PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

JAMP Minoxidil Solution

Minoxidil Topical Solution

20 mg/mL (2% w/v)

Manufacturer's Standard

Hair Regrowth Treatment

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

JAMP Minoxidil Solution (2% minoxidil topical solution) is indicated for:

- the treatment of male androgenetic alopecia (male pattern hair loss) on the top of the scalp (vertex).

JAMP Minoxidil Solution is not approved for use in women.

The effectiveness of minoxidil topical solution in the treatment of receding hairlines has not been demonstrated in clinical trials.

JAMP Minoxidil Solution: 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.

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (>65 years of age): The safety and efficacy of minoxidil topical solution in men over 65 have not been tested in clinical studies.

2 CONTRAINDICATIONS

JAMP Minoxidil Solution is contraindicated:

- in individuals with a history of hypersensitivity to minoxidil or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- in individuals with treated or untreated hypertension.
- in individuals whose baldness is not due to hereditary factors. JAMP Minoxidil Solution 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, recent discontinuation of birth control medication, 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 (e.g., cornrowing, tight ponytails), may also cause temporary hair loss which should not be treated with JAMP Minoxidil Solution.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

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

4.2 Recommended Dose and Dosage Adjustment

A total dose of 1 mL JAMP Minoxidil Solution should be applied twice per day to the scalp, beginning at the centre 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). After applying JAMP Minoxidil Solution, wash hands thoroughly. Do not apply JAMP Minoxidil Solution to any other area of the body.

Health Canada has not authorized an indication for pediatric use.

4.4 Administration

Pump-Spray Applicator

1. Remove the outer cap.
2. After opening the bottle, discard 3 sprays in order to obtain a uniform spray of the product.
3. After aiming the pump at the center of the thinning or bald area of the scalp, press the pump once and spread JAMP Minoxidil Solution with fingertips to cover all the thinning or bald area. Repeat for a total of 6 squirts, to apply a total dose of 1 mL. Avoid breathing spray mist.
4. Replace the cap.

4.5 Missed Dose

If a dose is missed, JAMP Minoxidil Solution 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.

5 OVERDOSAGE

Accidental ingestion of JAMP Minoxidil Solution can cause serious cardiac adverse effects. Contact your regional poison control centre immediately.

Because of the high concentration of minoxidil in JAMP Minoxidil Solution, accidental oral ingestion of these products 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.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients

Topical	Solution / 20 mg/mL (2%) minoxidil	Alcohol (63%), propylene glycol and purified water.

JAMP Minoxidil Solution (minoxidil topical solution) contains 20 mg minoxidil per mL (2%), as 60 mL of solution in a bottle with the pump spray. For external use only. JAMP Minoxidil Solution is a clear, colourless to light pink or yellow homogeneous solution, free from suspended particles. The light pink or yellow colour will not alter its effectiveness.

7 WARNINGS AND PRECAUTIONS

General

- JAMP Minoxidil Solution is for external use only. Apply only to scalp.
- Before applying JAMP Minoxidil Solution, 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.
- JAMP Minoxidil Solution contain 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 minoxidil topical solution 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 JAMP Minoxidil Solution and consult their doctor.
- JAMP Minoxidil Solution 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 JAMP Minoxidil Solution.
- Although the following systemic effects have not been associated with the topical use of minoxidil topical solution, 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 JAMP Minoxidil Solution 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.

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 JAMP Minoxidil Solution should be discontinued in the event of systemic effects and/or severe dermatologic reactions.

7.1 Special Populations

7.1.1 Pregnant Women

There are no adequate and well-controlled studies in pregnant women using minoxidil topical solution. These products should not be used in pregnant women.

7.1.2 Breast-feeding

Systemically absorbed minoxidil is secreted in human milk. JAMP Minoxidil Solution should not be used in nursing women.

7.1.3 Pediatrics

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

7.1.4 Geriatrics

Geriatrics (> 65 years of age): The efficacy and safety of minoxidil topical solution in men over 65 years of age have not been established. JAMP Minoxidil Solution should not be used in the male geriatric population.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most frequently encountered adverse events in clinical trials with minoxidil topical solution 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%).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in

real-world use.

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 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 topical solution as compared to patients treated with placebo

Primary System Organ Class	Medical Events by Preferred Terms	Minoxidil 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

8.3 Less Common Clinical Trial Adverse Reactions

Adverse Events seen in less than 1% of males using minoxidil 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.

8.5 Post-Market Adverse 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 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 Very rare	Tachycardia Palpitations
Vascular Disorders Very rare	Hypotension
Gastrointestinal Disorders Very rare Very rare	Nausea Vomiting
Skin and Subcutaneous Tissue Disorders Very rare Very rare Very rare Very rare	Application site reaction(these sometimes involve nearbystructures 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) Alopecia Hair colour changes Hair texture abnormal
General Disorders and Administration Site Conditions Very rare	Chest pain

9 DRUG INTERACTIONS

9.2 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 minoxidil topical solution may interact with vasodilators, e.g., hydralazine.

9.3 Drug-Behavioural Interactions

Interactions with lifestyle have not been established.

9.4 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 dipropionate 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.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

When applied topically, minoxidil 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 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.

10.2 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.

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.

10.3 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 provides serum minoxidil concentrations measured in clinical efficacy studies.

Table 3: Serum concentrations of total minoxidil after the application of 1 mL of minoxidil 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 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%).

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 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.

Animal Data

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 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 topical solution. The table 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 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.

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.

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.

Elimination
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.

11 STORAGE, STABILITY AND DISPOSAL

JAMP Minoxidil Solution should be stored at controlled room temperature between 15-30°C. Store in upright position. Caution: Flammable. Keep away from heat and open flame.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

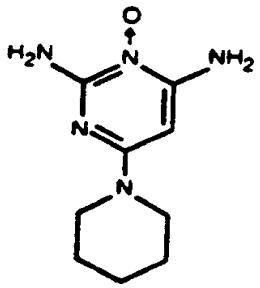
Drug Substance

Proper name: minoxidil

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

Molecular formula and molecular mass: $C_9H_{15}N_5O$; 209.25

Structural formula:



Physicochemical properties: A white or off-white, odourless, crystalline solid that is slightly soluble in water to the extent of approximately 2 mg/mL; is readily soluble in propylene glycol or ethanol, and is almost insoluble in acetone, chloroform, or ethyl acetate. It melts in the approximate range of between 248°C and 268°C, with decomposition.

14 CLINICAL TRIALS

14.2 Study Results

Minoxidil 20mg/mL [2% w/v]

The effectiveness of 2% minoxidil topical solution (MTS) for the treatment of androgenetic alopecia was studied in well-controlled protocols involving more than 2800 men and 850 women. 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 topical solution is not effective in all individuals. After 4 months of treatment with minoxidil 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 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.

The summary primary and secondary endpoint results of the MINALO3004 study comparing 2% MTS twice daily versus 5% MTF once daily in women are presented below.

Table 5: Adjusted Mean Change from Baseline in Total Area Hair Count (TAHC) (hairs/cm2) at Weeks 12 and 24 in MINALO3004*

Treatment Period # Weeks	2% MTS Twice daily Adjusted Mean Change (SE) TAHC per cm^2 from Baseline	5% MTF Once Daily Adjusted Mean Change (SE) TAHC per cm^2 from Baseline
12 (2° endpoint)	22.2 (2.1)	24.6 (2.1)
24 (1° endpoint)	24.2 (2.1)	23.9 (2.1)

* No significant difference in results between treatments for both 12 weeks and 24 weeks.

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 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.

14.3 Comparative Bioavailability Studies

This study was designed as a single-centre, two-arm, randomized, crossover, open-label clinical investigation with three different treatments. Thirty-three adult male subjects (18 to 65 years old), who were in good general health, with evidence of androgenetic alopecia of the vertex region of the scalp (Pattern 3, 4, 5, or 6), were enrolled in the trial. Thirty-four female subjects were enrolled and twenty- eight completed all phases. Thirty-two males and twenty-eight females were used in the statistical analysis.

The study consisted of three phases with a 7-day washout period between each phase. Each male subject used each of two 5% foam formulations and the 5% topical solution as a comparator over the course of the three phases (1 mL was applied twice daily for 5 days and 1 mL was applied on day 6). Each female subject used 2% Minoxidil Topical Solution twice daily and the 5% Minoxidil foam formulation once daily. Male subjects reported to the lab twice daily for 5 days and once on the 6th day for all treatments. Each female subject reported twice daily to the lab for 6 days for the 2% Minoxidil Topical Solution formulation and once daily for 6 days for the 5% foam formulations.

The absolute systemic absorption of Minoxidil after dermal application of the 5% solution is approximately 1-2%.

The table below presents the relative systemic absorption between Minoxidil Foam 5% BID and Minoxidil Solution 5% BID. In males the relative absorption rate of the 5% foam compared to the 5% solution was approximately one-half. In females, the relative absorption of the 2% solution applied twice daily was approximately the same as the 5% foam applied once daily.

Table 6: Minoxidil Foam 5% (50 mg/g) versus Minoxidil Solution 5% (50 mg/mL) Steady State Pharmacokinetic Parameters in Males on Day 6 (Mean ± SD)

Parameter	Test* Minoxidil Foam 5% (with glycerin)	Reference† Minoxidil Solution 5%	% Ratio of Geometric Means	90% Confidence Interval (p-value)
$AUC_{0-\tau}$ (0-12hrs) (ng.hr./mL)	8.81 (5.59)	18.71 (13.64)	49.0%	[39.3%,61.0%] (p<0.0001)
C_{MAX} (ng/mL)	1.11 (0.71)	2.13 (1.54)	58.9%	[46.8%, 74.1%] (p<0.0003)
T_{MAX} (hours)	5.42 (4.54)	5.79 (4.35)		

***, † source Pharmacia U.S.A.**

Table 7: Minoxidil Foam 5% (50 mg/g) Once Daily versus Minoxidil Solution 2% (20 mg/mL) Twice Daily Steady State Pharmacokinetic Parameters in Females on Day 6 (Mean±SD)

Parameter	Test Minoxidil Foam 5% (with glycerin)	Reference† Minoxidil Solution 2%	% Ratio of Geometric Means	90% Confidence Interval (p-value)
AUC0-τ (0-24hrs) (ng.hr./mL)	**12.00 (9.24)**	**12.46 (11.47)**	**101.9%**	**[67.6%, 153.7%] (p=0.9144)**
C_{MAX} (ng/mL)	**1.25 (1.51)**	**0.94 (0.77)**	**119.3%**	**[90.5%, 157.4%] (p=0.3466)**
T_{MAX} (hours)	**6.68 (6.03)**	**12.64 (8.07)**		

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Acute Toxicity

Table 8: 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	LD_{50} (mg/kg) ≥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.

Other Topical Application Studies

Rat

Notable toxicity was seen only in topical studies done in rats. When minoxidil topical solution was administered topically to rats, approximately 32% of the dose was absorbed. Therefore, 1 mL of minoxidil topical solution applied twice daily (20 mg/day), represents 2476 times the

human topical dose on the basis of a 250 g rat, a 50 kg human, 32% absorption in rats and an average of 1.4% absorption in man. One mL of minoxidil 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. The absorption of topical applications of minoxidil 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 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 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.

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 tumors but 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.

Genotoxicity: 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

Reproductive and Developmental Toxicology: 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.

Special Toxicology:

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 coronary 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.

17. SUPPORTING PRODUCT MONOGRAPHS

1. Men's ROGAINE® (Minoxidil Topical Solution, 20 mg/mL (2% w/v)), submission control 251296, Product Monograph, Johnson & Johnson Inc. JAN 20, 2022.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

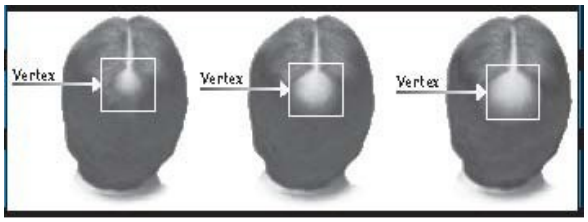
JAMP Minoxidil Solution

Minoxidil Topical Solution, Manufacturer's Standard

Read this carefully before you start taking **JAMP Minoxidil Solution** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **JAMP Minoxidil Solution**.

What is JAMP Minoxidil Solution used for?

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



- JAMP Minoxidil Solution 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.

How does JAMP Minoxidil Solution work?

JAMP Minoxidil Solution 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.

JAMP Minoxidil Solution 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 JAMP Minoxidil Solution 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 JAMP Minoxidil Solution. 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).

What are the ingredients in JAMP Minoxidil Solution?

Medicinal ingredient: Minoxidil

Non-medicinal ingredients: Alcohol (63%), propylene glycol and purified water.

JAMP Minoxidil Solution comes in the following dosage form:

20 mg / mL (2% w/v) solution with pump-spray applicator.

Do not use JAMP Minoxidil Solution if:

- You are a female, pregnant or breastfeeding
- You are allergic to minoxidil or to any ingredients in JAMP Minoxidil Solution
- You have treated or untreated high blood pressure
- You have baldness not due to male pattern baldness
- You have any conditions affecting your scalp, such as redness, inflammation, irritation, pain on touching, sunburn or psoriasis
- You have a shaved scalp or broken skin on the scalp
- You are treated with any kind of dressing or bandage (occlusive dressing) or other topical medication (e.g., anthralin, tretinoin or corticosteroids) on your scalp for any skin scalp problems
- You 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
- You have secondary syphilis.

JAMP Minoxidil Solution should not be used in males under 18 or over 65 years of age.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you apply JAMP Minoxidil Solution. Talk about any health conditions or problems you may have, including if you:

- Have high or low blood pressure or heart disease or irregular heartbeat (arrhythmia)
- Are under other treatment for any scalp conditions.

Other warnings you should know about:

- Apply JAMP Minoxidil Solution only on the scalp
- Avoid contact with eyes as JAMP Minoxidil Solution 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
- JAMP Minoxidil Solution 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
- JAMP Minoxidil Solution 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 JAMP Minoxidil Solution and consult their doctor.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with JAMP Minoxidil Solution:

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

How to apply JAMP Minoxidil Solution:

Application:

- JAMP Minoxidil Solution 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 JAMP Minoxidil Solution. However, if you wash your scalp before applying JAMP Minoxidil Solution, 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 JAMP Minoxidil Solution, to a sunburned or irritated, broken or shaved scalp.

- For JAMP Minoxidil Solution to work best, you should allow JAMP Minoxidil Solution 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 use of applicator. The applicator contains one dose of medicine.
- If you are planning to be in the sun after applying JAMP Minoxidil Solution, 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 JAMP Minoxidil Solution. You may use hair sprays, mousses, conditioners, gels, etc. However, you should apply JAMP Minoxidil Solution 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 JAMP Minoxidil Solution. However, to avoid possible scalp irritation, you should make sure all of the JAMP Minoxidil Solution has been washed off the hair and scalp before using these products.

USING THE APPLICATOR

1. Remove the outer cap.
2. After opening the bottle, discard 3 sprays in order to obtain a uniform spray of the product.
3. After aiming the pump at the center of the thinning or bald area of the scalp, press the pump once and spread JAMP Minoxidil Solution with fingertips to cover all the thinning or bald area. Repeat for a total of 6 squirts, to apply a total dose of 1 mL. Avoid breathing spray mist.
4. Replace the cap.

Usual dose:

- 1 mL applied twice daily to the scalp, beginning at the centre 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 JAMP Minoxidil Solution and seek the advice of your physician.
- One bottle of JAMP Minoxidil Solution should last for 25-30 days, if applied twice a day according to directions.

Overdose:

If you think you, or a person you are caring for, have applied too much JAMP Minoxidil Solution, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

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.

What are possible side effects from using JAMP Minoxidil Solution?

These are not all the possible side effects you may have when using JAMP Minoxidil Solution. If you experience any side effects not listed here, tell your healthcare professional.

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 JAMP Minoxidil Solution on areas of the skin other than the scalp.
- Scalp irritation such as local redness, itchiness, dryness, and 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 JAMP Minoxidil Solution.
- JAMP Minoxidil Solution 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.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	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 irregular heartbeat			✓
High or low blood pressure			✓
Shortness of breath or difficulty breathing			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

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.

Storage:

- Keep out of reach and sight of children.
- Store between 15-30°C in an upright position.
- Caution: Flammable. Keep away from heat and open flame. Do not use after the expiry date.
- Ask your pharmacist how to dispose of medicines no longer required.

If you want more information about JAMP Minoxidil Solution:

- Talk to your healthcare professional
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (www.jamppharma.com) or by calling at 1-866-399-9091.

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