PRODUCT MONOGRAPH

MINOX

Minoxidil Topical Solution USP

20 mg/mL (2% w/v)

Hair Regrowth Treatment

THIS PRODUCT IS FOR MEN ONLY

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20 mg/mL (2%)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Topical	Solution 2% (20 mg/mL)	Alcohol, propylene glycol and water

INDICATIONS AND CLINICAL USE

- MINOX (2% minoxidil topical solution) is indicated for the treatment of male androgenetic alopecia (male pattern hair loss) on the top of the scalp (vertex).
- MINOX is not approved for use in women.
- The effectiveness of MINOX in the treatment of receding hairlines has not been demonstrated in clinical trials.
- MINOX: the effect is maintained only for as long as the product is used. Cessation of treatment will result in loss of the newly re-grown hair within about 3 months and progressive hair loss will resume.

Geriatrics (> 65 years of age):

The safety and efficacy of MINOX in men over 65 have not been tested in clinical studies.

Pediatrics (< 18 years of age):

The safety and efficacy of MINOX have not been established in children under 18.

CONTRAINDICATIONS

MINOX is contraindicated:

- in Women.
- in individuals with a history of hypersensitivity to minoxidil or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.
- in individuals with treated or untreated hypertension.
- in individuals whose baldness is not due to hereditary factors. MINOX is only effective for the treatment of male vertex alopecia androgenetica.

- in individuals with any scalp abnormality (including psoriasis and sunburn).
- in individuals with a shaved scalp or whose scalp's skin is broken, inflamed, irritated, infected, or severely sunburned.
- if occlusive dressings or other topical therapeutic medications for treating disorders of the skin of the scalp are being used.
- Certain prescription and non prescription medications, certain treatments, such as cancer chemotherapy, or certain diseases, such as iron deficiency, thyroid disorders or secondary syphilis, as well as severe nutritional problems and certain grooming habits (eg. Cornrowing, tight ponytails), may also cause temporary hair loss which should not be treated with MINOX.

WARNINGS AND PRECAUTIONS

General

- MINOX is for external use only. Apply only to scalp.
- Before applying MINOX, the user should determine that the scalp is normal and healthy.
- Hands should be washed thoroughly after use.
- Inhalation of the spray should be avoided.
- MINOX contains ethanol (alcohol) which will cause burning and irritation of the eye. In the event of accidental contact with sensitive surfaces (eye, abraded skin, mucous membranes), the area should be bathed with large amounts of cool tap water.
- Some patients have experienced changes in hair colour and/or texture with MINOX use.
- Shedding of hair may occur within two to six weeks after initiating therapy, likely due to minoxidil's action on shifting hairs from the resting telogen phase to the growing anagen phase. If shedding persists for more than two weeks, users should stop applying MINOX and consult their doctor.
- MINOX should not be used when there is no family history of hair loss, hair loss is sudden and/or patchy, or the reason for hair loss is unknown.

Cardiovascular

- Patients with known cardiovascular disease or cardiac arrhythmia should contact a physician before using MINOX.
- Although the following systemic effects have not been associated with the topical use of MINOX, there is some absorption of minoxidil from the skin and the potential exists for systemic effects such as salt and water retention, hypertension, tachycardia, angina, and edema.
- The patient should stop using MINOX and see a doctor if hypotension is detected or if the patient is experiencing chest pain, rapid heartbeat, faintness or dizziness, sudden unexplained weight gain, swollen hands or feet, or persistent redness.

Special Populations

Women: MINOX is not approved for use in women.

Geriatrics (> 65 years of age): The efficacy and safety of MINOX in men over 65 years of age have not been established. MINOX should not be used in the geriatric population.

Pediatrics (< 18 years of age): The efficacy and safety of MINOX in children under 18 years of age have not been established. MINOX should not be used in the pediatric population.

Monitoring and Laboratory Tests: Patients should be monitored for signs of systemic effects of minoxidil such as hypotension, chest pain, rapid heartbeat, faintness or dizziness, sudden unexplained weight gain, swollen hands or feet, persistent redness or irritation of the scalp. The use of MINOX should be discontinued in the event of systemic effects and/or severe dermatologic reactions.

ADVERSE REACTIONS

ADVERSE DRUG REACTION OVERVIEW

The most frequently encountered adverse events in clinical trials with MINOX were minor respiratory events which included colds and respiratory infections (3.37%), rhinitis (1.26%), sinusitis (1.18%), and coughing (1.09%). Dermatological adverse reactions were the next most frequent adverse reactions reported and included scaling (1.35%), itching (1.94%), and rash (1.43%).

CLINICAL TRIAL ADVERSE DRUG REACTIONS

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The occurrence rates of adverse reactions seen in greater than 1% of male patients were obtained from placebo controlled clinical studies involving 2386 patients (1188 Minoxidil 2% Topical Solution and 1198 placebo) and are listed below in Table 1.

Table 1: Adverse Reactions observed in >1% of male patients treated with Minoxidil 2% Topical Solution as compared to patients treated with placebo

Primary System Organ Class	Medical Events by Preferred Terms	Minoxidil 2% Topical Solution (N=1188)		Placebo (N=1198)	
		N	%	N	%
General Disorders and Administration Site Conditions	Oropharyngeal pain	21	1.77	28	2.34
	Dental discomfort	12	1.01	7	0.58
Infections and Infestations	Bacterial infection	24	2.02	23	1.92
Musculoskeletal and Connective Tissue Disorders	Back pain / Muscle strain / Muscle spasms	13	1.09	7	0.58
Respiratory, Thoracic, and Mediastinal Disorders	Rhinitis	15	1.26	16	1.34
	Cough	13	1.09	6	0.50
	Nasopharyngitis / Upper respiratory tract infection	40	3.37	52	4.34
	Sinusitis	14	1.18	11	0.92
Skin and Subcutaneous Tissue Disorders	Rash	17	1.43	5	0.42
	Itching	23	1.94	15	1.25
	Skin exfoliation	16	1.35	13	1.09

Adverse Events seen in less than 1% of males using minoxidil 2% topical solution

Ear and Labyrinth Disorders: ear infection and ear inflammation.

Eye Disorders: conjunctivitis.

Gastrointestinal Disorders: abdominal pain, nausea, diarrhoea, vomiting, tonsillitis, gastroenteritis, hemorrhoids, and aphthous stomatitis.

General Disorders and Administration Site Conditions: pyrexia and fatigue.

Hepatobiliary disorders: hepatitis.

Immune System Disorders: hypersensitivity, seasonal allergy, influenza-like illness, and urticaria.

Injury, Poisoning, and Procedural Complications: injury.

Investigations: Weight increased.

Metabolism and Nutritional Disorders: oedema and weight gain.

Musculoskeletal and Connective Tissue Disorders: myalgia, fracture, arthralgia, musculoskeletal stiffness and myositis, muscle strain, and tendon, bursa, and ligament disorders.

Nervous system Disorders: dizziness, asthenia, headache, insomnia, paresthesia, and sciatica.

Renal and urinary Disorders: nephrolithiasis and urethritis.

Reproductive System and Breast Disorders: prostatitis and epididymal disorder.

Respiratory, Thoracic, and Mediastinal Disorders: pulmonary congestion, sneezing, pharyngitis, and bronchitis.

Skin and Subcutaneous Tissue Disorders: eczema, hypertrichosis, seborrhea, folliculitis, dry

skin, dermatitis, erythema, skin burning sensation, cellulitis, and skin irritation.

Vascular Disorders: hypotension, blood pressure increased, chest discomfort, tachycardia, and heart rate increased/decreased.

POST-MARKET ADVERSE DRUG REACTIONS

The following adverse drug reactions (ADRs) have been identified with the application of topical minoxidil during post-marketing use. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to the use of the drug. In the table 2 below, the ADRs are presented with ADR frequency categories estimated from spontaneous reporting rates according to the following convention:

Very common	≥1/10
Common	≥1/100 and < 1/10
Uncommon	≥1/1,000 and <1/100
Rare	≥1/10,000 and <1/1,000
Very rare	<1/10,000
Not known	(cannot be estimated from the available data)

Table 2: Adverse Drug Reactions Identified During Post-Marketing Experience with Topical Minoxidil by Frequency Category Estimated from Spontaneous Reporting Rates

System Organ Class	Adverse Event Preferred Term
Immune System Disorders	
Very rare	*Angioedema (the manifestations of angioedema may include the following: Lip oedema, Oedema mouth, Oropharyngeal swelling, Pharyngeal oedema, and Tongue oedema)*
Very rare	*Hypersensitivity (the manifestations of hypersensitivity reactions may include the following: Face oedema, Generalised erythema, Pruritus generalised, and Throat tightness)*
Very rare	*Dermatitis contact*
Psychiatric Disorders	
Very rare	*Depressed mood*
Nervous System Disorders	
Very rare	*Dizziness*
Eye Disorders	
Very rare	*Eye irritation*
Cardiac Disorders	
Very rare	*Tachycardia*
Very rare	*Palpitations*
Vascular Disorders	
Very rare	*Hypotension*
Gastrointestinal Disorders	
Very rare	*Nausea*
Very rare	*Vomiting*
Skin and Subcutaneous Tissue Disorders	

Very rare	*Application site reaction (these sometimes involve nearby structures like the ears and face and typically consist of pruritus, irritation, pain, rash, oedema, dry skin, and erythema but can sometimes be more severe and include exfoliation, dermatitis, blistering, bleeding, and ulceration)*
Very rare	*Alopecia*
Very rare	*Hair colour changes*
Very rare	*Hair texture abnormal*
General Disorders and Administration Site Conditions	
Very rare	*Chest pain*

DRUG INTERACTIONS

OVERVIEW

There are currently no known drug interactions associated with concomitant use of systemic drugs and topical minoxidil. Absorption of topical minoxidil is controlled and rate-limited by the stratum corneum. However, there is a potential risk that the minoxidil in MINOX may interact with vasodilators, e.g., hydralazine.

DRUG-DRUG INTERACTIONS

Topical drugs, e.g., tretinoin and anthralin, which alter the stratum corneum barrier, could result in increased absorption of topical minoxidil if applied concurrently. Betamethasone diproprionate has been shown to increase local tissue concentrations of Minoxidil and decreases systemic Minoxidil absorption in healthy volunteers. However, the effect of Betamethasone dipropionate on Minoxidil absorption with an inflamed scalp is not known. Although it has not been demonstrated clinically, there exists the theoretical possibility of absorbed Minoxidil potentiating orthostatic hypotension caused by peripheral vasodilators.

DRUG-FOOD INTERACTIONS

Interactions with food have not been established.

DRUG-HERB INTERACTIONS

Interactions with herbs have not been established.

DRUG-LABORATORY INTERACTIONS

Interactions with drug laboratory tests have not been established.

DRUG-LIFESTYLE INTERACTIONS

Interactions with lifestyle have not been established.

DOSAGE AND ADMINISTRATION

DOSING CONSIDERATIONS

MINOX is not approved for use in women.

FOR EXTERNAL USE ONLY. Use MINOX (minoxidil topical solution) only as directed. Apply MINOX **when the hair and scalp are thoroughly dry.** The safety and efficacy of MINOX in users aged under 18 or over 65 years of age have not been established.

RECOMMENDED DOSE AND DOSAGE ADJUSTMENT

A total dose of 1 mL MINOX (20 mg minoxidil) should be applied twice per day to the scalp, beginning at the center of the affected area. This dose should be used regardless of the size of the affected area. The total daily dose should not exceed 2 mL (40 mg minoxidil). The method of application varies according to the disposable applicator used, as indicated below. After applying MINOX, wash hands thoroughly. Do not apply MINOX to any other area of the body.

MISSED DOSE

If a dose is missed, MINOX should be applied as soon as remembered, if within a few hours of the time usually applied. Do not apply if it is almost time for the next dose. If a dose is missed, the amount used in the next regular dose should not be doubled.

ADMINISTRATION

A. Pump Spray Applicator

Works best for applying MINOX to large areas of the scalp.

1) Remove Child-Resistant cap by pushing down while turning the cap anti-clockwise. Retain Child-Resistant cap.
2) Insert the pump-spray applicator into the bottle and screw on tightly.
3) After aiming the pump at the centre of the thinning or bald area of the scalp, press the pump once and spread MINOX with fingertips to cover all the thinning or bald area. Repeat for a total of 4 times to apply a total dose of 1 mL. **Avoid breathing spray mist.**
4) To retain Child-Resistant feature, remove Pump-Spray applicator and retain for next application. Replace Child-Resistant cap by tightly screwing on in a clockwise direction.

B. Rub-On Applicator

Works best for applying MINOX to small areas of the scalp.

1) Remove Child-Resistant cap by pushing down while turning the cap anti-clockwise. Retain Child-Resistant cap.
2) Insert the rub-on applicator into the bottle and screw on tightly. Remove outer cap and keep it.
3) Hold the bottle upright and squeeze it once to half fill the upper chamber. The level of liquid in the chamber will automatically adjust to deliver one full dose (1 mL).
4) Hold the bottle upside down then rub applicator on your scalp to apply MINOX over the

whole thinning or bald area until the chamber is completely empty. Replace outer cap over the rub-on applicator when not in use.

5) To retain Child-Resistant feature, remove Rub-On applicator and retain for next application. Replace Child-Resistant cap by tightly screwing on in a clockwise direction.

C. Extended Spray-Tip Applicator

Works best for applying MINOX to small areas of the scalp or under hair.

1) Remove Child-Resistant cap by pushing down while turning the cap anti-clockwise. Retain Child-Resistant cap.
2) Insert the pump-spray applicator into the bottle and screw on tightly.
3) Remove small spray head from top of pump-spray applicator.
4) Fit the extended spray-tip applicator onto the spray shaft and push down firmly.
5) Remove the small cap on the end of the extended tip and keep it.
6) After aiming the applicator at the centre of the thinning or bald area of the scalp, press the pump once and spread MINOX with fingertips to cover all the thinning or bald area. Repeat for a total of 4 times to apply a total dose of 1 mL. **Avoid breathing spray mist.**
7) To retain Child-Resistant feature, remove Extended Spray-Tip applicator and retain for next application. Replace Child-Resistant cap by tightly screwing on in a clockwise direction.

OVERDOSAGE

Accidental ingestion of MINOX can cause serious adverse effects. Contact your regional Poison Control Centre immediately.

Because of the high concentration of minoxidil in MINOX, accidental oral ingestion could result in systemic absorption sufficient to cause the predictable cardiovascular effects of minoxidil (e.g., reduced blood pressure, reflex tachycardia, fluid retention).

Signs and symptoms of overdosage would most likely include cardiovascular effects associated with fluid retention, sudden weight gain, lowered blood pressure and tachycardia, faintness and dizziness. Fluid retention can be managed with appropriate diuretic therapy. Tachycardia can be controlled by administration of beta-adrenergic blocking agent.

Minoxidil and its metabolites are hemodialyzable, although this does not rapidly reverse its pharmacological effect.

Significant toxicity after minoxidil exposure, whether tablet or topical formulations, was associated with oral route, intentional reason, and co-ingestion of other products. A male who ingested 60 mL (one bottle) of 2% minoxidil with 12 ounces of cognac experienced tachycardia, hypotension, and a non-Q wave myocardial infarction. In another report, a patient who inadvertently drank minoxidil solution (he ingested 600 mg), developed syncope, hypotension, and acute renal failure.

There have been 27 spontaneous reports of unintentional oral exposure to minoxidil solution involving 12 pediatric patients and 15 adults. No adverse events were associated with 17 of the reports. Of the remaining 10 cases, one pediatric patient experienced lethargy, one pediatric patient had flushed cheeks, and one pediatric patient was more active and had diarrhea. One adult patient had tachycardia in addition to nausea and vomiting.

If exaggerated hypotension is encountered, it is most likely to occur in association with residual sympathetic nervous system blockade from previous therapy (guanethidine-like effects or alpha-adrenergic blockade). The recommended treatment is intravenous administration of normal saline.

Sympathomimetic drugs, such as norepinephrine or epinephrine, should be avoided because of their excessive cardiac-stimulating action. Phenylephrine, angiotensin II, vasopressin and dopamine, which reverse the effects of orally administered minoxidil, should only be used if inadequate perfusion of a vital organ is evident.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

When applied topically, minoxidil 2% topical solution has been shown to stimulate hair growth in males with androgenetic alopecia. The basic change in androgenetic alopecia is the conversion of terminal, non-vellus hair to vellus hair, i.e., hair which is thinner, shorter, and less pigmented.

Although the exact mechanism of action of minoxidil in the treatment of androgenetic alopecia is not known, there may be more than one mechanism by which minoxidil 2% topical solution stimulates hair growth; they include:

- vasodilation of the micro circulation around the hair follicles which may stimulate hair growth;
- direct stimulation of the hair follicle cells to enter into a proliferative phase; resting phase (telogen)
- follicles being stimulated to pass into growth phase (anagen) follicles.

Pharmacodynamics

The hemodynamic effects of minoxidil do not correlate directly with serum levels. There is a delay in onset relative to observable serum concentrations, peak hemodynamic effects lag one hour behind peak serum concentrations, and hemodynamic effects persist long after nearly all the minoxidil has disappeared from the circulation. It appears that minoxidil requires bioactivation before exerting its hemodynamic activity. The active metabolite is considered to be minoxidil sulphate. Sulfotransferase enzyme which converts minoxidil to minoxidil sulphate has been isolated from various human tissues including liver, platelets, scalp skin, hair follicles and epidermal keratinocytes. The effects of minoxidil on hair regrowth are possibly mediated by this active metabolite as well. In clinical studies, no correlation was established between serum or tissue minoxidil concentrations and hair regrowth.

Pharmacokinetics

Absorption

Absorption of topical minoxidil averages about 1.4% (range 0.3 to 4.5%) from normal intact scalp. Absorption is about 2% when applied topically to shaved scalps of hypertensive patients. Increasing the amount of drug applied or increasing the frequency of application of topical minoxidil also results in increased absorption. The use of minoxidil in conjunction with occlusion (plastic dressing) application to sunburn areas, and increasing the surface area of application has minimal to no effect on the absorption of topical minoxidil.

Results of extensive pharmacokinetic studies indicate that the three major factors by which topical minoxidil absorption is increased are:

- increasing the magnitude of the dose applied;
- increasing the frequency of dosing; and
- decreasing the barrier function of the stratum corneum.

The following table (table 3) provides serum minoxidil concentrations measured in clinical efficacy studies.

Table 3: Serum concentrations of total minoxidil after the application of 1 mL of minoxidil 2% topical solution twice daily

Serum minoxidil concentration (ng/mL)	Interval of exposure to Treatment					Summary		
	0-6 mths N	7-12 mths N	13-24 mths N	25-36 mths N	37-54 mths N	N	%	Cumulative %
<0.1	601	320	211	121	84	1337	31.2	31.2
0.1-2.0	1082	692	510	340	140	2764	64.5	95.6
2.1-5.0	65	38	28	17	7	155	3.6	99.3
5.1-8.0	6	3	2	4	0	15	0.3	99.6
8.1-12.0	4	3	2	0	0	9	0.2	99.8
12.1-15.0	1	0	0	0	0	1	0	99.8
15.1-18.0	1	0	0	0	0	1	0	99.9
18.1-21.0	0	1	0	0	1	2	0	99.9
> 21.0	1	3	0	0	0	4	0.1	100
Total	1761	1060	753	482	232	4288	100	100

Although the percutaneous drug absorption data are highly variable, the table 3 shows that more than 99% of the values are below 5 ng/mL and less than 0.2% exceeds 12 ng/mL.

Absorption from the gastrointestinal tract following oral administration of minoxidil tablets is essentially complete (at least 95%).

Distribution

Minoxidil does not bind to plasma proteins; its renal clearance corresponds to glomerular filtration rate and it does not cross the blood brain barrier. Minoxidil and its metabolites are hemodialyzable, although this does not rapidly reverse its pharmacological effect.

Metabolism

Approximately 90% of orally administered minoxidil is metabolized, predominantly by conjugation with glucuronic acid at the N-oxide position in the pyrimidine ring and by conversion to more polar products.

Excretion

Serum minoxidil levels and systemic effects resulting from administration of topical minoxidil are governed by the drug's absorption rate through the skin. Following cessation of topical dosing of minoxidil, approximately 95% of systemically absorbed drug is eliminated within four days. Minoxidil and its metabolites are excreted principally in the urine.

STORAGE AND STABILITY

MINOX should be stored at controlled room temperature (15-30 °C).

DOSAGE FORMS, COMPOSITION AND PACKAGING

Each kit of MINOX contains the following:

MINOX (minoxidil topical solution) 20 mg minoxidil per mL (2%), as 60 mL of solution in a HDPE bottle with one or more of the following metered disposable applicators: Pump Spray, Extended Spray Tip and a Rub-On-Applicator. For external use only.

MINOX (minoxidil topical solution) contains minoxidil, at a concentration equivalent to 20 mg minoxidil per mL in a solution composed of alcohol, purified water and propylene glycol. MINOX is a clear, colourless to slightly yellow solution. The yellow colour will not alter its effectiveness.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

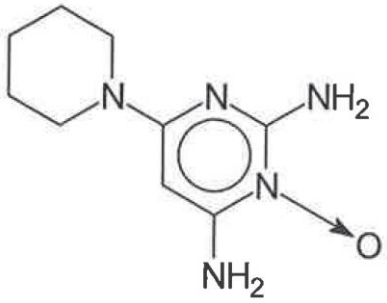
Proper Name: minoxidil

Chemical Name: 2,4,-Pyrimidinediamine,6-(1-piperidinyl)-,3-oxide;
2,6-Diamino-4-piper-idinopyrimidine 1-oxide

Molecular weight: 209.25 g/mol

Molecular Formula : $C_9H_{15}N_5O$

Structural Formula:



Description: A white to off-white, crystalline powder. Soluble in Alcohol and in Propylene Glycol; soluble in Methanol; slightly soluble in Water; practically insoluble in Chloroform, in Acetone, in Ethyl Acetate and in Hexane. It has a melting point of 248°, a pKa of 4.60, a logP of 0.6 (octanol/water partition coefficient), and a pH in an aqueous solution of 7.0 (due to very low solubility in water).

CLINICAL TRIALS

CLINICAL EFFICACY AND SAFETY STUDIES

MINOXIDIL 2% TOPICAL SOLUTION (Minoxidil 20 mg/mL [2% w/v])

The effectiveness of 2% topical minoxidil solution (MTS) for the treatment of androgenetic alopecia was studied in well-controlled protocols involving more than 2800 men and 850 women[1]. The results are summarized as follows:

A 6-month, placebo-controlled, dose-response study was conducted in 503 men with androgenetic alopecia to compare the efficacy/safety of (0.01%, 0.1%, 1% and 2%) of topical minoxidil vs. placebo[2]. This study demonstrated that 2% MTS was significantly more effective than placebo for mean change from baseline in non-vellus hair count. There was no significant difference between 1% MTS and placebo for this variable. In addition, 2% MTS was significantly more effective than 1% MTS for new hair growth.

Results of 4-month, placebo-controlled protocols in men showed that the mean change from baseline in hair counts at Month 4 were significantly greater in 2% MTS-treated patients than in placebo-treated patients. Between Month 4 and 12, patients treated with 2% MTS continued to show significant increases in hair counts.

A multicentre double-blind and randomized study of 285 patients, with mild to moderate hypertension, was conducted to ascertain if topical minoxidil can produce systemic physiologic changes in patients with hypertension, in the absence of concomitant antihypertensive therapy.

Six treatment groups were evaluated: 1%, 2%, and 5% topical minoxidil solutions, 2.5 mg and 5 mg oral minoxidil doses, and placebo were given twice daily for 4 consecutive days. Systemic pharmacologic effect of absorbed minoxidil was monitored primarily in terms of reductions of mean diastolic blood pressure (seated) and increased pulse rate. Other similar measurements were also performed. Based on all primary and supportive measures, 2% topical minoxidil did not demonstrate systemic pharmacologic effects (blood pressure reduction, tachycardia and edema) seen with the oral dosage forms.

Minoxidil 2% topical solution is not effective in all individuals. After 4 months of treatment with minoxidil 2% topical solution, only 26% of individuals reported moderate (defined as new individual hairs that covered all or some of the thinning areas but not as close together as hairs on the rest of the head) to dense hair regrowth (new hairs that cover or almost completely cover the thinning area and are as close together as hairs on the non-thinning areas of the head). A similar response was obtained in 11% of the subjects using the vehicle control. Thirty-one percent of the vehicle users and 33% of the minoxidil 2% topical solution users reported minimal regrowth at 4 months.

The net increase of non-vellus hair attributable to minoxidil was a mean of 33 hairs in a circle one inch in diameter. The investigator's global improvement rating showed no statistically significant difference in terminal hair growth between treatment groups.

After further 8 months of treatment, the 2% group had an additional 112 non-vellus hairs. Based on the investigator's assessment, 39% of the subjects achieved moderate to dense terminal hair while 40% of the users rated their regrowth as moderate and 8% as dense; 36% reported minimal regrowth (some new hairs which do not grow as close together as hairs on non-thinning areas and not enough to cover the thinning areas) while 16% had no regrowth.

A temporary hair loss may occur upon initiation of therapy; this increase in shedding generally occurs 2 - 6 weeks after the beginning of treatment and subsides within a few weeks. This shedding upon initiation of therapy is due to hair shifting from resting phase (telogen) to growth phase (anagen).

The response time differs greatly between individuals. It takes at least 4 months of twice daily applications. The effect is maintained only for as long as the product is used. Cessation of treatment will result in loss of the newly regrown hair within about 3 months and progressive hair loss will resume.

It is not known which individuals may show a satisfactory response, but younger men who have been balding for a shorter period of time (less than 10 years) or who have a smaller area of hair loss (less than a diameter of 4 inches) tend to respond better than older men who have been balding for longer periods of time and/or have a large area of hair loss or in those with an area of baldness that is devoid of all hair.

Skin Irritation/Hypersensitivity

Minoxidil 2% topical solution did not cause phototoxicity, skin sensitization, or photoallergic reactions in four studies conducted to determine skin sensitization/phototoxic/allergenic potential and the effect of UV-B induced erythema[3].

DETAILED PHARMACOLOGY

Animal Data

Pharmacokinetics

In Vivo studies

Results from a long-term dermal toxicity study in rats concluded that there was no apparent relationship between the nadir minoxidil levels and gross cardiac pathology. These nadir minoxidil levels in the rat were approximately 40 to 500 times higher than those documented in humans.

Results from a long-term dermal toxicity in rabbits concluded that increased heart and liver weights were drug-related; however no concomitant histopathologic lesions were seen.

The following table (table 4) provides a comparison of topically absorbed doses from a 2-year dermal carcinogenicity study in mouse and rat, compared to results obtained from humans using the recommended twice daily dose of Minoxidil 2% topical solution. The table 4 demonstrates that on a mg/kg basis, the animals received higher doses than humans. In addition, the % minoxidil absorbed was much higher in the animals. Both of these factors indicate that the systemic exposure

to minoxidil in animals (in preclinical toxicity studies) is several hundred times greater than that associated with clinically recommended doses in man.

Table 4: Comparison of Minoxidil Absorption from different doses in Mouse and Rat to that from Minoxidil 2% topical solution BID in Humans

	Mouse			Rat			Man
Dose (mg/kg/day)	8	25	80	8	25	80	0.57
% absorbed	-	47.6	-	-	32.4	-	1.4
Available dose (mg/kg/day)	3.8	11.9	38.1	2.59	8.10	25.9	0.009
Ratio (animal/man)	422	1322	4233	288	900	2878	1.0

Following topical application, the urinary metabolite profiles in the rat corresponded closely to those observed after systemic administration, suggesting that metabolism was not altered by entry across the skin.

Characteristics of the topical absorption of ^{14}C-labelled minoxidil differ appreciably in monkey scalp. During the 10-16 days the monkeys were chaired, approximately 4% of the 1% solution and 1% of the 4% solution appeared in the urine. When returned to metabolism cages, a larger component of total urinary excretion occurred; urinary excretion did not follow first order kinetics. Total absorption in the monkeys was 17.4% of a 1% solution and 5.7% of a 4% solution.

Human Data

Pharmacodynamics

In Vitro/in Vivo Studies

Exploratory in vivo and in vitro studies, designed to determine the mechanism by which minoxidil stimulates hair growth in patients with male pattern baldness have been completed, but have not been successful in definitely demonstrating the mechanism of action of minoxidil in stimulating hair growth. Studies have shown that there appears to be an immediate vasodilation of the micro circulation after topical application of minoxidil and that there is no significant alteration of the effects of androgens on scalp hair. These studies have also shown that cultured epidermal cells appear to be stimulated to divide under the influence of minoxidil and that in vitro cell cultures of lymphocytes are inhibited in their response to mitogens when minoxidil is present in culture. The overall significance of any of these studies is unknown.

In Vivo Studies

Results of two studies evaluating minoxidil tablets in doses up to 5 mg twice daily for up to 28 days in normotensive patients show that there were no clinically significant effects on blood pressure measurements or on pulse rate. In addition, there were no clinically significant changes in maximum heart rate response to standard treadmill test, pulse and blood pressure response to a dynamometer grip device, forearm blood flow, plasma renin levels or urine epinephrine and norepinephrine levels. No evidence of fluid retention was seen. The conclusion was made that low-to-moderate, short-term doses of minoxidil tablets, in normotensive volunteers, do not lower blood

pressure, and side effects commonly observed during minoxidil tablet therapy for hypertensive patients do not occur in normotensive subjects.

No clinically significant systemic effects were noted in a 16-week, placebo-controlled, randomized study of 98 treated hypertensive patients (involving B-blockers, diuretics) who were also treated with minoxidil topical solution 3%.

Untreated hypertensive patients were evaluated in an IV minoxidil study. The subjects achieved pharmacokinetic steady-state within 6 hours after the start of infusion. The heart rate and diastolic blood pressure effects observed indicated that IV infusions of 1.37 mg and 3.43 mg of minoxidil did not result in clinically significant cardiovascular effects. The 6.86 mg dose, which resulted in a mean serum minoxidil concentration of 21.7 ng/mL, was the lowest dose clearly distinguishable from placebo, based on heart rate data.

Immune Function

A pilot study compared the immune status of 11 patients with male pattern baldness who were treated with topical minoxidil for 30 months, with the immune status of 12 untreated male control subjects. Peripheral leukocytes were examined for the presence of various cell subpopulations using monoclonal antibodies coupled with cytofluorometry and for blastogenic responses to phytohemagglutinin (PHA), concanavalin A (Con A), and pokeweed mitogen (PWM). The results of this study revealed no effect on helper T-cell, suppressor T-cell, B-cell, or natural killer cell numbers. In addition, no difference was observed in mitogenic responses of the minoxidil-treated patients (to any of the mitogens) as compared to responses of the control subjects.

Effect on Cardiac Function

An analysis of echocardiographic parameters such as left ventricular diameters in systole and diastole, septal and posterior wall thickness, cardiac output and cardiac index revealed no differences in patients exposed to 3% minoxidil solution for up to 5 years when compared to healthy patients that had not been exposed to 3% minoxidil during this time period.

Pharmacokinetics

In Vitro Studies

The transdermal metabolism of ^{14}C-minoxidil in fresh human skin in an in-vitro diffusion system was studied. The dermal metabolism of minoxidil in human skin under these in-vitro conditions was minimal at 4.8 to 6.0% of the applied dose.

In Vivo studies

Extent of Absorption

A three-way cross-over study in 14 male volunteers demonstrated that the extent of minoxidil absorption, by the topical route, is low; with bioavailability averaging 1.4% and 1.2%, for 2% and 3% topical solutions respectively, relative to oral doses of 2.5 mg minoxidil tablet.

The disappearance of minoxidil from the systemic circulation was found to be controlled by its rate of absorption, which is slow, and appears to occur by a zero-order process at steady state.

Absorption of minoxidil from topically applied solution is greater in individuals with whom a simulated bald spot was generated by shaving (2.4% of applied dose) than in individuals who were naturally bald (1.4% of applied dose).

A four-way cross-over study in 23 male subjects demonstrated that the contact time of minoxidil 2% topical solution affects absorption. Treatment involved dosing of 1mL q12h for 6 days applied to a constant surface area of the scalp. The scalp was washed one, two, four, and 11.5 hours post dose. With increased contact time, absorption increased disproportionately. More than 50% of the minoxidil that is eventually absorbed is absorbed in the first hour post dose, and absorption is nearly complete after 4 hours.

The concomitant topical application of minoxidil with corticosteroids or tretinoin cream causes an increased absorption of minoxidil.

Effect of Surface Area

A four-way cross-over study documented that when 1 mL of 2% minoxidil solution was spread over surface areas ranging from 100 cm^2 to 200 cm^2, the amount of minoxidil absorbed was minimally affected. Less than a 20% increase in the amount absorbed was observed with a 100% increase in surface area.

Dose Proportionality

Results of a parallel design study of subjects applying 1 mL of a 0.01%, 0.1%, 1%, or 2% minoxidil solution twice daily to the scalp for two weeks indicate that absorption increases nearly linearly over the dose range studied. A cross-over study evaluating higher strength solutions demonstrated that the amount of minoxidil recovered in the urine increases less than in proportion to an increase in dose for the dose range evaluated. Subjects in this study had applied 1 mL of a 1%, 2%, or 5% solution to a constant 200 cm^2 surface area every 12 hours.

Frequency of Application

Percutaneous absorption is increased when the frequency exceeds twice daily dosing. Absorption for minoxidil that is applied to a healthy scalp does reach a threshold maximal level. It has been documented that the average amount of minoxidil recovered in the urine following 1 mL of 1% minoxidil solution administered every six hours was equivalent to that observed following 1 mL of 2% minoxidil administered every 12 hours.

Volume of Solution

A cross-over study evaluated the effect of the volume of application on the amount of minoxidil absorbed. This study documented that for a constant applied dose (10 mg) over a constant surface area, the volume applied has no influence on the amount of drug absorbed. Subjects received 1 mL of 1% minoxidil solution, 2 mL of 2% minoxidil solution, and 1/3 mL of 3% minoxidil solution.

Location of Application

No significant accumulation of minoxidil occurred as a result of applying up to four times the recommended dose of 3% minoxidil solution to the scalp or chest. In this parallel-design study,

subjects received 1 mL of 3% minoxidil solution (30 mg) between two and eight times within a 12-hour interval for fourteen consecutive days. The results also demonstrated that there was no difference in absorption of minoxidil between the scalp and chest if applied less than eight times per day. Absorption of minoxidil appeared to be slightly greater in the scalp than in the chest at eight applications per day. Overall, the results indicate that absorption of minoxidil solution was independent of the number of applications within a twelve-hour period for the doses administered in this study. This dosage range (60 to 240 mg per day) was significantly greater than that used in previous studies which demonstrated a significant but less than proportional increase in the amount absorbed, following doses of 10 to 50 mg. The lack of an increase in serum or urine minoxidil levels with increased frequency of application seen in this study is probably the result of saturation of the stratum corneum with initial doses of minoxidil.

After application of minoxidil topical solution 2% q12h to the scalp, forearm and upper back, it has been shown that systemic absorption is three-fold greater after application to the scalp compared to the forearm or back.

TOXICOLOGY

Acute Toxicity

Table 5: LD_{50} (mg/kg) in Mouse and Rat by Route of Administration

SPECIES	ROUTE	LD_{50} (mg/kg)
Mouse	Oral	2457
	Intraperitoneal	1001
	Intravenous	51
Rat	Oral	1321
	Intraperitoneal	759
	Intravenous	49
Rat	Cutaneous	$\geq$ 2007

Signs of Toxicity

CNS depression and acute pulmonary congestion.

Concomitant therapy with either prednisone and anti-thymocyte globulin, hydrochlorothiazide and propranolol, or digoxin and furosemide did not appreciably alter the LD_{50} for minoxidil. Acute toxicity evaluations of cutaneous administration of minoxidil did not result in mortalities at 999 and 1998 mg/kg, therefore the LD_{50} was not determined.

Repeat Dose Toxicity

Oral Studies

3-Day Studies (Rat, Dog)

Minoxidil was administered orally to rats and dogs at daily doses up to 100 and 10 mg/kg/day respectively for 3 days. In rats, a dose related slight increase in the number of mitoses in hepatocytes was seen. In beagle dogs, epicardial and myocardial cellular infiltrations, hypertrophy and hyperplasia of the mesothelial cells, small focal hemorrhages, and myocardial atrial lesions

were observed at 1.0 and 10 mg/kg doses. These findings were more frequent and severe at the higher dose. In mongrel dogs, there were minimal to mild subepicardial hemorrhages present in the right atrium and/or right auricle which may represent the early stages of right atrial lesions as seen in the longer-term studies.

1-Month Studies (Monkey, Dog, Minipig, Rat)

Minoxidil was administered orally to monkeys at 20 mg/kg/day; to dogs at 0.5 and 1 mg/kg/day, and at 20 and 100 mg/kg/day; to minipigs at 20 mg/kg/day; and to rats at 300 mg/kg/day. Grossly observed cardiac hypertrophy was reported in the monkey study (the 4-OH metabolite of minoxidil at the same dose showed no effect). In dogs, lesions of the right atrium and/or auricle were seen at all doses. Local myocardial cell atrophy and/or degeneration were reported at doses as low as 1 mg/kg/day. The 20 mg/kg dose produced degenerative right auricular heart lesions as did the 4-OH metabolite of minoxidil. The high dose resulted in the death of all dogs probably due to profound alteration in electrolyte balance. In the minipig study blood pressure was depressed, heart rate elevated and total body water and exchangeable sodium were increased. Cardiac lesions due to minoxidil were not seen. In rats, repression of body weight gain, decreased food consumption, reduced erythrocyte levels increased liver and heart weights, indications of cardiac hypertrophy and electrolyte imbalance were observed.

1-Year Studies (Rat, Monkey, Dog)

Minoxidil was administered orally to rats at 10, 30 and 100 mg/kg/day, monkeys at 3.5, 7 and 14 mg/kg/day and dogs at 3, 10 and 30 mg/kg/day. In rats, repression in body weight gain occurred and a dose related increase in liver, kidney, adrenal and heart weights was seen. One high dose female monkey with chronic glomerulonephritis died from cardiac failure and minoxidil probably contributed because of its salt and water retaining action. In the dog study, degenerative right auricular heart lesions were found at all dose levels. Evidence of chronic electrolyte disturbance was noted in dogs at the highest dose.

22-Month Study (Rat)

Minoxidil was administered orally to rats at 3, 10 and 30 mg/kg/day. Increased heart weights were observed at the highest dose. No carcinogenic potential was apparent.

Topical Application Studies

91 - Day (Beagle Dog)

Minoxidil was administered topically to male and female dogs at doses of 0.6, 1.2 and 4.8 mg/kg/day. Hemorrhagic atrial lesions were seen in the right atrium of the heart at all doses over a treatment period of 91 days. Cardiomyopathy and epicarditis of the atrial wall, increased organ weights and decreased inorganic phosphorous levels were reported. The hemorrhagic right atrial lesions reported in this study have not been observed in seven other species (including man) following minoxidil administration.

13-Day (Beagle Dog)

^{14}C-minoxidil was administered topically and orally to female dogs at a dose of 4.8 mg/kg/day for 3 days followed by non-radioactive minoxidil for 10 days. Hemorrhagic right atrial lesions,

papillary muscle necrosis/paleness and epicarditis of the right atrium were evident in topically and orally treated groups. Since the percutaneous absorption of minoxidil in dogs is 39% and 2 - 4% in man, the potential of the development of right atrial lesions is not applicable to man.

Special Toxicity Studies

Cardiovascular Mechanistic Studies (dog)

The mechanisms of the various cardiovascular lesions induced by minoxidil are considered to be related to the exaggerated pharmacologic/hemodynamic effects of the drug rather than to a direct toxicity of the drug. The mechanism of cardiovascular toxicity of minoxidil (an ATP-sensitive potassium channel opener) was studied by blocking its pharmacologic effects with glyburide (an ATP-sensitive potassium channel antagonist) in beagle dogs that were treated orally for two days either with minoxidil alone or in combination with glyburide. Glyburide did not influence the pharmacokinetics of minoxidil but prevented or markedly attenuated the minoxidil-induced carotid pulsation, hypotension, and tachycardia. None of the cardiovascular lesions (right atrial hemorrhagic lesions, subendocardial necrosis, or coronoary arteritis) occurred in dogs whose minoxidil -induced hemodynamic effects were effectively blocked by glyburide. These findings led to the conclusion that the cardiovascular toxicity of minoxidil in dogs is related to its exaggerated pharmacologic (hemodynamic) effects rather than by a direct toxic effect of minoxidil on the heart.

The threshold serum concentrations of minoxidil for hemodynamic effects and cardiovascular lesions were determined in dogs administered minoxidil by continuous infusion at doses ranging from 0.05 to 4.32 mg/kg/day for three days. Classic minoxidil-induced cardiovascular lesions were observed after profound hemodynamic changes occurred at doses of 0.43 mg/kg/day or higher. The absence of these lesions at 0.14 mg/kg/day, in which there was tachycardia without significant hypotension, indicated that hypotension may be important for the development of cardiovascular lesions.

The threshold dose/serum concentrations of minoxidil for hemodynamic effects (heart rate) and cardiovascular toxicity were approximately 0.05 mg/kg/day (2.0 ng/mL) and 0.14 mg/kg/day (7.96 ng/mL), respectively.

Since dogs are particularly sensitive to the cardiac effects of minoxidil and other vasodilating agents, they are not considered to accurately predict human risk for these compounds. Human exposure would be about 0.028 mg/kg/day (assuming a 60 kg individual using twice daily applications of 1 mL of 5% minoxidil topical solution and a mean level of minoxidil absorption in humans of 1.7%), which provides a difference in exposure between humans and dogs of 8-fold or more for a 5% solution. There is no clinical or autopsy evidence that orally administered minoxidil causes similar cardiac toxicity in humans.

Drug Interaction Studies

There was no evidence of alteration in toxicity when minoxidil was given concomitantly with (a) hydrochlorothiazide and propranolol in rats and monkeys for up to 1 month, and (b) furosemide and digoxin in rats for 1 month. Hydrochlorothiazide partially reduced increases in heart weight and total body exchangeable sodium produced by minoxidil in a 1-month monkey study.

Longer term treatment in rats, dogs and monkeys showed cardiac hypertrophy and cardiac dilation (in rats). Hydrochlorothiazide partly reversed the increased heart weight in monkeys.

Reproduction Studies

Male rats received minoxidil in oral doses of 3 or 10 mg/kg/day for 60 days prior to and during the 14 day breeding period. Female rats received the same dose for 14 days prior to and during breeding, and throughout gestation. A reduction in conception rate was observed. No increase in the incidence of fetal resorption in treated dams was seen. The average number of live pups per litter was significantly decreased in both treatment groups, but live pups from treated dams were significantly heavier than live pups from control dams.

Minoxidil, when given orally to pregnant rats and rabbits on gestation days 6 through 15 and 18 respectively, at dose levels of 3 and 10 mg/kg/day showed no teratogenic effect. Increased fetal resorption occurred in rabbits. The same dose administered to rats from the 15th day of gestation until pups were weaned at 21 days showed no effect of treatment on various parameters related to gestation, parturition and lactation.

When a minoxidil suspension was given subcutaneously to pregnant rats in doses of 0,1,11, and 120 mg/kg, no teratogenic changes were found in the fetuses from the rats dosed at 0, 1 and 11 mg/kg of minoxidil. Increased fetal mortality, still birth, external malformations and skeletal anomalies and variations were observed at 120 mg/kg. This dose also caused decreased maternal weight gain and food consumption and thus the fetal effects noted could have resulted from maternal toxicity.

Minoxidil administered subcutaneously to pregnant rats at 80 mg/kg/day was maternally toxic (manifested by general malaise and weight loss) but not teratogenic. This is about 2000 times the maximum daily systemic human exposure after topical administration.

Higher doses (120 and 160 mg/kg/day) produced some fetal malformations. The no adverse effect level (NOAEL) for maternal toxicity was 40 mg/kg/day while the NOAEL for developmental toxicity was 80 mg/kg/day.

Other Topical Application Studies

Rat

Notable toxicity was seen only in topical studies done in rats. When minoxidil 2% topical solution was administered topically to rats, approximately 32% of the dose was absorbed. Therefore, 1 mL of minoxidil 1% topical solution applied twice daily (20 mg/day), represents 2476 times the human topical dose on the basis of a 250 gm rat, a 50 kg human, 32% absorption in rats and an average of 1.4% absorption in man. One mL of minoxidil 5% topical solution applied twice daily (100 mg/day) represents 12381 times the human topical dose.

In the 94-day dermal rat study (1 mL/day), signs of toxicity were mainly noted in the 6% minoxidil solution group (60 mg/day). The toxicity consisted of dose-related increased nasal and ocular porphyrins; area of soreness in the treatment area (also noted in one control rat); and fecal stains in a few rats of the 6% group. Females had decreased body weight gains, and the following organ

weight changes were seen: increased spleen weights for both sexes at all dose levels; increased heart weights for males at all dose levels and for females in the 1% group (10 mg/day); and increased liver weights for males in the 3% (30 mg/day) and 6% (60 mg/day) groups. There were, however, no drug-related lesions involving the skin or internal organs.

A one-year dermal toxicity study in male and female rats at doses of 1 mL b.i.d. of 1%, 3% and 5% minoxidil resulted in decreased body weight gains, increased urinary protein, slight enlargement and/or dilatation of the heart, increased organ weights and histopathologic findings such as cardiac and hepatocellular hypertrophy, myocardial degeneration and increased nephritis. Most of the effects were evident in the 3% (60 mg/kg/day) and the 5% (100 mg/kg/day) groups.

The decreased body weights in females, increased organ weights and histopathologic findings are associated with high systemic doses of minoxidil and, therefore, do not constitute new findings. The systemic doses reached in this study are approximately 2,000 to 12,000 times the human topical dose. The minimal irritation and thickening of the skin were not considered drug-related or of consequence.

Rabbit

On a volume basis (4 mL/day), the dose levels tested in rabbits represent one to five times the human dose. However, on the basis of a 2.5-kg rabbit and a 50-kg man, the dose levels represent 20 to 100 times the human topical dose of minoxidil 2% topical solution. The absorption of topical applications of minoxidil topical solution has not been investigated in the rabbit.

In the 21-day dermal study in the rabbit, drug-related clinical signs were absent. Relative and/or absolute heart weights were significantly increased in the males which received the 3% and 5% minoxidil topical solutions, as compared to the controls. No histopathologic lesions were seen.

A one-year dermal toxicity study in male and female rabbits at doses of 2 mL b.i.d. of 1%, 3% and 5% minoxidil resulted in dilated ventricles of the heart, increased organ weights, and slight to moderate irritation. Except for site irritation, none of these effects were evident in the 1% group.

Eye Irritation Studies

A single 0.1 mL dose of a 2% minoxidil solution was instilled into the conjunctival sac of the right eye of New Zealand white rabbits. The left eye served as a control. It was concluded that minoxidil topical solution 2% is an irritant.

A single 100 mg dose of 2% minoxidil gel was instilled into the conjunctival sac of the right eye of three male and three female New Zealand White rabbits. The left eye was untreated and served as control. At one-hour post-instillation, all six treated eyes exhibited slight-to-moderate conjunctival irritation, as indicated by slight redness, slight-to-moderate swelling, and discharge. By 24 hours, the eye irritation remained at approximately the same level for five rabbits, while the irritation in the eye of one female rabbit deteriorated to include slight corneal opacity and iridal capillary injection. However, the irritation gradually subsided by 96 hours post-dosing. By day 7 post-treatment, all the treated eyes appeared normal.

A single 100 mg dose of 3% minoxidil gel was instilled into the conjunctival sac of the right eye of three male and three female New Zealand White rabbits. The left eye was untreated and served as control. Slight-to-moderate conjunctival redness and swelling, and slight-to-severe discharge were observed in all treated eyes from 1-96 hours post-dosing.

In addition, the treated eyes of two males and one female also exhibited slight corneal opacity and corneal epithelial exfoliation for 1-24 hours post-dosing. However, the treated eyes of all six rabbits appeared normal by day 7 post-treatment.

Gel formulations of minoxidil used in the eye irritation studies; contain the same excipients that are present in minoxidil 2% topical solution, with the exception that a gelling agent and a stabilizer are present in the gel formulation. The alcohol content in the gel formulations is lower than that of the topical solution. Since alcohol is a known eye irritant, it can be concluded that minoxidil 2% topical solution is also an eye irritant.

Phototoxic/Photoallergic Study

Guinea Pig

Minoxidil topical solution 2% in guinea pigs caused no reaction in a phototoxicity/photoallergic study.

Mutagenicity

Minoxidil was not genotoxic in the Salmonella (Ames) test (TA-98-100, TA-98-1535, TA-98-1537, TA-98-1538), the DNA damage alkaline elution assay, the *in vitro* rat hepatocyte unscheduled DNA synthesis (UDS) assay, the rat bone marrow micronucleus assay, or the mouse bone marrow micronucleus assay. An equivocal result was recorded in an in vitro cytogenetic assay using Chinese hamster ovary cells at long exposure times, but a similar assay using human lymphocytes was negative.

Carcinogenicity

Two-year carcinogenicity studies of minoxidil have been conducted by the dermal and oral (dietary) routes of administration in mice and rats.

In the two-year dermal study in mice, an increased incidence of mammary adenomas and adenocarcinomas in the females at all dose levels (8, 25 and 80 mg/kg/day) was attributed to increased prolactin activity. Mechanistic studies in female mice objectively demonstrated an increased prolactin secretion in mice treated topically with minoxidil for 90 days.

Other hormonal changes, including decreased LH, FSH, and estrogen, which are consistent with hyperprolactinemia, were also observed in these studies. In addition, histological changes consistent with a hyperprolactinemic state were observed in the 90 day and 2-year studies. Hyperprolactinemia is a well-known mechanism in the enhancement of mouse mammary tumorsbut has not been associated with mammary tumorigenesis in women. Additionally, topical minoxidil has not been shown to cause hyperprolactinemia in women on clinical trials. Absorption of minoxidil through rodent skin is greater than would be experienced by patients treated topically with minoxidil for hair loss. In a dietary study of minoxidil in mice for up to 2 years, malignant

lymphomas were seen earlier in females which failed to survive for 2 years in the high dose (63 mg/kg/day) compared to controls. However, this finding was not observed in 2-year topical studies and higher systemic studies. In the 2-year dermal study in mice there was an increased incidence of hepatic nodules in males (63 mg/kg/day); however there was no effect of dietary minoxidil on malignant lymphomas.

In the two-year dermal study in rats there were significant increases in incidence of pheochromocytomas in males and females and preputial gland adenomas in males. Mechanistic studies in male rats objectively demonstrated an increased prolactin secretion in rats treated topically with minoxidil for 90 days.

Other hormonal changes consistent with hyperprolactinemia in males were also observed in these studies. The increased incidence of preputial gland adenomas observed in male rats is consistent with the increased prolactin levels observed in this species and sex.

Changes in incidence of neoplasms found to be increased in the dermal or oral carcinogenicity studies were typical of those expected in rodents treated with other hypotensive agents (adrenal pheochromocytomas in rats), treatment-related hormonal alterations (mammary carcinomas in female mice; preputial gland adenomas in male rats) or representative of normal variations within the range of historical incidence for rodent neoplasms (malignant lymphomas, liver nodules/adenomas in mice). Based on differences in absorption of minoxidil and mechanisms of tumorigenesis in these rodent species, none of these changes were considered to be relevant to the safety of patients treated topically with minoxidil for hair loss.

There was no evidence of epithelial hyperplasia or tumorigenesis at the sites of topical application of minoxidil in either species in the 2-year dermal carcinogenesis studies. No evidence of carcinogenicity was detected in rats or rabbits treated topically with minoxidil for one year. Topical minoxidil (2% and 5%) did not significantly ($p< 0.05$) reduce the latency period of UV light-initiated skin tumors in hairless mice, as compared to controls, in a 12-month photocarcinogenicity study.

Positive carcinogenicity findings which occurred in the topical rodent studies did not occur in the oral studies. A comparative bioavailability study using the identical routes and methods of administration used in the topical and oral (drug-in-diet) studies indicated that a 45-fold C_{max} and a 3 fold C_{av} higher systemic exposure to minoxidil occurs after topical vs oral treatment in rodents. Additionally, a study which compared the route dependent absorption, excretion and metabolism of minoxidil-[^{14}C] after topical and oral administration in the female mouse and rat suggested intrinsically greater percutaneous absorption of the topically applied minoxidil-[^{14}C] in the mouse relative to that in the rat.

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PART III: CONSUMER INFORMATION

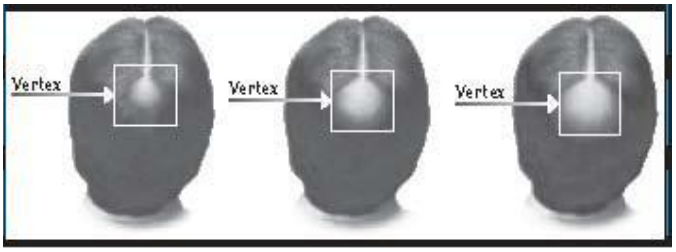
MINOX
Minoxidil Topical Solution USP
20 mg/mL (2% w/v)

This leaflet is part III of a three-part "Product Monograph" published when MINOX was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about MINOX. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

MINOX is used for the treatment of male pattern baldness (androgenetic alopecia) on the top of the scalp (vertex) in men aged 18 to 65 years. It prevents further hair loss and helps hair re-growth.



MINOX has no effect on receding hairlines. It does not permanently reverse male pattern baldness; most new hair is lost within three to four months after stopping the medication.

What it does:

MINOX contains minoxidil, which is thought to work by aiding the blood flow to hair follicles on your scalp and thereby helping hair re-growth. Initial hair re-growth may look soft, downy ("vellus") hair and may be barely visible. After further treatment, hair re-growth may change and become the same colour and thickness as the rest of the hair.

MINOX is more effective if you are experiencing gradually thinning hair or gradual hair loss on the top of the head (as shown in the image).

Gradual hair loss on the top of the scalp

Male Pattern Baldness or Hereditary Hair Loss is recognizable because:

- Of the pattern of hair loss (see diagrams above).
- Hair loss starts gradually and progresses.
- You have a family history of hair loss.
- No other symptoms are present with your hair loss.

You must use MINOX for at least 4 months, and possibly for up to 1 year, before you see any effect.

The amount of hair regrowth is different for each person. Not everyone will respond to MINOX. The response to this medicine cannot be predicted. No one will be able to grow back all of their hair.

You may respond better if you have been losing your hair for a shorter period of time (less than 10 years) or have little initial hair loss (less than a diameter of 10 cm).

When it should not be used:

Do not use this medicine if you:

- are female;
- have an allergic reaction (hypersensitivity) to minoxidil or any of the other ingredients in MINOX;
- have treated or untreated high blood pressure;
- have baldness not due to male pattern baldness;
- have any condition that affects your scalp such as redness, inflammation, irritation, pain on touching, sunburn, or psoriasis;
- have a shaved scalp or broken skin on the scalp;
- are treated with any kind of dressing or bandage (occlusive dressing) or other topical medication (eg. anthralin, tretinoin, or corticosteroids) on your scalp for any skin scalp problems;
- have temporary hair loss as a result of taking certain medications (cancer chemotherapy) or having certain disease state or nutritional problems, as well as poor grooming habits.
- have secondary syphilis

What the medicinal ingredient is:

Minoxidil

What the important nonmedicinal ingredients are:

Alcohol, Purified Water and Propylene Glycol.

What dosage forms it comes in:

MINOX is available as a 60 mL solution in a bottle with one or more of the following metered disposable applicators: Pump Spray, Extended Spray Tip and a Rub-On-Applicator

WARNINGS AND PRECAUTIONS

- Apply MINOX only on the scalp.
- Inhalation of spray mist should be avoided.
- Avoid contact with eyes as MINOX contains alcohol, which would cause burning or irritation of the eyes or sensitive skin areas. If contact occurs, rinse thoroughly with large amounts of cool tap water. Stop use and speak to your doctor if irritation persists.
- MINOX may rarely cause low blood pressure, salt and

water retention that lead to chest pain (angina), rapid heartbeat (tachycardia), swollen hands and feet.
- May change colour/texture of hair.
- MINOX should not be used when there is no family history of hair loss, hair loss is sudden and/or patchy, or the reason for hair loss is unknown.
- Shedding of hair may occur within two to six weeks after using the product. If shedding persists for more than two weeks, users should stop applying MINOX and consult their doctor.

MINOX should not be used in males under 18 or over 65 years of age.

BEFORE using MINOX, talk to your doctor or pharmacist if any of the following conditions applies to you:

- High or low blood pressure or heart disease or irregular heartbeat (arrhythmia).
- Under other treatment for any scalp conditions.

INTERACTIONS WITH THIS MEDICATION

Before using MINOX talk to your pharmacist or doctor if you are taking or have recently taken Prescription drugs, non-prescription drugs or natural health product.

The following medications may increase the absorption of minoxidil:

- Anthralin – used to treat psoriasis
- Tretinoin – used to treat acne or other skin conditions

MINOX (Minoxidil) also may increase the effect of hydralazine (drug to treat high blood pressure).

PROPER USE OF THIS MEDICATION

Application:

- MINOX is for topical and external use only. It should only be applied directly to the scalp area. Make sure your hair and scalp are completely dry before applying the solution.
- Shampooing is not required before applying MINOX. However, if you wash your scalp before applying MINOX, use a mild shampoo. Dry hair and scalp before application.
- Do not apply to areas of the body other than the scalp.
- Do not apply MINOX to a sunburned or irritated, broken or shaved scalp.
- For MINOX to work best, you should allow MINOX to remain on the scalp for at least 4 hours.
- Wash your hands thoroughly before and after applying the solution and rinse other areas that have come into contact with the solution.
- Please see special instructions below for 3 different applicators. Each applicator contains one dose of medicine.
- If you are planning to be in the sun after applying MINOX, use headwear. Do not use sunscreens or sun-blocking agents.
- Avoid swimming, showering or physical activity involving excessive sweating or wetting in rain for at least 4 hours after application.
- To minimize breakage of existing hair, the scalp should be massaged gently. Comb hair with a widely spaced, round tooth comb to avoid excessive pulling.
- There is no need to change your usual hair care routine when using MINOX. You may use hair sprays, mousses, conditioners, gels, etc. However, you should apply MINOX first and wait for it to dry before applying your styling aids.
- It is not known if hair colouring, perming or relaxing agents change the effect of MINOX. However, to avoid possible scalp irritation, you should make sure all of the MINOX has been washed off the hair and scalp before using these products.

Usual dose:

- 1 mL applied twice daily to the scalp, beginning at the center of the affected area; for example, once in the morning and once at night. Do not exceed 2 mL in a day. Exceeding the recommended dosage may cause increased side effects.
- If you do not see any results after 1 year, stop using MINOX and seek the advice of your physician.
- One bottle of MINOX should last for 25 - 30 days, if applied twice a day according to directions.

Missed Dose:

If a dose is missed, use as soon as remembered if it is within a few hours of the usual time applied. Do not apply if it is almost time for the next dose. If a dose is missed, the amount used in the next dose should not be doubled.

Overdose:

In case of drug overdose or accidental ingestion, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

INSTRUCTIONS FOR USE OF APPLICATORS

APPLICATOR OPTIONS

Hair styles and degree of hair loss can be very different for each person. We have included three applicators that have been designed especially for men. You can choose whichever one works best for you.

A. Pump-Spray Applicator
B. Rub-On Applicator
C. Extended Spray-Tip Applicator

USING THE APPLICATORS

A. Pump-Spray Applicator

Works best for applying MINOX to large areas of the scalp.

1) Remove Child-Resistant cap by pushing down while turning the cap anti-clockwise. Retain Child-Resistant cap.

2) Insert the pump-spray applicator into the bottle and screw on tightly.
3) After aiming the pump at the centre of the thinning or bald area of the scalp, press the pump once and spread MINOX with fingertips to cover all the thinning or bald area. Repeat for a total of 4 times to apply a total dose of 1 mL. **Avoid breathing spray mist.**
4) To retain Child-Resistant feature, remove Pump-Spray applicator and retain for next application. Replace Child-Resistant cap by tightly screwing on in a clockwise direction.

B. Rub-On Applicator

Works best for applying MINOX to small areas of the scalp.

1) Remove Child-Resistant cap by pushing down while turning the cap anti-clockwise. Retain Child-Resistant cap.
2) Insert the rub-on applicator into the bottle and screw on tightly. Remove outer cap and keep it.
3) Hold the bottle upright and squeeze it once to half fill the upper chamber. The level of liquid in the chamber will automatically adjust to deliver one full dose (1 mL).
4) Hold the bottle upside down then rub applicator on your scalp to apply MINOX over the whole thinning or bald area until the chamber is completely empty. Replace outer cap over the rub-on applicator when not in use.
5) To retain Child-Resistant feature, remove Rub-On applicator and retain for next application. Replace Child-Resistant cap by tightly screwing on in a clockwise direction.

C. Extended Spray-Tip Applicator

Works best for applying MINOX to small areas of the scalp or under hair.

1) Remove Child-Resistant cap by pushing down while turning the cap anti-clockwise. Retain Child-Resistant cap.
2) Insert the pump-spray applicator into the bottle and screw on tightly.
3) Remove small spray head from top of pump-spray applicator.
4) Fit the extended spray-tip applicator onto the spray shaft and push down firmly.
5) Remove the small cap on the end of the extended tip and keep it.
6) After aiming the applicator at the centre of the thinning or bald area of the scalp, press the pump once and spread MINOX with fingertips to cover all the thinning or bald area. Repeat for a total of 4 times to apply a total dose of 1 mL. **Avoid breathing spray mist.**
7) To retain Child-Resistant feature, remove Extended Spray-Tip applicator and retain for next application. Replace Child-Resistant cap by tightly screwing on in a clockwise direction.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

MINOX may cause side-effects.

If you experience any of the following, stop using the medicine and tell your doctor.

- Faintness or dizziness – if affected do not drive or operate machinery
- Sudden unexplained weight gain.
- Swollen hands or feet.
- Headache.
- Muscle pain.
- Depressed mood

Other side effects include:

- Unwanted non-scalp hair. This may be due to the frequent applying of MINOX on areas of the skin other than the scalp.
- Scalp irritation such as local redness, itchiness, dryness, flaky skin have all been reported. This is usually only a temporary effect, but if it is persistent you should stop using this product.
- Temporary hair loss may occur during the first 2-6 weeks of use. If this hair loss continues for longer than 2 weeks, stop using the product and talk to your doctor.
- Change in hair colour and/or texture may occur. If this happens you should stop using MINOX.
- MINOX should be applied only to the scalp. The risk of side effects may be greater when it is applied to other parts of the body.

This is not a complete list of side effects. For any unexpected effects while taking MINOX, contact your doctor or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Very rare	Swollen face, lips, mouth, tongue, and throat			✓
	Skin redness, rash, severe irritation, throat tightness			✓
	Chest pain			✓
	Rapid or			✓

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SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
	irregular heartbeat			
	High or low blood pressure			✓
	Shortness of breath or difficulty breathing			✓

HOW TO STORE IT

- Keep out of the reach and sight of children.
- Store at a controlled temperature range of 15-30 °C.
- Do not use after the expiry date
- Ask your pharmacist how to dispose of medicines no longer required.

REPORTING SIDE EFFECTS

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor, Laboratoire Riva Inc., at: 1-800-363-7988.

This leaflet was prepared by:

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