

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-812

PHARMACOLOGY REVIEW

NDA NUMBER: 21-812

SERIAL NUMBER: 000

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PRODUCT: 5% Minoxidil Topical Foam

INTENDED CLINICAL POPULATION: Adult males and females

SPONSOR: Pharmacia & Upjohn-A Pfizer Company

DOCUMENTS REVIEWED: Vol. 1.1-1.3

REVIEW DIVISION: Division of Dermatologic and Dental Drug Products
HFD-540

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability: Approvable from non-clinical safety point of view.

B. Recommendation for nonclinical studies: None

C. Recommendations on labeling: The labeling draft submitted by the sponsor is almost identical to the one approved for the over-the-counter 5% minoxidil solution. It includes the appropriate information for the safe use of foam formulation. No additional recommendation is warranted.

II. Summary of non-clinical findings

A. Brief overview of non-clinical findings: A majority of the animal studies conducted to evaluate the safety of minoxidil had employed non-topical (intravenous, oral, intraperitoneal) routes for drug administration. In these studies, moderate to severe adverse effects mostly associated with the morphology and functioning of the cardio-renal systems included degeneration, fibrosis, nuclear enlargement and hypertrophy of the heart, and extensive nephritis. In addition, some pulmonary (increased alveolar macrophages in the lungs) and hepatic lesions (hepatocellular hypertrophy) were also observed. In rodents, at high intravenous and intraperitoneal dose levels, minoxidil also caused decreased motor activity, tremors, and labored respiration.

Among the test species (mouse, rat, mini pig, rabbit, dog, and monkey), monkeys were least susceptible to local and systemic toxicity of minoxidil. All other species because of high topical absorption and resulting high serum drug levels were much more sensitive to minoxidil. The pharmacokinetic behavior and systemic toxicity in monkeys were more near to humans. Whereas, mini pigs developed papillary muscle necrosis, atrial and ventricular hemorrhage and coronary arteritis only after two days of oral treatment with 1mg minoxidil/kg/day, it took monkeys 32 days of daily oral treatment with 20mg minoxidil/kg to develop hypertrophy of the heart.

A similar pattern was observed in the topical studies. For instance, in one-year rabbit study with 1, 3 or 5% minoxidil solution, the increased liver and heart weights and dilated ventricles were observed in the mid- (60mg/kg/day) and high-dose (100mg/kg/day) females. In a similar one-year study in monkeys, absolutely no systemic toxicity was observed at 100mg/kg/day dose level. This NOEL (60mg/m²/day using actual absorption of 5%) for systemic toxicity in monkeys is 24 times greater than the human dose of 2.5mg/m²/day (using actual absorption of 4%).

In humans, rare cases of visual disturbance (decreased visual acuity) with the topical use of minoxidil have been reported.

The maximum topical absorption of minoxidil reported in humans was 4 percent. In monkeys, the average mean absorption was 5 percent. In rodents and dogs dermal absorption was much greater (32-48%). The average plasma half-life of 4 hours in humans was not associated with any drug accumulation. In all species including humans, irrespective of the route of administration the peak plasma drug levels were achieved within 6 hours.

In rats, minoxidil was absorbed through placenta; however, the level of drug in the fetus was much lower than in the maternal plasma. The drug related radioactivity in milk increased with time.

In all the test species and humans, minoxidil goes through extensive first pass metabolism. Eight metabolites have been identified. Whereas in monkeys and humans, glucuronides (detoxified metabolites) comprised a major portion of the urinary metabolites, the parent drug was the major excretory component in the rodents.

In a spectrum of *in vitro* and *in vivo* assays, minoxidil tested nongenotoxic.

In rodent dermal carcinogenicity studies (8, 25, and 80mg/kg/day), no drug related gross or histopathological lesions were observed in rats. In mice, lesions restricted to the mid- and high-dose animals included basophilic cell foci and hyperplasia along with hepatocellular adenomas and myocardial fibrosis of heart in males, and hyperplasia along with adenocarcinomas in the mammary glands and the adenomas in the pituitary gland of females. Using the mid-dose of 25mg/kg/day in mice, the margin of safety in $\text{mg}/\text{m}^2/\text{day}$ will be 14 times of the proposed human dose of $2.5\text{mg}/\text{m}^2$. However, it must be mentioned that neither the individual nor the combined tumor burden revealed any statistical significance.

In the photo carcinogenicity study in hairless mice, minoxidil did not induce or promote the development of papillomas or carcinomas.

In a segment II subcutaneous rat study, no teratogenic changes were observed at 80mg/kg/day. Considering this dose as NOEL for developmental toxicity, and 4% absorption in humans versus 32% absorption in rats, the margin of safety will be 60 times (mg/m^2). In another subcutaneous segment II rat study, the teratogenic effects were observed at 120mg/kg/day dose level. This dose was 92 times (mg/m^2) greater than the clinical dose.

Whereas, the systemic toxicity in humans via the intravenous route occurred at the serum minoxidil level of 20ng/mL or above, the highest amount of serum minoxidil level achieved in humans with the proposed topical foam formulation was 3.52ng/mL. It was approximately 6 times lower than the threshold level for systemic toxicity.

The data obtained from the non-clinical and clinical dermal studies support the safe use of foam formulation in humans.

B. Pharmacologic activity: The primary pharmacodynamic action of oral minoxidil involves the activation of ATP-modulated potassium channel. The opening of these channels in the smooth muscle permits potassium efflux, causing hyperpolarization and relaxation of smooth muscle. The secondary pharmacodynamic (side effects) activity of minoxidil leads to fluid and salt retention and hair growth (hypertrichosis) on the face, back arms, and legs. For the therapeutic activity, the parent drug is converted by liver sulfotransferase to active minoxidil-N-O sulfate.

The primary mechanism of action for the topical minoxidil is not clear. It may involve 1) enhanced microcirculation around the hair follicles, 2) direct stimulation of hair follicles, and 3) alteration of androgen effect on the genetically programmed hair follicles. Probably, all these changes involve the action of minoxidil-N-O-sulfate on the potassium channels in the hair follicles.

Irrespective of the mechanism of action, the direct and indirect pharmacologic actions of minoxidil cause pathological and functional changes in the cardio-renal systems of the test species.

C. Nonclinical safety issues relevant to clinical use: None

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2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY: Minoxidil was originally recognized for its hypotensive action in 1965. In 1979 it was developed as an oral antihypertensive agent (LONITEN[®], Upjohn). During the early period of its clinical use, it was serendipitously observed that patients on minoxidil developed hypertrichosis. This unexpected finding led to the development of its topical formulations for the treatment of androgenic alopecia of the vertex. The first formulation Men's Rogaine[®] Regular Strength (2% Minoxidil Solution) was marketed in the USA in 1987; it was switched from the Rx to OTC product in 1996. The second topical formulation Men's Rogaine[®] Extra Strength (5% Minoxidil Solution) was approved as an OTC product in 1997. Under the current submission, the sponsor has proposed the development of 5% Minoxidil Topical Foam as an OTC drug product.

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Information to sponsor: No

Sponsor and/or agent: Pharmacia & Upjohn-A Pfizer Company

Pfizer Inc.

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Manufacturer for drug substance: Pfizer Inc.

Reviewer name: Kumar D. Mainigi

Division name: Dermatologic and Dental Drug Products

HFD #: 540

Review completion date:

Drug:

Trade name: Men's Rogaine[®] Extra Strength
Minoxidil 5% Topical Foam

Generic name: Minoxidil

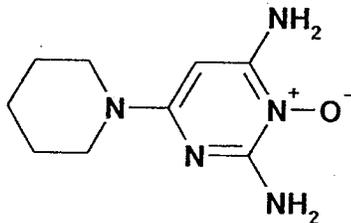
Code name: U-10858

Chemical name: 2, 4-pyrimidinediamine-6-(1-piperidinyl)-3-oxide

CAS registry number: 38304-91-5

Molecular formula/molecular weight: C₉H₁₅N₅O/209.25

Structure:



Relevant INDs/NDAs/DMFs:

INDs: ~~_____~~
 13, 267 (Minoxidil topical solutions 2% and 5%)

 50, 063 (Minoxidil 5% Topical Foam)
 NDAs: 18-154
 19-501 (2% Rogaine Topical solution)
 20-492 (Rogaine 5% solution, withdrawn)
 20-834 (Rogaine 5% Topical solution)
 DMF: ~~_____~~ (~~_____~~)

Drug class: Vasodilator, hair growth stimulator

Intended clinical population: Hair Regrowth Treatment

Clinical formulation:

<u>Ingredient</u>	<u>Concentration</u>		<u>Function</u>
	(% w/w without _____)		
	<u>Fragranced</u>	<u>Unfragranced</u>	
<u>Active Phase Ingredients</u>			
Minoxidil USP	5.00	5.00	Active ingredient
Alcohol SD 40B	T		
_____ water			
BHT			
Lactic acid			
Citric acid			
Glycerin			
Fragrance ¹			
Nitrogen ²			
Alcohol _____			
Cetyl alcohol			
Polysorbate 60			
Total	L	J	

1- _____ Fragrance
 2- _____
 3- _____

Route of administration: Topical

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Data reliance: Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 21-812 are owned by Pfizer Inc. Any information or data necessary for approval of NDA 21-812 that Pfizer Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 21-812.

Studies reviewed within this submission: None

Studies not reviewed within this submission: The following relevant studies were reviewed by Dr. Javier Avalos under NDA 20-834 in May 1997.

Safety pharmacology:

Three-day oral cardiovascular study in rats
Cardiac hypertrophy and reversal study in rats

Pharmacokinetics:

Pharmacokinetics of minoxidil in rats, dogs, and monkeys
Pharmacokinetics and biotransformation in mouse
The comparative bioavailability of oral and solution formulations
Pharmacokinetics of minoxidil
The comparative bioavailability of oral and topical formulations
Absorption and excretion in rats and monkeys after subcutaneous and topical applications
Pharmacokinetics in rats and monkeys
Tissue distribution in rats
Dermal absorption in rats and monkeys
Plasma drug levels and excretion in female mice and rats
Pharmacokinetics in three and twelve month dermal studies in monkeys
Percutaneous absorption in man
Biotransformation in rats, dogs, and monkeys following oral administration
Metabolites in rat bile
Investigation of route (topical and oral) dependent pharmacokinetics in mouse and rat
In vitro transdermal metabolism in human skin

Toxicology:

Single dose studies

Acute dermal toxicity in mice
Acute oral toxicity in two strains of mice
Acute LD₅₀ in mouse and rat
Acute intraperitoneal LD₅₀ in mouse
Acute subcutaneous toxicity in mouse
Acute oral toxicity in rat
A single oral dose lotion study in rats
Acute subcutaneous toxicity in rats
Acute subcutaneous toxicity in monkeys.
Single oral dose study with 1% minoxidil lotion in mice
Single oral dose study with 1% minoxidil lotion in rats

Subchronic and chronic studies

Dermal

Twenty-day study in rats
Three-month study in rats
One-year study in rats
Twenty-one-day study in rabbits
One-year study in rabbits
Three-month study in dogs
One-month study in monkeys
Three-month study in monkeys
One-year study in monkeys

Systemic

Chronic oral study in rats
Subacute oral study in dogs
One-month oral study in dogs
Two-week oral study in monkeys
One-year oral study in monkeys

Tolerance studies

Two-week subcutaneous tolerance study in rats
Two-week intravenous tolerance study in monkeys
Delayed type contact dermal sensitization in guinea pigs
Delayed sensitization potential of topical solution in guinea pigs
Evaluation of dermal phototoxic and photoallergic potentials in guinea pigs
Ocular irritation in rabbits
Cumulative skin irritation study
Primary dermal irritation in rabbits

Intramuscular irritation in rabbits

Genetic toxicity studies

Ames reverse mutation test

DNA damage/alkaline elution assay

In vitro unscheduled DNA synthesis in rat primary hepatocytes

In vitro chromosome aberration test

In vitro cytogenetics assay in human lymphocytes

The micronucleus test

Carcinogenicity studies

Oral dietary study in mice

Oral dietary study in rats

Dermal study in mice

Dermal study in rats

Photocarcinogenicity study in hairless mice

Reproductive and developmental toxicity studies

Rat segment I study

Fertility study in rats

Rat segment II study

Additional teratology study in rats

Segment II study in rabbits

Rat segment III study

Rat segment III study

Special toxicity studies

Histological re-evaluation of selective endocrine and reproductive organs of female mice from the oral and topical carcinogenicity studies

Histological re-evaluation of selective endocrine and reproductive organs of male and female rats from the oral and topical carcinogenicity studies

Seven-day preliminary toxicity study to evaluate the effect of oral minoxidil on serum and pituitary prolactin levels in female mice

Three-month toxicity study to evaluate the effect of oral minoxidil on the serum and pituitary prolactin levels in female mice

Estrogenic activity bioassay in ovariectomized mice

Immunohistochemical study on tissues of female mice treated with minoxidil for 24 months

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary: The oral minoxidil is a peripheral vascular smooth muscle vasodilator. The parent molecule is converted in the liver by sulfotransferase to the active drug minoxidil-N-O-sulfate. This molecule is also minor excretory metabolite. The drug is mostly eliminated via conjugation with glucuronic acid in the liver. After absorption, the plasma drug level remains high for 3-4 hours; however, its hypotensive action occurs within 30 minutes.

The drug increases blood flow to the gastrointestinal tract, skeletal muscles, skin, and heart, and to a lesser extent to the central nervous system. The increase in the cardiac output is due to an increase in venous return. The primary action of minoxidil involves the activation of ATP-modulated potassium channel. The opening of these channels in the smooth muscle permits potassium efflux, causing hyperpolarization and relaxation of smooth muscle. The side effects (secondary pharmacodynamics) of oral minoxidil include fluid and salt retention, and hair growth (hypertrichosis) on the face, back arms and legs. To overcome the cardiovascular and renal side effects, minoxidil is always administered with a beta blocker and diuretic.

The topical formulations of minoxidil have been used to treat alopecia androgenetica (male pattern baldness) variably expressed in males as hair loss at the vertex of the scalp, and in females as thinning of frontoparietal areas. The primary mechanism of action for the topical minoxidil is not clear. It may involve 1) enhanced microcirculation around the hair follicles, 2) direct stimulation of the hair follicles, and 3) alteration of androgen effect on the genetically programmed hair follicles. Probably, all these changes involve the action of minoxidil-N-O-sulfate on the potassium channels of the hair follicles. Reportedly, the therapy is actually more effective at arresting further hair loss, and to a lesser extent to the regrowth of the miniaturized follicles.

In general, the topical minoxidil is well tolerated. A few dermatological side effects such as irritation, allergic contact dermatitis and hair growth in the undesirable areas have been reported. There are no systemic side effects since very little drug is absorbed topically. There are no known drug interactions with the topical minoxidil.

2.6.2.4 Safety pharmacology: No specific safety pharmacology studies were conducted to support the proposed foam formulation. However, data from the previously conducted sub-chronic and chronic animal studies had indicated that most of the adverse effects due to oral minoxidil were associated with the cardio-renal systems.

Much of the information provided below is extracted from the original NDA (20-834) review of Dr. Avalos Javier, and a few published reports.

Neurological and Pulmonary effects: In rodents, at high intravenous and intraperitoneal dose levels (mice 1350mg/kg, rats 900mg/kg), minoxidil in propylene glycol caused decreased motor activity, tremors, and also inhibited the respiration. In humans, rare cases of visual disturbance (decreased visual acuity) with the topical use of mioxidil have been reported.

Cardiovascular and Renal effects: In animals as well as in humans, the systemic toxicity of minoxidil included edema, salt and water retention, hirsutism, and pericardial lesions (pericardial effusion, pericarditis, and tamponade) (Table 1).

Table 1. Adverse effects following oral treatment with minoxidil

<u>Species</u>	<u>Dose</u> (mg/kg/day)	<u>Duration</u>	<u>Adverse Effects</u>
Rat	10-30	One-year	Dilation and hypertrophy of heart
Monkey	20	32 days	Hypertrophy of heart, renal tubular water and salt retention
Mini pig	1	2 days	Papillary muscle necrosis, atrial and ventricular hemorrhage, and coronary arteritis
Dog	0.5	30 days	Atrial hemorrhage, hypertrophy of heart, degeneration of muscle cells, coronary arteritis, and epicarditis on right arterial wall

Except for monkey, in all other species, similar cardio-renal changes were observed at higher topical doses after a longer period of treatment (Table 2). Whereas, an oral dose of 20mg/kg/day in monkeys caused severe adverse effects in 32 days, the topical dose of 100mg/kg/day for one year did not produce any cardio-renal changes. In this regard, monkey is a more appropriate model for risk determination. On the contrary, rodents were much more sensitive to minoxidil by all routes of administration.

Table 2. Adverse effects following topical treatment

Rat	10, 30, 50	One year	4/6 died in high-dose group due to cardiac failure
Rabbit	20, 60, 100	One year	Dilated ventricles of heart and increased heart weight
Monkey	1, 10, 100	One year	No changes at study end
Dog	2.5, 5, 20	3 months	In high-dose group increased heart weight, epicarditis, and chronic proliferative inflammation of atrial myocardium

Because of very limited dermal absorption in humans, the systemic adverse effects were not commonly observed, however, in a few reported cases, minoxidil had been associated with some cardio-renal changes.

Gastrointestinal effects: No effects were reported in animals. In humans, occasional incidences of diarrhea, nausea, and vomiting have been reported.

Abuse liability: None reported

Pharmacodynamic drug interactions: Not known with the topical treatment.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary: The topical absorption of minoxidil in humans and monkeys is much lower (humans 4%, monkeys mean average 5%) than in rodents and dogs (32-48%). In all species including humans, irrespective of the route of administration the peak plasma drug levels were achieved within 6 hours. Minoxidil is absorbed through placenta in rats; however, the level of drug in the fetus is much lower than in the maternal plasma. The drug related radioactivity in the rat milk increased with time. Irrespective of the route of administration, the drug distribution profiles in all the species were similar, the highest amount was present in the liver. In the test species and humans, minoxidil goes through extensive first pass metabolism. However, some qualitative and quantitative interspecies differences in the metabolic profiles were observed. In rat, eight metabolites had been identified, and most (above 80%) of these pharmacologically inactive compounds were excreted in the urine. The average plasma half-life for minoxidil in humans is 4 hours.

Absorption: In various species (rats, mice, dogs, monkeys, humans), over 90% of the orally administered minoxidil is absorbed. However, the topical absorption of drug varied from mean average of 5% in monkey to 32%, 39%, and 48% in rat, dog, and mouse, respectively. In a 21-day rat subcutaneous study, the steady state was achieved on day 12, and at that time point the C_{max} and AUC were 4 and 6.5 times greater than on day 1. In one-year rat dermal study with 2mL of 1, 3, or 5% minoxidil solution per day (equivalent to 20, 60, and 100mg/day), the mean C_{max} values for males were 34, 253, and 224ng/mL, respectively. The corresponding values in females were 96, 756, and 1364 ng/mL. The greater absorption in females was attributed to thinner stratum corneum. The topical absorption in monkeys indicated no gender difference during one year of drug treatment. The peak plasma levels of topically absorbed minoxidil were achieved within 6 hours in all the test species.

Following the subcutaneous doses of ¹⁴C-minoxidil to pregnant rats on gestation days 13 or 18, the C_{max} in fetuses was achieved at 30 minutes post-dose; however, at that point, the levels of radioactivity in the fetuses were 40% lower than the maternal levels.

In humans, the oral drug is well absorbed through the gastrointestinal tract; at one hour post-dose, the oral doses of 2.5 and 5mg of minoxidil provided the peak serum concentrations of 18.5 and 41ng/mL, respectively. The drug recovery following the oral administration was 97 percent. The topical absorption in humans is only 0.5-4% of the applied dose. In human cadaver skin, over 72 hours only 3.2%±1 of the applied dose was found in the receptor fluid, and 32.7%±7.8% of it was found within the skin. The low systemic toxicity in monkeys and humans is directly related to low dermal absorption.

2.6.4.4 Distribution: Irrespective of the route of administration (oral, subcutaneous, topical), the distribution profiles of drug-related radioactivity in all the species were similar. In a three-week rat subcutaneous study, no drug accumulation was observed; and the distribution patterns on days 1 and 21 were identical. The level of radioactivity was in the following decreasing order: liver, kidney, intestine, urinary bladder, and aorta. In a rat oral reproductive study, the major portion of radioactivity was found in the liver and kidney of fetuses. Most of the radioactivity after the topical dose (s) was found at the application sites.

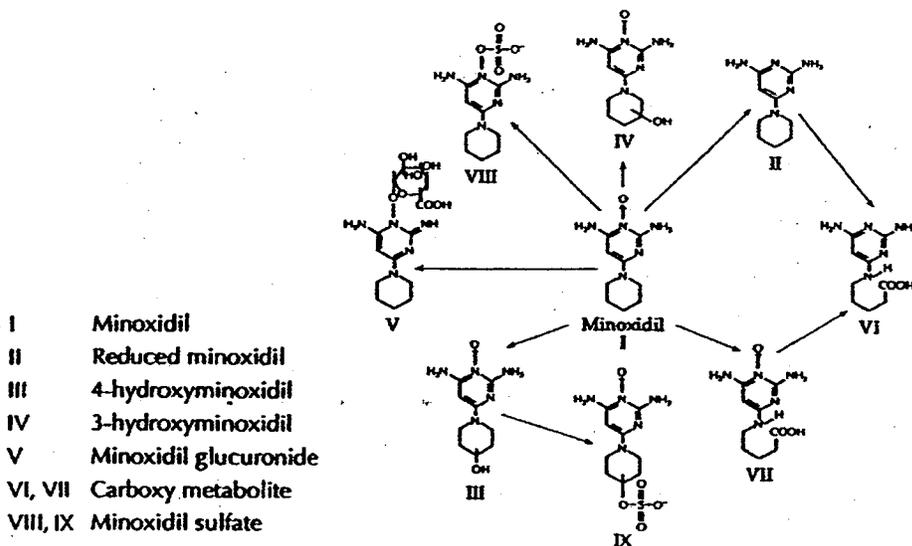
2.6.4.5 Metabolism: In all the test species and humans, minoxidil goes through extensive first pass metabolism. In general, in all species after the oral dose, same metabolites were excreted in the urine, but in different relative amounts. For instance, in rats following a subcutaneous dose, 50% of the radioactivity was found in the intact drug, the next major component was a carboxyminoxidil metabolite (Figure 1). In monkey on the other hand, 50% of the radioactivity was found in a glucuronide conjugate (V), followed by the parent drug. The metabolites in humans were very similar to monkeys. Except for the topical route, some qualitative differences in metabolism were observed between the other routes of administration. Following a subcutaneous dose (0.9mg/kg), eight metabolites were identified in organs and plasma of rat.

In rats, the major urinary metabolite was the parent drug, and the major fecal metabolites were a glucuronide (V) and a de-*N*-oxide (VI). In humans and monkeys, the major metabolite was a glucuronide conjugate at the *N*-oxide position in the pyrimidine ring. This pharmacologically less active metabolite permits longer stay in the body than the parent drug. In dogs, the major metabolite was 4-hydroxyminoxidil (III); other metabolites were found in smaller amounts. Although the plasma half-life for minoxidil in humans averages about 4 hours, the duration of hypotensive action may be significantly longer, since it is affected by the hepatic blood flow.

The metabolic profile in the skin of rodents was determined at 24 and 216 hours postapplication. The drug was more extensively metabolized in mouse than rat skin. At least 11 additional peaks were detected in the former. The rat skin mainly contained the parent drug.

In a transdermal study using fresh human epidermis (breast/foreskin), at 72 hours only 3% of the applied radioactivity was found in the receptor fluid. Approximately 60% of the radioactivity was extracted in the skin surface swabs, and ~33% was present in the extract of homogenized skin. The *in vitro* dermal metabolism in humans consumed between 4-6% of the applied dose; the transdermal penetration was low and similar to that observed *in vivo*.

Figure 1. Biotransformation of Minoxidil



2.6.4.6 Excretion: Following a subcutaneous dose of minoxidil (0.9mg/kg) to rats, within a week 90% of the radioactivity was excreted in the urine, rest was found in the feces. It was inferred that most metabolites were hydrophilic in nature. The corresponding values in monkeys were only one-tenth of rats (0.9% and 1%), indicating a much reduced subcutaneous absorption. After the topical application, within the same post-dose period, only 9.5% and 0.7% of the radioactivity was excreted in the rat urine and feces; the rate of excretion in the females was two-fold greater than males. In monkeys approximately 5% of the radioactivity was found in the urine.

In rats, the amount of excretory metabolites after multiple dosing was not much different from that recovered after the single dose. The peak level of radioactivity in the rat milk was achieved at 30 minutes after the subcutaneous dose; at that time point the amount in milk (457ng/mL) was similar to that found in the maternal plasma (448ng/mL). However, the level of radioactivity in the milk increased with time; the levels were 41%, 720%, and 400% of the plasma levels at 2, 6, and 24 hours. After the topical application (0.9mg/kg), the amount of radioactivity in the rat milk was only 4% of that found after the subcutaneous dose. However, in this case as well the radioactivity in the milk increased with time, and the levels at 0.5, 1, 6, and 24 hours were 72%, 41%, 400%, and 100% greater than the plasma. At 48 hour, no radioactivity was detected in either of the fluids.

In humans, 80% of the orally administered minoxidil is excreted in the urine as metabolites.

2.6.4.7 Pharmacokinetic drug interactions: There are no known drug interactions with the topical minoxidil.

2.6.4.8 Other Pharmacokinetic Studies: None

2.6.4.9 Discussion and Conclusions: The low topical absorption, short half-life, fast metabolism, and insignificant drug accumulation suggests a sound safety profile for minoxidil.

2.6.6 TOXICOLOGY:

2.6.6.1 Overall toxicology summary: No new studies were reported. The information provided in this section is mostly extracted from the original NDA (20-834) review of Dr. Avalos Javier.

General toxicology: A single 6 hours topical exposure to minoxidil in rodents (mice up to 1350 and rats up to 900mg/kg) did not cause any systemic toxicity. Depending on the vehicle and the route of administration (oral, intravenous, intraperitoneal, and subcutaneous), the range for LD₅₀ in various species was as follows: mice 50-2400, rats 42-1900, and monkeys 1290-1670mg/kg. While mice had no gross lesions, vacuolization and necrosis in hepatocytes, and slight thickening of splenic capsule were observed in rats. In monkeys, the histopathologic lesions in the renal (tubular dilation, cellular debris/hyaline casts in tubular lumina), hepatic (vacuolar change), and cardiovascular (subacute myocarditis and moderate coagulative necrosis of myocardium) systems were observed.

In an oral rat study (10, 30, or 50mg minoxidil /kg/day in propylene glycol for one month, three month or one year), 4/6 deaths in the high-dose group were attributed to the drug treatment. In addition, in the mid- and high-dose rats, weights of liver, kidney and spleen were increased. The histopathologic examinations revealed a number of cardiovascular (degeneration, fibrosis, nuclear enlargement), hepatic (hepatocellular hypertrophy), pulmonary (increased alveolar macrophages in the lungs), and renal lesions (extensive nephritis). The mean plasma drug levels in males and females were 34, 253, 244 and 96, 754, and 1364ng/mL, respectively.

In one year rabbit dermal study (20, 60, 100mg minoxidil kg/day in propylene glycol), increased liver and heart weights and dilated ventricles were observed in the mid- and high-dose females. However, these changes were not associated with any histopathologic lesions. In a similar study in monkeys (1, 10 or 100mg/kg/day in propylene glycol), no systemic toxicity was observed.

In a 3-month dermal study in dogs (5, 10, or 40mg/kg/day), more extensive and severe adverse effects such as increased heart and liver weights, chronic proliferative epicarditis, chronic active inflammation of the atrial myocardium, hemorrhage and pigment, fibroblastic proliferation, neovascularization, and myocardial necrosis, were observed.

More severe cardio-renal toxicity occurred via the non-topical routes. In a rat oral (10, 30, or 100mg/kg/day) study, dilation and hypertrophy of heart were observed at the end of one year treatment. However, similar changes in other species were observed within much shorter period of treatment. For instance, in monkeys the hypertrophy of heart was observed after 32 days of oral treatment with 20mg minoxidil/kg/day; however, the same lesions at 14mg/kg/day took one year to develop. On the other hand, more sensitive

mini pigs only after two days of treatment with 1mg/kg/day oral dose, developed papillary muscle necrosis, atrial and ventricular hemorrhage, and coronary arteritis, Similar changes (atrial hemorrhage, hypertrophy, degeneration of muscle cells, coronary arteritis, and epicarditis on right atrial wall) were observed in dogs treated with an oral dose of 0.5mg/kg/day for 2-30 days.

In dogs at minoxidil blood level of 6-7ng /mL, 50% increase in heart rate was associated with minimum decrease in blood pressure. In hypertensive humans, the heart rate was changed only by 5 beats/minute at 25ng/mL level.

Genetic toxicology: Minoxidil was evaluated as non-mutagenic in Ames (125-2800µg/plate), DNA damage/alkaline elution (up to 10mM), unscheduled DNA synthesis (up to 100mg/plate), and chromosome aberration (up to 1880µg/mL) assays. The drug also tested negative in the rat (single oral dose of 5, 50 or 150mg/kg) and mouse (single oral dose of 250, 500, and 1,000mg/kg, or 250mg/kg for 4 days) bone marrow micronucleus assays. All tests were conducted at the appropriate dose levels, and validated with the use of proper controls.

Carcinogenicity: The potential carcinogenicity of minoxidil was evaluated in three oral and two dermal rodent bioassays. In addition, a photocarcinogenicity study was also conducted.

<u>Study type</u>	<u>Species</u>	<u>Dose (mg/kg/day)</u>	<u>Duration (months)</u>
Dietary admix	ICR mice	0, 3, 10, 30	18*
Dietary admix	—————	0, 10, 25, 63	24
Dietary admix	S-D rats	0, 3, 10, 30	22
Topical**	—————	0, 8, 25, 80	24
Topical**	Fischer rats	0, 8, 25, 80	24

*This compromised study was terminated after 16 months

** Vehicle: 50% propylene glycol+31.6%+18.4% water

Critical findings: Because of epizootic *Pseudomonas* infection (first detected at week 34) and resulting high mortality, the study in ICR mice was terminated after 16 months. In the second mouse study, the high-dose females developed malignant lymphomas; the males in the same group had hepatic nodules. A high mortality rate and shortened life were also recorded in the high-dose females. A positive dose response in the combined incidence of hemangiosarcomas was observed in males. However, the statistical significance of this incidence remained doubtful.

No drug related macro- or microscopic lesions were observed in the rat study.

In the mouse dermal study, drug related changes were mostly restricted to the high-dose groups. In males, it included increased incidence of basophilic cell foci, hyperplasia along with hepatocellular adenomas and the myocardial fibrosis in the heart. Females developed

hyperplasia along with adenoma and adenocarcinomas in the mammary gland, adenomas in the pituitary gland and infiltration in the urinary bladder. The development of adenocarcinomas was attributed to the chronic hormonal stimulation of the mammary gland. The positive linear trend for pituitary adenomas in females and hepatocellular adenomas and carcinomas in males were statistically insignificant. The inter-group survival rates were comparable.

In the rat dermal study as well, most of the non-neoplastic and neoplastic growths were observed in the high-dose animals. An increased incidence of chronic nephropathy, myocardial fibrosis, and capillary infiltration in the skin, and a dose-dependent formation of adrenal pheochromocytomas were observed in both the sexes. In addition, in males, the bile duct hyperplasia and vacuolated cell foci in the liver, and in females, cysts in the pituitary gland, were reported. The probable cause for the development of pheochromocytomas was attributed to a continual neurogenic stimulation of the adrenal gland due to hypotensive action of minoxidil. The survival rate was also reduced in the high-dose rats.

In the photocarcinogenicity bioassay, the hairless mice received daily topical applications of 0.1mL of the vehicle [ethanol+propylene glycol+water (30:50:20)], and 2% or 5% minoxidil 5 times per week for 40 weeks. During the treatment period, the animals were also exposed to either 273 or 545 Robertson-Berger Units (RBU) of solar stimulated irradiation (>280nm) for 5 days per week. The drug applications and UV exposure were alternated. Minoxidil did not promote UV induced (545 RBU) development of papillomas or carcinomas. Minoxidil also did not provide any photo protection.

Reproductive toxicology:

<u>Study type</u>	<u>Dose (mg/kg/day)</u>	<u>Route</u>	<u>Critical findings/conclusions</u>
Rat segment I	0, 3, 10	oral	Dose related decrease in conception
Rat segment II	up to 80	sc	No teratogenicity
Rat segment II	120mg	sc	Skeletal abnormalities and variations, Increased embryonic and fetal mortality, Decreased fetal weights. <u>Teratogenic</u>
Rabbit segment II	0, 3, 10	oral	No teratogenicity
Rabbit segment II	up to 49	sc	No teratogenicity

In a segment II subcutaneous rat study, no teratogenic changes were observed at 80mg/kg/day. Considering this dose as NOEL for developmental toxicity, and only 4% absorption in humans versus 32% absorption in rats, the margin of safety will be 60 times (mg/m^2). In another subcutaneous segment II rat study, the teratogenic effects were observed at 120mg/kg/day dose level. This dose was 92 times (mg/m^2) greater than the clinical dose.

In the original NDA (20-834) review, no segment III study was reviewed.

2.6.6.7 Local tolerance: No studies were conducted with the foam formulation. Previously conducted studies evaluated the contact sensitization, phototoxic, photoallergic, ocular and dermal irritation potential of minoxidil. The drug at 1-3% strength (in propylene glycol:ethanol:water) did not elicit any delayed contact sensitization response in guinea pigs after the topical or intradermal induction. In guinea pigs, no phototoxic or photoallergic responses were achieved with the topical applications of 2% solution followed by 90 minutes exposure to UVA and UVB. No dermal irritation developed in rabbits with applications of 1-5% minoxidil solutions. No dermal irritation occurred in rabbits receiving topical applications of 0.1-1% minoxidil solutions previously exposed to sunlight for 6 months. Intramuscular injection (in lumbar muscle) of 5mg minoxidil/mL to rabbits also failed to cause any dermal irritation in rabbits. In a rabbit assay, 1-2% minoxidil solution tested as a moderate ocular irritant.

2.6.6.8 Special toxicology studies: The sponsor conducted a number of studies to explain the development of neoplastic and non-neoplastic lesions in the rodent carcinogenicity studies. The endocrine and reproductive organs obtained from the carcinogenicity studies were used in these investigations. These organs were re-evaluated histologically to confirm the original findings. The re-examination of pituitary glands from the oral carcinogenicity study revealed an increase in adenomas in female mice (control 22/60, low-dose 37/60, mid-dose 39/60, and high-dose 33/60). This increase was statistically significant in the low-and mid-dose ($p=0.01$) and high-dose ($p=0.05$) groups. A significant increase in the epithelial development of seminal vesicles was also reported in male rats. However, none of these findings were linked to any drug induced change in the hormonal environment as suggested by the sponsor.

Prolactin levels in the serum and pituitary gland were determined in female mice prior to proestrus period and after the oral administration of minoxidil for 7, 30, and 90 days. The level of prolactin in the serum, weights of uterus and vagina, and the cell activity in two organs were decreased within 7-11 days of treatment. At the same time, the concentration of prolactin in the pituitary was increased. The findings in a 7-day study in mice with normal estrous cycle were just the opposite, suggesting that the changes observed in the first study were influenced by the status of estrous cycle itself.

In the 90-day topical study (80mg/kg/day) in diestrous and proestrous mice, the serum prolactin levels at various time points were similar to reserpine (positive control) treated animals. A decrease in serum prolactin was observed during the diestrous period both in minoxidil and reserpine treated mice. However, during proestrous period, the serum prolactin levels in the negative control (bromocriptine) and minoxidil treated mice were similar, but an increase in level was observed in the reserpine group. It was inferred that the topical minoxidil increased the serum hormone level during the estrous period and decreased it during the diestrous period. Since the findings of oral and topical studies were different, the suggestion made by the sponsor that the chronic treatment with minoxidil may have induced the mammary tumors in mice by hormonal (prolactin) changes is questionable.

The potential estrogenic activity of minoxidil was evaluated in ovariectomized B₆C₃F₁ mice receiving oral doses of 300mg/kg/day for 7 days, or 80mg/kg/day topically for 7 days with or without 0.1-1.0µg of diethylstilbestrol. The weights of uterus and ovary were not affected indicating lack of any estrogenic activity.

In 90-day topical (80mg/kg/day) studies in male rats and mice, the pituitary prolactin level and FSH (follicle stimulating hormone), and liver weights were increased in rats. The histological examination in male mice revealed dilatation of secretory ducts, decreased glandular cell activity of the coagulating gland, increased glandular vacuolation of the preputial gland, and increased epithelial cell activity in the epididymis.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: Minoxidil had been extensively tested non-clinically and clinically. In the first two decades, it was evaluated as an oral and intravenous anti-hypertension agent. As expected, the majority of these studies were conducted in rodents, and to a limited extent in other species. Mostly non-topical routes (oral, intravenous, intraperitoneal) of drug administration were used for these investigations. In the last two decades, the topical formulations of this drug had also been tested for the treatment of male pattern baldness (androgenic alopecia of the vertex). These studies were conducted mainly using the dermal route.

An interspecies comparison of pharmacokinetic behavior and systemic toxicity of minoxidil has revealed good similarity between monkeys and humans. The use of monkey as an appropriate model to evaluate the clinical safety of minoxidil has also been supported by the fact that like adult humans, adult stump tail macaques monkeys (*Macaca arctoides*) also develop bald foreheads. This strain of monkey had also been used in the experimental dermatology to evaluate other topical drugs.

Irrespective of the route of drug administration, all test species with the sole exception of monkeys, are highly sensitive to minoxidil treatment. The major reason for extensive systemic toxicity in these species is a greater topical absorption, resulting in plasma drug levels crossing the threshold for systemic toxicity. Thus, mini pigs within two days of daily treatment with just 1mg oral minoxidil/kg developed papillary muscle necrosis, atrial and ventricular hemorrhage, and coronary arteritis. On the other hand, dogs exhibited similar lesions within 30 days at 0.5mg/kg/day dose level. However, in monkeys it took 32 days of daily oral dosing with 20mg minoxidil/kg to produce limited adverse cardio-renal changes.

Whereas absolutely no systemic toxicity was observed in monkeys treated topically for one year with 100mg/kg/day (24 times the proposed topical dose in humans in mg/m²), dogs on the other hand, developed cardio-renal lesions within 3 months of daily applications with 2.5 mg minoxidil/kg (~8 times the human dose).

A similar interspecies pattern was observed for pharmacokinetics. The topical absorption of minoxidil in monkeys and humans was low (mean average 5% in monkeys, and 4% in

humans), in rodents and dogs it ranged between 32-48% of the applied amounts. However, there were also some similarities between the species. In all species including humans, irrespective of the route of administration, the C_{max} in the plasma was achieved within 6 hours. Second, minoxidil goes through extensive first pass metabolism in all the species. Third, irrespective of the route of administration, the distribution profiles in the test species were similar. Fourth, in various species, urinary metabolic profiles were similar. However, among various species, some quantitative differences were observed in relative amounts of metabolites. For instance, in monkeys and humans, glucuronides (detoxified metabolites) comprised the major portion of urinary metabolites, in rodents (especially rats) the parent drug (active metabolite) was the major excretory product. Fifth, no significant drug accumulation was observed in any of the tested species, indicating fast metabolism.

The half life for minoxidil in humans is about 4 hours, and there is no pharmacokinetic evidence of any drug accumulation.

Some serious deficiencies were observed in the non-clinical pharmacokinetic studies, especially in rodents. A dose-response relationship was not established. The data of two parallel pharmacokinetic studies in the same strain of a species were widely different. These differences were attributed to different protocols and stock solutions.

No systemic toxicity in monkeys was observed at the topical dose level of 100mg/kg/day. At a maximum absorption of 4% in humans and 5% in monkeys, the NOEL in monkeys will be 60mg/m²/day. That means the proposed human topical dose is 24 times lower than the NOEL in monkeys.

Whereas, the systemic toxicity in humans via the intravenous route occurred at the serum minoxidil level of 20ng/mL or above, the highest level of serum drug level achieved with the foam formulation was only 3.52ng/mL, i.e. approximately 6 times lower than the threshold level for systemic toxicity.

In two rodent dermal carcinogenicity studies (8, 25, or 80mg/kg/day for 24 months), no drug related gross or histopathologic lesions were found in rats. In mice, lesions restricted to the mid- and high-dose animals included basophilic cell foci, hyperplasia along with hepatocellular adenomas and myocardial fibrosis of heart in males, and hyperplasia along with adenocarcinomas in the mammary glands and the adenomas in the pituitary of females. Of the applied topical dose in mice, 48% was absorbed. The proposed clinical dose for the foam formulation is 2 grams/day (equivalent to 100mg/day). The maximum absorption in humans was 4% (2.5mg/m²/day), providing a margin of safety 14 times the proposed clinical dose. In addition, revised statistical analyses indicated that the incidences of individual or combined tumor were insignificant.

In a photocarcinogenicity study in hairless mice, minoxidil did not induce or promote the development of papillomas or carcinomas

There was no true dermal study among the reported segment II studies. Irrespective, in the rat subcutaneous study, no teratogenic changes were observed at 80mg/kg/day. Accounting

for 4% and 32% dermal absorption in humans and rats, respectively, the proposed clinical dose is 62 times lower than the NOEL for the developmental toxicity in rats.

Taking into account all the safety factors such as low human topical absorption, fast metabolism, lack of drug accumulation, fair safety margins for systemic toxicity, carcinogenicity and teratogenicity, it is expected that Minoxidil 5% Topical Foam will be safe to use.

Unresolved toxicology issues (if any): None

Recommendations: From the non-clinical point of view, I have no objection to the approval of New Drug Application number 21-812.

Suggested labeling: The labeling draft submitted by the sponsor is almost identical to the one approved for 5% minoxidil solution. It includes the appropriate information for the safe use of foam formulation. No additional recommendation is warranted.

Signatures (optional):

Reviewer Signature _____

Supervisor Signature _____ Concurrence Yes ___ No ___

APPENDIX/ATTACHMENTS

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/s/

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