PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Men's GLN-MINOXIDIL

Minoxidil Foam

Aerosol Foam, 50 mg/g (5% w/w), topical

Hair Regrowth Treatment

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Date of Authorization:
November 21, 2024

Submission Control Number: 282501

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Men's GLN-MINOXIDIL (5% minoxidil topical foam) is indicated for:

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

The effectiveness of Men's GLN-MINOXIDIL in the treatment of receding hairlines has not been demonstrated in clinical trials.

Men's GLN-MINOXIDIL: the persistence of effect after cessation of treatment for 16 weeks in men has not been demonstrated in clinical trials.

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 Men's GLN-MINOXIDIL in men over 65 have not been tested in clinical studies.

2 CONTRAINDICATIONS

Men's GLN-MINOXIDIL is contraindicated:

- in Women
- 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. Men's GLN-MINOXIDIL 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 (e.g., cornrowing, tight ponytails), may also cause temporary hair loss which should not be treated with Men's GLN-MINOXIDIL.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- FOR EXTERNAL USE ONLY. Use Men's GLN-MINOXIDIL (5 % minoxidil topical foam) only as directed. Apply Men's GLN-MINOXIDIL when the hair and scalp are thoroughly dry. The safety and efficacy of Men's GLN-MINOXIDIL in users aged under 18 or in men over 65 years of age have not been established.

4.2 Recommended Dose and Dosage Adjustment

Men's GLN-MINOXIDIL

A dose of half (½) capful (equal to 1 gram of foam or 50 mg minoxidil), Men's GLN-MINOXIDIL should be applied to the total affected hair loss areas of the scalp (not on the hair) twice daily. The total daily dosage should not exceed 2 grams of foam (100 mg minoxidil) in men.

It may take twice-daily applications for 2 months or more before evidence of hair growth can be expected. If hair regrowth occurs, twice daily applications of Men's GLN-MINOXIDIL are necessary for continued hair growth. Regrown hair may disappear three to four months after stopping Men's GLN-MINOXIDIL application and the balding process will continue. Treatment should be discontinued if there is no improvement after one year.

Health Canada has not authorized an indication for pediatric use.

4.4 Administration

Men's GLN-MINOXIDIL

1) To open container: Match arrow on can ring with arrow on cap. Pull off cap.
2) Hold the can upside down and press nozzle to dispense the foam. The total amount of foam applied should not exceed half (½) capful (equivalent to one gram of foam)
3) The foam may begin to melt on contact with warm skin. If your fingers are warm, rinse them in cold water first. Be sure to dry them thoroughly before handling the foam.
4) The foam should be massaged lightly into the affected areas of the scalp.

4.5 Missed Dose

Men's GLN-MINOXIDIL
If one or two applications are missed, the missed application(s) should be skipped, and treatment should be resumed with the next scheduled application/dose. Do not use twice as much, or twice as often, the prescribed dose.

5 OVERDOSAGE

Accidental ingestion of Men's GLN-MINOXIDIL can cause serious cardiac adverse effects. Contact your regional Poison Control Centre immediately.

Because of the high concentration of minoxidil in Men's GLN-MINOXIDIL, accidental oral ingestion of this product 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 FORM, STRENGTH, COMPOSITION AND PACKAGING

Table – Dosage Form, Strength, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Topical	Foam / 50 mg/g (5%) minoxidil	Anhydrous Citric Acid, Butylated Hydroxyl Toluene, Cetyl Alcohol, Dehydrated Alcohol, Glycerin, Hydrocarbon Propellant (propane, isobutane, n-butane), L-Lactic Acid, Purified Water, Polysorbate 60, and Stearyl Alcohol.

Men's GLN-MINOXIDIL (5% minoxidil topical foam) is available in a lined (polyamide-imide) aluminum pressurized container with a translucent round dust cap, containing 60 grams of product. Packs contain either one or three cans. The foam is creamy in appearance.

7 WARNINGS AND PRECAUTIONS

General

- Men's GLN-MINOXIDIL is for external use only. Apply only to scalp.
- Before applying Men's GLN-MINOXIDIL, 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.
- Men's GLN-MINOXIDIL 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.
- Men's GLN-MINOXIDIL also contain butylated hydroxytoluene, cetyl alcohol, and stearyl alcohol. Butylated hydroxytoluene may cause local skin reactions (e.g., contact dermatitis), or irritation to the eyes or mucous membranes. Cetyl alcohol and stearyl alcohol may cause local skin reactions (e.g., contact dermatitis).
- Some patients have experienced changes in hair colour and/or texture with Men's GLN-MINOXIDIL 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 Men's GLN-MINOXIDIL and consult their doctor.
- Men's GLN-MINOXIDIL 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 Men's GLN-MINOXIDIL.
- Although the following systemic effects have not been associated with the topical use of Men's

GLN-MINOXIDIL, 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 Men's GLN-MINOXIDIL 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 Men's GLN-MINOXIDIL 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 Men's GLN-MINOXIDIL. This product should not be used in pregnant women.

7.1.2 Breast-feeding

Systemically absorbed minoxidil is secreted in human milk. Men's GLN-MINOXIDIL should not be used in nursing women.

7.1.3 Pediatrics

Pediatrics (<18 years of age): The efficacy and safety of Men's GLN-MINOXIDIL 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 Men's GLN-MINOXIDIL in men over 65 years of age have not been established. Men's GLN-MINOXIDIL should not be used in the male geriatric population.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Men's MINOXIDIL FOAM 5%

In the short-term treatment with Men's Minoxidil FOAM 5% BID in males with androgenetic alopecia (16-week Placebo-controlled phase of Study 006), serious events (1.1% for Minoxidil Foam 5% group and 1.7% for Placebo Foam group) were not considered drug related, and no serious event resulted in discontinuing study participation. Most of the drug-related adverse events (6.7% in the Minoxidil

Foam 5% group, 7% in the Placebo Foam group) reflected mild to moderate pain or skin irritation. Adverse events related to study withdrawal (1.7% in the Minoxidil Foam 5% group, 1.2% in the Placebo Foam group) were headache, alopecia, and rash (one case each) in the Minoxidil Foam 5% group, and tachycardia, nausea, and hyperventilation (one case each) in the Placebo Foam group.

The most frequently reported adverse drug reaction following the short-term 16-week treatment with Men's Minoxidil FOAM 5% was Headache (1.7% for Minoxidil Foam 5%, 1.2% for Placebo Foam).

Dermatological adverse reactions included Pruritis (1.1% for Minoxidil Foam 5%, 0.0% for Placebo Foam), and Rash (1.1% for Minoxidil Foam, 0.0% for Placebo Foam). The most frequently reported dermatological adverse events were erythema (4.0% for Minoxidil Foam 5% group, 4.9% for Placebo Foam group), rash (3.9% for Minoxidil Foam 5%, <1.0% for Placebo Foam), acne (2.8% for Minoxidil Foam 5%, 1.7% for Placebo Foam), and pruritis (2.2% for Minoxidil Foam 5%, 1.2% for Placebo Foam).

The most frequently reported adverse events at week 16 were infections (11.1% for Minoxidil Foam 5%, 12.8% for Placebo Foam), accidental injury (2.8% for Minoxidil Foam 5%, 7.6% for Placebo Foam), pain (2.2% for Minoxidil Foam 5%, 1.2% for Placebo Foam), flu syndrome (2.2% for Minoxidil Foam 5%, 1.7% for Placebo Foam), bronchitis (2.2% for Minoxidil Foam 5%, 1.2% for Placebo Foam), and pharyngitis (2.2% for Minoxidil Foam 5%, 0.0% for Placebo Foam).

Adverse events that differed in incidence of more than 1% in the Minoxidil Foam 5% group relative to the Placebo Foam group at week 16 included headache (7.2% for Minoxidil Foam 5%, 3.5% for Placebo Foam), pharyngitis (2.2% for Minoxidil Foam 5%, 0.0% for Placebo Foam vehicle), hypersensitivity (1.7% for Minoxidil Foam 5%, 0.0% for Placebo Foam), pyrexia (1.1% for Minoxidil Foam 5%, 0.0% for Placebo Foam), and myalgia (1.1% for Minoxidil Foam 5%, 0.0% for Placebo Foam).

For the long-term treatment with Men's Minoxidil FOAM 5% BID (an open-label safety extension phase of Study 006), 114 subjects out of 143 subjects completed one year of treatment. 53.1% of the subjects reported adverse events. The most frequently reported non-serious adverse events were infection (6.7%), headache (3.7%), and accidental injury (2.3%). Two events were considered serious in nature; accidental injury (<1.0%) and pain (<1.0 %) but were not considered to be drug related. All other adverse events were considered mild or moderate in nature. The incidence of drug-related adverse events was 7.0% of subjects overall and 13.2% of the subjects reporting adverse events. The incidence of adverse events leading to withdrawal was low (2.8% overall).

In general, the overall post-marketing safety experience to date has been consistent with that observed in the clinical trial program.

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.

Men's MINOXIDIL FOAM 5%

In a randomized, double-blind, placebo-controlled, multi-centre (involving 14 centers) trial (Study 006), the efficacy and safety of a topical 5% Minoxidil Foam formulation for the treatment of male androgenetic alopecia were evaluated. A total of 352 male subjects with androgenetic alopecia were enrolled. Subjects were randomized in a ratio of 1:1 to receive either 5% Minoxidil Foam twice daily (180 subjects) or placebo foam twice daily (172 subjects) for 16 weeks. Safety was assessed by means of clinical assessments of local tolerance, laboratory tests, and vital signs, as well as reported adverse events.

Table 1 summarizes the Adverse Events reported in study 006 for ≥1% of subject by Primary System Organ Class and Preferred Term.

Table 1 Adverse Events occurring in ≥1% of male patients treated with Men's MINOXIDIL FOAM 5% as compared to male patients treated with Placebo for 16 weeks

Primary System Organ Class: Preferred Term	**Number (%) of Subjects**	
	5% Minoxidil Foam (N=180)	**Foam Vehicle (N = 172)**
Gastrointestinal Disorders		
Abdominal Pain	2 (1.1)	1 (<1.0)
Diarrhea	2 (1.1)	3 (1.7)
Gastrointestinal Disorder	1 (<1.0)	3 (1.7)
Hernia	2 (1.1)	2 (1.2)
Nausea	2 (1.1)	2 (1.2)
General Disorders and Administration Site Conditions		
Flu Syndrome	4 (2.2)	3 (1.7)
Pain	4 (2.2)	2 (1.2)
Pyrexia	2 (1.1)	0 (0.0)
Periodontal Abscess Complication	1 (<1.0)	2 (1.2)
Immune System Disorders		
Hypersensitivity	3 (1.7)	0 (0.0)
Infection and Infestations		
Infection	20 (11.1)	22 (12.8)
Infection Viral	2 (1.1)	1 (<1.0)
Infection Bacterial	1 (<1.0)	2 (1.2)
Periodontal Abscess Complication	1 (<1.0)	2 (1.2)

Primary System Organ Class: Preferred Term	Number (%) of Subjects	
	5% Minoxidil Foam (N=180)	Foam Vehicle (N = 172)
Injury, Poisoning, and Procedural complications		
Accidental Injury	5 (2.8)	13 (7.6)
Metabolism and Nutritional Disorders		
Hyperglycemia	1 (<1.0)	5 (2.9)
Hyperuricemia	0 (0.0)	2 (1.2)
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	2 (1.1)	1(<1.0)
Myalgia	2 (1.1)	0 (0.0)
Nervous System Disorders		
Headache	13 (7.2)	6 (3.5)
Dizziness	1 (<1.0)	3 (1.7)
Psychiatric Disorders		
Depression	1 (<1.0)	2 (1.2)
Renal and Urinary Disorders		
Urine abnormality	4 (2.2)	6 (3.5)
Haematuria	3 (1.7)	7 (4.1)
Albuminuria	0 (0.0)	2 (1.2)
Glycosuria	0 (0.0)	4 (2.3)
Respiratory, Thoracic, and Mediastinal Disorders		
Bronchitis	4 (2.2)	2 (1.2)
Pharyngitis	4 (2.2)	0 (0.0)
Pneumonia	1 (<1.0)	3 (1.7)
Rhinitis	1 (<1.0)	4 (2.3)
Skin and Subcutaneous Tissue Disorders		
Rash	7 (3.9)	1 (<1.0)
Acne	5 (2.8)	3 (1.7)
Pruritis	4 (2.2)	2 (1.2)
Photosensitivity Reaction	1 (<1.0)	4 (2.3)
Dry Skin	0 (0.0)	2 (1.2)

Primary System Organ Class: Preferred Term	Number (%) of Subjects	
	5% Minoxidil Foam (N=180)	Foam Vehicle (N = 172)
Vascular Disorders		
Hypertension	2 (1.1)	1 (<1.0)

8.3 Less Common Clinical Trial Adverse Reactions

Adverse Drug Reactions observed in <1% of males treated with Men's MINOXIDIL FOAM 5% for 16 weeks

General Disorders and Administration Site Conditions: headache and pain (not otherwise specified).
Vascular Disorders: hypertension.
Skin and Subcutaneous Tissue Disorders: acne, rash, pruritis, and hirsutism.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings
The following table summarizes the Clinical Chemistry Abnormal Values noted in male patients treated with Men's Minoxidil 5% FOAM compared to male patients treated with Placebo Foam Vehicle for 16 weeks (STUDY 006).

Table 2: Values at Week 16 vs. Baseline (Men's MINOXIDIL Foam 5% Study 006)

Notable Criteria		5% Minoxidil Foam BID (N=180)	Placebo Foam Vehicle BID (N =172)
Parameter	ULN (U/L)	Number (%) of Subjects with Increase > ULN	Number (%) of Subjects with Increase > ULN
ALT	43	2 (1.1%)	0 (0.0)
AST	36	3 (1.7)	2 (1.2)
GGT	61	3 (1.7)	2 (1.2)

ULN=Upper Limit of Normal, ALT=Alanine aminotransferase, AST=Aspartate aminotransferase, GTT=Gamma-glutamyltransferase.

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 6 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 3: 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

System Organ Class	Adverse Event Preferred Term
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

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 Men's Minoxidil FOAM 5% 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 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 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 4: Serum concentrations of total minoxidil after the application of 1 mL of Men's Minoxidil 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 Men's 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 Men's 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 5: Comparison of Minoxidil Absorption from different doses in Mouse and Rat to that from Men's 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

Men's GLN-MINOXIDIL should be stored at controlled room temperature range of 15-30 °C. Do not puncture or incinerate container. Do not expose to heat or temperature above 50°C. Store in upright position.

PART II: SCIENTIFIC INFORMATION

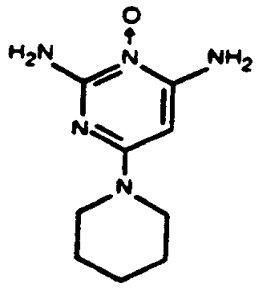
13 PHARMACEUTICAL INFORMATION

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, crystalline solid that is slightly soluble in water, soluble in propylene glycol and in alcohol, sparingly soluble in methanol, and practically insoluble in acetone, chloroform, ethyl acetate and in hexane. It melts in the approximate range of 248°C.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Men's MINOXIDIL FOAM 5% (Minoxidil 50mg/g [5% w/w])

The efficacy of minoxidil 5% foam was evaluated in a Phase 3, randomized, double-blind, placebo-controlled, multi-centre trial involving 14 centers (Study 006). In this study, the efficacy of a topical 5% Minoxidil Foam formulation was compared to that of the product vehicle without the minoxidil active ingredient for the treatment of male androgenetic alopecia. A total of 352 male subjects with androgenetic alopecia were enrolled. Subjects were randomized in a ratio of 1:1 to receive either 5% Minoxidil Foam twice daily (180 subjects) or Placebo Foam twice daily (172 subjects) for 16 weeks. More than 80% of the subjects in each group were Caucasians. The primary efficacy endpoints were the mean change in non-vellus hair count within the target region between Baseline and Week 16, as determined by a validated computer-assisted dot-mapping technique, and subject rating of treatment benefit via the use of global photographs of the vertex region, assessed as an overall improvement from baseline, and collected on a subject questionnaire.

Table 6: Summary of Patient Demographics in Study 006

Study #	Study design	Dosage, route of administration and duration	Study subjects (n) Minoxidil/ Placebo	Mean age (Range) Minoxidil/ Placebo	Sex
006	Phase 3, multiple-centre, double-blind, randomized placebo-controlled study, 16 weeks	5% minoxidil topical foam or placebo, twice daily, topical application to the affected area on the scalp	172 / 180	40.1 (21-49) / 38.3 (20-49)	Male
	Open label safety phase following the 16-week controlled study, duration up to one year	5% minoxidil topical foam or placebo, twice daily, topical application to the affected area on the scalp	75/68	39.6 (21-49)	Male

14.2 Study Results

Men's MINOXIDIL FOAM 5% (Minoxidil 50mg/g [5% w/w])

The Minoxidil 5% Foam treatment group showed a statistically significant greater increase in hair count compared to the Vehicle Foam group (21.0 versus 4.3 hairs per cm^2) at week 16. A clear difference between treatment groups was evident at week 8, increasing at week 12, and again at week 16. The subject's rating of treatment benefit was statistically significantly better for the Minoxidil 5% Foam treatment group compared to the Placebo treatment group (1.4 vs. 0.5) at week 16.

Table 7: Summary of Efficacy Results for Men's MINOXIDIL FOAM 5% after 16 weeks of treatment in the controlled-phase of Study 006

Primary Endpoints	Minoxidil FOAM 5% Mean Scores	Placebo Foam Vehicle Mean Scores
Mean change in non-vellus hair count in the target region between baseline and weeks 8,12 & 16	Week 8: 16.0 hairs/cm^2 Week 12: 19.9 hairs/cm^2 Week 16: 21.0 hairs/cm^2 P<0.0001 at each visit	Week 8: 4.9 hairs/cm^2 Week 12: 4.5 hairs/cm^2 Week 16: 4.3 hairs/cm^2

Primary Endpoints	Minoxidil FOAM 5% Mean Scores	Placebo Foam Vehicle Mean Scores
Subject rating of treatment benefit based on global photographs of change from baseline	Week 16: 1.4 points P<0.0001	Week 16: 0.5 points

14.3 Comparative Bioavailability Studies

Men's GLN-MINOXIDIL (Minoxidil Foam, Aerosol Foam 50 mg/g (5% w/w)) has satisfied the criteria for a biowaiver in comparison to Men's ROGAINE® FOAM 5% (Minoxidil Foam 50 mg/g (5% w/w)) (Johnson & Johnson Inc).

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Acute Toxicity

Table 8: LD50 (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 Men's Minoxidil 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 g 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 Men's Minoxidil Topical Solution. The absorption of topical applications of Men's 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 Men's 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 Men's 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)), Men's ROGAINE® FOAM 5% (Aerosol Foam, 50 mg/g (5% w/w)), Women's ROGAINE® FOAM 5% (Minoxidil Foam 50 mg/g (5%w/w)) Submission Control # 251296, Product Monograph, Johnson & Johnson Inc. (JAN 20, 2022).

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

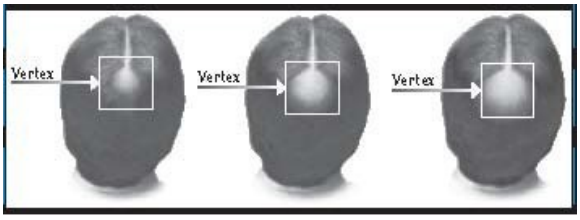
Men's GLN-MINOXIDIL

Minoxidil Foam

Read this carefully before you start taking **Men's GLN-MINOXIDIL** 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 **Men's GLN-MINOXIDIL**.

What is Men's GLN-MINOXIDIL used for?

- Men's GLN-MINOXIDIL 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 (vertex only, as shown below).



- Men's GLN-MINOXIDIL 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 Men's GLN-MINOXIDIL work?

Men's GLN-MINOXIDIL 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.

Men's GLN-MINOXIDIL 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 below).

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 Men's GLN-MINOXIDIL for at least 4 months before you see any results.

The amount of hair regrowth is different for each person. Not everyone will respond to Men's GLN-MINOXIDIL. 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 Men's GLN-MINOXIDIL?

Medicinal ingredients: minoxidil

Non-medicinal ingredients: Anhydrous Citric Acid, Butylated Hydroxyl Toluene, Cetyl Alcohol, Dehydrated Alcohol, Glycerin, Hydrocarbon Propellant (propane, isobutane, n-butane), L-Lactic Acid, Purified Water, Polysorbate 60, and Stearyl Alcohol.

Men's GLN-MINOXIDIL comes in the following dosage form:

Foam that contains 50 mg minoxidil per gram (5% w/w) and is delivered from a pressurized container

Do not use Men's GLN-MINOXIDIL if:

- you are female, pregnant, or breastfeeding
- you are a male under 18 or over 65 years of age
- you have no family history of hair loss, hair loss is sudden and/or patchy, or the reason for hair loss is unknown
- you are allergic to minoxidil or to any ingredients in Men's GLN-MINOXIDIL
- 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.
- have secondary syphilis

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Men's GLN-MINOXIDIL. 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 Men's GLN-MINOXIDIL only on the scalp.
- Avoid contact with eyes as Men's GLN-MINOXIDIL 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.
- Men's GLN-MINOXIDIL may cause local skin reactions (contact dermatitis), irritation to the eyes or mucous membranes.
- May change colour/texture of hair
- Avoid inhalation of the spray
- In rare cases, Men's GLN-MINOXIDIL may cause low blood pressure, salt and water retention that lead to chest pain (angina), rapid heartbeat (tachycardia), swollen hands and feet
- Shedding of hair may occur within two to six weeks after using the product; this is not uncommon and is temporary. If shedding persists for more than two weeks, users should stop applying Men's GLN-MINOXIDIL and consult their doctor
- If you do not see any results after 4 months, stop using Men's GLN-MINOXIDIL and seek advice of your 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 Men's GLN-MINOXIDIL:

- Anthralin – used to treat psoriasis
- Tretinoin – used to treat acne or other skin conditions
- Men's GLN-MINOXIDIL (Minoxidil) also may increase the effect of hydralazine (drug to treat high blood pressure).

How to take Men's GLN-MINOXIDIL:

- Men's GLN-MINOXIDIL 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 foam.

<u>Pre-Application</u>:

- Shampooing is not required before applying Men's GLN-MINOXIDIL. However, if you wash your scalp before applying, 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 to a sunburned or irritated, broken, or shaved scalp.

Application:

1. PREP HANDS WITH COLD WATER
Rinse your fingers in cold water and dry them. Note: foam will melt on contact with warm surfaces.

2. OPEN THE CAP
Be sure to align arrow on the cap with arrow on blue ring. Tilt cap back and pull off.

3. HOLD CAN STRAIGHT UPSIDE DOWN AND DISPENSE ONTO A COLD SURFACE
If you hold the can at an angle, foam may not dispense properly. Press nozzle to dispense half a capful of foam onto a cold surface (e.g. dish, or cold hands).

4. APPLY TO SCALP, NOT HAIR
Part your hair to expose hair loss area. Massage foam into scalp, not hair. Repeat until all hair loss areas have been covered.

5. CLOSE CAP AND WASH HANDS
Snap cap back into place. Be sure arrows do not line up. Wash hands and any surface thoroughly after use.

- For Men's GLN-MINOXIDIL to work best, you should allow it to remain on the scalp for at least 4 hour

Post-Application:

- Do not dry the foam with a hair dryer.
- If you are planning to be in the sun after applying Men's GLN-MINOXIDIL, 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.
- You may use hair sprays, mousses, conditioners, gels, etc. However, you should apply Men's GLN-MINOXIDIL 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 Men's GLN-MINOXIDIL. However, to avoid possible scalp irritation, you should make sure all of the foam has

been washed off the hair and scalp before using these products.

Usual dose:

- Half (½) capful (equivalent to 1 gram of foam) applied twice daily to the entire affected area; **for example, once in the morning and once at night.**
- Do not exceed two doses of half (½) capful (equivalent to 2 grams of foam) in a day. Exceeding the recommended dosage may cause increased side effects.

One can of Men's GLN-MINOXIDIL should last for 30 days (one month), if applied twice a day according to directions.

Overdose:

If you think you, or a person you are caring for, have taken too much Men's GLN-MINOXIDIL, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

- If you miss one or two applications, skip the missed dose and continue your regular dosing schedule. Do not apply a double dose to make up for a missed one.

What are possible side effects from using Men's GLN-MINOXIDIL?

These are not all the possible side effects you may have when taking Men's GLN-MINOXIDIL. 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 Men's GLN-MINOXIDIL 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 Men's GLN-MINOXIDIL.
- Men's GLN-MINOXIDIL 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 at a controlled room temperature range of 15-30°C, in an upright position.
- Do not use after the expiry date on the base of the can.
- The product in this pressurized container is extremely flammable, therefore exposure of the container or its contents to open flames should be avoided.

- Protect from sunlight and do not expose to temperatures above 50°C.
- Do not pierce or burn the container, even when empty.
- Do not use while smoking.
- Do not use near, or place container on, polished or painted surfaces.
- Medicines should not be disposed of via wastewater or household waste.
- Ask your pharmacist how to dispose of medicines no longer required.
- These measures will help to protect the environment.

If you want more information about Men's GLN-Minoxidil:

- 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; or contacting Glenmark Pharmaceuticals Canada Inc. at 1-844-801-7468.

This leaflet was prepared by Glenmark Pharmaceuticals Canada Inc.

Last Revised: November 21, 2024