CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-812

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology/Biopharmaceutics Review

PRODUCT (Generic Name):	Minoxidil (5%) Topical Foam
PRODUCT (Proposed Brand Name):	Men's Rogaine Extra Strength
DOSAGE FORM:	Topical Foam
DOSAGE STRENGTH:	5% Foam
NDA:	21-812
PROPOSED INDICATIONS:	Androgenic Alopecia
NDA TYPE:	505(b)(2)
SUBMISSION DATE:	March 23, 2005
SPONSOR:	Pfizer
REVIEWER:	Tapash K. Ghosh, Ph.D.
TEAM LEADER:	Edward D. Bashaw, Pharm.D.
OCPB DIVISION:	DCPB III, HFD 880
OND DIVISION:	HFD 540

EXECUTIVE SUMMARY

The subject drug product is a topical foam containing 5% w/v minoxidil, and is indicated for over-the-counter (OTC) use in the treatment of androgenic alopecia in men. Pfizer Consumer Healthcare intends to market the product under the Rogaine® trade name.

Rogaine products are currently approved for OTC use in 2% and 5% minoxidil topical solutions (MTS) pursuant to NDAs 19-501 and 20-834 respectively. According to the sponsor, the proposed dosage from offers several advantages including ease of application, quick drying, minimal residue, and non-greasy feel. The product will be packaged in 60 grams aerosol cans, and will be available in three different fragrances (two scented and one unscented).

The sponsor started with two foam formulations (with propylene glycol and with glycerin respectively as humectants) and finally decided to continue with glycerin formulation as glycerin provided less greasy feeling when compared to propylene glycol. The sponsor

seeks approval of two formulations (same composition but with and without fragrance) of the foam. The PK studies were conducted with the formulation without fragrance. Inclusion of 0.6% fragrance is not expected to make any difference in percutaneous absorption and therefore, no additional PK studies are necessary.

According to the current draft of the clinical review, the application is not approvable due to lack of a sufficient demonstration of effectiveness. Effectiveness for the proposed indication has been demonstrated in one clinical study, but this needs to be replicated in a second study. The design of the additional study should incorporate the recommendations made by the Agency on the design of the pivotal clinical study (Study 006), some of which were not followed by the sponsor. The sponsor also needs to provide a cumulative irritation study which is in accord with our current requirements.

The clinical pharmacology studies demonstrate that serum minoxidil levels from the proposed foam product in males were similar to, or lower than that of the marketed 5% topical solutions.

Recommendation:

The Clinical Pharmacology and Biopharmaceutics section of NDA 21-812 is acceptable with no suggested labeling changes.

Primary Reviewer: Tapash K. Ghosh, Ph.D.
Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation III

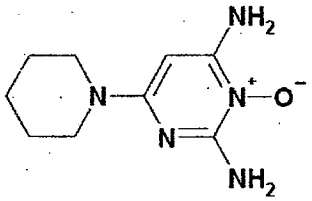
Team Leader: Edward D. Bashaw, Pharm.D._____

GENERAL ATTRIBUTES

Trade name: Men's Rogaine® Extra Strength Minoxidil 5% Topical Foam
Generic name: Minoxidil
Chemical name: 2, 4-pyrimidinediamine-6-(1-piperidinyl)-3-oxide

Molecular formula/molecular weight: $C_9H_{15}N_5O$/209.25

Chemical Structure:



Formulation:

Ingredient	Concentration (% w/w without propellant)		Function
	Fragranced	Unfragranced	
Active Phase Ingredients			
Minoxidil USP	5.00	5.00	Active ingredient
Alcohol			
Purified water			
BHT			
Lactic acid			
Citric acid			
Glycerin			
Fragrance[1]			
Nitrogen[2]			
Alcohol			
Cetyl alcohol			
Stearyl alcohol			
Polysorbate 60			
Total			

Brief Overview of Clinical Program: The clinical program consisted of the following studies:

- Study MINOB-9140-001: The systemic bioavailability of two 5% foam formulations of minoxidil vs 5% minoxidil topica solution in males and 2% topical solution in females.
- Study MINOB-9140-005: The systemic absorption of minoxidil after the application of increasing doses of 5% minoxidil foam in males.
- Study MINOB-9140-004: Contact sensitization.
- Study MINOB-9140-006: A double blind, randomized, placebo controlled trial of the efficacy and safety of 5% minoxidil foam in the treatment of androgenic alopecia in males.

Efficacy: Study 006 was a multi-center, double-blind, randomized, placebo controlled trial of the efficacy and safety of 5% minoxidil foam in the treatment of androgenic alopecia of the vertex region of the scalp in males. Applications of 5% minoxidil foam or the foam vehicle were made twice daily for 16 weeks. The primary efficacy variables were a) the mean change in hair counts in a target area of the scalp as determined by a computer assisted dot mapping technique, and b) a subject rating of treatment benefit by use of global photographs of the vertex region.

According to the current draft of clinical review, the application is not approvable due to lack of a sufficient demonstration of effectiveness. Effectiveness for the proposed indication has been demonstrated in one clinical study, but this needs to be replicated in a second study. The design of the additional study should incorporate the recommendations made by the Agency on the design of the pivotal clinical study (Study 006), some of which were not followed by the sponsor. The sponsor also needs to provide a cumulative irritation study which is in accord with our current requirements.

Safety: To be reviewed by the OTC division.

Clinical Pharmacology and Biopharmaceutics (CPB): The clinical pharmacology and biopharmaceutics review of this NDA 21-812 consists of 2 studies:

- Study MINOB-9140-001: The systemic bioavailability of two 5% foam formulations of minoxidil vs 5% minoxidil topical solution in males and 2% topical solution in females.
- Study MINOB-9140-005: The systemic absorption of minoxidil after the application of increasing doses of 5% minoxidil foam in males.

A comparison of the pharmacokinetic (PK) parameters of minoxidil from the proposed foam formulation from both CPB studies (001 and 005) along with the parameters from marketed 5% MTS is presented below:

Males	Foam (5%) Study # 001*			Foam (5%) Study # 005			MTS (5%)		
	AUC_{0-12} (ng.hr/ml)	C_{max} (ng)	T_{max} (hr)	AUC_{0-12} (ng.hr/ml)	C_{max} (ng)	T_{max}	AUC_{0-12} (ng.hr/ml)	C_{max} (ng)	T_{max} (hr)
n	32	32	32	31	31	31	29	29	29
Mean	9.62	1.14	6.31	8.81	1.11	5.42	18.71	2.13	5.79
SD	4.55	0.59	4.37	5.59	0.71	4.54	13.64	1.54	4.35
Median	9.77	1.04	6.00	7.95	0.96	6.00	12.29	1.45	6.00
Min	1.23	0.35	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Max	18.99	3.10	12.00	21.05	3.52	12.00	60.53	7.23	12.00

* Data from Foam formulation with glycerin.

Overall, it has been observed that serum minoxidil levels from the proposed foam product in males were similar to, or lower than that of the marketed 5% topical solutions. Individual CPB study reviews are as follows:

NDA: 21-812/Study MINOB-9140-001 **Study Dates: Jul'02 – Sep '02**

Evaluation of the Systemic Bioavailability of Two Investigational 5% Foam Formulations of Minoxidil vs. 5% Minoxidil Topical Solution in Males and vs. 2% Topical Solution in Females

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Objectives

Primary: The primary objective of this study was to establish the steady-state percutaneous absorption and relative systemic bioavailability of two new formulations of a 5% minoxidil foam preparation compared to the commercially available 5% Minoxidil Topical Solution (MTS) used twice daily in male subjects, or once daily application of the 5% foam preparations compared to twice daily administration of commercially available 2% MTS in female subjects, with androgenic alopecia.

Secondary: The secondary objective of this study was to assess product safety, as documented by the type, severity and duration of adverse events, if such occurred during the course of the study.

Overall Study Design: This study was a single-center, two-arm, randomized, crossover, open-label clinical investigation. Thirty-three adult male subjects with evidence of androgenic alopecia of the vertex region of the scalp were enrolled in the male arm of the trial. In the other arm of this study, thirty-four adult female subjects with evidence of androgenic alopecia of the anterior-frontal region of the scalp were enrolled. Fifty seven subjects (29 male, 28 female) completed all phases of the study. The total length of this study was six weeks including screening. Subjects were assigned to a treatment arm and group as shown below:

Male Arm	Phase 1	Phase 2	Phase 3
Subjects 101-110, 131	5% MTS (A)	Foam #1(B)	Foam #2 (C)
Subjects 111-120, 132	Foam #1 (B)	Foam #2 (C)	5% MTS (A)
Subjects 121-130, 133	Foam #2 (C)	5% MTS (A)	Foam #1 (B)

Female Arm	Phase 1	Phase 2	Phase 3
Subjects 501-510, 531-534	2% MTS (D)	Foam #1(B)	Foam #2 (C)
Subjects 511-520	Foam #1 (B)	Foam #2(C)	2% MTS (D)
Subjects 521-530	Foam #2 (C)	2% MTS(D)	Foam #1 (B)

A = 5% MTS Commercial lot number: 29HSB
B = Foam #1 w/glycerin: Formulation No. P902853A00 (F128/12/01); Manufacturing Lot: SFDF-C
C = Foam #2 w/propylene glycol: Formulation No. P902854A00 (F112/29/03); Manufacturing Lot: SFDI-C
D = 2% MTS Commercial lot number: 94HPJ

All applications of clinical test material (CTM) were performed at the investigative site. Each one mL dose of either 2% or 5% MTS was carefully measured to provide 20 mg or 50 mg, respectively, of minoxidil using the medication dropper provided with each bottle. Each dose of the 5% foam preparations was weighed to ensure that a dose of 50 mg of minoxidil (1 gram of foam) was used. The study consisted of three phases with a 7-day washout period between each phase. Each male subject used each of two 5% foam formulations and the 5% MTS over the course of the three phases. Each female subject used each of the two 5% foam formulations and the 2% MTS over the course of the three phases. Male subjects reported to the lab twice daily for 5 days and once on the 6th day for all treatments. Female subjects reported twice daily for 6 days for 2% MTS and once daily for 6 days for the 5% foam formulations.

Each phase consisted of 5 days of twice daily dosing and once on the 6th day for a total of 11 applications per phase followed by a seven (7) day washout period between phases.

Serum samples were collected for all subjects at screening and prior to CTM application on Days 2, 4, 6, 15, 16, 18, 20, 29, 30, 32 and 34. On Days 6-7, 20-21 and 34-35 additional serum samples were drawn at hour 1, 2, 3, 4, 6, 8, 12 and 24 hours following application for male subjects. Female subjects had serum samples drawn on Days 6-7, 20-21 and 34-35 at hour 1, 2, 3, 4, 6, 8, 12, 13, 14, 15, 16, 18, 20 and 24 hours after application.

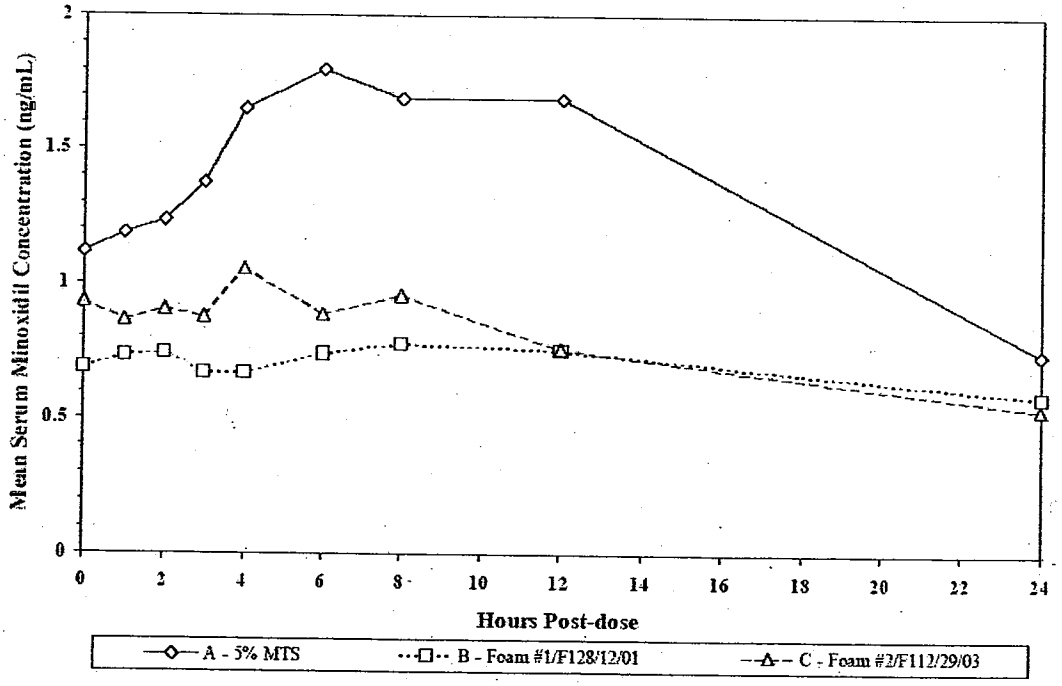
Concentrations of minoxidil in serum samples were analyzed [redacted] using a validated [redacted] high-performance liquid chromatography (HPLC) on a [redacted], with ultraviolet absorbance detection at [redacted] with a lower limit of quantitation of [redacted] The relationship between the peak height ratio and concentration was linear in the curve range from [redacted] ng/mL. All values recorded as [redacted] ng/mL (the lower limit of quantitation for the method) were treated as zero levels.

Results: The purpose of this study was to evaluate systemic absorption of minoxidil in two foam preparations when compared to the commercially-available minoxidil solution for men (5% MTS) and women (2% MTS). *However, as the target population for the minoxidil foam for this NDA is male only, data on the female population has not been reviewed and will not be discussed.*

Steady state pharmacokinetic parameters in males are summarized in the following Table and Mean Serum Minoxidil Concentrations, Days 6/20/34 (Males) is presented in the following figure.

Males	**MTS**			**Foam B**			**Foam C**		
	AUC_{0-12} (ng.hr/ml)	C_{max} (ng)	T_{max} (hr)	AUC_{0-12} (ng.hr/ml)	C_{max} (ng)	T_{max}	AUC_{0-12} (ng.hr/ml)	C_{max} (ng)	T_{max}
n	29	29	29	31	31	31	30	30	30
Mean	18.71	2.13	5.79	8.81	1.11	5.42	10.83	1.64	4.13
SD	13.64	1.54	4.35	5.59	0.71	4.54	9.02	1.65	4.50
Median	12.29	1.45	6.00	7.95	0.96	6.00	7.25	1.02	2.00
Min	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Max	60.53	7.23	12.00	21.05	3.52	12.00	32.47	9.19	12.00

Mean Serum Minoxidil Concentrations, Days 6/20/34 (Males)



Discussion: Being a new formulation, it was necessary to evaluate systemic exposure of minoxidil from the to be marketed formulation. As evident from the above table and figure, in male subjects, the systemic exposure of minoxidil from both 5% foams with twice daily application were about half of that of 5% MTS with twice daily application. Foam B had a somewhat lower absorption rate than that of Foam C.

At no time point did any minoxidil level reach 10 ng/mL. In the male arm, the highest level attained at any time point was 7.23 ng/mL (5% MTS), 3.52 ng/mL (Foam B) and 9.19 ng/mL (Foam C). Therefore, it demonstrates that serum minoxidil levels from either foam product in males were similar to, or lower than that of the marketed 5% topical solutions.

According to the sponsor, no cardiovascular or hemodynamic adverse events were reported.

NDA: 21-812/Study MINOB-9140-005 **Study Dates: Sep'02 – Nov '03**

Evaluation of the Systemic Absorption of Minoxidil After the Application of Increasing Doses of 5% Minoxidil Foam in Adult Males

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Objectives:
Primary: The primary objective of this study was to establish the steady-state percutaneous absorption and relative systemic absorption of minoxidil with enhanced volumes of 5% minoxidil foam applied twice daily in men.
Secondary: The secondary objective of this study was to assess product safety, as documented by the type, severity and duration of adverse events.

Overall Study Design: This was a single-center, three-treatment group, randomized, cross-over, open-label study. Thirty-five adult male subjects (average was 44 years (22-62). Approximately 83% were white, 9 % were black, 6 % were Hispanic and 3% were Other) with evidence of androgenic alopecia of the vertex region of the scalp were enrolled in the trial. Each subject participated in three active phases: 1 gram (gm), 2 gram and 3 gram applications of 5% minoxidil foam. Each phase consisted of 5 days of twice daily dosing and once on the 6th day for a total of 11 applications per phase followed by a seven (7) day washout period between phases.

Systemic minoxidil bioavailability was measured in serum levels drawn at screening and on Days 1, 2, 4, 6-7, 15, 16, 18, 20-21, 29, 30, 32, and 34-35 prior to test product application. On Days 6, 20 and 34 serum collections were performed at 1, 2, 3, 4, 6, 8, 12 and 24 hours after final application for the male subjects.

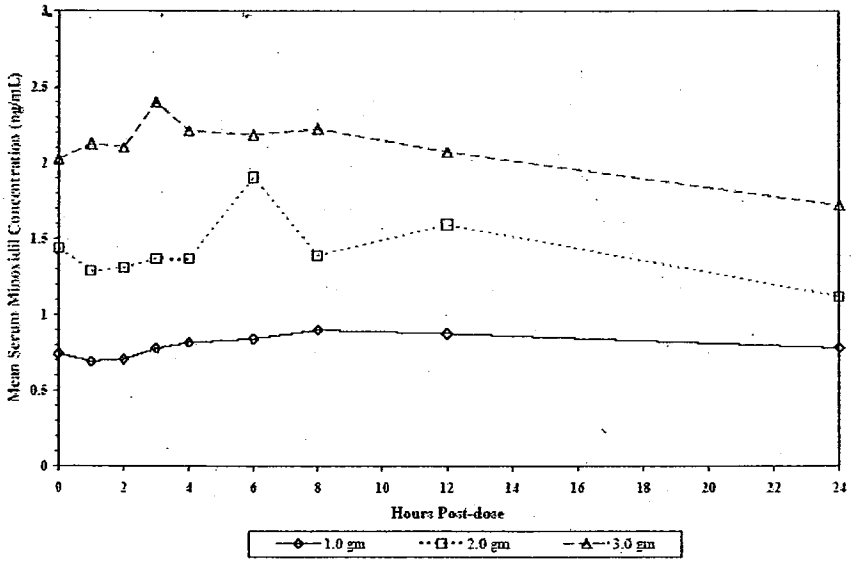
Concentrations of minoxidil in serum samples were analyzed by [redacted] using a validated [redacted] high-performance liquid chromatography (HPLC) on a [redacted] with ultraviolet absorbance detection at [redacted] nm with a lower limit of quantitation of [redacted] ng/mL. The relationship between the peak height ratio and concentration was linear in the curve range from [redacted] ng/mL. All values recorded as [redacted] ng/mL (the lower limit of quantitation for the method) were treated as zero levels.

Results: Steady state pharmacokinetic parameters are summarized in the following Table.

Male	1 gm			2 gm			3 gm		
	AUC_{0-12} (ng.hr/ml)	C_{max} (ng)	T_{max} (hr)	AUC_{0-12} (ng.hr/ml)	C_{max} (ng)	T_{max}	AUC_{0-12} (ng.hr/ml)	C_{max} (ng)	T_{max}
n	32	32	32	31	31	31	30	30	30
Mean	9.62	1.14	6.31	18.04	2.59	6.13	26.11	3.03	4.70
SD	4.55	0.59	4.37	9.28	3.03	4.97	11.37	2.23	4.06
Median	9.77	1.04	6.00	15.43	1.85	6.00	24.76	2.42	4.00
Min	1.23	0.35	0.00	7.07	0.71	0.00	8.82	0.94	0.00
Max	18.99	3.10	12.00	46.26	16.80	12.00	52.31	11.50	12.00

Mean steady state serum minoxidil concentrations are graphically presented in the following Figure.

Figure 1. Mean Serum Minoxidil Concentrations, Days 6/20/34



Discussion: This study was conducted to compare the systemic bioavailability and the risks of increasing the dose of the foam up to three times the recommended dose. Although systemic exposure increased linearly with increasing dose, the maximum observed blood level of 5% minoxidil foam at the highest exaggerated dose of 3.0 gram used twice a day (11.5 ng/ml) is far below the level associated with any systemic effects, which is approximately 20 ng/mL. According to the sponsor, no cardiac or hemodynamic events were reported in association with any dosing group. Three adverse events considered related to treatment occurred at the lower doses, were mild and did not increase in severity with increased applications.

In conclusion, the serum blood levels for the minoxidil foam preparation were significantly lower than the currently approved 5% minoxidil solution used twice a day. The exaggerated use of the foam preparation up to three times the recommended dose, used twice a day does not produce blood levels associated with systemic effects.

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