecular Weight: 209.25
Melting Range: 240°C (dec)
CAS Number: [38304-91-5]

PATENT STATUS**A. Patent Information**

Below are listed all patents known to the applicant that claim the drug or a method of using the drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, sale, or use of the drug.

1. U.S. Patent No.: 4,113,619
Issue Date:
Expiration Date: 13-FEB-1996
Patent Owner: Upjohn
Claims For: Compound

2. U.S. Patent No.: 4,843,086
Issue Date:
Expiration Date: 13-FEB-1996
Patent Owner: Upjohn
Claims For: Method of treatment for alopecia with minoxidil and solvent

A period of three years of market exclusivity has been requested by the applicant (Vol. 1.1).

SUPPORTING DOCUMENTS:

DMF

~~DMF~~

DMF

DMF

DMF

DMF

RELATED DOCUMENTS:

NDA 18-154, LONITEN® Tablets, Pharmacia and Upjohn.

NDA 19-501, ROGAINE® 2% Topical Solution, Pharmacia and Upjohn.

Letter from
for

regarding specifications

material.

No DMF has been submitted for this

CONSULTS:

Trade name acceptability consultation was sent to the FDA Labeling and Nomenclature Committee; the decision of the LNC was that the proposed Trade name "ROGAINE Extra Strength for Men" is acceptable. A copy of their finding is attached.

CONCLUSIONS & RECOMMENDATIONS:

APPROVED

This application, after review of the chemistry, manufacturing and controls information, is approvable. The following changes in the labeling should be made by the applicant before approval:

The following is not a condition of approvability, but is a request strongly supported by the reviewer:

4. The revisions above should also be applied to the packaging of Rogaine 2% Topical Minoxidil Solution for Men, and Rogaine 2% Topical Minoxidil Solution for Women at the next printing of these materials.

11/5/97
J. S. Hathaway, Ph.D.
Reviewing Chemist, DNDC III

Original to NDA 20-834

cc: NDA 19-501
IND 13,267
HFD-540/DivisionFile
HFD-540/DivDir/JKWilkin
HFD-540/Chem/JSHathaway
HFD-540/MedOffr/PHeune
HFD-540/Pharm/JAvalos
HFD-540/Stat/SFarr
HFD-160/Micro/BUratani
HFD-880/Biopharm/AEITahtawy
HFD-540/ProjMgr/MJKozmaFornaro
HFD-540/ChemTeamLdr/WHDeCamp
HFD-560/MedOffr/SAurecchia

11/5/97
filename: C:\WPFILES\NDAS\NDA20834\N20834RW.0GA

11/6/97
11/14/97
APPROVABLE

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-834

PHARMACOLOGY REVIEW(S)

**Review and Evaluation of Pharmacology and Toxicology Data
Division of Dermatologic and Dental Drug Products (HFD-540)**

NDA 20-834 (009) - INSERT LABELING

Date Submitted: August 4, 1997

Number of Volumes: 1

Date CDER Received: August 5, 1997

Date Assigned: August 8, 1997

Drug: Rogaine® Extra Strength for Men (5% minoxidil topical solution)

Category: Hair growth stimulant

Sponsor: The Upjohn Company
700 Portage Road
Kalamazoo, Michigan 49001-0199
(616) 329-5671

Indication: Androgenic Alopecia in male subjects

Introduction:

In this submission, the Sponsor is submitting a revised draft of the consumer booklet for their Rogaine 5% product. Revisions have also been made to the bottle and carton label. Revisions were made to the carton following suggestions made by the Nonprescription Drug Advisory Committee (NDAC) on July 16, 1997. Not all suggestions made by the NDAC were incorporated. The Sponsor provides a brief statement as to why those suggestions were not incorporated. The revisions made are consistent within all three labels.

Comments:

My suggestions regarding these labels are also consistent. The suggestions I have recommended for the carton and bottle labels should be applied for the booklet label. These are: highlighting the sentence- - to improve compliance and decrease potential overdosing (page 7); adding the word (page 10); and deleting the sentence which suggests (pages 5, 7, and 10).

Additional changes are suggested for the booklet. On page 6, the Sponsor has incorporated in the booklet an explanation for continued hair loss once treatment with Rogaine has been initiated. Evidence that the Rogaine treatment is causing the removal of old hair for the growth of new hair is not provided. This section of the label should remain (e.g., without the added statement) as originally proposed by the Sponsor in the NDA. On page 8 and 10, the Sponsor has added the name of a mild shampoo. Inclusion of this statement is not necessary and should be omitted. On page 9, the swimming or rain question and answer have been omitted from the revised draft label. The Sponsor considers this paragraph as unnecessary since only a few consumers have inquired via the Rogaine 800 number about use

of Rogaine while swimming or going out in the rain. Such a statement would be important to those concerned individuals. I would recommend that this paragraph be included in the label.

Recommendations:

1. Delete sentence: on
pages 5, 7, and 10.

2. Highlight in the sentence - on
page 7.

3. Add the word in the statement: This sentence on page
10 should read:

4. On page 6, removal of the following sentences from the revised draft label is encouraged:

5. On page 8 and 10, the Sponsor is encouraged not to include the name of the

6. On page 9, inclusion of the paragraph regarding the question is encouraged.

8/13/97

Javier Avalos, Ph.D.
Toxicologist

cc:
NDA 20-834
HFD-540
HFD-540/Pharm/Jacobs
HFD-540/Pharm/Avalos
HFD-540/CSO/Anderson *Koymed*
HFD-540/MO/Huene
HFD-540/Chem/Higgins

For Concurrence Only:
HFD-540/DD/JWilkin 9/7/97
HFD-540/Team Leader/Jacobs *of 8/13/97*
HFD-560/ 11/14/97

Review and Evaluation of Pharmacology and Toxicology Data
Division of Dermatologic and Dental Drug Products (HFD-540)

SEP 7 1997

NDA 20-834 (008) - BOTTLE LABELING

Date Submitted: August 4, 1997

Number of Volumes: 1

Date CDER Received: August 5, 1997

Date Assigned: August 8, 1997

Drug: Rogaine® Extra Strength for Men (5% minoxidil topical solution)
Category: Hair growth stimulant

Sponsor: The Upjohn Company
700 Portage Road
Kalamazoo, Michigan 49001-0199
(616) 329-5671

Indication: Androgenic Alopecia in male subjects

Introduction:

The Sponsor has submitted a revised label for the bottle of their rogaine 5% product. Revisions made to the bottle are consistent with those made to the carton. Revisions were made to the carton following suggestions of the Nonprescription Drug Advisory Committee (NDAC) on July 16, 1997. Not all suggestions made by the NDAC were incorporated. The Sponsor provides a brief statement as to why those suggestions were not incorporated.

Comments:

The suggestions I have for change in the bottle label are identical to those made to the carton label. In the _____ section, the sentence- _____ should be highlighted with white letters to improve compliance and decrease potential overdosing. In the _____ section, the word _____ should be added to the _____ statement. The incorporation of this word would address the concern the NDAC had regarding this potential side effect. Following the _____ section, the sentence suggesting _____ should be deleted. This statement does not assist in defining the _____ conditions for this product.

Recommendations:

1. Delete sentence:
2. Highlight in white letters the sentence:
3. Add the word _____ to the statement:

This sentence should read:

Javier Avalos, Ph.D.
Toxicologist

8/13/97

cc:

NDA 20-834

HFD-540

HFD-540/Pharm/Jacobs

HFD-540/Pharm/Avalos

HFD-540/CSO/Anderson *Kayma*

HFD-540/MO/Huene

HFD-540/Chem/Higgins

For Concurrence Only:

HFD-540/DD/JWilkin

HFD-540/Team Leader/Jacobs *0.5 8/13/97*

HFD-540/DD/

1/14/97

JUL 31 1997

**Review and Evaluation of Pharmacology and Toxicology Data
Division of Dermatologic and Dental Drug Products (HFD-540)**

NDA 20-834 (006) - LABELING ADDENDUM

Date Submitted: July 23, 1997

Number of Volumes: 1

Date CDER Received: July 24, 1997

Date Assigned: July 30, 1997

Drug: Rogaine® Extra Strength for Men (5% minoxidil topical solution)
Category: Hair growth stimulant

Sponsor: The Upjohn Company
700 Portage Road
Kalamazoo, Michigan 49001-0199
(616) 329-5671

Indication: Androgenic Alopecia in male subjects

Introduction:

The Sponsor has submitted a revised label for their Rogaine 5% product. Revisions were made following the suggestions made at the Nonprescription Drug Advisory Committee (NDAC) meeting, held on July 16, 1997. Not all suggestions made by the NDAC were incorporated. The Sponsor provides a brief statement as to why those suggestions were not incorporated.

Comments:

The revisions made to the label are improvements on the label. As the label reads now, I have several suggestions for change. On the back panel in the _____ section, the sentence suggesting _____ should be deleted. This statement does not assist in defining the _____ conditions for this product. On the back panel in the _____ section, the sentence- _____ should be highlighted with white letters to improve compliance and decrease potential overdosing. In the _____ section, the word _____ should be added to the end of the _____ statement. The incorporation of this word would address the concern the NDAC had regarding this potential side effect.

Recommendations:

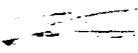
On back panel:

1. Delete sentence:
2. Highlight in white letters the sentence:

3. Add the word

at the end of the statement:

This sentence should read:

 Javier Avalos, Ph.D.
Toxicologist

7/30/97

cc:

NDA 20-834

HFD-540

HFD-540/Pharm/Jacobs

HFD-540/Pharm/Avalos

HFD-540/CSO/Anderson

HFD-540/MO/Huene

HFD-540/Chem/Higgins

For Concurrence Only:

HFD-540/DD/JWilkin

HFD-540/Team Leader/Jacobs

8/1/97

7/31/97

MEMORANDUM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Date: June 18, 1997

To: Jonathan Wilkin, MD, Director 6/20/97
Division of Dermatologic and Dental Drug Products

From: Javier Avalos, Ph.D.
Pharmacologist (HFD-540)

Through: Abby Jacobs, Ph.D. 0.4
Toxicologist-Team Leader (HFD-540)

Subject: Rogaine 5% (NDA 20-834) - Photosensitivity Label Not Recommended

In my review of NDA 20-834, I recommended that the Sponsor include a statement in the label warning consumers to avoid solar exposure when using this product. The recommendation was based on the summary of human photosensitivity reactions reported for the 2% minoxidil product from the FDA's Spontaneous Reporting System (40 reports of photosensitivity).

After searching the literature and reading each adverse event report, the data indicate that minoxidil 2% is an irritant and allergen. However, the potential for minoxidil to elicit a photosensitivity reaction still needs to be confirmed. I have found only two reports which describe photopatch testing on two individuals with positive reactions. Many of the adverse MedWatch reports had extenuating circumstances which interfered with identifying a causative agent for the itching, scaling, or scalp burn reported. Furthermore, the number of "photosensitivity" reports made to the Spontaneous Reporting System has been constant the last three years (1/year) in lieu of a increase in the number of 60-ml Rogaine 2% packages sold for the same time period.

Although the evidence of minoxidil 2% to elicit a phototoxic reaction in man is not extensive, the ability of Rogaine 5% to photosensitize consumers may be of greater concern. For the proposed 5% product, irritation, allergenicity, and photosensitization reactions may be more prevalent in consumers due to the higher concentrations of minoxidil and propylene glycol compared to Rogaine 2%.

Based on the current data available, a statement in the label warning consumers to avoid solar exposure following application of this product is not warranted. Routine examination, however,

of the Spontaneous Reporting System is recommended in order to reassess the photosensitivity potential of Rogaine 5%.

cc:

NDA 20-834

HFD-540

~~HFD-540/Pharm/Jacobs~~

HFD-540/Pharm/Avalos

HFD-540/CSO/Anderson

HFD-540/MO/Huene

HFD-540/Chem/Higgins

**Review and Evaluation of Pharmacology and Toxicology Data
Division of Dermatologic and Dental Drug Products (HFD-540)**

NDA 20-834 (000)

Date Submitted: February 28, 1997

Number of Volumes: 43 (1.1, 1.2, 1.6-1.43, 1.339-1.340, 1.359)

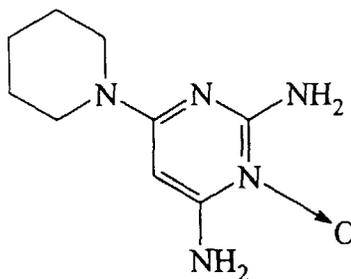
Date CDER Received: March 3, 1997

Date Assigned: March 5, 1997

Drug: Rogaine 5 Topical Solution (minoxidil topical solution 5%)

Chemical Name: 6-(1-piperidiny)-2,4-pyrimidinediamine 3-oxide

Chemical Structure:



Ultraviolet Absorption: 200 to 320 nm; max=230, 261, 285 nm in ethanol

Molecular Weight: 209.25

Molecular Formula: C₉H₁₅N₅O

Category: Hair growth stimulant

Sponsor: The Upjohn Company
700 Portage Road
Kalamazoo, Michigan 49001-0199
(616) 329-5671

Indication: Androgenic Alopecia in male subjects

Route of Administration: Topical

Submissions Cross-referenced: IND IND IND NDA 18-154,
NDA 19-501

Composition:	<u>Ingredient</u>	<u>Concentration</u>
	✓Minoxidil, USP	mg/ml
	✓Alcohol, USP	%
	✓Propylene Glycol, USP	%
	✓Purified Water, USP	.

Background: Minoxidil is approved for the treatment of androgenic alopecia (NDA 19-501) as Rogaine™ and hypertension (NDA 18-154) as Loniten™. Upjohn received approval for marketing of Loniten on August 18, 1979 and for Rogaine on August 17, 1988. For the alopecia indication, Rogaine 2% was switched from a prescription drug to an Over-the Counter drug product on February 9, 1996. The current submission is a resubmission of Pharmacia & UpJohn's previously submitted NDA

Revisions to NDA

have been made and are incorporated in the current submission. The revisions do not affect the Pharmacology/Toxicology review of NDA

Most of the pharm/tox review

for NDA 20-834 is identical to the pharm/tox review of NDA

except for the label recommendation.

Index of Studies:

A. Pharmacokinetics

1. Metabolism of minoxidil, a new hypotensive agent I: absorption, distribution, and excretion following administration to rats, dogs, and monkeys. *J. Pharm Sci* 1975;64:1360-1366.
2. Metabolism of minoxidil, a new hypotensive agent. IV. Pharmacokinetics and biotransformation in the mouse (Report No. 7256-83-017, May 23, 1983).
3. Pharmacokinetic studies of minoxidil. *Clin Pharmacol Ther* 1972;13:436-441.
4. The oral bioavailability of minoxidil in tablets as compared with a solution of minoxidil and the effect of minoxidil on blood-pressure (Report No. 7243-76-7261-002, May 4, 1976).
5. Bioavailability of 2% and 3% minoxidil topical solution relative to a 2.5 mg oral minoxidil tablet (Report No. 9111-85-016, May 22, 1985).
6. Absorption and excretion of minoxidil in rats and monkeys after subcutaneous and topical application (Report No. 7256-92-028, June 17, 1992).
7. Pharmacokinetics of minoxidil in rats and monkeys (Report No. 7256-92-052, June 17, 1992).
8. Tissue distribution of minoxidil in rats (Report No. 7256-92-027, June 18, 1992).
9. The percutaneous absorption of topically applied ¹⁴C-labeled minoxidil in the conscious rat and monkey (Report No. 7243-85-056, September 5, 1985).
10. Plasma concentrations, percutaneous absorption, and excretion of minoxidil-[¹⁴C] after topical administration to female mice and rats under the experimental conditions (Report No. 7256-91-046, November 25, 1991).
11. Effect of minoxidil on heart weights and serum minoxidil concentration in rats after

- repeated dermal application (Report No. 7256-92-022, June 2, 1992).
12. Development of radioimmunoassay for minoxidil concentration in rat and monkey serum (Report No. 7256-92-025, June 12, 1992).
 13. Topical minoxidil extent of percutaneous and oral absorption and appearance of cardiac lesions in the dog (Report No. 7256-88-030, March 31, 1988).
 14. Minoxidil concentrations in serum obtained during three month and twelve month dermal toxicity studies in cynomolgus monkeys (Report No. 7256-92-026, June 12, 1992).
 15. Percutaneous absorption of minoxidil in man. *Arch Dermatol* 1985;121:203-206.
 16. The effect of changes in frequency of application and applied dose on the absorption of topically applied minoxidil solution (Report No. 9111-86-004, March 19, 1986).
 17. Tissue distribution and hypotensive effects of minoxidil in normotensive rats. *J. Lab Clin Med* 1972;79:639-647.
 18. Metabolism of minoxidil, a new hypertensive agent II: Biotransformation following oral administration to rats, dogs, and monkeys. *J. Pharm Sci* 1975;64:1366-71.
 19. Metabolites of minoxidil in rat bile (Report No. 7243-81-7243-005, February 10, 1981).
 20. Investigation and comparison of the route dependent absorption, excretion and metabolism (including cutaneous metabolism) of minoxidil- ^{14}C after topical and oral administration in the female mouse and rat (Report No. 7256-91-045, November 26, 1991).
 21. Transdermal metabolism of ^{14}C -minoxidil in fresh human skin in an in vitro diffusion system (Report No. 7256-92-010, April 2, 1992).

B. Single Dose Dermal Toxicity Studies

1. Acute dermal toxicity of minoxidil in mice (Upjohn Technical Report No. 7219-92-005, March 16, 1992).
2. Acute dermal toxicity of minoxidil in rats (Report No. 7219-92-006, March 16, 1992).

C. Single Dose Systemic Toxicity Studies

1. U-10858 (minoxidil); a comparison of acute oral toxicity in Upj:TUC(ICR)spf and $\text{B}_6\text{C}_3\text{F}_1$ hybrid mice (Report No. 7243-77-7263, September 22, 1977).
2. Acute oral toxicity of minoxidil in mice (Report No. 7219-92-017, March 16, 1992).
3. A study of single oral dose toxicity of 1% minoxidil lotion in mice (Report No. 7219-94-028, April 18, 1992).
4. U-10858 sterile solution: LD_{50} determinations in the rat and mouse (Report No. 7243-73-7263-014, November 6, 1973).
5. Acute toxicity report on U-10858 (January 23, 1964).
6. Acute LD_{50} in mice and rats (Report No. 4301-71-7263-016, November 17, 1971).
7. U-10858; an acute intraperitoneal LD_{50} in the mouse (Report No. 7243-79-7263-063, June 6, 1979).
8. Acute intraperitoneal toxicity of minoxidil in mice (Report No. 7219-92-018, March 16, 1992).

9. Acute Subcutaneous toxicity of minoxidil in mice (Report No. 7219-92-019, March 16, 1992).
10. U-10858; acute oral LD₅₀ study in the rat comparing two manufacturing processes (Report No. 7243-76-7263-009, May 14, 1976).
11. Acute oral toxicity of minoxidil in rats (Report No. 7219-92-020, March 16, 1992).
12. A study of single oral dose toxicity of 1% minoxidil lotion in rats (Report No. 7219-94-030, April 18, 1994).
13. U-10858; an acute intraperitoneal LD₅₀ in the rat (Report No. 7243-79-7263-002, June 4, 1979).
14. Acute intraperitoneal toxicity of minoxidil in rats (Report No. 7219-92-021, March 16, 1992).
15. Acute subcutaneous toxicity of minoxidil in rats (Report No. 7219-92-022, March 16, 1992).
16. Acute subcutaneous toxicity study in cynomolgus monkeys (Report No. 7219-92-023, March 16, 1992).

D. Repeated-Dose Dermal Toxicity Studies

1. 28-Day epidermic toxicity study with minoxidil in rats-dose range finding study (Report No. 7219-94-032, April 18, 1994).
2. 90-Day epidermic toxicity study with minoxidil in rats (Report No. 7219-92-007, March 16, 1992).
3. 3-Month dermal subacute toxicity study of minoxidil lotion in rats (Report No. 7219-94-033, April 18, 1994).
4. Minoxidil topical; 94-day dermal toxicity study in the rat (Report No. 7205-76-7263-015, December 30, 1976).
5. 52-Week percutaneous toxicity study of minoxidil in rats (Report No. 7219-94-034, April 27, 1994).
6. One-year dermal toxicity study of U-10858 in Sprague-Dawley rats (Report No. 7263-85-065, November 4, 1985).
7. A 21-day dose finding study of U-10858 in Dutch belted rabbits (Report No. 7263-85-031, May 28, 1985).
8. U-10858; one-year dermal toxicity study in Dutch belted rabbits (Report No. 7263-85-066, November 1, 1985).
9. 91-Day Percutaneous toxicity study in dogs (Report No. 7219-92-031, March 16, 1992).
10. 4-Week dermal dose range-finding study in Cynomolgus monkeys (Report No. 7219-92-008, March 16, 1992).
11. 3-Month dermal toxicity study in Cynomolgus monkeys (Report No. 7219-92-009, March 16, 1992).
12. One-year dermal toxicity study in Cynomolgus monkeys (Report No. 7219-92-010, March 16, 1992).

E. Repeated-Dose Systemic Toxicity Studies

1. U-10858; 3-day oral toxicity study in the rat with emphasis upon the cardiovascular system (Report No. 7243--76-7263-002, January 26, 1976).
2. U-10858; cardiac hypertrophy and reversal study in rats (Report No. 4301-71-7263-004, February 5, 1971).
3. Histology addendum to the cardiac hypertrophy reversal study in rats (Report No. 4301-71-7263-012, June 24, 1971).
4. Chronic oral toxicity in the rat (Interoffice memorandum, April 27, 1965).
5. U-10858; 14-day subcutaneous tolerance study in the rat (Report No. 7243-74-7263-003, May 8, 1974).
6. U-10858; pathology addendum on special study to attempt to produce the early cardiac lesions in the dog reported by Balazs et al. (Report No. 7243-75-7263-008, October 6, 1975).
7. U-10858; 3-day oral toxicity study in the beagle dog (Report No. 7243-76-7263-005, March 26, 1975).
8. U-10858; subacute oral toxicity study in the dog (Report No. 4301-69-7263-019, December 31, 1969).
9. U-10858; subacute oral toxicity study in the dog at dose levels of 0.5 and 1.0 mg/kg/day (Report No. 4301-70-7263-014, June 18, 1970).
10. U-36464; subacute (30-day) oral toxicity study in the dog (Report No. 4301-72-7263-005, May 19, 1972).
11. U-10858; one-year oral toxicity study in the monkey (Report No. 7243-75-7263-003, March 4, 1975).
12. U-10858; 14-day intravenous tolerance in the monkey (Report No. 7243-74-7263-006, May 8, 1974).
13. U-10858; one month oral toxicity study in the monkey (Report No. 7243-73-7263-002, March 8, 1973).

F. Carcinogenicity Studies

1. U-1085: 12-Month photocarcinogenesis interaction study in hairless mice (Report No. 7227-91-051, October 25, 1991).
2. Dermal carcinogenicity study of minoxidil in rats and mice - A 2 year study (Report No. 7219-92-002[091 and 092], November 16, 1990).
3. U-10858; 16 month long-term oral tolerance and carcinogenicity test in ICR mice (Report No. 7243-77-7263-002, June 29, 1977).
4. U-10858; a chronic oral bioassay for carcinogenic potential in the Hap:(B₆C₃F₁)Br mouse (Report No. 7243-81-7263-012, October 30, 1981).
5. U-10858; twenty-two-month oral toxicity study in rats (Report No. 7243-75-7263-006, August 6, 1975).

G. Reproductive Toxicity Studies

1. U-10858; a segment I study in the rat (Report No. 7243-75-7263-002, March 10, 1975).
2. Reproduction studies of minoxidil-fertility study in rats (Report No. 72129-92-024, March 16, 1992).
3. Teratology study in the rat (Report No. 7243-73-7263-016, November 30, 1973).
4. U-10858; final report on evaluation of folded retinas in rat fetuses (Report No. 7243-74-7263-007, August 1, 1974).
5. Retinal folds reported in rats in previous studies represent fixation artifacts (Report No. 7243-74-7263-011, October 14, 1974).
6. U-10858; a segment II teratology study (subcutaneous) in the rat (Report No. 7227-88-169, October 24, 1988).
7. Reproduction studies of minoxidil-teratology study in rats (Report No. 7219-92-025, March 16, 1992).
8. Reproduction studies of minoxidil-additional teratology study in rats (Report No. 7219-92-026, March 16, 1992).
9. U-10858; teratology study in the rabbit (Report No. 7243-74-7263-004, March 27, 1974).
10. Reproduction studies of minoxidil-teratology study in rabbits (Report No. 7219-92-027, March 16, 1992).
11. U-10858; a segment III study in rats (Report No. 7243-75-7263-001, January 1, 1975).
12. Reproduction studies of minoxidil-perinatal and postnatal study in rats (Report No. 7219-92-028, March 16, 1992).

H. Mutagenic Potential

1. Evaluation of U-10858 in the *Salmonella*/microsome test (Report No. 7243-78-7263-013, May 17, 1978).
2. Further evaluation of minoxidil in the *Salmonella*/microsome test (Report No. 7243-80-7263-001, July 3, 1980).
3. Mutagenicity studies of minoxidil-bacterial reverse mutation test (Ames) (Report No. 7219-92-002, March 16, 1992).
4. Evaluation of U-45806F in the *Salmonella*/microsome test (Report No. 7268-83-009, May 31, 1983).
5. Evaluation of U-68394E in the *Salmonella*/microsome test (Report No. 7268-83-010, May 31, 1983).
6. Evaluation of U-10858 in the DNA damage/alkaline elution assay (Report No. 7268-85-015, September 24, 1985).
7. Evaluation of u-10858 in the *in vitro* unscheduled DNA synthesis assay in rat primary hepatocytes (Report No. 7227-88-026, October 28, 1988).
8. The primary hepatocyte unscheduled DNA synthesis assay with U-45806F, U-68394E, and ultraviolet light (Report No. 7268-83-035, November 28, 1983).
9. Mutagenicity studies of minoxidil - *in vitro* chromosome aberration test (Report No. 7219-92-004, March 16, 1992).
10. U-10858; evaluation of U-10858 in an *in vitro* cytogenetics assay in human lymphocytes (Report No. 7228-91-082, February 4, 1992).

11. The micronucleus test with minoxidil (Report No. 7243-80-7263-002, July 11, 1980).
12. Mutagenicity studies of minoxidil - the micronucleus test (Report No. 7219-92-003).

I. Local Tolerance

1. Delayed-type contact dermal sensitization study on minoxidil solutions in albino guinea pigs (Report No. 7277-85-007, October 3, 1985).
2. Dermal sensitizing potency of the 1% minoxidil topical solution in guinea pigs (Report No. ~~7219-94-035~~, April 18, 1994).
3. I-245, Test to evaluate the acute toxicity using a single cutaneous administration in the rat. I-246, Evaluation of phototoxic and photoallergic potential by topical application in the guinea pig. I-247, Evaluation of ocular irritation in the rabbit (Report No. 7263-86-038, July 14, 1986).
4. Phototoxicity study of minoxidil (Report No. 7219-92-011, March 16, 1992).
5. Cumulative skin irritation study of minoxidil (Report No. 7219-92-012, March 16, 1992).
6. Local irritation study of minoxidil (Report No. 7219-92-013, March 16, 1992).
7. Primary dermal irritation test of the 1% minoxidil degradation topical solution in rabbits (Report No. 7219-94-037, April 18, 1994).
8. U-10858; intramuscular irritation study in the rabbit (Report No. 7243-73-7263-013, September 6, 1973).
9. Local irritation study of minoxidil (Report No. 7219-94-013, March 16, 1992).
10. Ocular irritation test of the 1% minoxidil topical solution in rabbits (Report No. 7219-94-036, April 18, 1994).

J. Special Toxicity Studies

1. U-1085; histological re-evaluation of selected endocrine and reproductive tissues of female B6C3F1 mice from chronic oral carcinogenicity study and comparison with similar observations from a chronic topical carcinogenicity study (Report No. 7228-91-062, October 2, 1991).
2. U-10858; histological re-evaluation of selected endocrine and reproductive tissues of male and female F344/DuCrj rats from a chronic topical carcinogenicity study (Report No. 7228-91-071, November 7, 1991).
3. U-10858; immunohistochemical stain of pituitary prolactin and quantitation by image analysis (Report No. 7228-91-061, October 2, 1991).
4. U-10858; 7-day preliminary toxicity study to evaluate the effect of oral U-10858 on serum and pituitary prolactin levels in the female B6C3F1/CrIBR mouse (Report No. 7228-91-058, September 30, 1991).
5. U-10858; 7-day preliminary toxicity study to evaluate the effect of oral U-10858 on serum and pituitary prolactin levels in the female B6C3F1/CrIBR mouse (Report No. 7228-91-059, October 2, 1991).
6. U-10858; a 30-day preliminary toxicity study to evaluate the effect of oral U-10858 on serum and pituitary prolactin levels in the female B6C3F1/CrIBR mouse (Report No.

- 7228-91-060, October 2, 1991).
7. U-10858; a 90-day preliminary toxicity study to evaluate the effect of oral U-10858 on serum and pituitary prolactin levels in the female B6C3F1/CrIBR mouse (Report No. 7228-91-057, November 19, 1991).
 8. In vitro estrogen receptor binding of U-10858, U-45806E, U-58838, U-10752, U-78968, U-38472, U-36464 (Report No. 7228-91-067, October 4, 1991).
 9. U-10858, U-58838, U-45806E: Estrogenic activity bioassay in ovariectomized female B6C3F1/CrIBR mice (Report No. 7228-91-079, November 14, 1991).
 10. U-10858 oral route: Estrogenic activity bioassay in ovariectomized female B6C3F1/CrIBR mice, interaction with diethylstilbestrol (Report No. 7228-91-087, December 2, 1991).
 11. U-10858: Estrogenic activity bioassay in ovariectomized female B6C3F1/CrIBR mice, interaction with diethylstilbestrol (Report No. 7228-91-086, December 2, 1991).
 12. Estrus cycle duration of female B6C3F1 mice housed in the absence or presence of male mice (Report No. 7228-91-041, May 29, 1991).
 13. Serum prolactin levels in the female B6C3F1 mouse: variations with the light/dark cycle (Report No. 7228-91-068, October 4, 1991).
 14. Stress induction of serum prolactin levels in female B6C3F1 mice following blood collection by orbital puncture (Report No. 7228-91-069, October 4, 1991).
 15. Bioavailability of minoxidil in female B6C3F1 mice; topical vs. drug-in-diet- (Report No. 7228-93-042, September 9, 1993).
 16. U-10858; 90-day topical repeated dose investigative toxicity study in male mice (Report No. 7228-94-026, January 26, 1995).
 17. U-10858; 90-day topical repeated dose investigative toxicity study in male mice (Report No. 7228-94-025, January 27, 1995).
 18. U-10858; 90-day topical repeated dose investigative toxicity study in male rats- neurochemical analysis of the brain (Report No. 7228-94-029, March 17, 1994).
 19. U-10858; 90-day topical repeated dose investigative toxicity study of pulsative prolactin secretion in male rats (Report No. 7228-94-027, February 22, 1995).
 20. U-10858; determination of prolactin in plasma and pituitary from minoxidil-treated mice (Report No. 7219-95-020, June 16, 1995).
 21. U-10858; comparison study of blood and pituitary levels in female mice treated percutaneously and feed additively with minoxidil (Report No. 7219-95-018, June 16, 1995).
 22. U-10858; immunohistochemical study on tissue of female mice receiving minoxidil for 24-months-immunostaining of mammary tissue (Report No. 7219-95-016, June 16, 1995).
 23. U-10858; The blood minoxidil concentration in mice (Report No. 7219-95-017, June 16, 1995).
 24. U-10858; analysis of minoxidil-assay of minoxidil in mouse plasma (Report No. 7219-95-019, June 16, 1995).
 25. Antigenicity study of minoxidil (2) (Report No. 7219-94-014, March 16, 1992).
 26. Antigenicity study of minoxidil (3) (Report No. 7219-92-015, March 16, 1992).
 27. Antigenicity study of minoxidil (5) (Report No. 7219-92-016, March 16, 1992).

28. Study of vehicle for minoxidil solution (Report No. 7219-94-039, April 18, 1994).
29. Effects on drug-metabolizing enzyme system in the liver (Report No. 7219-94-038, April 18, 1994).

A. Pharmacokinetics

The absorption, distribution, metabolism, and excretion of minoxidil have been examined in rat, mouse, dog, and monkey following single and multiple administrations of oral, subcutaneous, intravenous, and topical doses. At least 90% of the oral dose is absorbed in each of these species. However, mean levels of absorption following a topical administration varied between species: mouse 48%, rat 32%, dog 39%, and monkey 5%. The administration of 1 ml of 1%, 3%, and 5% minoxidil (twice a day) to rats for 1 year resulted in mean plasma levels of 34.2, 253.4, and 224.5 ng/ml in males and 95.7, 753.9, and 1363.7 ng/ml in females. The higher blood levels and urinary excretion in female animals were attributed to a sex difference in the thickness of the corneal layer in the epidermis. Topical administration of 1.5 and 7.5 mg/kg/day (1.5 ml/kg of 0.1% and 0.5%) to male Wistar rats resulted in serum plasma values of 9.76-10.99 ng/ml at 2 hours post dosing in the 1.5 mg/kg/day group and 2-5 times greater for the high dose group. These values were maintained irrespective of administration period (1, 2, 4, or 13 weeks). Additionally, heart weight increases (9%) were first noted at 2 weeks and 1 week after administration of 1.5 mg/kg/day and 7.5 mg/kg/day, respectively. Overall, the maximum percutaneous absorption of minoxidil in rats, mice, and dogs was approximately 37%, 50%, and 39%, respectively, of the administered dose. Maximal serum concentrations were achieved within 6 hours in all species. In monkeys, the maximum percutaneous absorption of minoxidil observed was 17% of a topically administered dose. The monkeys had no gender-related differences in serum concentration during a 12 month study.

Following absorption, similar distribution patterns were noted in animals after oral, subcutaneous, and topical administrations. The distribution was rapid and encompassed the liver, kidney, intestine, bladder, and aorta. The absorption and distribution pattern after 21 repeated subcutaneous administrations demonstrated no bioaccumulation of radioactivity in rats. The radioactivity concentration was increased by repeated administrations, but reached a steady state after the 12th day. C_{max} and AUC were much higher (4 and 6.5 times, respectively) than those observed after a single sc administration. After the 21st administration in rats, the distribution of ^{14}C -minoxidil was similar to the distribution following a single sc administration. However, the levels of radioactivity were much higher (2-9 times; 17 for skin). No radioactivity was observed in the brain. For the topical administration, the majority of the radioactivity was observed at the site of application. In addition, the levels of radioactivity observed in the tissues of female animals was twice the level observed in male animals.

The subcutaneous administration of radiolabeled minoxidil to pregnant rats (gestation day 13 or 18) demonstrated that the radioactivity was absorbed by the fetuses. The maximum level of radioactivity in fetal tissue occurred at 30 minutes after dosing during the middle or late gestation periods. The levels of radioactivity in the fetus at either gestation period were 40% less than the maternal plasma levels of 491 and 690 ng/ml, respectively. The radioactivity in fetus

was greatest in the liver and kidney. A similar distribution pattern and exposure level was observed in fetuses after a topical administration of ^{14}C -minoxidil was administered (0.9 mg/kg) to dams.

Extensive first pass metabolism was evident in all species examined. Eight metabolites were characterized 30 minutes after a sc administration (0.9 mg/kg) in the rat. The greatest amount of radioactivity remained as unchanged minoxidil (50%) followed by the carboxy-minoxidil metabolite. In the monkey, a glucuronide conjugate of minoxidil accounted for the greatest radioactivity (50%) followed by the unchanged drug. Most of the characterized metabolites of minoxidil were also identified in several of the organs in the rat. However, no qualitative differences in metabolism were noted between species after a single and multiple topical applications. At the site of application following a topical administration, the unchanged drug was the predominant component (70-80%). Additionally, some qualitative differences were noted between metabolite profile from an oral administration and the metabolite profile from a topical administration.

As in the plasma, the major urinary and biliary metabolite of minoxidil in rats was the metabolite with a large portion of the radioactivity remaining as unchanged minoxidil. In monkeys, the major product in urine was the metabolite. This pattern of metabolites was observed after dosing with either route of administration (topical and subcutaneous). The main fecal metabolites in rats were the and the metabolite.

The metabolite profile in urine following a 21-day consecutive administration was similar to that of a single administration. Eight metabolites were characterized with being the most abundant and the parent compound accounting for 50% of the radioactivity.

After both subcutaneous and topical administrations of minoxidil to rats and monkeys, radioactivity was almost exclusively excreted in urine. The rates of excretion into the urine and feces up to 168 hours after administration were 89.7% and 9%, respectively, of the dose in rats, and 9.2% and 0.9% in monkeys. Following a topical administration, 9.5% and 0.7% of the radioactivity were excreted up to 168 hours into urine and feces, respectively, in rats, and 4.9% was excreted into urine in monkeys. In rats, the excretion rate in female-treated rats was about two times greater than male-treated rats. The levels of biliary excretion (>10%) also reflect the fecal excretion rates.

Excretion rates of radioactivity into urine and feces did not differ in rats treated subcutaneously for 21 consecutive days from rats given a single administration. Up to 168 hours after the final administration, 82.9% and 8.1% of the cumulative dose was recovered in the urine and feces, respectively, in rats. However, the excretion rates of radioactivity into urine and feces observed in rats treated with 7 daily topical (1%) administrations decreased with the number of administrations. The decreased rates were assumed to be caused by a decrease in the percutaneous absorption as a result of the repeated applications and wiping of test material.

Excretion of minoxidil into milk was also examined in rats. Radioactivity in milk reached a maximum 30 minutes following the single subcutaneous administration of 0.9 mg/kg. The levels of radioactivity present in milk (457 ng/ml) were similar to the levels observed in plasma (448 ng/ml) at 30 minutes. At 2, 6, and 24 hours following dosing, the levels of radioactivity in milk were 41%, 720%, and 400%, respectively, greater than the

plasma levels. The levels of radioactivity in milk following a topical administration were 4% (13 ng/ml) of those found after a subcutaneous administration. However, the levels of radioactivity in milk were greater (72%, 41%, 400%, and 100%) than the levels reported in plasma at 0.5, 1, 6, and 24 hours following the topical administration of 0.9 mg/kg minoxidil. Within 48 hours, no radioactivity was detected in either milk or plasma following both routes of administration.

In man, oral doses of 2.5 and 5 mg of minoxidil resulted in peak serum concentrations of 18.5 ng/ml and 41 ng/ml, respectively. Minoxidil recovery following an oral administration was 97%. The recovery of minoxidil following a dermal application of a 5% solution (1 ml twice a day to a 60 kg individual) was 0.3-4.5% of an oral dose. As reported in the animal studies, minoxidil is also extensively metabolized and distributed in man. The distribution and metabolic pattern are also qualitatively similar to those reported for the animal studies. Quantitatively, the metabolite profile for man is similar to that observed for monkeys. In an in vitro transdermal system using human skin (foreskin and breast), $3.2\% \pm 1\%$ of the applied dose penetrated into the receptor phase over a 72 hour period while $32.7\% \pm 7.8\%$ of the applied dose was found within the skin.

B. Single Dose Dermal Toxicity Studies

In summary, minoxidil was topically administered to male and female ICR mice (7219-92-005) and Wistar rats (7219-92-006). Both studies were conducted between September 1987 and December 1987 in Japan. Minoxidil was first dissolved in propylene glycol at a concentration of _____ mg/ml (9% solution) and applied as a 15 and 10 ml/kg, respectively, dose to a surface area approximating 24 cm². Mice were treated with 1350 mg/kg and rats were treated with 900 mg/kg. Test material was left on the site for 6 hours. No treatment-related gross observations, lesions at site of application or histopathological effects were reported for either study.

C. Single Dose Systemic Toxicity Studies

These studies have been previously submitted to IND _____ NDA 19-501 and NDA 18-154. Reviews for two of these studies (Report Nos. 7243-77-7263-005 and 4301-71-7263-016) are attached. In summary, minoxidil was administered orally, intravenously, intraperitoneally, and subcutaneously to mice and rats. Cynomolgus monkeys were subcutaneously administered minoxidil. LD₅₀ values were calculated for each species: mice ranged from _____ mg/kg, rats had a range from _____ mg/kg, and monkeys from _____ mg/kg. The values were dependent on route of administration and vehicle. Clinical signs reported were ptosis, decreased motor activity, inhibited respiration, and muscle tremors (iv and ip high doses). No gross lesions or histopathological findings were reported in mice while in rats, vacuolization and necrotic changes of hepatocytes and slight thickening of splenic capsule. In monkeys, histopathology revealed tubular dilatation, presence of cellular debris/hyaline casts in the tubular lumina, hepatic vacuolar change, subacute myocarditis, and moderate coagulative necrosis of the myocardium.

D. Repeated-Dose Dermal Toxicity Studies

These studies have been previously submitted to IND NDA 19-501 and NDA 18-154. Reviews for most of these studies are attached. In summary, minoxidil was administered topically to rats, rabbits, dogs, and monkeys. Irritation at the site of application, increased heart weights, and cardiovascular changes (increased heart rate, hypotension, and cardiac lesions) were observed in the treated animals. Wistar and Sprague-Dawley rats were treated with vehicle (propylene glycol:ethanol:water), 0.2%, 1%, 3%, 5%, or 6% solutions of minoxidil for 1 month, 3 months, or 1 year. In the one year Sprague-Dawley study, rats were treated twice daily with 1 ml of 1%, 3%, or 5% minoxidil in propylene glycol:ethanol:water (5:3:2) vehicle. The concentration of minoxidil applied on a daily basis would then correspond to 10, 30, and 50 mg/ml. Four of the 6 animal deaths in the high dose group prior to study termination were directly attributed to cardiac failure as a result of drug treatment. Besides the increased heart weight reported, the liver, kidney, and spleen weights were also increased in the mid and high dose animals. The drug-related histologic findings in all treated rats were degeneration & fibrosis, nuclear enlargement, and cytoplasmic vacuolation (heart); increased alveolar macrophages (lung); and hepatocellular hypertrophy (liver) at necropsy. Extensive kidney nephritis was also observed in the mid and high dose male treated animals. Terminal plasma levels of minoxidil was determined for males and females. The administration of 1 ml of 1%, 3%, and 5% minoxidil (twice a day) resulted in mean plasma levels of 34.2, 253.4, and 224.5 ng/ml in males and 95.7, 753.9, and 1363.7 ng/ml in females.

Similar findings (organ weight increases; site of application, hepatic, renal, and cardiac histological findings) were reported in Wistar rats treated with 1.35 ml/kg of 0.3, 4.5, and 67.5 mg/kg/day minoxidil in a propylene glycol:ethanol:water (5:3:2) vehicle. Two animals died due to severe chronic nephropathy and marked myocardial fibrosis. The no-observable-effect level determined in this study was 0.3 mg/kg/day. This dose would correspond to a concentration of 0.22 mg/ml/day.

A one-year dermal toxicity study was also conducted in Dutch Belted rabbits. The rabbits received 2 ml of a 1%, 3%, or 5% minoxidil solution in propylene glycol:ethanol:water (5:3:2) vehicle. None of the deaths during the study (18) were considered to be treatment-related. As in the rat studies, irritation and thickening at the site of application was noted in all animals. Dilated ventricles of the heart were reported in female rats treated with 3% and 5%. Increases in heart and liver were noted in female rabbits of the mid and high dose groups. No histological lesion were noted. The administration of 2 ml of 1%, 3%, and 5% minoxidil (twice a day) resulted in mean plasma levels of 67, 52.8, and 505.3 ng/ml in males and 41.1, 193.2, and 361.8 ng/ml in females.

Cynomolgus monkeys also received vehicle (propylene glycol:ethanol:water, 5:3:2), 1, 10, or 100 mg/kg/day of minoxidil at a volume of 2 ml/kg/day. This corresponds to a concentration of 1, 10, or 100 mg/ml/day for each application. Although some treatment-related findings (scabbing at application site, slight increased heart rate, and systolic murmur at 3 months) were reported with identical dosing in earlier range-finding studies, no treatment-related changes in clinical observations, percussions and auscultations of the heart and lungs, electrocardiographic examinations, or histologic examinations of heart, liver, or kidney were

reported after one year of treatment.

Beagle dogs were only treated chronically for 91 days. A dose of vehicle (1% oleyl alcohol), 0.25%, 0.5%, or 2% minoxidil at a volume of 1 ml was applied twice daily. Treatment-related findings for the high dose group included increased heart and liver weights, chronic proliferative epicarditis, chronic active inflammation of the atrial myocardium, hemorrhage and pigment in some animals, fibroblastic proliferation and neovascularization in some animals, and myocardial necrosis. Similar changes were noted in one and three of the animals treated with 0.25% and 0.5% minoxidil, respectively.

E. Repeated-Dose Systemic Toxicity Studies

These studies have been previously submitted to IND NDA 19-501 and NDA 18-154. Reviews for these studies are attached. In summary, minoxidil was administered orally, intravenously, or subcutaneously to dogs, monkeys, miniature swine, or rats. As discussed in earlier reviews, minoxidil caused renal tubular water and electrolyte retention, arterial dilation, tachycardia, and hypotension in rats, monkeys, dogs, and pigs. In the rat, dilatation and hypertrophy of the heart was observed at oral doses of 10, 30, and 100 mg/kg/day after one year. In the Rhesus monkey, hypertrophy of the heart was observed in animals orally treated with 20 mg/kg/day for 32 days. Cardiac alterations were also observed in monkeys orally treated with 14 mg/kg/day for 1 year. Papillary muscle necrosis, atrial and ventricular hemorrhage, and coronary arteritis were reported in miniature pigs treated orally with 1 mg/kg/day after 2 days of treatment. Cardiac alterations (atrial hemorrhage, hypertrophy, degeneration of muscle cells, coronary arteritis, and epicarditis on right atrial wall) in dogs were noted with oral doses of 0.5 mg/kg/day after 2 days or 30 days. Beagle dogs treated orally with 3 mg/kg/day for 1 year also had similar findings.

Dogs were also intravenously infused with minoxidil (0.05-4.3 mg/kg/day) for 3 days while blood minoxidil levels, heart rate, blood pressure, and then hearts were examined for any gross or microscopic pathological changes. Dose-related changes in all parameters were obtained (see Table 1 and 2). Steady state for minoxidil serum levels and cardiovascular changes were obtained within 12 hours and 24 hours, respectively. Minimal heart rate increases and blood pressure decreases were observed with minoxidil serum levels of 2 ng/ml following 3 days of minoxidil infusion. At this plasma level, no cardiac lesions were observed. At a serum level of 6-7 ng/ml, heart rate increased by 45% without a concurrent decrease in BP. No cardiac lesions were reported in these animals. Infusion doses of 0.43 mg/kg/day or greater (serum levels of 14 ng/ml or greater) for 3 days caused cardiac lesions with concurrent increases in heart rate greater than 50% and concurrent decreases in BP greater than 20%. Thus, a 7-10 fold difference in blood levels separates a blood level (2 ng/ml) that causes a detectable heart rate increase and a blood level (14-22 ng/ml) that causes hypotension and associated heart lesions.

Each of the cardiac findings (hemorrhagic lesions, coronary arteritis, papillary muscle and ventricular subendocardial necrosis, cardiac dilatation and hypertrophy, and epicarditis) observed in the treated animals have been addressed by the Division of Cardio-Renal Drug Products. In their reviews, the cardiac vascular findings in the treated animals were reported

Table 1. Placebo-corrected heart rate and mean blood pressure, and average serum plasma levels in dogs following intravenous administration of minoxidil for 3 days.

Dose (mg/kg/day)	Serum Level (ng/ml)	Heart Rate (% increase)	Blood Pressure (% decrease)
0.05	2	15	10
0.14	6-7	45	10
0.43	14-22	58	30
1.44	30-60	58	20
4.32	170-250	72	25

Table 2. Treatment-related cardiovascular findings in dogs continuously infused with minoxidil for 3 days.

Findings	Dose (mg/ kg / day)					
	0.0	0.05	0.14	0.43	1.44	4.32
Right Atrium/Auricle						
Inflammation/hemorrhage, epicardium	0	0	0	3	4	4
Hemorrhage, epicardium, focal	0	0	1	0	0	0
Left Atrium/Auricle						
Hemorrhage epicardial/endocardial	0	0	0	0	2	0
Left Ventricular Wall/Septum						
Necrosis, subendocardium (ischemic)	0	0	0	0	0	1
Hemorrhage, endocardium	0	0	0	1	2	3
Dorsal/Ventral Papillary Muscle						
Necrosis, subendocardium (ischemic)	0	0	0	0	1	2*
Necrosis, hemorrhagic	0	0	0	1	1	0
Hemorrhage, endocardium	0	0	0	1	3	2
Right Coronary Artery						
Medial hemorrhage/necrosis	0	0	0	3	4	4
Left Coronary Artery						
Medial hemorrhage/necrosis	0	0	0	2	2	3

* - One dog also had lesions in both dorsal and ventral papillary muscles.

to occur "only in the context of profound hypotension and tachycardia of one day or more duration with minoxidil". These changes reflected "hemodynamic and/or hypoxic stress rather than direct cytotoxicity". The blood level which caused a 50% increase in heart rate in the dog was 6-7 ng/ml, with only a minimal decrease in blood pressure. In hypertensive humans, a 25 ng/ml blood level of minoxidil only increased HR by 5 beats/min.

F. Carcinogenicity Studies

These studies have been previously submitted to IND [REDACTED], IND [REDACTED], and NDA 19-501. Reviews for these studies are attached. In summary, minoxidil was administered orally and topically to mice and rats. In the oral studies, minoxidil (0, 3, 10, or 30 mg/kg/day) was given in the diet to ICR mice for 16 months, to B₆C₃F₁ mice (0, 10, 25, and 63 mg/kg/day) for 24 months, and to Sprague-Dawley rats (0, 3, 10, or 30 mg/kg/day) for 22 months. In rats, no treatment-related changes were reported in gross or microscopic observations. In mice, the first mouse study was terminated early (16 months vs. 18 months) due to low number of survivors. This study was compromised by disease (epizootic of Pseudomonas infection at week 34 and aggravated by renal amyloidosis). No conclusions were drawn from this study. In the second mouse study, malignant lymphomas were reported earlier in female mice treated with 63 mg/kg/day when compared to vehicle control animals and hepatic nodules were reported in the high dose males. Female animals treated with 63 mg/kg/day also had a shortened survival time. In addition, Division of Biometrics observed a positive dose response relationship at the p=0.01 level in the incidence of hemangiosarcomas for all sites combined in male treated mice (CDER Division of Biometrics Review dated 11/4/88). The incidence of hemangiosarcomas in male mice was 4/60, 6/60, 7/60, and 12/60 in the control, low, mid, and high (63 mg/kg/day) dose animals, respectively. In the Fisher's exact test, the incidence of hemangiosarcomas in the high dose was statistically significant at p=0.05 for the pairwise comparison.

These findings were addressed in Dr. Linda De Witt's review of April 4, 1990, in which she proposed that the findings be incorporated into the label. Although a statistically significance (for 1988 criteria) was obtained at a p value of 0.01 and 0.05 for common tumors in the trend test and pairwise comparisons, respectively, the findings were not incorporated into the label. In my review of the Divisional file, no documentation was found which described why the findings were not incorporated into the label. In Dr. De Witt's review, only the hemangiosarcomas are identified. No mention of hemangiomas are observed. In evaluating a lesion, both the benign and malignant lesion type are generally included in the evaluation. The combination incidence of hemangiosarcoma and hemangioma are 8/60, 6/60, 7/60, and 13/60 in the control, low, mid, and high dose animals, respectively. Therefore, statistical significance would not be obtained and findings would not be incorporated into the label. Additionally, p value levels for statistical significance have been modified since the approval of Loniten and Rogaine 2%. The 1988 criteria for statistical significance was a p value of 0.05 for pairwise comparison and 0.01 for common tumors in the trend test. The current (1997) p values for statistical significance is 0.005 for common tumors in the trend test and 0.025 for the pairwise comparison. Thus, the hemangiosarcoma/ hemangioma lesions

reported in male mice should not be incorporated in the current labels for Loniten, Rogaine 2%, or Rogaine 5%.

Dermal carcinogenicity studies were conducted in B6C3F1 mice and Fischer rats. Minoxidil was applied in doses of 0, 8, 25, or 80 mg/kg/day in a 50% propylene glycol and 31.6% ethyl alcohol aqueous mixture. In rats, survival rates were decreased in male and female animals treated with 80 mg/kg/day. Body weight gains were also suppressed in males (9-14%) treated with 80 mg/kg/day at week 76-88 and in females (9%) treated with 80 mg/kg/day at week 44-76. An increased incidence of non-neoplastic and neoplastic lesions was reported in treated male and female animals. An increased incidence of chronic nephropathy, myocardial fibrosis, and capillary proliferation at the skin site was noted in both genders. In males, bile duct hyperplasia and vacuolated cell focus in the liver were also reported while cyst formation in the pituitary gland was reported in female animals. Dose-related increases in pheochromocytomas in both male and female animals and increases in preputial gland adenomas in male treated rats were reported (Table 3). The Sponsor has concluded that a probable cause for the adrenal pheochromocytomas noted was the result of a continual neurogenic stimulation of the adrenal gland caused by the hypotensive action of minoxidil. In this study, an increased incidence of mammary adenomas or carcinomas was not reported.

In the mouse study, survival rates did not differ among control and treated animals. An increased incidence in basophilic cell foci and hyperplasia in the liver and myocardial fibrosis in the heart were reported in male animals given 80 mg/kg/day. The high dose female mice had an increased incidence of hyperplasia in the mammary gland and lymphocytic infiltration in the urinary bladder. An increased incidence of hepatocellular adenomas in male mice was noted (Table 4). In female mice, an increased incidence of adenomas in the pituitary and mammary gland adenocarcinomas was reported (Table 4). The mammary gland adenocarcinomas were proposed to be the result of chronic hormonal stimulation of the mammary gland. Mechanistic studies were conducted to determine if minoxidil was capable of stimulating prolactin secretion (see Special Toxicology Studies section).

Following the review of the data by CDER Division of Biometrics (Pharm/Tox review dated 9/23/1993 for NDA 19-501), several of the increased incidences of neoplastic lesions were considered not to have a statistically significant linear trend. Biometrics came to the following conclusion: "Since pituitary adenomas, hepatocellular adenoma/carcinomas in the concurrent controls are greater than 1% and are considered common tumors in this strain of mice, that for a positive linear trend not to occur by chance or variation, the p-value should be smaller than 0.01. Therefore, we do not regard the positive linear trend in pituitary adenoma in female mice and liver hepatocellular adenoma and carcinoma in male mice as statistically significant." The increased incidences of pheochromocytomas in female rats were also found to be not statistically significant by the Division of Biometrics.

A photocarcinogenicity assay using hairless mice was also conducted with minoxidil. In the assay, hairless mice were topically treated with 0.1 ml/day (5 days/week) of vehicle (30% ethanol:50% propylene glycol:20% water), 2% or 5% minoxidil for 40 weeks followed by a 12-week observation period. In addition, animals were exposed to either 273 or 545 Robertson-Berger Units (RBU; 400 RBU equals one mouse minimal erythema dose and 1000 RBU equals one human minimal erythema dose) of solar simulated irradiation (>280 nm) for

5 days/week. Minoxidil administration and UV irradiation were alternated during the week. On Monday, Wednesday, and Friday, minoxidil was administered first and followed by UV irradiation. On Tuesday and Thursday, UV irradiation was conducted first and then minoxidil was administered. Administration of minoxidil did not promote either papillomas or carcinomas initiated by UV with a RBU dose of 545. Furthermore, minoxidil did not afford any photoprotection to the hairless mice under these test conditions. The Sponsor should conduct a more robust statistical analysis in order to provide a lack of evidence of a real effect.

Table 3. Neoplastic lesions reported in rats topically treated with minoxidil for 24 months.

Dose (mg/kg) Tumor/species/sex	Incidence			
	0	8 mg/kg/day	25 mg/kg/day	80 mg/kg/day
Adrenal pheochromocytoma:				
Rat/Male	7/50	10/50	18/50	19/50
Rat/Female	1/50	2/50	4/50	6/50
Preputial gland adenoma:				
Rat/Male	4/50	12/50	10/50	10/50

Table 4. Neoplastic lesions reported in mice topically treated with minoxidil for 24 months.

Dose (mg/kg) Tumor/species/sex	Incidence			
	0	8 mg/kg/day	25 mg/kg/day	80 mg/kg/day
Hepatocellular adenoma:				
Mice/Male	12/50	11/50	16/50	22/50
Hepatocellular carcinoma:				
Mice/Male	10/50	8/50	10/50	10/50
Mammary gland adenocarcinoma:				
Mice/Female	2/50	12/50	12/50	27/50
Pituitary gland adenoma:				
Mice/Female	9/48	12/49	14/47	17/50
Pituitary gland carcinoma:				
Mice/Female	0	0	0	2/50

G. Reproductive Toxicity Studies

These studies have been previously submitted to IND IND NDA 18-154, and NDA 19-501. Reviews for these studies are attached. In summary, minoxidil was administered orally or subcutaneously to rabbits and rats. In a segment I study, oral administration of 0, 3, or 10 mg/kg/day of minoxidil to Sprague-Dawley rats resulted in a dose dependent decrease in conceptions. An increase in fetal resorptions was observed in Dutch Belted rabbits after receiving oral administrations of 3 and 10 mg/kg/day of minoxidil during a Segment II study. No teratogenic findings were noted in either rats or rabbits following oral administrations. Subcutaneous administrations of 80 mg/kg/day or lower to pregnant rats were also not teratogenic. In pregnant rabbits (Japanese White rabbit), no fetotoxicity or teratogenicity was observed after subcutaneous administrations of 49 mg/kg/day or lower. This dose caused maternal toxicity. However, skeletal abnormalities and variations (abnormal thoracic bodies, fusion of vertebral arches, fusion of ribs, hypoplasia or absence of cervical vertebral arch, supernumerary thoracic cerebral arch, or supernumerary ribs), increased embryonic/fetal mortality, and decreased fetal body weights were reported in Wistar rats administered subcutaneously 120 mg/kg/day during a Segment II study. These findings were reconfirmed in animals treated specifically with 120 mg/kg/day during Day 7 to 10 of gestation. However, the 120 mg/kg/day dose caused a statistically significant decrease in maternal body weight gain (4.7% and 8%) beginning at day 13 of gestation for the first study and day 18 of gestation for the second study, respectively. Body weight gain was not decreased in dams treated during gestation day 7-10, 10-13 or 13-15 in the second study. Additionally, emaciation was noted from day 22 of gestation to delivery for both studies.

The dose of 120 mg/kg/day corresponds to approximately 132 times the maximum recommended human dose. This calculation is based on the treatment of a 200 g rat (325 cm² surface area) and a 70 kg individual applying 1 ml of 5% minoxidil twice daily. The rat subcutaneous dose (100% absorption) of 120 mg/kg/day would then equal to 0.0738 mg/cm²/day. The human recommended dose would then equal to 0.00055 mg/cm²/day. However, human absorption is 0.3 to 4.5 percent following a topical application. This would then correspond to an expected exposure of 0.0000247 mg/cm²/day. Thus, an exposure of a 120 mg/kg/day dose in Wistar rats would be 2952 times greater than an expected human exposure while a dose of 80 mg/kg/day would correspond to 1969 times an expected human exposure.

H. Mutagenic Potential

These studies have been previously submitted to IND IND , and NDA 19-501. Reviews for these studies are attached. In summary, minoxidil was not mutagenic in the *Salmonella* microsome assay, DNA damage/alkaline elution assay, unscheduled DNA synthesis (UDS) assay, chromosome aberration assay, or in the bone marrow micronucleus assay. For the in vitro assays, minoxidil concentrations ranged from ug/plate for the *Salmonella* assay, up to 10 mM in the DNA damage assay, up to 100 mg/plate in the UDS assay, and up to 1879 ug/ml in the chromosome aberration assay. The doses for the

micronucleus assays were single administrations of 5, 50, or 150 mg/kg to Sprague-Dawley rats and either a single administration of 250, 500, or 1000 mg/kg, or 4 administrations of 250 mg/kg over a 4 day period to the mouse.

I. Local Tolerance

These studies have been previously submitted to IND NDA 19-501 and NDA 18-154. Reviews for these studies are attached. The potential for minoxidil to elicit a delayed contact sensitization, phototoxic, photoallergic, ocular and dermal irritation, and intramuscular irritation response was evaluated in guinea pigs or rabbits. A 1, 2, or 3% solution of minoxidil in a propylene glycol:ethanol:water vehicle did not elicit a delayed contact sensitization response in Hartley guinea pigs after induction with topical or intradermal administrations. A 2% solution (50 ml) of minoxidil also did not elicit phototoxic or photoallergic responses in male and female guinea pigs. Animals were irradiated with UVA and UVB (290-400 nm) or UVA (340-420 nm) 90 minutes following application of test material. No dermal irritation responses were noted in New Zealand White rabbits following treatment 10, 30, or 50 mg/ml (1%, 3%, or 5%, respectively) of minoxidil in a propylene glycol:ethanol:water vehicle to abraded and intact skin. In addition, no dermal irritation responses were observed in Japanese White rabbits following treatment with 0.1 ml of 1% minoxidil topical solution (in a propylene glycol:ethanol:water vehicle), which had been exposed to sunlight for 6 months. In the intramuscular irritation study, a single 1-ml intramuscular injection of minoxidil (5 mg/ml) in benzyl alcohol:propylene glycol:water was given to Dutch Belted rabbits in the lumbar muscle. The vehicle was moderately irritating while minoxidil did not contribute to the musculoirritant property of the vehicle alone. The vehicle may also be responsible for the ocular irritation reported in minoxidil-treated rabbits. A 1% or 2% solution of minoxidil in propylene glycol:ethanol:water was instilled (0.1 ml) into the right eye while the left eye was untreated. Under the conditions of the assay, the minoxidil solution was classified as a moderate eye irritant. Although the components of the vehicle were shown to cause similar ocular responses (discharge, conjunctival swelling, corneal opacity, and iris hyperemia), instillation of this agent in this vehicle will elicit a moderate ocular irritation response. Rinsing of the eye after treatment will reduce the severity of the reactions.

J. Special Toxicity Studies

These studies have been previously submitted to IND IND and NDA 19-501. Although these studies have been submitted, reviews were not found. These studies will be summarized below. The majority of the studies in this section were conducted in order to better defined the role of hormonally responsive endocrine and reproductive organs. In particular, the tissues from mice treated orally and dermal treated rats in the carcinogenicity studies. The reevaluation of these organs was stimulated by the findings observed (increase in mammary gland tumors, pituitary adenomas, pituitary hyperplasia, and mammary gland hyperplasia) in mice given dermal administrations of 8 to 80 mg/kg/day for 2 years. Tissues

from the oral and dermal carcinogenicity studies were stained or histologically reevaluated (for NDA to confirm the presence of the findings. The results of the reevaluation of the oral carcinogenicity study found a treatment related increase in mammary gland hyperplasia and pituitary gland adenomas. The new numbers of pituitary adenomas reported were 22/60, 37/60, 39/60, and 33/60 in the control, low, mid, and high dose female treated mice, respectively. Although the incidence of pituitary lesions increased, a statistical significance (Fischer's Exact test) was obtained for the low and mid dose groups at $p=0.01$ compared to control and at $p=0.05$ for the high dose compared to control. In the rat tissues reevaluated, an increased incidence of interstitial fibrous connective tissue of the mammary gland was observed in all male and female rats topically treated. However, no mammary adenomas or carcinomas were reported in either gender. Additionally, a significant increase in epithelial development of the seminal vesicle was reported in all treated male rats. Although the incidence of pituitary adenomas/carcinomas was increased in both genders, the incidence was not statistically significant compared to control incidence. The findings reported in the reevaluation of tissues in male and female mice and rats either treated topically or orally may not be consistent with alterations to hormonal environments due to minoxidil treatment as reported by the Sponsor. Hyperplasia of the mammary gland was observed after minoxidil treatment in dermally treated rats and orally treated mice for 2 years. However, corresponding tumor findings were not observed in either study.

Serum and pituitary prolactin levels were determined in female B6C3F1 mice prior to proestrus and after oral administrations of 300 mg/kg minoxidil for 7, 30, and 90 days. Serum prolactin levels, uterine and vaginal weights, and cell activity in these organs all decreased with treatment for 7 to 11 days. However, significant increases in pituitary prolactin concentrations were noted in treated mice. A second 7-day study with mice exhibiting normal estrous cycles resulted in opposite findings. The changes reported in uterine and vaginal weights, serum and pituitary prolactin levels were influenced by the status of the estrous cycle. In a 30-day oral study, minoxidil did not cause hormonal changes in normally cycling (4-6 days) mice. The average serum levels of prolactin for the vehicle and treated (300 mg/kg/day) female mice were 56 ng/ml during diestrus and 53 ng/ml during proestrus for the vehicle treated, and 43 ng/ml during diestrus and 40 ng/ml during proestrus for the minoxidil treated mice.

In a 90-day study, minoxidil (80 mg/kg/day) was topically given to diestrus and proestrus mice. In addition, positive (reserpine; 0.05-1 mg/kg/day, ip) and negative (bromocriptine; 0.2 mg/kg/day, sc) control groups were included. The estrous cycle during the 90 day study for these animals were 4-6 days for the vehicle, minoxidil, and bromocriptine-treated mice, and 8-10 days for the reserpine-treated mice. The pattern of increased and decreased serum prolactin level observed during the study for minoxidil was almost similar to the positive control (Table 5 and Table 6). Decreases in circulating serum prolactin levels are observed during diestrus in minoxidil and reserpine-treated mice. However, serum levels do increase following administration of perphenazine in minoxidil-treated diestrus mice at day 14-20 and day 70-76 of the study, and in reserpine diestrus mice at day 70-76 of the study. During proestrus, circulating levels of serum prolactin do not differ from control in minoxidil treated mice while increases are observed in reserpine-treated

animals. Again, serum prolactin levels do increase following administration of perphenazine in both the minoxidil and reserpine-treated mice. With the administration of perphenazine, differences between control and treated animals are obtained. This would indicate that an increase of prolactin is observed in the pituitary. However, no such increase is noted when the pituitary is examined post-mortem at day 90 (Table 7). Therefore, topical administrations of minoxidil to normally estrous cycling female mice does sporadically increase the pituitary prolactin levels and decrease circulating serum prolactin levels during diestrus.

Other similarities with the positive control include decreases in LH, estrogen, and uterine endometrial gland dilatation. However, only minoxidil increased immunohistochemical staining for pituitary prolactin. Based on the overall findings, the Sponsor concluded that minoxidil may have induced mammary tumors in mice (chronically treated) by hormonal mechanisms similar to those previously reported for reserpine. However, the hypothesis of a hormonal mechanism for the induction of mammary tumors remains equivocal. Induction of prolactin levels in female mice orally treated with minoxidil was not confirmed. Thus, a comparison of the two routes can not be determined.

Other studies were conducted to determine the effect of blood collection methods and light/dark cycle on the serum prolactin levels in female B6C3F1 mice. Serum prolactin levels were 3 to 4 fold increased following blood collection via the orbital plexus versus decapitation. This suggests that the orbital puncture method induced a stress related increase in prolactin levels. Additionally, peak prolactin secretion in the female mouse occurs on the afternoon or evening of proestrus and diestrus levels are higher than the proestrus levels.

Table 5. Serum prolactin levels (ng/ml) in female mice in diestrus and topically treated with minoxidil (80 mg/kg/day).

Treatment	Base	Pre-Per* Day 14-20	Post-Per Day 14-20	Pre-Per Day 70-76	Post-Per Day 70-76	Day 90-96
Untreated Control	78.54	117.63	311.67	113.50	331.67	106.03
Vehicle Control	89.21	119.11	289.86	102.27	358.82	114.84
Bromocryptine	57.57	14.03 [‡]	6.21 [‡]	16.32 [‡]	28.00 [‡]	51.68 [‡]
Reserpine	96.55	134.45	265.89	30.27 [‡]	572.80 [‡]	67.18 [‡]
Minoxidil	93.32	84.48	377.20 ^{††}	69.19 [‡]	372.14 [‡]	85.27 [†]

*- Perphenazine (1 mg/kg; ip) was administered to release most of the pituitary stores of prolactin in order to assess total stored prolactin levels in the pituitary.

[‡]- A statistical significance of $p < 0.05$ (Ranks of Observations) was obtained when compared to the untreated control.

[†]- A statistical significance of $p < 0.05$ (Ranks of Observations) was obtained when compared to the vehicle control.

Table 6. Serum prolactin levels (ng/ml) in female mice in proestrus and topically treated with minoxidil (80 mg/kg/day).

Treatment	Base	Pre-Per* Day 14-20	Post-Per Day 14-20	Pre-Per Day 70-76	Post-Per Day 70-76	Day 90- 96
Untreated Control	38.38	48.10	280.07	15.41	360.87	40.08
Vehicle Control	34.39	62.35	354.54	18.00	324.14	33.63
Bromocryptine	43.32	9.76 [‡]	20.50 [‡]	7.44	31.42 [‡]	29.42 [‡]
Reserpine	62.27	220.00 [‡]	364.00	59.07 [‡]	766.40 [‡]	103.28 [‡]
Minoxidil	48.82	45.44	337.60	21.98	430.69 ^{††}	46.32 [†]

*- Perphenazine (1 mg/kg; ip) was administered to release most of the pituitary stores of prolactin in order to assess total stored prolactin levels in the pituitary.

[‡]- A statistical significance of $p < 0.05$ was obtained when compared to the untreated control.

[†]- A statistical significance of $p < 0.05$ was obtained when compared to the vehicle control.

Table 7. Pituitary prolactin levels in female mice during diestrus or proestrus following a topical treatment of minoxidil (80 mg/kg/day) for 90 days.

Treatment	Diestrus (ug/mg)	Proestrus (ug/mg)	Diestrus Stained (%)	Proestrus Stained (%)
Untreated Control	6.59	8.41	ND	ND
Vehicle Control	6.44	8.15	7.56	8.06
Bromocryptine	6.07	7.39 [‡]	5.52	9.43
Reserpine	6.29 [‡]	6.66 [‡]	8.66	8.93
Minoxidil	5.50	8.04	11.16 [†]	10.83 [†]

[‡]- A statistical significance of $p < 0.05$ was obtained when compared to the untreated control.

[†]- A statistical significance of $p < 0.05$ was obtained when compared to the vehicle control.

The potential for minoxidil to have estrogenic activity after oral and topical administrations was also examined in ovariectomized female mice. The ability of minoxidil and six metabolites to compete with [3H]-estradiol binding to the receptor site was first examined in vitro. Only two metabolites had weak activity ($K_i = 0.8-3$ mM). Minoxidil had a weaker, non-clinically relevant activity ($K_i = 20$ mM). Similar results were obtained in vivo. Ovariectomized B6C3F1 female mice received 300 mg/kg/day orally for 7 days or 80 mg/kg/day topically for 7 days with or without diethylstilbestrol (0.01-1.0 ug/mouse). No

increases in weight were observed in the uterus or vagina of the minoxidil-treated animals.

The effect of topical minoxidil on the levels of plasma prolactin (Prl) and other hormones (FSH, LH, T, and MSH) were examined in the male B6C3F1 mouse and male Fischer 344 rats. Minoxidil-5% (80 mg/kg/day, top), reserpine (0.1 mg/kg/day; ip), or bromocryptine (10 mg/kg/day; sc) were administered for 90 days. In blood collected via retro-orbital punctures on Day 45 and 85 and via decapitation on termination from mice, pituitary prolactin levels, FSH, and liver weights were increased with minoxidil and reserpine treatment. However, prolactin levels were not increased at every time period nor had a similar pattern as reserpine (Table 8). Increases in circulating levels of prolactin (143.7%, 280.3%, and 127.2%) were observed in animals treated with reserpine at day 45, 85 and 90, respectively. In minoxidil-treated male mice, no changes were reported for the same time period. Following perphenazine injection, male mice treated with reserpine had non-statistically significant increases on day 45 (10%) and 85 (10%), while minoxidil-treated mice had a statistically significant increase on day 45 (20%) and a non-statistically significant increase on day 85 (16%). In the bromocryptine-treated animals, statistically significant decreases were reported at all time periods. Unlike minoxidil, reserpine and bromocryptine statistically significantly decreased FSH. Only reserpine treatment decreased (85%) the levels of MSH. Finally, no differences in LH and testosterone plasma levels were noted by all three treatments.

Table 8. Serum prolactin levels (ng/ml) in male mice topically treated with minoxidil (80 mg/kg/day).

Treatment	Pre-Per* Day 45	Post-Per Day 45	Pre-Per Day 85	Post-Per Day 85	Day 90
Vehicle Control	14.69	74.73	12.84	61.95	6.47
Bromocryptine	6.01 [‡]	12.41 [‡]	5.65 [‡]	8.94 [‡]	8.01 [‡]
Reserpine	35.67 [‡]	82.30	48.83 [‡]	69.20	14.62 [‡]
Minoxidil	13.73	89.83 [‡]	13.23	72.19	5.52

*- Perphenazine (1 mg/kg; ip) was administered to release most of the pituitary stores of prolactin in order to assess total stored prolactin levels in the pituitary.

[‡]- A statistical significance of $p < 0.05$ (Least Square Difference or Ranks of Observations) was obtained when compared to the untreated control.

Histologically, both minoxidil and reserpine caused a dilatation of secretory ducts and decreased glandular cell activity of the coagulating gland of male mice. Minoxidil treatment also caused an increase in glandular vacuolation of the preputial gland and increased activity of the epithelial cell activity in the epididymis.

In blood obtained from rats via identical method as mice, the levels of Prl and MSH

were decreased and LH was increased in minoxidil-treated animals. The decreases in plasma prolactin levels were statistically significant at 30.8%, 25.1%, and 41.2% on day 45, 85, and 90, respectively. Following perphenazine injection, the prolactin levels in minoxidil and bromocryptine-treated male rats were statistically significantly decreased at day 45 and 85, respectively. Minoxidil treatment to rats also caused a decrease in testicular weight, decrease in vacuolation of the adrenal cortex, and increased liver weight. Reserpine treatment also caused a decrease in testicular weight, but caused an increase in pituitary Prl levels only on day 45 following perphenazine injection, vacuolation of the adrenal cortex, and secretion of the preputial gland and mammary gland. Bromocryptine had similar effects on both species (decreased serum prolactin, reduced preputial gland weight, and decreased morphological evidence of secretory activity).

The effect of minoxidil on serum Prl levels was re-examined in the male rat. Fischer 344 male rats were topically treated with either vehicle or 5% minoxidil (80 mg/kg/day) for 90 days. On day 83, each rat was implanted with a jugular cannula. Five minutes after the last dose on day 90, blood samples (200 ul/sample) were collected at 5-minute intervals for 6 hours. A mixture of suspended washed blood cells collected from age and sex matched donor rats in a steroid-free 5% human plasma protein fraction was infused following each sample collection. Serum prolactin levels were increased as indicated by the increases in mean Prl pulse duration (38%), mean duration of ascending phase of the Prl pulse (56%), mean AUC of Prl pulses (53%), mean number of pulses/6 hour (26%), and mean duration of descending phase of the Prl pulse (28%). Statistical significance was observed in the mean ascending phase of the prolactin pulse and pulse duration. Associated changes reported were liver and seminal weight increases, testis and dorsal prostate weight decreases, decreased secretion of the coagulating gland, vacuolation of the liver, glandular degeneration of the mammary gland, increased activity of the mammary gland and pituitary chromophobe cell, and increased secretion of the dorsal prostate. No effect on FSH secretion was observed and the effect on LH secretion was uncertain due to technical considerations.

In summary, male and female mice topically treated with 5% minoxidil (80 mg/kg/day) for 90 days had equivocal increases in pituitary prolactin levels. An increase in prolactin due to minoxidil treatment was highly dependent on stage of estrus, sampling time and method, and day of sampling. Some histological changes such as decreased secretion of the coagulating gland, vacuolation of the liver, glandular degeneration of the mammary gland, increased activity of the mammary gland and pituitary chromophobe cell, and increased secretion of the dorsal prostate were reported to be associated with changes in the prolactin increase. Based on these findings, the Sponsor concluded that minoxidil may have induced mammary tumors in mice by hormonal mechanisms after being chronically treated. Additionally, estrogenic activity was not observed in ovariectomized female mice treated with 5% minoxidil (80 mg/kg/day) for 7 days. However, the observations noted for rats regarding prolactin increase are contradictory. The results of the 90-day studies varied due to sampling method. No increase in prolactin is observed following blood sampling via the orbital plexus while an increase in various markers were noted following blood sampling via an implanted jugular cannula. Although in previous studies to determine the effect of sampling method revealed a increase in prolactin levels in samples collected via the orbital plexus, the stress-

induced levels of the control animals may have masked any increases in prolactin in animals treated with minoxidil.

Comments

Administration of minoxidil can reduce mean arterial pressure by relaxing the arteriolar resistance vessels. The decrease in blood pressure is accompanied by a reflex mediated increase in cardiac output and heart rate. In addition, administration of minoxidil results in retention of electrolytes and renal tubular water, which increases plasma volume and interstitial fluid volume. The pharmacologic properties of minoxidil lead to the pathological changes in the heart of all treated species (dogs, rats, mice, and monkeys). Whether the effect is caused by indirect mechanisms or direct cardiocytotoxicity, the final outcome is due to the exposure of minoxidil.

Both oral and dermal applications will cause either hemorrhagic lesions, coronary arteritis (small vessels), papillary muscle and ventricular subendocardial necrosis, cardiac dilatation and hypertrophy, and epicarditis. These nonclinical findings have been reviewed by the Division of Cardio-Renal Drug Products. As reported by the Division of Cardio-Renal Drug Products, the cardiac findings in the treated animals occur "only in the context of profound hypotension and tachycardia of one day or more duration with minoxidil".

In order to achieve the hypotension and tachycardia, the material must be absorbed after exposure to the drug product. Absorption of minoxidil after topical administration ranged from 17% to 50% of the applied dose for monkeys, rats, mice, and dogs. In humans, 0.5-4% of the applied dose was reported in the plasma. However, a dose-response relationship does not exist for serum minoxidil concentration. A concentration of 10 mg/ml applied to Sprague-Dawley rats twice a day for 1 year, which did not result in an observable adverse effect, had a corresponding serum level at the end of the study of 34.2 ng/ml. However, a 30 mg/ml concentration applied under similar conditions resulted in a serum level of 253.4 ng/ml, which did correspond to an adverse effect. This discrepancy may be due to the protocol design of the study. Although doses of 10, 30, and 50 mg/ml were applied twice daily for 1 year, the 1 ml application of test material was obtained from stock test material of differing concentrations (i.e., 1%, 3%, and 5%). Absorption of minoxidil or any other compound is dependent on the concentration of material, duration of exposure, and other factors. Since the Sponsor employed various stock concentrations of test material, this difference may be the cause for the lack of dose dependent increases in serum concentration.

Still, in order for the pharmacologic effects of minoxidil to occur, critical levels of minoxidil must be observed in the serum. Thus, many of the pharmacological effects reported in animals may not be observed in humans. As discussed in previous pharmacology/toxicology reviews, identifying cardiovascular changes in hypertensive humans receiving oral minoxidil has been very difficult.

In addition to the cardiovascular changes observed in treated animals, neoplastic lesions were also observed in the initial studies. Oral administration of minoxidil resulted in malignant lymphomas in female mice at all doses tested and hepatic nodules in male mice given 63 mg/kg/day. No findings were reported in rats receiving oral dietary administrations of

minoxidil. In the dermal studies, adrenal pheochromocytomas were observed in both male and female rats receiving 8, 25, and 80 mg/kg/day. Preputial gland adenomas in male rats were also reported in all treated animals. Mice administered minoxidil topically had increased incidences of hepatocellular adenomas/carcinomas, pituitary gland adenoma/carcinoma, and mammary gland adenomas/carcinomas. However, the pituitary adenomas/carcinomas and hepatocellular adenomas/carcinomas were determined not to be statistically significant because statistical significance was not obtained when the same type of tumors in the concurrent (vehicle treated) controls were greater than 1%. A p value of 0.01 was the cut-off in 1988. [The current cut-off is 0.005].

In addition to the hepatic nodules reported in the male mice receiving oral minoxidil for 2 years, a statistically significant increase in the incidence of hemangiosarcomas was observed. In Dr. De Witt's review, the combination of both hemangiosarcomas and hemangiomas for this group was not included. Upon reviewing the incidence of hemangiosarcomas and hemangiomas (8/60, 6/60, 7/60, and 13/60 in the control, low, mid, and high dose animals, respectively), a statistical significance would not be observed. Therefore, these findings should not be incorporated into the label. Additionally, p value levels for statistical significance have been modified since the approval of Loniten and Rogaine 2%. As mentioned earlier, the 1988 criteria for statistical significance was a p value of 0.05 for pairwise comparison and 0.01 for common tumors in the trend test. The current (1997) p values for statistical significance is 0.005 for common tumors in the trend test and 0.025 for the pairwise comparison. Thus, the statistical significance observed in Dr. De Witt's review (4/9/90) would not meet the current criteria for statistical significance and the hemangiosarcoma/hemangioma lesions reported in male mice should not be incorporated in the current labels for Loniten, Rogaine 2%, or Rogaine 5%.

In regards to the mammary tumors observed in the mice treated topically, the Sponsor has concluded that "the higher level of exposure received by animals in the topical carcinogenicity studies compared to the oral carcinogenicity study provides a rational explanation for the positive carcinogenicity results in the topical studies compared to the negative results in the oral study". In a study to determine the bioavailability of minoxidil via three different routes in the female B6C3F1 mice, a increase in C_{max} (12.76 vs 0.28 ug/ml) was obtained in mice receiving topical minoxidil (80 mg/kg/day) compared to drug-in-diet (63 mg/kg/day). In addition, a 3-fold increase in C_{av} (0.35 vs 0.12 ug/ml) was reported for the two groups. This difference in systemic exposure occurred even though the actual dose of minoxidil consumed in the drug-in-diet route was approximately 1.5 times higher than the topical route. Compared to the oral gavage route, a higher peak serum concentration was reported in mice treated topically.

The higher levels of minoxidil in female mice following topical absorption may be a rational explanation for the lack of tumors in the orally treated mice. However, the difference in systemic exposure between topically treated mice and topically treated rats is not as significant. Therefore, the incidence of tumors reported in topically treated rats should have been similar to the findings observed in the mice. Especially if, as proposed by the Sponsor, the mechanism for the observed tumors is an induction of prolactin levels. Changes in serum prolactin or pituitary prolactin levels will depend on the time of analysis, cycle of estrus,

several environmental conditions, route of drug administration, and length of administration. In the studies conducted by the Sponsor to ascertain the involvement of prolactin, no similarities were observed between minoxidil and reserpine, a positive control, in the potential to increase serum prolactin levels. Prolactin levels were increased in the pituitary at several time periods in topically minoxidil-treated male and female mice. However, the Sponsor did not provide data as to the effect of minoxidil on prolactin levels in the female rat. These data would be instrumental in determining whether the lack of mammary tumors in the female rats was really due to a lack in serum prolactin increase.

The role of minoxidil in increasing the levels of prolactin should be re-evaluated in male and female rats and mice. As proposed by the Sponsor in the second male rat 90-day study, stressful conditions resulting from sample collection procedures can markedly affect prolactin secretion. Jugular cannulation provides more consistent results as a sampling method than using the orbital plexus method. Additionally, blood sampling via cannulation resulted in drug-related findings of increased circulating prolactin at the end of the study. All other previous studies which sampled via the orbital plexus did not find an increase in prolactin at study termination (Day 90). The used of a positive control, reserpine, would also provide a valuable comparison in the evaluation of the new studies.

A concern with drug products chronically administered topically to areas of the body exposed to solar radiation is the potential of the drug product to enhance UV carcinogenesis. Minoxidil applied topically to hairless mice that were irradiated with solar simulated radiation did not promote either papillomas or carcinomas initiated by UV and did not afford any photoprotection to the hairless mice under these test conditions. Additionally, no photosensitization reactions were observed in rabbits treated with minoxidil (2%) and irradiated with solar simulated radiation. Phototoxic reactions were also not reported in 10 human subjects treated with minoxidil (5%) and irradiated with UVA. Although minoxidil did not elicit a phototoxic reaction in rabbits or man nor enhance UV carcinogenesis, human photosensitivity reactions have been reported for the 2% minoxidil product. Human photosensitivity reactions have been reported as part of the FDA's Spontaneous Reporting System (SRS) for topically administered minoxidil products (Rogaine 2%). Roger Goetsch of the Division of Pharmacovigilance and Epidemiology examined the number of sensitization reports for minoxidil. Between 1983 and May 13, 1997, the FDA has received 16,829 reports with topical minoxidil. Sensitization was reported 4096 times (25%). Of the sensitization reports, 21 reported a serious outcome; 1 of these serious reports was a death. Included in the sensitization reports were 40 reports of photosensitivity. The Sponsor is recommended to include a statement in the label warning product users to avoid solar exposure.

Conclusion: From a pharmacological standpoint, this NDA is approvable.

Recommendations:

1. The Sponsor is recommended to reevaluate the role of minoxidil in prolactin secretion in the male and female mouse and rat.

2. The Sponsor is recommended to include in the label of this product that the material is a potential sensitizer and photosensitizer.

Label:

A warning should be placed in the label which advises potential users of this product to avoid solar exposure. Additionally, the label contains a couple of misleading statements which need to be corrected. The statements are: the only product for hair growth. Rogaine 5% Extra Strength is not the only hair growth product available to the public.

5/20/97

Javier Avalos, Ph.D.
Toxicologist

cc:

HFD-540
HFD-540/Pharm/Jacobs
HFD-540/Pharm/Avalos
HFD-540/CSO/Anderson
HFD-540/MO/Huene
HFD-540/Chem/Higgins

For Concurrence Only:

HFD-540/DD/JWilkin
HFD-540/Team Leader/Jacobs 5/20/97
HFD-540 [signature] 11/1/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-834

STATISTICAL REVIEW(S)

CLINICAL/STATISTICAL REVIEW AND EVALUATION

JUN 20 1997

NDA/Drug Class: 20-834

APPLICANT: The Upjohn Company

NAME OF DRUG: Rogaine Extra Strength for Men
(Minoxidil topical solution 5%)

INDICATION(S): Androgenetic Alopecia in Males and Females

TYPE OF REVIEW: Clinical/Statistical

DOCUMENTS REVIEWED: Volumes 1.1, 1.2, 1.181-1.280,
Study# M/7415/0001 & Study# M/7410/0285

CLINICAL INPUT: Dated December 22, 1995
Phillis Huene, M.D. (HFD 540)

I. INTRODUCTION

Rogaine Topical Solution 2% (2% minoxidil solution) was the first drug approved for the treatment of male pattern baldness in the United States in 1988 and for androgenetic alopecia in females in 1991. The sponsor claims that data from clinical studies that included minoxidil concentrations greater than 2% suggested that, dosing modifications (ie, applying higher concentrations of topical minoxidil solution) may enhance the therapeutic efficacy, which is the purpose of this new drug application.

The sponsor intends to demonstrate the safety and superiority of 5% Rogaine to 2% Rogaine and Placebo. The sponsor has submitted the results of two studies (studies M/7415/0001 and M/7410/0285) which are the basis for the approval of the new drug application of Rogaine Extra Strength for Men for the treatment of androgenetic alopecia to be approved for OTC purposes.

Study M/7415/0001 has used hair count as the sole primary endpoint to demonstrate the efficacy of Regain 5, whereas, study M/7410/0285 provides questionnaires to assess the satisfaction of the patients and global assessment of the investigator, in addition to hair count (total of three endpoints).

The FDA requires two **independent**, randomized, adequate and well-controlled, double blind, **multi center** studies for its approval. However, it was observed that study M/7415/0001 is a one center trial. Moreover, it was noted that a few of the investigators participated in more than one trial. In particular, center# 11917 participated in studies

M/7415/0001 and M/7410/0285 which are both male studies. These violations make the validity of these trials questionable. To resolve these problems in a certain extent, one of the centers which was in common in both studies was eliminated from study M/7410/0285 (n=100).

The table below summarizes the studies under review.

Table I, Overview of Pivotal Studies

Study #	Study Design	Treatment (n)	N	Treatment Duration	Endpoints	# of Centers
M/7415/0001 (Male)	Double Blind, PBO/Controlled	PBO (85) 2% (86) 5% (174)	345	32 Weeks	Hair Count	1
M/7410/0285 (Male)	Double Blind, PBO/Controlled	PBO (78) 2% (158) 5% (157)	393	48 Weeks	Hair Count Patient Questionnaire Investigator Questionnaire	6

In order to gain approval for the new formulation, the sponsor should show statistical superiority of the following: 1) Rogaine 5% to placebo, and 2) Rogaine 5% to Rogaine 2% at a two-sided, 5% significance level. The sponsor has performed Analysis of Variance test in their data analyses.

The main focus of this review is on patient's hair growth at the end of the treatment period on the evaluable population.

For study M/7410/0285 two different approaches were made. First, the analyses were performed on the data set based on all randomized subjects whose end of treatment hair count was available. This data set will be referred to as FDA-Evaluable (FDA_Eval) data. Second, in order to maintain the integrity of the randomization, an intent-to-treat analysis was done. For the subjects who did not finish the 48-week treatment, the baseline hair count value was carried forward to replace their missing week 48 hair count value. In other words, subjects with missing hair count at the end of 48 weeks will show no change from the baseline. Because of the non-linearity of the hair count distribution throughout the 48 weeks, we found it inappropriate to attempt to carry the last observation forward.

II. REVIEW OF STUDIES, **EFFICACY**

Study No. M/7415/0001 (Male):

Objectives, Design, Patient Enrollment and Statistical Methods:

The objective of this study was to evaluate the safety and efficacy of 5% Topical Minoxidil Solution (TMS) for the treatment of androgenetic alopecia and to compare results with those obtained with Rogaine Topical Solution 2% and PBO (vehicle for 5% solution) after thirty-two weeks of treatment in males.

This was a 32-week, double-blind, single-center, parallel design, phase III study of male patients with androgenetic alopecia. Patients were randomly assigned (approximately 2:1:1 ratio) to 5% TMS, 2% TMS and Placebo. Patients were instructed to apply 1.0 ml of the test solution to the affected area twice daily, 12 hours apart.

The primary endpoint for this study was nonvellus hair counts.

A total of three hundred and forty-five otherwise healthy male patients with androgenetic alopecia were randomly assigned to 5% TMS (n=174), 2% TMS (n=86), and placebo (n=85). Three hundred and twenty-one patients completed the entire 32 week study period.

A one-way analysis of variance statistical methodology was used to look at the difference among the three treatment groups in the primary endpoint variable, change in hair growth. The sponsor has used protected LSD (least significant difference) test for pairwise comparisons of the three treatment groups. In this review both the LSD method and the contrast method were used.

Evaluable Subjects:

A total of twenty-four subjects did not complete the 32-week treatment. Eleven (6%) of these patients had been assigned to the 5% TMS, 7 (8%) to the 2% TMS and 6 (7%) to the placebo arm. These subjects were eliminated from the analysis of efficacy.

Baseline Comparability:

The distribution of demographic and baseline characteristics were not statistically different among all three treatment groups. The FDA requires a multi-center studies for its approval. This was a single center study. For this reason there might be some potential bias in this trial. The demographic and baseline information are summarized in table II below:

**Table II
Demographics and Baseline Characteristics of All Randomized Subjects
M/7415/0001 (Male)**

	Whole Population (N=345)	5% TMS (n=174, 50%)	2% TMS (n=86, 25%)	Placebo (n=85, 25%)	P-Value
Age (Mean):	35	35	35	36	0.58
Race (n):					0.57
White	314 (91%)	157 (90%)	78 (91%)	79 (93%)	
Hispanic	24 (7%)	14 (8%)	5 (6%)	5 (6%)	
Black	2 (0.6%)	1 (0.6%)	1 (1%)	0 (0%)	
Oriental	1 (0.3%)	0 (0%)	0 (0%)	1 (1%)	
Other	4 (1%)	2 (1%)	2 (2%)	0 (0%)	
Baseline Hair Count (Mean):	105	107	103	105	0.80
Years of Hair Loss (Mean):	8	8	7	7	0.28
Duration of Hair Loss Category (n):					0.08
1 to <3	35 (10%)	20 (11%)	9 (10%)	6 (7%)	
3 to <5	60 (17%)	24 (14%)	20 (23%)	16 (19%)	
5 to < 10	144 (42%)	72 (41%)	29 (34%)	43 (51%)	
10 to < 15	69 (20%)	36 (21%)	23 (27%)	10 (12%)	
15 to <20	19 (6%)	9 (5%)	4 (5%)	6 (7%)	
>= 20	18 (5%)	13 (7%)	1 (1%)	4 (5%)	

Efficacy Analysis:

A total of 42 subjects lost hair in the 32-week study period.

**Table III
Subjects with decrease hair count among three treatment groups
M/7415/0001 (Male)**

Treatment	n	Mean (hair loss)	Range (hair loss)
5% TMS	7	17	
2% TMS	8	8	
Placebo	26	10	

Hair loss at the end of the study was not statistically different among the three treatment groups ($p > 0.2$). (These results should be interpreted with caution, since the sample size being used is too small).

The table IV lists the mean hair count at baseline and mean hair count at week-16, week-32 and the mean changes for each treatment group.

Table IV
Comparison of change in hair count by treatment group (FDA_Eval)
M/7415/0001 (Male)

	5% TMS (Mean)	2% TMS (Mean)	Placebo (Mean)	P-Value (5% vs. 2% vs. PBO)	P-Value (5% vs. 2%)
Week_0	107	103	105	0.80	0.52
Week_16	142	129	110	0.0001	0.03
Week_32	145	133	110	0.0001	0.06*
Week_16 - Week_0	36	26	5	0.0001	0.002
Week_32 - Week_16	3	4	1	0.55	0.54
Week_32 - Week_0	39	30	5	0.0001	0.006

* At week 32, the average hair count is not statistically different between 5% and 2% solutions.

The mean change hair count from baseline to the end of the 32-week period was still statistically significant when the results were adjusted for age, baseline hair count and years of hair loss among the three treatment groups, $p < .001$; pairwise comparison between 5%TMS vs. 2%TMS, yielded $p < .05$.

Conclusions:

The results of the male study, M/7415/0001 indicated a strong statistical superiority of 5% Rogaine to 2% Rogaine and placebo relative to hair growth in males ($p = .001$) after 32-weeks treatment period.

Study No. M/7410/0285 (Male):

Objectives, Design, Patient Enrollment and Statistical Methods:

The purpose of this study was to determine the safety and efficacy of 5% Topical Minoxidil Solution (TMS) for the treatment of androgenetic alopecia and to compare results with those obtained with Rogaine Topical Solution 2% and PBO (vehicle for 5% solution) after forty-eight weeks of treatment in males.

This was a 48-week, double-blind, randomized, placebo controlled, six-center, parallel design, phase III study of male patients with androgenetic alopecia. Patients were randomly assigned (approximately 2:2:1 ratio) to 5% TMS, 2% TMS and Placebo. Patients were instructed to apply 1.0 ml of the test solution to the affected area twice daily, 12 hours apart.

This study was designed to evaluate the nonvellus hair counts and also density ratings questionnaires from both the patient and investigator perspectives. The sponsor has selected three primary endpoints for the final results. These were: 1) Change in nonvellus hair count, 2) Change in scalp coverage (from the patient questionnaire), 3) Benefit from treatment (patient questionnaire). In this review, also three primary endpoints have been analyzed. However, instead of the 'Benefit from treatment, from the patient questionnaire', 'Change in scalp coverage from baseline from the investigator questionnaire' was chosen by the medical officer as the third primary endpoint. In order to gain approval, the sponsor should show statistical significance for all three primary endpoints, at a significance level of 0.05.

A total of 393 otherwise healthy male patients with androgenetic alopecia were randomly assigned to 5% TMS (n=157), 2% TMS (n=158), and placebo (n=78). Of these, a total of 346 subjects completed the entire 48 week.

A one-way analysis of variance statistical methodology was used to look at the difference among the three treatment groups in the primary endpoint variables, change in hair growth. The sponsor has performed a protected LSD (least significant difference) test for pairwise comparisons of the three treatment groups. In this review both the LSD method and the contrast method were used, but only the results from the contrast procedure will be reported. Questionnaire variables from visual analog scale, change in scalp coverage according to the patient and change in scalp coverage according to the investigator, were also treated as continuous variables and analyzed in the same manner.

Sample Size:

As was mentioned before in the introduction section, this study and study M/7415/0001 had investigator # 11917 in common. To maintain the independence of these two trials, this center was eliminated from the analysis of this study. A total of 100 subjects had been enrolled to this center. The entire population were removed from the data set. Therefore,

the number of subjects decreased from 393 to 293. This reduces the power of the study. Hence, the results of this trial should be interpreted with caution, since the analysis might not have enough statistical power.

Evaluable Subjects:

A total of thirty-five (12%) subjects did not complete their 48-week treatment. Of these, 14 (12%) had been assigned to the 5% TMS, 16 (14%) to the 2% TMS and 5 (9%) to the placebo arm. All of these patients were excluded from the 48-week FDA_Evaluable data for the purpose of efficacy analysis.

Baseline Comparability:

Eliminating center 11917 did not change the distribution of demographic and baseline characteristics among the three treatment groups. The demographic and baseline information are summarized in table IX:

**Table IX
Demographics and Baseline Characteristics of All Randomized Subjects
M/7410/0285 (Male)**

	Whole Population (N=293)	5% TMS (n=117, 40%)	2% TMS (n=118, 40%)	Placebo (n=58, 20%)	P-Value
Age (Mean):	37	36	37	37	0.56
Race (n):					0.09
White	230 (79%)	86 (74%)	97 (82%)	47 (81%)	
Hispanic	52 (18%)	27 (23%)	17 (14%)	8 (14%)	
Black	5 (2%)	1 (0.9%)	4 (3%)	0 (0%)	
Oriental	3 (1%)	2 (2%)	0 (0%)	1 (2%)	
Other	3 (1%)	1 (0.9%)	0 (0%)	2 (3%)	
Baseline Hair Count (Mean):	150	149	148	156	0.53
Years of Hair Loss (Mean):	10	10	10	10	0.95
Duration of Hair Loss Category (n):					0.59
1 to <3	11 (4%)	3 (3%)	4 (3%)	4 (7%)	
3 to <5	35 (12%)	15 (13%)	15 (13%)	5 (9%)	
5 to <10	101 (34%)	42 (36%)	42 (36%)	17 (29%)	
10 to <15	76 (26%)	32 (27%)	25 (21%)	19 (33%)	
15 to <20	44 (15%)	14 (12%)	23 (19%)	7 (12%)	
>= 20	26 (9%)	11 (9%)	9 (8%)	6 (10%)	
Investigator:					1.0
9225	55 (19%)	22 (19%)	22 (19%)	11 (19%)	
9677	60 (20%)	24 (21%)	24 (20%)	12 (21%)	
10225	62 (21%)	25 (21%)	25 (21%)	12 (21%)	
13470	55 (19%)	22 (19%)	22 (19%)	11 (19%)	
13471	61 (21%)	24 (21%)	25 (21%)	12 (21%)	

Efficacy Analysis:

1. Hair Count:

A total of 46 subjects lost hair in the 32-week study period.

**Table X
Subjects with decrease hair count at week 32 among three treatment groups
M/7410/0285 (Male)**

Treatment	n	Mean (hair loss)	Range (hair loss)
5% TMS	12	11	
2% TMS	19	11	
Placebo	15	11	

The mean hair loss at the end of the 32 weeks was not statistically different among the three treatment groups ($p>0.99$). (These results should be interpreted with caution, since the sample size being used is too small).

A total of 80 subjects lost hair in the 48-week study period.

**Table XI
Subjects with decrease hair count at week 48 among three treatment groups
M/7410/0285 (Male)**

Treatment	n	Mean (hair loss)	Range (hair loss)
5% TMS	28	12	
2% TMS	26	14	
Placebo	26	17	

Hair loss at the end of the 48 weeks was not statistically different among the three treatment groups ($p>0.4$).

Table XII illustrates the mean hair count at baseline and mean hair count at week-16, week-32, week-48 and the mean changes for each treatment group based on FDA_Evaluable subjects. This data represents subjects whose week 48 hair count was available (n=258). This approach interfered with the randomization scheme. The distribution of race was statistically different after removing non-compliant patients from the analysis ($p=.03$).

Table XII
Comparison of change in hair count by treatment group (FDA_Eval)
M/7410/0285 (Male)

	5% TMS (n=103) (Mean)	2% TMS (n=102) (Mean)	Placebo (n=53) (Mean)	P-Value (5% vs. 2% vs. PBO)	P-Value (5% vs. 2%)
Week_0	150	145	154	0.5	0.4
Week_16	183	173	166	0.09	0.1
Week_32	179	167	161	0.04	0.06
Week_48	166	155	155	0.18	0.1
Week_16 - Week_0	33	27	12	0.0001	0.06
Week_32 - Week_16	-4	-5	-5	0.8	0.5
Week_48 - Week_32	-13	-12	-6	0.09	0.6
Week_32 - Week_0	30	22	7	0.0001	0.02
Week_48 - Week_0	17	10	1	0.0004	0.04

From table XII, it is seen that the mean hair growth for the 5% Rogaine group and the 2% Rogaine group are not statistically different, at week_16 ($p=0.1$), week_32 ($p=0.06$), and week_48 ($p=0.1$).

The mean in change hair count from baseline, however, was highly statistically significant among the three arms at week_32 and week_48 ($p<0.001$) and statistically significant at point 0.05 between the 5% and 2% groups.

Adjusting for age yielded to a border-line significance between the 5% and 2% solutions ($p>.06$).

In order to sustain the integrity of randomization, the baseline hair count value was carried forward for subject whose week 48 hair count was missing. This translates to no change in hair growth at week 48 for these subjects ($n=293$).

Table XIII shows the comparison of change in hair count by treatment group for the Intent-to-Treat population:

Table XIII
Comparison of change in hair count by treatment group (Intent - to - Treat)
M/7410/0285 (Male)

	5% TMS (n=117) (Mean)	2% TMS (n=118) (Mean)	Placebo (n=58) (Mean)	P-Value (5% vs. 2% vs. PBO)	P-Value (5% vs. 2%)
Week_0	149	148	156	0.5	0.9
Week_16	180	174	167	0.3	0.3
Week_32	179	166	161	0.05	0.06
Week_48	163	156	157	0.5	0.3
Week_16 - Week_0	33	27	13	0.0001	0.1
Week_32 - Week_16	-4	-6	-5	0.8	0.5
Week_48 - Week_32	-13	-12	-6	0.09	0.7
Week_32 - Week_0	29	21	7	0.0001	0.01
Week_48 - Week_0	15	9	1	0.0006	0.04

As can be seen from the tables XII and XIII, the results of the intent-to-treat analysis are not different from the results presented for evaluable subjects.

2. Change in Scalp Coverage Since Baseline. (Patient Questionnaire):

A total of 275 subjects, 112 (96%) in 5% TMS group, 109 (92%) in 2% TMS group and 54 (93%) in placebo group responded to the questionnaire regarding change in their scalp coverage at the 48th week since baseline. Each patient rated this change in scalp coverage from 0 to 100. An analysis of variance test was performed to compare these ratings.

Table XIV shows the means of change in scalp coverage at week 48 from baseline, based on the patients' questionnaires:

**Table XIV
Comparison of Change in Scalp Coverage at Week 48 from Baseline
According to the Patients
M/7410/0285 (Male)**

	5% TMS (n=112) (Mean)	2% TMS (n=109) (Mean)	Placebo (n=54) (Mean)	P-Value (5% vs. 2% vs. PBO)	P-Value (5% vs. 2%)
Change in 48th Week from Baseline	62	57	52	0.0001	0.01

Patients in the 5% TMS group were satisfied with their scalp coverage more than the other treatment groups at the end of the treatment.

3. Change in Scalp Coverage Since Baseline, (Investigator Questionnaire):

A total of 365 responses were collected from the investigators regarding the change in scalp coverage of the subjects at the 48th week since baseline. Of these responses 147 (94%) were in 5% TMS group, 146 (92%) in 2% TMS group and 72 (92%) in placebo group. Each investigator rated the current scalp coverage. The change in scalp coverage was then calculated by subtracting the baseline scalp coverage from the current value. An analysis of variance test was performed to compare these changes.

Table XV shows the means of change in scalp coverage at week 48 from baseline based on the investigators' questionnaires:

**Table XV
Comparison of Change in Scalp Coverage at Week 48 from Baseline
According to the Investigators
M/7410/0285 (Male)**

	5% TMS (n=147) (Mean)	2% TMS (n=146) (Mean)	Placebo (n=72) (Mean)	P-Value (5% vs. 2% vs. PBO)	P-Value (5% vs. 2%)
Change in 48th Week from Baseline	12	7	2	0.004	0.03

Investigators rated change in scalp coverage for patients in the 5% TMS group more favorably than the other treatment groups at the end of the treatment period.

In order to detect an investigator bias in this analysis, another test was run controlling for the investigator effect. The above results did not change.

Conclusions:

The results of the male study, M/7410/0285, indicated a strong statistical superiority of 5% Rogaine to 2% Rogaine and placebo in regards to hair growth in males ($p=.001$). Patients and the investigators noticed a significantly higher change in scalp coverage at week 48 from baseline with 5% Rogaine than the 2% ($p<.05$).

III. CONCLUSIONS (which may be conveyed to the sponsor):

Studies M/7415/0001 and M/7410/0285 provide a statistical evidence to the applicant's claim that 5% Rogaine induces more nonvellus hair increase in a male population in 48 weeks. However, it is not clear whether or not the hair growth effect will remain after the 48 week period.

SAFETY

The adverse events considered in this review are, dryness, erythema, folliculitis, itching and stinging. These elements were reviewed for each one of the studies separately. In addition, the two studies were pooled together and analyzed as the integrated safety summary. The p-values for the Chi-Square statistics are reported in tables I, II and III.

Study No. M/7415/0001

The safety data for the total of 345 patients who had participated in this study was analyzed. Table I summarizes the number of subjects with adverse events, the percentages in each treatment group and the corresponding p-values for all treatment groups together and for 5% TMS vs. 2% TMS:

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Table I
ADVERSE REACTIONS
MALE STUDY M/7415/0001

Adverse Events	5% TMS	2% TMS	PBO	p-value	
				All Trts.	5% vs. 2%
Dryness				0.08	0.02*
None	71 (41%)	51 (59%)	45 (53%)		
Mild	78 (45%)	30 (35%)	31 (36%)		
Moderate	23 (13%)	5 (6%)	9 (11%)		
Severe	2 (1%)	0 (0%)	0 (0%)		
Erythema				0.08	0.05*
None	158 (91%)	85 (99%)	79 (93%)		
Mild	12 (7%)	1 (1%)	6 (7%)		
Moderate	4 (2%)	0 (0%)	0 (0%)		
Severe	—	—	—		
Folliculitis				0.89	0.78
None	161 (93%)	80 (93%)	80 (94%)		
Mild	12 (7%)	6 (7%)	5 (6%)		
Moderate	1 (0.6%)	0 (0%)	0 (0%)		
Severe	—	—	—		
Itching				0.10	0.21
None	121 (70%)	70 (81%)	72 (85%)		
Mild	32 (18%)	11 (13%)	10 (12%)		
Moderate	18 (10%)	4 (5%)	2 (2%)		
Severe	3 (2%)	1 (1%)	1 (1%)		
Stinging				0.71	0.57
None	160 (92%)	81 (94%)	80 (94%)		
Mild	12 (7%)	5 (6%)	5 (6%)		
Moderate	2 (1%)	0 (0%)	0 (0%)		
Severe	—	—	—		

As it is shown in table I, more subjects in the 5% TMS arm suffered from dryness and erythema than the 2% TMS.

* Statistically significantly more adverse events were found in the 5% TMS arm.

Study No. M/7410/0285

The safety data for the total of 393 patients who had participated in this study was analyzed. The data for erythema and folliculitis were not collected for this study. Table II summarizes the number of subjects with adverse events, their percentages in each treatment group and the corresponding p-values for all treatment groups together and for 5% TMS vs. 2% TMS:

**Table II
ADVERSE REACTIONS
MALE STUDY M/7410/0285**

Adverse Events	5% TMS	2% TMS	PBO	p-value	
				All Trts.	5% vs. 2%
Dryness				0.001	0.001*
None	72 (46%)	119 (75%)	44 (56%)		
Mild	71 (45%)	34 (22%)	26 (33%)		
Moderate	12 (8%)	5 (3%)	8 (10%)		
Severe	2 (1%)	0 (0%)	0 (0%)		
Itching				0.001	0.001*
None	86 (55%)	116 (73%)	79 (63%)		
Mild	42 (27%)	36 (23%)	22 (28%)		
Moderate	23 (15%)	4 (3%)	7 (9%)		
Severe	6 (4%)	2 (1%)	0 (0%)		
Stinging				0.42	0.47
None	128 (82%)	135 (85%)	71 (91%)		
Mild	22 (14%)	19 (12%)	6 (8%)		
Moderate	5 (3%)	4 (3%)	1 (1%)		
Severe	2 (1%)	0 (0%)	0 (0%)		

It can be seen from table II that a statistically significant number of subjects suffered from dryness and itching in the 5% TMS group as compared to the 2% TMS.

* Statistical significance indicating a higher number of subjects with adverse events in the 5% TMS arm.

Integrated Safety Summary (ISS):

The safety data for the total of 738 patients who had participated in the both pivotal male studies (study M/7410/0001 & study M/7410/0285) were pooled and analyzed. Table III summarizes the number of subjects with adverse events and their percentages in each treatment group and the corresponding p-values for all treatment groups together and for 5% TMS vs. 2% TMS:

**Table III
ADVERSE REACTIONS
MALE STUDIES M/7415/0001 & M/7410/0285
(ISS)**

Adverse Events	5% TMS	2% TMS	PBO	P-value			
				All Trts.	5% vs. 2%	5% vs. PBO	2% vs. PBO
Dryness None Mild Moderate Severe	143 (43%) 149 (45%) 35 (11%) 4 (1%)	170 (70%) 64 (26%) 10 (4%) 0 (0%)	89 (55%) 57 (35%) 17 (10%) 0 (0%)	0.001	0.001*	0.05*	0.003**
Erythema None Mild Moderate Severe	158 (91%) 12 (7%) 4 (2%) ---	85 (99%) 1 (1%) 0 (0%) ---	79 (93%) 6 (7%) 0 (0%) ---	0.08	0.05*	0.37	0.05**
Folliculitis None Mild Moderate Severe	161 (93%) 12 (7%) 1 (0.6%) ---	80 (93.6%) 6 (7%) 0 (0%) ---	80 (94%) 5 (6%) 0 (0%) ---	0.89	0.78	0.74	0.77
Itching None Mild Moderate Severe	207 (63%) 74 (22%) 41 (12%) 9 (3%)	186 (76%) 47 (19%) 8 (3%) 3 (1%)	121 (74%) 32 (20%) 9 (6%) 1 (1%)	0.001	0.001*	0.02*	0.66
Stinging None Mild Moderate Severe	288 (87%) 34 (10%) 7 (2%) 2 (1%)	216 (89%) 24 (10%) 4 (2%) 0 (0%)	151 (93%) 11 (7%) 1 (1%) 0 (0%)	0.43	0.64	0.22	0.35

A statistically significantly greater number of subjects suffered from dryness, erythema (The numbers and the percentages for erythema and folliculitis are the same as study

* Statistical significance indicating a higher number of subjects with adverse events in the 5% TMS arm.
** Statistical significance indicating a higher number of subjects with adverse events in the vehicle arm.

M/2415/0001, since these values were not collected for study M/7410/0285) and itching in the 5% TMS group as compared to the 2% TMS. Also, a higher number of people had dryness and itching in 5% TMS, as compared to placebo. Furthermore, it was observed that the subjects in the vehicle arm had more incidences of dryness and erythema than the patients in the 2% TMS group.

III. RESULTS:

Studies M/7415/0001 and M/7410/0285 indicated that 5% Rogaine induces more dryness (p=0.001), erythema (p=0.05) and itching (p=0.001) in subjects than the 2% TMS. In addition, more subjects suffered dryness (p=0.003) and erythema (p=0.05) in the vehicle treatment arm than the 2% TMS group.

IV. CONCLUSIONS (which may be conveyed to the sponsor):

Studies M/7415/0001 and M/7410/0285 provide statistical evidence that 5% Rogaine induces more dryness, erythema and itching than the 2% TMS. In addition, the vehicle used in these trials caused more dryness and erythema than the 2% TMS in patients.

Therefore, it can be concluded that according to these findings the 5% Rogaine is not as safe as the 2% Rogaine or the vehicle.

6/18/97

Shahla S. Farr, M.S.
Mathematical Statistician, Biometrics IV

06/20/97

concur: R. Srinivasan, Ph.D.
Team Leader, Biometrics IV

cc:
Archival NDA 20-834
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HFD-540/Ms. Anderson *Anna*
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Chron.

This review contains 17 pages.
Farr\X7-2037\wpfiles\sriini\rogaine\nda20834.rev Dated 6/18/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-834

BIOEQUIVALENCE REVIEW(S)

AUG 22 1997

5% Minoxidil Topical Solution
Rogaine® Extra Strength For Men
NDA 20-834
Reviewer: E.D. Bashaw, Pharm.D.
APW

Pharmacia & UpJohn Co.
Kalamazoo, MI

Submission Date:
Feb. 28, 1997

Review of an Rx to OTC Switch

Background

UpJohn Pharmaceuticals, the fore-runner of Pharmacia-UpJohn, currently markets 2% minoxidil topical solution as an OTC product. It was originally approved under NDA 19-501 in 1988 for male pattern baldness (a/k/a androgenic alopecia). A supplement for use in women was approved in 1991 and a supplement for an Rx to OTC switch was approved in 1996. In 1996 a new NDA for a 5% topical solution was submitted by the applicant and subsequently found to be approvable in Dec. 1996 for male (but not female) androgenic alopecia. Late in the review of NDA the applicant attempted to change the indication of the NDA from an Rx to an OTC product. Because of the nature of this change it was decided by Agency management that this would require a separate NDA and the change in the pending NDA was not allowed. At this time the applicant has chosen not to pursue NDA to approval, but instead has chosen to file a new NDA for OTC use in male androgenic alopecia. In doing so the applicant has re-submitted all of the material originally contained in NDA to NDA 20-834 along with some additional clinical indications. No new pharmacokinetic information has been submitted.

Review History

The original pharmacokinetic review for the Rx 5% NDA was undertaken by Dr. Ahmed El-Tahtawy. In his review (dated 12/19/95) the pharmacokinetic portion of the Rx 5% product was found to be acceptable for marketing. Subsequent to his review appropriate labeling for this product, based on Dr. El-Tahtawy's review was developed by this reviewer. There are no outstanding pharmacokinetic phase IV requirements.

Current NDA

In filing this NDA the applicant has merely copied the pharmacokinetic portion of the Rx NDA and re-labeled it for the OTC indication. No new pharmacokinetic studies were undertaken to support the OTC indication for 5% minoxidil. Examination of the documentation submitted in this NDA and the material submitted in support of the Rx NDA have revealed no differences or discrepancies in the data submitted under either NDA. On the basis of the identical nature of the data submitted and the lack of influence of OTC vs. Rx marketing on the inherent pharmacokinetics of a drug, a new review of this material will not be undertaken at this time. As Dr. El-Tahtawy's review is still acceptable and as there are no outstanding pk review or pk-OTC specific issues, a formal review of this package will not be undertaken at this time.

Recommendation

As this NDA is merely a re-submission of the data that was previously reviewed in NDA and found to be acceptable, a formal review of this data (beyond checking for consistency between the NDA's) will not be performed. As there are no outstanding biopharmaceutic issues for this product, the product is acceptable from a biopharmaceutic standpoint for OTC marketing.

E. Dennis Bashaw, Pharm.D.
Senior Pharmacokineticist (HFD-550)
Division of Pharmaceutical Evaluation-III

 Secondary Review, John Lazor, Pharm.D. _____

8/24/97

CC: NDA 20-834 (ORIG),
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