SUBMISSION FOR THE RECLASSIFICATION OF A MEDICINE

Topical Minoxidil

January 2010

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EXECUTIVE SUMMARY

Background to the Submission

Our application is intended to support the reclassification of Minoxidil preparations in 5% or less for dermal use from Pharmacy Only to General Sales Medicine by demonstrating that they are safe and effective treatments, and therefore suitable for sale in the general retail environment for people with androgenetic alopecia (common baldness).

We will show that a detailed examination of the safety profile of Topical Minoxidil demonstrates little difference between 2% and 5% preparations of Minoxidil and therefore the two strengths can be viewed as having virtually the same level of safety. There has not been any detectable change in the safety profile of Topical Minoxidil since its reclassification to Pharmacy Only in 2001.

We note that the Medicines Classifications Committee has previously considered a similar submission in 1999 by another sponsor which was subsequently rejected. The concerns raised by Committee at the time will be addressed in this submission.

Currently, there are no treatments evaluated for safety and efficacy available to consumers for the treatment of androgenetic alopecia in the general retail environment. The current treatments sold in general retail channels are either complementary medicines or cosmetic products which have not been evaluated by Medsafe for efficacy and safety.

For any Topical Minoxidil product to be effective, it must be used regularly and continuously. If the product is discontinued, hair loss reverts to the level it would have reached had the product never been used. In this situation, the wider availability of Topical Minoxidil will benefit consumers in terms of convenience and its presence on the shelf in retail outlets will prompt consumers to purchase when they might otherwise have forgotten and thereby assist with compliance. The availability of Topical Minoxidil in general retail outlets would also be a convenience to those consumers who might suffer embarrassment when asking for treatment for this condition. Given the safety of the product, these benefits are considered sufficient to outweigh any advantage gained from professional advice at the point of sale.

There are numerous products and procedures that are marketed for the treatment of hair loss (Table 1). In general, the treatments can be classed as those requiring medical intervention and those that do not require medical intervention. Topical Minoxidil is the only OTC medicine that is evaluated and approved for the treatment of androgenetic alopecia, and as such, is the only clinically proven option available for consumers to self-medicate.

The Therapeutic Guidelines: Dermatology (Version 3, 2009) recommends Topical Minoxidil 5% as first-line therapy for androgenetic alopecia and that the basis for treatment of androgenetic alopecia is to arrest further hair loss and, where possible, stimulate new hair growth (Dermatology Expert Group, 2009).

Table 1 – Current Treatments for Androgenetic Alopecia in New Zealand

Evaluated by Medsafe	NOT evaluated by Medsafe
Topical Minoxidil 2 & 5% (REGAINE®, and other brands)	Herbal/Vitamin formulations in topical and oral formats. Not evaluated by Medsafe for safety and efficacy.
	Shampoos, Conditioners and Hair Tonics
	Coloured hair sprays, wigs and toupees conceal hair loss but are **not** treatments.

Classification of minoxidil overseas

Topical Minoxidil solutions have been down scheduled and are available for general sale in the USA (since 1997) and the UK for the 2% strength only (since 2002) (however, a GSL submission was made in 2009 for the 5% strength which is still being evaluated).

The following table (Table 2) shows the scheduling status of Topical Minoxidil in other countries.

Table 2 - Classification Status of Topical Minoxidil 2% and 5% in other countries

COUNTRY	CURRENT CLASSIFICATION	COMMENTS
AUSTRALIA	2% Strength – Pharmacy Only 5% Strength – Pharmacy Only	Both strengths are available for self-selection in pharmacies, the same as NZ.
UNITED KINGDOM	2% Strength – General Sales Medicine	Reclassified to GSL in **2002** (7 years of GSL experience)
	5% Strength – Pharmacy Only	GSL reclassification application submitted to MHRA in late 2009 is pending evaluation. But is currently available for self selection in pharmacies.
UNITED STATES OF AMERICA	2% and 5% Strengths – General Sales Medicine	Reclassified to GSL in **1996** (14 years of GSL experience). Available in hairdressers, pharmacies and other outlets by self selection.

COUNTRY	CURRENT CLASSIFICATION	COMMENTS
CANADA	2% and 5% - Pharmacy Only	Since 2000, sold in drugstores only, but available for self-selection in all provinces except for Nova Scotia, Quebec and Alberta where it is held behind the counter (like Pharmacist Only Medicines). Each of the various provinces is responsible for determining the conditions of sale for medications.

Topical Minoxidil is considered to be a safe and effective medicine for the treatment of androgenetic alopecia. The first reclassification of Topical Minoxidil making it available for general sale was almost 14 years ago in the USA and then subsequently 7 years ago in the UK for the 2% formulation.

Conclusion

The excellent safety profile, established efficacy, and minimal risk associated with its reclassification, as demonstrated overseas, makes Topical Minoxidil an ideal candidate for rescheduling to a General Sales Medicine. It will allow greater access via the general retail channel, increasing awareness of a safe and efficacious treatment and giving better outcomes to those with androgenetic alopecia when compared to currently available offerings in the general retail environment.

PART A

1. International Non-proprietary Name (or British Approved Name or US Adopted Name) of the Medicine

- Minoxidil (BAN)
- Minoxidil (INN)

2. Proprietary Name

- Regaine® (previously known as Rogaine®)

3. Name of company/organisation/individual requesting reclassification

Johnson & Johnson Pacific
Locked Bag 5, Broadway, NSW 2007 Australia
45 Jones Street, Ultimo, NSW 2007 Australia

Contact Person: Paul Melas

DDI: +61 2 8260 8419
Fax: +61 2 8260 8518
pmelas@ its.jnj.com

4. Dose form (s) and strength(s) for which a change is sought

Minoxidil 5% solution for Men

5. Pack size and other qualifications

60mL x1, 60mL x3

6. *Indications for which change is sought*

For the treatment of androgenetic alopecia (common baldness) in healthy men and women.

7. *Present classification of medicine*

Ingredient	Conditions (if any)	Classification
Minoxidil	For dermal use in medicines containing 5% or less	Pharmacy Only

8. *Classification sought*

Ingredient	Conditions (if any)	Classification
Minoxidil	For dermal use in medicines containing 5% or less	General Sale

9. *Classification status in other countries (especially Australia, UK, USA, Canada)*

Table 2 - Classification Status of Topical Minoxidil 2% and 5% in other countries

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COUNTRY	CURRENT CLASSIFICATION	COMMENTS
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Topical Minoxidil is considered to be a safe and effective medicine for the treatment of androgenetic alopecia, being first reclassified for general sale almost 14 years ago in the USA and 7 years ago in the UK for the 2% formulation. The ability for consumers to self-select in pharmacy has been possible since 2002 in New Zealand and Australia.

10. Extent of usage in NZ and elsewhere (e.g. sales volumes) and dates of original consent to distribute

The sales data presented in this section is considered COMMERCIAL IN CONFIDENCE.

Currently, only Regaine for Men 5% solution is available for sale in New Zealand. Rogaine for Women was discontinued since 2006. Rogaine and Regaine are have the same formulation but with different brand names.

Table 3 -
Usage of Regaine/Rogaine in New Zealand from 2004-2009

Year	Product	Units
Year 2004	ROGAINE	720
	ROGAINE FOR WOMEN	22
	REGAINE	36
Year 2005	ROGAINE	12,904
	ROGAINE FOR WOMEN	402
	REGAINE	266
Year 2006	ROGAINE	8,946
	ROGAINE FOR WOMEN	169
	REGAINE	50
Year 2007	ROGAINE	5,980
Year 2008	ROGAINE	4,067
Year 2009	ROGAINE	4,073
TOTAL over 5 years		**37635**

New Zealand usage over the last 5 years is 37635 units which is equal to 2,258,100 mL. This compares to approximately 1.9 billion mL over 10 years worldwide.

11. Labelling of draft labelling for the proposed new presentation (s)

Please refer to the copy of the carton label attached for REGAINE for Men 5% solution.

12. Proposed warning statements if applicable

The current warnings on the carton label are:

Keep out of reach of children. For external use only. Avoid contact with eyes. Do not take orally.

Do not use if you:

- Do not have a family history of hair loss
- Have a sudden and/or unexplained hair loss
- Have a red, inflamed, irritated, infected or painful scalp
- Have had an allergic reaction to REGAINE or any of its ingredients
- Are under 18 years or over 65 years of age
- Are a woman who is pregnant or breastfeeding

Tell your doctor of pharmacist before use if you:

- Have any heart problems

13. Other products containing the same active ingredient(s) and which would be affected by the proposed change.

Table 4 – Topical Minoxidil Products Registered in New Zealand

Product	Sponsor	Status
Apo-Gain Topical solution, 2% (Pharmacy only)	Apotex NZ Ltd	Consent given
Apo-Gain Topical solution, 5%w/v (Pharmacy only)	Apotex NZ Ltd	Consent given
Hair A-Gain Scalp Application Topical solution, 50mg/mL (Pharmacy only)	Arrow Pharmaceuticals (NZ) Limited	Consent given
Headway Topical solution, 2%w/v (Pharmacy only)	Mylan New Zealand Limited	Not marketed
Headway 5 Topical solution, 5%w/v	Mylan New Zealand	Not

(Pharmacy only)	Limited	marketed
Men's Regaine Regular Strength Topical solution, 2% (Pharmacy only)	Johnson & Johnson (New Zealand) Limited	Not Marketed
Men's Regaine Extra Strength Topical solution, 5% (Pharmacy only)	Johnson & Johnson (New Zealand) Limited	Consent given
Regaine (see Rogaine Topical gel, 2%w/w (Pharmacy only))	Johnson & Johnson (New Zealand) Limited	Not Marketed
Regaine (see Men's Regaine Regular Strength Topical solution, 2% (Pharmacy only))	Johnson & Johnson (New Zealand) Limited	Not Marketed
Regaine (see Men's Regaine Extra Strength Topical solution, 5% (Pharmacy only))	Johnson & Johnson (New Zealand) Limited	Consent given
Rogaine Topical gel, 2%w/w (Pharmacy only)	Johnson & Johnson (New Zealand) Limited	Not Marketed
Rogaine (see Men's Regaine Regular Strength Topical solution, 2% (Pharmacy only))	Johnson & Johnson (New Zealand) Limited	Not Marketed
Rogaine (see Men's Regaine Extra Strength Topical solution, 5% (Pharmacy only))	Johnson & Johnson (New Zealand) Limited	Not Marketed
Rogaine (Women's) Topical solution, 2% (Pharmacy only)	Johnson & Johnson (New Zealand) Limited	Not Marketed

Part B

Reasons for requesting classification changes

This section should be supported where relevant by the following:

1. A statement of the benefits to both the consumer and to the public expected from the proposed change

Although scalp hair provides no known vital physiological function for humans, it is an important facet of human appearance, which is commonly used for recognition and is one determinant of physical attractiveness. Consumers search for ways to halt or reverse the course of their condition and to restore their body image integrity (Cash, Price, & Savin, 1993). The high level of desire to self-treat their hair loss condition leads many individuals to turn to unapproved, scientifically unproved, non-prescription hair growth products some of which undoubtedly represent real or potential public health hazards, or at best are marginally effective. Unproved preparations for treating androgenetic alopecia have been sold and used for many years and only contribute to the distress a person is already suffering when they are found to be ineffective.

Thus reclassification of Topical Minoxidil preparations would have the following main advantages:

- Increases availability or access to a product with clinically demonstrated efficacy and safety.
- It improves consumer awareness that safe and efficacious treatment is available.

Other benefits are in terms of convenience and its presence on the shelf in retail outlets which will prompt consumers to purchase when they might otherwise have forgotten and thereby assisting with compliance. The availability of Topical Minoxidil in general retail outlets would also be a convenience to those consumers who might suffer embarrassment when asking for treatment of this condition.

As already stated, when compared to other products for hair loss that are available without prescription, Topical Minoxidil is the only treatment that is currently available to consumers that has clinically proven safety and efficacy and been evaluated by Medsafe. Other products are either cosmetic or

complementary medicines in nature. Complementary medicines are not free of adverse events. (ADRAC reports for Hair Skin and Nail tablets and for Saw Palmetto products, 2010).

The General Sale Medicine status would also result in Topical Minoxidil being made available for purchase through hairdressers who can increase awareness of this treatment option to those who may be in the early stages of hereditary hair loss, resulting in better outcomes for those individuals, as the goal of treatment is to “arrest further hair loss and, where possible, stimulate new growth”. (Dermatology Expert Group, 2009)

Topical Minoxidil has proven efficacy and safety and is an excellent candidate for reclassification as a General Sales Medicine. With the included consumer information leaflet in each pack, the consumer has enough information to treat their condition safely. Given its safety, these benefits are considered sufficient to outweigh any advantage gained from professional advice at point of sale.

2. Ease of self-diagnosis or diagnosis by a pharmacist for the condition indicated

Androgenetic alopecia can be self-diagnosed easily because of the nature of the condition, namely:

- The pattern of hair loss – although this is less distinct in women,
- The gradual onset and progression of hair loss,
- A positive family history of androgenetic alopecia, and
- The lack of associated local or systemic signs and symptoms as aspects of the condition.

There is a low risk of masking a serious disease. Hair loss (but not androgenetic alopecia) may infrequently present as the earliest sign of systemic disease, but it is unusual for this situation to continue, and a short delay in diagnosis is unlikely to be harmful. Examples of such diseases are alopecia areata, hypothyroidism, second-stage syphilis and systemic lupus erythematosus.

The conditions discussed above have other signs and symptoms which point to the need for medical care, but the overall outcome of the conditions are not likely be affected adversely by a short delay in diagnosis.

Lastly, as androgenetic alopecia has a family history and gradual onset, the product label states, “Do not use if you do not have a family history of hair loss” and “Do not use if you have a sudden and/or unexplained hair loss” providing guidance to consumers wishing to self treat.

3. Relevant comparative data for like compounds

There are no similar compounds on the market. Some comparative data on Saw Palmetto is included below. Saw Palmetto is a traditional herbal remedy. Other complementary medicines have no proven efficacy in androgenetic alopecia, due to the nature of the condition, supplementation with vitamins and minerals will not assist in stopping the progression of this type of condition.

Saw Palmetto (Serenoa repens)

It has been suggested that saw palmetto may by an antagonist of block some effects of testosterone and therefore reduce male pattern hair loss, similar to the medication finasteride (Propecia®). Although, Medline Plus of the US National Library of Medicine states that, “More studies are necessary before saw palmetto can be recommended for this use” and has classified the evidence of efficacy as “unclear”. (Natural Standard Research Collaboration, 2009)

4. Local data or special considerations relating to NZ

Safety data presented in this section is considered COMMERICAL IN CONFIDENCE.

The following points address the concerns raised in previous submissions by the Committee. They will show that

Foeto-toxicity

The label clearly states “Do not use if you are a woman who is pregnant or breastfeeding”

The summary of Minoxidil in Drugs in Pregnancy and Lactation edition 8 states,

“Minoxidil is not teratogenic in rats and rabbits, but some fetotoxicity was observed in rabbits. The human pregnancy experience is too limited, after both oral dosing and topical application, to determine the risk of teratogenicity. A possible exception involves the two infants exposed in utero to oral minoxidil who had hypertrichosis. This is a known adverse effect in adults, and, indeed, one of the mothers had hypertrichosis. However, the causes of the multiple congenital malformations observed in one of these infants and the heart defects in the other are unknown. Similarly, the causes of the multiple anomalies observed in two fetuses after minoxidil topical application also are unknown. Although the doses applied in these two cases were not specified, only small amounts of topically applied minoxidil are absorbed into the systemic circulation. Of interest, both mothers had a flulike illness in the 1st trimester. Even if these malformations are not related to drug exposure, the potential toxicity of oral minoxidil is severe enough to preclude its use in

pregnancy. One of these toxicities includes large orthostatic decreases in blood pressure that could severely jeopardize placental perfusion. Although the possibility of a causal relationship to malformations after topical application appears to be remote, the safest course is to avoid applying the agent during the 1st trimester." (Briggs, Freeman, & Yaffe, 2008)

The label clearly states to avoid use in pregnancy or breastfeeding, however, the risk of foetal harm is low if Topical Minoxidil is administered inadvertently during pregnancy.

Loss of libido

Only 2 cases of decreased libido have been reported as an adverse event in the PSUR analysis using events over a 10 year period from 1998 to 2008 (Shah, Shur, & Van Loon, 2008).

Adverse Events / Side Effects

Please refer to Part B Section 8 Adverse events – nature, frequency, etc.

The analysis of adverse events in relation to 2% and 5% formulations demonstrates that the two formulations have similar safety profiles.

Furthermore, post marketing data supports the safety profile of Topical Minoxidil for reclassification as General Sales Medicine.

Interactions with other medications

Please refer to Part B Section 5 Interactions with other medicines.

There are no known drug interactions associated with the use of Topical Minoxidil.

Use by consumers with cardiovascular conditions including hypertension.

The product label clearly states, "Tell your doctor or pharmacist before use if you have any heart problems". See "Part B Section 8 Adverse Events – nature, frequency, etc" for more detail.

The risk of clinically important cardiovascular effects following use of 5% TMS is extremely remote.

Rescheduling would cause the product to be treated more like a cosmetic than a medicine by those selling and using the product

The advertising of therapeutic medication in New Zealand is regulated. Medication included as General Sales Medicines are still required to comply with the "Advertising Requirements of the Medicines Act 1981 (sections 56 to 62) and the Medicines Regulations 1984 (regulations 7 to 11). The "Guidelines for Advertising Over the Counter Medicines Direct to Consumers" are intended to assist in this compliance.

The Guidelines state that there is a responsibility to inform the consumer in advertisements that:

- There are risks to be considered
- Further information is available
- If the need arises, the use of the medicine can be discussed with an appropriate healthcare professional.

These mandatory requirements assist in keeping the fact that topical minoxidil is a medication in the mind of the consumer.

Lastly, advertisements are pre-vetted by the Therapeutic Advertising Pre-vetting System (TAPS), which is a barrier to illegal or unethical advertising behaviour. Claims and context of the advertisement is reviewed by TAPS ensuring that the medication is not promoted as a cosmetic product.

The current guidelines, regulations and approval processes are sufficient to ensure that a medicine that is classified as a General Sale Medicine is advertised and sold ethically and that the product is not viewed as a cosmetic product by consumers.

5. Interactions with other medicines

The current approved datasheet states:

"There are currently no known drug interactions associated with the use of ROGAINE. Although it has not been clinically demonstrated, there exists the theoretical possibility of absorbed minoxidil potentiating orthostatic hypotension in patients currently taking peripheral vasodilators. In vitro studies have shown that paracetamol and diethylcarbamazine may inhibit the stimulation of hair growth by minoxidil.

Drugs for cutaneous use, e.g., tretinoin and anthralin/dithranol, which alter the stratum corneum barrier, could result in increased absorption of cutaneously used minoxidil if applied concurrently".

A literature search of EMBASE (Ovid, 2010) was conducted and no new interactions were discovered. The EMBASE database was used as it relates to medical literature in humans.

Reports of possible interactions of topical minoxidil with hair care products were mostly minor irritant type reactions or changes in hair colour or texture, which, apart from the effects on appearance, posed no risk to the physical health of the patient. These interactions are well able to be managed by the consumer.

Interactions for oral minoxidil were for drugs or herbal substances that increase blood pressure which counteract the antihypertensive effects of oral minoxidil (Healthcare Series Volume 142, 2009). These interactions do not hold any relevance for topically applied minoxidil.

6. Contraindications

Topical minoxidil is contraindicated in patients with a history of hypersensitivity to minoxidil, propylene glycol or ethanol.

Although, a warning for use in people with cardiovascular disease or cardiac arrhythmias is present in the datasheet, it is not a contraindication.

7. Possible resistance

Not applicable

8. Adverse events – nature, frequency etc

The safety data and discussion of internal reports contained in this section is considered COMMERCIAL IN CONFIDENCE.

The Australian REGAINE® approved prescribing information states:

“The most frequently encountered adverse effect in clinical trials with REGAINE was mild dermatitis of the scalp. The dermatological events were of a similar type and severity in the 2% and 5% groups, but the incidence was greater in the 5% group.

Most frequently reported adverse reactions with 2% and 5% topical minoxidil in commercial marketing experience are dermatological reactions and include: local erythema, itching and dry skin, scalp flaking. Increased hair shedding can occur due to minoxidil’s action of shifting hairs in the resting telogen phase to

the growing anagen phase (old hairs fall out as new hairs grow in their place). This temporary increase in shedding generally occurs two to six weeks after beginning treatment and subsides within a couple of weeks (first sign of action of minoxidil).

Other adverse reactions that have been reported very rarely (<0.01%) include irritant dermatitis (redness/erythema, scaling/rash scaly and burning), non-specific allergic reactions, hives, hypersensitivity, allergic contact dermatitis, allergic rhinitis, facial swelling, folliculitis, alopecia, hypertrichosis, hair abnormalities, seborrhoea, , shortness of breath, headache, neuritis, dizziness/light-headedness , syncope, vertigo, oedema, chest pain, blood pressure changes (decreased and increased blood pressure, hypotension, hypertension), palpitations and pulse rate changes, rapid heartbeat/tachycardia.

Rare cases of hypertrichosis (unwanted non-scalp hair including facial hair growth in women) have been reported." (Australian Approved Prescribing Information, 2010)

In general, Topical Minoxidil is well tolerated and the majority of side effects are dermatological in nature, due to skin intolerance of the topical formulation in some patients. These side effects resolve upon discontinuation of the product. There has been no change in severity of reported side effects (Shah, Shur, & Van Loon, 2008). Minoxidil serum levels measured after topical application of a 5% minoxidil solution are generally considerably lower than the mean threshold level for haemodynamic effects. In the clinical studies, no associations between minoxidil serum levels and medical events, cardiovascular events, or abnormal diagnostic test results were evident.

Type A Events
A type A event is one that is due to an extension of the active pharmacologic properties of the drug; A indicates *augmented*. Serious type A adverse reactions (those that result from exaggeration of the drug's expected pharmacological actions when given in the usual therapeutic dose) have never been reported for Topical Minoxidil.

Type B Events
A type B event is one that is not due to an extension of the active pharmacologic properties of the drug; the B indicates *bizarre*. The risk of serious type B adverse reactions (those that represent a novel response not expected from known pharmacological action) seems to be very low in view of the widespread clinical use for 18 years and the extensive post-marketing experience.

Topical Minoxidil is not likely to present any danger to patients with concomitant diseases/conditions, as will be described in the following:
Concomitant cardiovascular disease/condition:

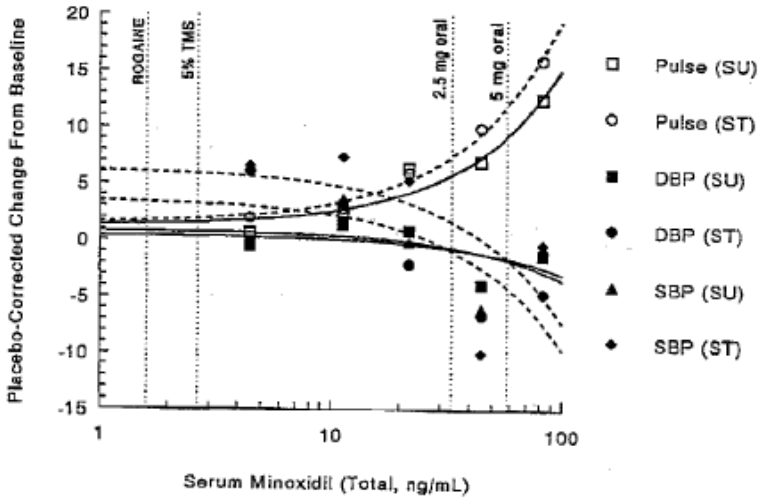
HYPERTENSION
a) Untreated hypertensives

Based on measurable haemodynamic effects, a mean minoxidil serum concentration of 21.7 ng/ml, was the lowest dose clearly distinguishable from placebo with regard to changes in heart rate (without significant change in blood pressure) (Ferry, Turner, Albert, Dietz, & Luderer, 1993).

A composite summary of the haemodynamic response-serum minoxidil concentration relationships determined in this study is shown in Figure 1. The fitted lines drawn through the symbols are best-fit lines determined using single regression (plotted semi-logarithmically) for each of the haemodynamic endpoints evaluated in the intravenous study in mild-to-moderate hypertensive subjects. Superimposed on the figure are vertical lines (labelled Rogaine i.e. 2% TMS, 5% TMS, 2.5 mg oral, and 5 mg oral) representing the mean peak serum minoxidil concentrations determined at steady-state in patients enrolled in the multicenter, placebo-controlled trial in untreated hypertensive patients (Baumgartner & Spindler, 1985) (Eller & Della-Coletta, 1985). In this study, Topical Minoxidil treatments were applied to a shaved rather than a naturally bald area of the scalp. Applying minoxidil to a shaved scalp has been shown to increase percutaneous absorption by approximately 70% (Szpunar & Dalm, 1985c). This finding needs to be considered in referring to the figure to evaluate the margin of safety in bald subjects using Topical Minoxidil.

(DBP = Diastolic Blood Pressure, SBP = Systolic Blood Pressure, SU = Supine measurement, ST = Standing measurement)

Figure 1



Overview of Concentration Hemodynamic Response Relationships

Blood pressure and pulse are placebo-subtracted and are the mean of the last two values (Hours 14 and 24 after the beginning of the infusion) for each dose level. Vertical lines are steady-state mean concentrations after topical dosing to a shaved area of the scalp and the peak steady-state serum concentrations following oral dosing.

As shown in Figure 1 above, a wide margin, more than a 30 times difference exists between serum minoxidil concentrations observed after topical dosing of Topical Minoxidil (i.e.: 2% and 5% TMS) and those associated with minimal effects on blood pressure and pulse in hypertensive subjects observed after

treatment with 2.5 mg oral minoxidil. The risk of patients with untreated hypertension experiencing haemodynamic effects when using Topical Minoxidil solution was examined in structured clinical studies (Baumgartner & Spindler, 1985). It is important to observe that the study of Baumgartner & Spindler (1985) was performed in patients with shaved scalps. **The results revealed no statistically significant variation in pulse rate, decreases in blood pressure or changes in body weight as a measure for fluid retention in treated and untreated hypertensive patients who used Topical Minoxidil** (2% TMS, or 5% TMS).

Figure 2 below shows the mean steady state concentration of topical Minoxidil solution and Minoxidil tablet in a more traditional concentration versus time graph. This reinforces the vast difference in concentrations between oral and topical dosing of Minoxidil and therefore the expected lack of haemodynamic effect of the topically applied formulation. (Eller & Della-Coletta, 1985)

Figure 2

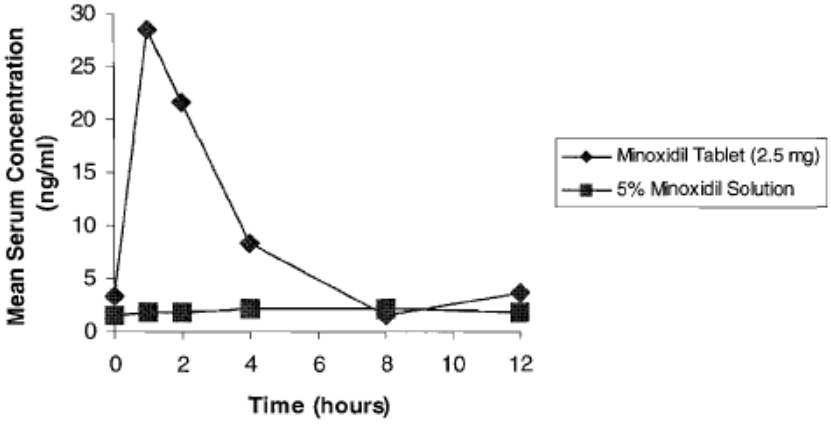


Figure 1: Mean Steady State Serum Concentration of Minoxidil Following Oral (2.5 mg tablet, twice daily) or Topical (5% minoxidil solution, twice daily) Administration.

b) Treated hypertensives

The risk for haemodynamic effects when using Topical Minoxidil solution in treated hypertensive patients was examined in a study in which 3% TMS was administered to patients with androgenetic alopecia who were receiving various medications for hypertension including vasodilators (Friedman, Seckman, & Royer, 1988). Vital signs including changes in blood pressure were monitored throughout this 16 week study. **No clinically significant changes in blood pressure attributable to Topical Minoxidil were detected.** Serum minoxidil drug levels did not correlate with clinical effects. **Additionally, no evidence was found of any interaction between Topical Minoxidil and the concomitant anti-hypertensive therapies being used by the patients in the study**.

HYPOTENSION

While Topical Minoxidil has not been specifically studied in hypotensive patients, world-wide marketing experience of both prescription and non-prescription use of 2% and 5% TMS demonstrates a reasonable safety record.

Between the period of 1 April 1996 to 31 March 2001, 7 reports on hypotension have been received for Topical Minoxidil 2%, 3 of which involve overdosing (2 oral ingestion and 1 topical application) and ne case of oral overdose for 5% TMS. **Topical Minoxidil has not been shown to affect blood pressure in normotensive subjects** (Royer, Seckman, & Neill, 1985a), nor has there been an effect on blood pressure in normotensive subjects by oral doses of minoxidil up to 10 mg/day (Royer, Seckman, & Schwartz, 1985b) or by 12-hour intravenous infusions of minoxidil at rates of 0.384 mg/ hour (total dose = 4.61 mg) and 1.53 mg/hour (total dose=18.36 mg) (Ferry, Turner, Froeschke, Sinkula, Luderer, & Hopkins, 1992). **Thus, Topical Minoxidil would not be expected to have an effect on blood pressure in hypotensive patients.**

A precautionary statement regarding the use of Topical Minoxidil whilst taking antihypertensive medication or when experiencing cardiovascular adverse effects is included in the CMI (see pack label and pack insert included for Part A Section 11 – Labelling of draft labelling for the proposed new presentation).

However, there is a very low likelihood of any cardiovascular effects due to the poor absorption and low serum levels of Topical Minoxidil.

Other Concomitant diseases

SCALP DISORDERS

Percutaneous studies investigating the use of minoxidil in the presence of scalp disorders have not been formally conducted. Percutaneous minoxidil absorption is controlled, and rate limited, by penetration into the stratum corneum. Any condition that results in a disruption of the integrity of the stratum corneum (e.g.: trauma, disease processes) will, most likely, result in an increase in percutaneous minoxidil absorption. The magnitude of this increase is dependent on the magnitude of damage to the stratum corneum. Since minoxidil is formulated in an alcohol-based solution, application of minoxidil in these circumstances is likely to be accompanied by stinging and burning. For these reasons, Topical Minoxidil is not recommended for use by patients treated for other scalp disorders, or when application is accompanied by stinging and burning.

The use of Topical Minoxidil is contra-indicated in the presence of other scalp disorders. This warning is stated on the pack label and CMI included in the pack (see pack label and pack insert included for Part A Section 11 – Labelling of draft labelling for the proposed new presentation).

POST MARKETING SAFETY UPDATE REPORTS

Review of the post-marketing data suggests that the safety profile of both strengths of Topical Minoxidil is favourable. The nature, frequency and severity

of reported serious AEs with the use of either 2% or 5% minoxidil formulations are similar.

Introduction

The analysis of safety data in this section is from the main safety PSUR dated 1999-2004. The remaining PSURs, Bridging Report and Addendum demonstrate that there is no change in safety profile of Topical Minoxidil up from 1st April 1996 to 1st July 2009.

The analysis will show that 2% and 5% Minoxidil preparations for dermal use have very similar safety profiles and that they may be treated in the same manner when considering safety.

The international birth date for minoxidil is 04 April 1986 (Guatemala). Topical Minoxidil was first approved for marketing in New Zealand on 3rd July 1987. The safety profile of Minoxidil has been summarized in the 3 Periodic Safety Update Reports (PSURs), Bridging Report and Addendum as outlined in Table 5.

TABLE 5 – Safety Data from 1996 to 2009

Report number	Reporting Period
1 – PSUR	**01 April 1996 to 31 March 2001 (5 years)**
2 – PSUR	**20 September 1999 to 30 June 2004 (4 years & 9 months)**
3 – PSUR	**01 July 2004 to 31 May 2005 (1 year)**
4 - Bridging Report	**01 June 2005 to 15 March 2009 (3 years 9 months)**
5 - Addendum	**16 March 2009 to 01 July 2009 (4 months)**

DATA ANALYSIS of Adverse Events from 3Q1998 through to 1Q2008

Available cumulative distribution data are derived from “units of volume measurement” from the Intercontinental Marketing Services (IMS) Global Services for the period 3Q1998 through 1Q2008. There were approximately 1.9 billion milliliters (mL) of minoxidil distributed during the period above.

Of the 1.9 billion mL, approximately 820 million mL (42%) were distributed as the 2% strength formulation and 1.1 billion mL (58%) were distributed as the 5% strength formulation.

Definitive conversion of packages distributed into numbers of patients exposed is not possible as the product may not be used as directed and may be used

by more than one member of the family. However, when used as directed, a 60-mL bottle is expected to provide a one-month supply.

RESULTS

DEMOGRAPHICS

The full line listing of medically confirmed cases for consumers using 2% and 5% minoxidil is included in the Safety/Efficacy Summary 2008 (Shah, Shur, & Van Loon, 2008).

Demographics of patients using 2% minoxidil formulations

This line listing contains 1,877 AEs from 942 cases (114 males; 754 females; 74 sex unreported). Of the 1,877 AEs, 1,707 were non-serious and 170 were serious. Fifty-three (6%) of the 942 cases contained AEs that were classified as serious. The age of the individuals, where reported, ranged from 4 to 85 years.

Demographics of patients using 5% minoxidil formulations

This line listing contains 1,695 AEs from 885 cases (469 males; 309 females; 107 sex unreported) reported from 26 different countries. Of the 1,695 AEs, 1,436 were non-serious and 259 were serious. Eighty-eight (10%) of the 885 cases contained adverse events that were classified as serious. The age of the individuals, where reported, ranged from 1.5 to 83 years.

Table 6 presents the number of cases, country, legal classification status and seriousness for the 5% minoxidil formulation.

Table 6: Number of Cases, with Country of Origin and Legal classification Status in that Country, by Case-Seriousness for the 5% Minoxidil Formulation

Country	Legal Classification	Serious	Non-serious	Total
Germany	OTC (P)	23	236	259
USA	GSL	31	187	218
Australia	OTC (P)	5	177	182
United Kingdom	OTC (P) & GSL	4	48	52
Austria	Rx	1	23	24
Switzerland	OTC (P)	2	17	19
Greece	Rx	2	14	16
Israel	OTC	2	13	15
Japan	OTC	11	4	15

Ireland	OTC (P)	2	11	13
France	OTC (P)	0	12	12
Hong Kong	OTC	0	8	8
Denmark	OTC	0	7	7
New Zealand	OTC (P)	1	6	7
Sweden	OTC (P)	1	6	7
Singapore	OTC	0	6	6
Canada	Rx	2	3	5
Brazil	Rx	0	4	4
Norway	OTC (P)	0	4	4
Finland	OTC (P)	0	3	3
Korea	OTC	0	3	3
Philippines	Rx	0	2	2
Czech Republic	OTC (P)	0	1	1
Italy	Rx	1	0	1
Malaysia	OTC	0	1	1
Malta	OTC (P)	0	1	1
Total		**88**	**797**	**885**

OTC: Over the counter (P: Pharmacy Only)

Rx: Prescription medication;

GSL: General Retail Sale

The vast majority (75%) of the cases originated from Germany, the United States, Australia, or the UK. New Zealand accounted for 7 (0.8%) cases in total over the 10 year period.

Most frequently occurring adverse events

Reporting rates grouped by strength of minoxidil formulation for AEs representing 1% or more of the total reported AEs

Table 7 presents the estimated reporting rates for the most frequent AEs grouped by event-seriousness and by strengths of minoxidil formulation.
Overall, the estimated reporting rates for individual AEs were higher for the 2% minoxidil formulation compared to those for the 5% minoxidil formulation.
Exceptions included Medication error, Wrong drug administered, Dandruff, Dermatitis, Skin irritation and Hypertrichosis.
It should be noted that reported cases contain one or more of the AEs listed in these frequency reports. Thus, the number of AEs far exceeds the number of cases.

The number of cases in which the strength of the minoxidil formulation was not reported is small. Therefore, the unknown category will not be taken into account for further analyses.

Table 7

Estimated Reporting Rates for AEs Representing 1% or more of Total Reported AEs Grouped by Seriousness and by Strengths of Minoxidil Formulation

AEs	2%			5%		
	Serious	Non-serious	Total	Serious	Non-serious	Total
	Estimated Reporting Rate[d] Per 1 Billion mLs of Minoxidil Distributed (Number of Cases)					
Cardiac Disorders SOC						
Palpitations[a]	3.7 (3)	22.0 (18)	25.6 (21)	0.9 (1)	12.8 (14)	13.7 (15)
Tachycardia[a]	6.1 (5)	18.3 (15)	24.4 (20)	2.7 (3)	5.5 (6)	8.2 (9)
Gastrointestinal Disorders SOC						
Nausea[a]	1.2 (1)	31.7 (26)	32.9 (27)	1.8 (2)	11.9 (13)	13.7 (15)
General Disorders and Administration Site Conditions SOC						
Application site irritation[b]	1.2 (1)	111.0 (91)	112.2 (92)	2.7 (3)	37.4 (41)	40.1 (44)
Application site pruritus[b]	1.2 (1)	93.9 (77)	95.1 (78)	0.9 (1)	36.5 (40)	37.4 (41)
Application site erythema[b]	0	91.5 (75)	91.5 (75)	1.8 (2)	43.8 (48)	45.6 (50)
Drug ineffective[b]	1.2 (1)	29.3 (24)	30.5 (25)	1.8 (2)	18.2 (20)	20.1 (22)
Immune System Disorders SOC						
Hypersensitivity[b]	4.9 (4)	56.1 (46)	61.0 (50)	2.7 (3)	25.5 (28)	28.3 (31)
Injury, Poisoning and Procedural Complications SOC						
Medication error[c]	0	11.0 (9)	11.0 (9)	13.7 (15)	45.6 (50)	59.3 (65)
Wrong drug administered[c]	0	6.1 (5)	6.1 (5)	3.7 (4)	24.6 (27)	28.3 (31)
Nervous System Disorders SOC						
Dizziness[b]	8.5 (7)	74.4 (61)	82.9 (68)	7.3 (8)	21.9 (24)	29.2 (32)
Headache[b]	4.9 (4)	64.6 (53)	69.5 (57)	1.8 (2)	40.1 (44)	42.0 (46)
Burning sensation[b]	1.2 (1)	24.4 (20)	25.6 (21)	0	20.1 (22)	20.1 (22)
Skin and Subcutaneous Tissue Disorders SOC						
Pruritus[b]	3.7 (3)	203.6 (167)	207.3 (170)	1.8 (2)	124.0 (136)	125.9 (138)
Alopecia[b]	2.4 (2)	140.2 (115)	142.7 (117)	1.8 (2)	69.3 (76)	71.1 (78)
Rash[b]	1.2 (1)	80.5 (66)	81.7 (67)	0.9 (1)	42.0 (46)	42.9 (47)
Erythema[b]	1.2 (1)	63.4 (52)	64.6 (53)	0.9 (1)	35.6 (39)	36.5 (40)
Skin exfoliation[b]	1.2 (1)	51.2 (42)	52.4 (43)	0	50.2 (55)	50.2 (55)
Dandruff[c]	0	7.3 (6)	7.3 (6)	0	21.0 (23)	21.0 (23
Dermatitis contact[b]	6.1 (5)	22.0 (18)	28.1 (23)	6.4 (7)	13.7 (15)	20.1 (22)
Dermatitis[c]	0	7.3 (6)	7.3 (6)	0	17.3 (19)	17.3 (19)
Dry skin[b]	0	26.8 (22)	26.8 (22)	0	26.4 (29)	26.4 (29)
Skin irritation[b]	0	25.6 (21)	25.6 (21)	0	27.4 (30)	27.4 (30)
Swelling face[a]	4.9 (4)	19.5 (16)	24.4 (20)	0	8.2 (9)	8.2 (9)
Hypertrichosis[b]	1.2 (1)	20.7 (17)	22.0 (18)	0.9 (1)	45.6 (50)	46.5 (51)
Hair colour changes[b]	0	22.0 (18)	22.0 (18)	0	17.3 (19)	17.3 (19)

a: AEs representing 1% or more of the total reported AEs in patients using 2% minoxidil formulation.

b: AEs representing 1% or more of the total reported AEs in patients using 2% and in patients using 5% minoxidil formulations.

c: AEs representing 1% or more of the total reported AEs in patients using 5% minoxidil formulation.

d: Estimated Reporting Rate = Number of cases reporting a specific AE for a specific strength of minoxidil during a specific time period/Total mL* of the same strength of minoxidil sold during the same time period.

* Total mL of 2% minoxidil formulation sold = 820 million mL; Total mL of 5% minoxidil formulation sold = 1.1 billion mL

Non-serious AEs by strength of minoxidil formulation

For both the 2% and the 5% minoxidil formulations, the most frequently reported non-serious AEs (>10% of all reported non-serious events) according to MedDRA SOC (Medical Dictionary for Regulatory Activities System Organ Class) were General Disorders and Administration Site Conditions (such as Application site irritation and Application site pruritus), and Skin and Subcutaneous Tissue Disorders (such as Pruritus and Alopecia).

Serious Type A and Type B AEs by strength of minoxidil formulation

Table 8 presents serious AEs classified as Type A or Type B, and grouped by strength of minoxidil formulation.

Table 8

Serious Type A and Type B AEs Grouped by Strengths of Minoxidil Formulation

		2%	5%
Type A[a] AEs	**Cardiac Disorders SOC**		
	Acute myocardial infarction	0	1
	Angina pectoris	0	3
	Arrhythmia	5	4
	Atrial fibrillation	2	4
	Atrioventricular block	0	1
	Cardiac failure	1	1
	Cardiac flutter	0	1
	Cardiovascular disorder	1	0
	Myocardial infarction	0	3
	Palpitations	3	1
	Sick sinus syndrome	0	1
	Sinus bradycardia	1	0
	Sinus tachycardia	0	2
	Supraventricular tachycardia	2	0
	Tachycardia	5	3
	Tachycardia paroxysmal	0	1
	General Disorders and Administration Site Conditions SOC		
	Oedema peripheral	1	2
	Investigations SOC		
	Blood pressure decreased	2	2
	Blood pressure diastolic decreased	0	1
	Nervous System Disorders SOC		
	Dizziness	7	8
	Syncope	3	0
	Syncope vasovagal	1	1
	Vascular Disorders SOC		
	Hypotension	3	3
Type B[b] AEs	**Immune System Disorders SOC**		
	Anaphylactic shock	0	1
	Drug hypersensitivity	0	1
	Hypersensitivity	4	3

a: A type A event is one that is due to an extension of the active pharmacologic properties of the drug; A indicates *augmented*.

b: A type B event is one that is not due to an extension of the active pharmacologic properties of the drug; the B indicates *bizarre*.

Note: Each case may contain 1 or more of the AEs mentioned above, therefore the number of cases is lower than the number of AEs reported.

For some cardiac events, such as Angina pectoris and Myocardial infarction, the number of AEs was higher in the patients using the 5% minoxidil formulation.

It should be noted that reported cases may contain one or more of the AEs listed in Table 7. Thus the number of the AEs exceeds the number of cases. For example, although there were 25% more cardiac AEs reported with the use of 5% minoxidil compared to 2% minoxidil, the number of cases reporting one or more of these cardiac AEs with 2% or 5% minoxidil use was 13 and 16, respectively.

Frequency reports for all serious AEs occurring in medically confirmed cases of patients using 2% and 5% minoxidil are provided in the Safety/Efficacy Summary 2008 (Shah, Shur, & Van Loon, 2008).

Fatal cases

Elective abortion

There were 2 literature reports that described maternal use of 2% minoxidil during the first trimester of pregnancy. In both cases, the pregnancies were terminated due to multiple life-threatening foetal malformations. In a case from Italy, the foetus had sub-aortic stenosis, cardiac enlargement, and cranial malformation. The other case, from Israel, described a foetus with caudal regression syndrome: absence of sacrum, lower limbs and urinary tract; single umbilical artery, oesophageal atresia, tracheo-oesophageal fistula. The reporter causality assessment for these 2 reports was “possibly related” to minoxidil.

The other reported deaths were not found to be associated with the use of Topical Minoxidil.

DISCUSSION

The majority of the AEs were non-serious. The most frequently reported AEs, for both 2% and 5% minoxidil formulations, were non-serious skin disorders such as pruritus and alopecia. These AEs are already identified and included in the datasheet and consumer medicine information for Topical Minoxidil preparations.

Both the reporting rates and reporting ratios for individual AEs were higher for the 2% minoxidil formulations as compared to the 5% minoxidil formulations with the exception of medication error, wrong drug administered, and certain skin disorders such as skin exfoliation, dandruff, dermatitis, dry skin, skin irritation and hypertrichosis.

Medication errors were mostly due to the use of 5% minoxidil by females. It should be noted that Company policy is to code “medication error” in reports of unapproved use of Topical Minoxidil for Men Extra Strength by females, even if

the product was medically prescribed. (NB: 5% Minoxidil is not approved in all countries for use by females)

There were no marked differences seen in the nature or frequency of the serious Type A and Type B[1] AEs reported for patients using the 2% versus the 5% minoxidil formulation. Although there were a greater number of cardiac AEs reported with the use of 5% minoxidil, the number of cases reporting one or more of these AEs was 13 for the 2% and 16 for the 5% minoxidil formulation.

There were no reports of fatal outcomes associated with the use of 5% minoxidil formulations.

CONCLUSION

Review of the post-marketing data suggests that the safety profile of Topical Minoxidil 2% and 5% is favourable. The nature, frequency and severity of reported serious AEs with the use of either 2% or 5% minoxidil formulations are similar.

The analysis of adverse events in relation to 2% and 5% formulations demonstrates their similar safety profiles.

Overall the adverse event profile of Topical Minoxidil preparations demonstrates that it is a well tolerated drug. The most commonly reported adverse events were mild to moderate in nature. Serious events were of low incidence and occurred rarely in the post marketing data.

Thus, post-marketing data supports the safety profile of Topical Minoxidil preparations for sale as EXEMPT medicines.

<u>CARM Reports from New Zealand</u>

CARM was requested to supply adverse events reports in December 2009. Unfortunately, ARM has not been able to provide the reports in time for this submission. If information is forthcoming within the review period, an addendum will be submitted reviewing the data from CARM.

<u>ADRAC reports - Australia</u>

A database report was requested from ADRAC for Minoxidil covering the period 01 January 2002 – 23 December 2009 (Adverse Drug Reactions Advisory Committee, 2010). ADRAC could not provide a report specific to only Topical Minoxidil. In 9 cases, the format of minoxidil was not reported, and so we will focus our analysis on cases where Topical Minoxidil is clearly identified.

[1] A type A event is one that is due to an extension of the active pharmacologic properties of the drug; A indicates *augmented*. A type B event is one that is not due to an extension of the active pharmacologic properties of the drug; the B indicates *bizarre.*

There were 27 reports that involved Topical Minoxidil. Nine reports were for an unidentified dose form of minoxidil. 5 reports were for minoxidil tablets and 1 report for a topical product that does not contain minoxidil. The single case that was reported for a product not involving minoxidil was for "Revivogen Scalp Therapy" (see report number 217641 dated 24/04/2006 in the ADRAC line listing (Adverse Drug Reactions Advisory Committee, 2010)). The table below displays the number of reports and their breakdown by strength. Over this time period approximately 490,000 units[2] of REGAINE® brand Topical Minoxidil were sold (this data does not include sales of generic brands). The rate of reported adverse events is low when compared to the number of units of medication that were used.

Table 9 - ADRAC reports by strength and dose form

Strength and Dose Form	Number of Cases
Topical Minoxidil 2%	7
Topical Minoxidil 5%	12
Topical Minoxidil Unknown Strength	8
Minoxidil Unknown Dose Form	9
Minoxidil Tablets	5
Product Incorrectly identified as containing minoxidil	1
TOTAL	42

Since minoxidil is poorly absorbed systemically from the skin with an average of 1.7% (ranging from 0.3%-4.5%) of the applied dose reaching the systemic circulation, we will not address the reports involving minoxidil tablets where it is almost 100% absorbed into the systemic circulation, and where adverse events are more likely to occur due to the higher serum concentrations.

The 9 cases where the dose form is unknown will not be addressed as there is a likelihood that they involve minoxidil tablets.

The product incorrectly identified as containing minoxidil is Revivogen Scalp Therapy which does not contain minoxidil and is an unregistered cosmetic product.

Table 10 lists the ADRAC reported adverse events by organ group.

Table 10 - ADRAC reported adverse events for Topical Minoxidil

Organ Group	Reported Adverse Event
Cardiovascular	Arrhythmia, Palpitations, Tachycardia, Syncope, Chest discomfort, Pericarditis, Abnormal ECG, Chest pain, Elevated cardiac enzymes, myocardial infarction,

[2] MAT Data 2001 to 2009

	Abnormal coronary arteriogram, Elevated troponin, Hypotension, Erectile dysfunction
CNS	Dizziness, Vertigo, Pain, Balance disorder, Migraine, Loss of consciousness
Skin	Rash, Facial oedema/swelling, acne, Skin cancer, Blepharitis, Erythema nodosum, Skin reaction, Alopecia, paraesthesia, Maculo-papular rash, Hyperhidrosis, Pruritus,
Gastrointestinal	Vomiting, Abdominal pain, Nausea, Dyspepsia, Abdominal distension
Respiratory	Dyspnoea
Musculo-skeletal	Arthralgia
Non-specific	Malaise

The events described in the 27 Topical Minoxidil ADRAC reports are consistent with adverse events that are already known and described in the approved prescribing information and have been reported in global PSURs.

The reactions described in the ADRAC line listing are usually very rare at less than 0.01%.

It is noted that adverse reaction reports for 5% Topical Minoxidil were greater than for 2% Topical Minoxidil. That is due to much higher sales volumes of this particular strength when compared to the lower strength and is not an indication of greater toxicity. [3]

There were no reported deaths attributed to Topical Minoxidil in Australia in the ADRAC line listing.

The post-marketing information from the ADRAC reports supports the excellent safety profile of Topical Minoxidil preparations as medicine available for sale through general retail channels.

Overdosage

In cases of oral ingestion, Topical Minoxidil could result in systemic absorption sufficient to cause the predictable cardiovascular effects of minoxidil (e.g., reduced blood pressure, reflex tachycardia, fluid retention). Excessive, non-intentional ingestion of Topical Minoxidil, however, is not likely to occur because of the foul taste of the topical formulation, the replaceable safety closure of the container, and the design of the applicator (which does not

[3] The percentage of total sales of all Topical Minoxidil SKUs MAT were 78% from 5% TMS and 22% from 2% TMS. Sales data is available upon request.

deliver a continuous flow of medication). Specific discussion of overdose cases is available in the Post-marketing Safety Update Reports section.

9. Potential for abuse or misuse

Overuse of Topical Minoxidil (Increased Frequency and/or Increased Dose)

Pharmacokinetic studies of topically applied minoxidil have shown that minoxidil is poorly absorbed following topical dosing, and with increased applications, percutaneous minoxidil absorption appears to reach a maximal level beyond which no further absorption can occur. Thus, except in situations of substantial trauma to the stratum corneum, the potential for systemic minoxidil effects to occur under conditions of topical overdose or misuse is low. Further, because the alcohol content of the formulation would cause unpleasant symptoms on inflamed skin, it is unlikely that a patient with severe rash, sunburn, or trauma of the scalp would apply REGAINE in amounts far in excess of the recommended regimen.

Abuse & dependence

Topical Minoxidil Solutions contain minoxidil, alcohol, and propylene glycol, and are not likely to present a substantial risk of medical abuse, to lead to addiction, or to be misused for illegal purposes.

Misuse

Literature reports in the past described the use of Topical Minoxidil applied to the genitalia for the treatment of erectile dysfunction. Consequences of using Topical Minoxidil, which contains alcohol, for this purpose, may result in local irritation at the site of application. It is unlikely for such cases to occur now, with the availability of oral medications specifically indicated for erectile dysfunction (Viagra, Levitra, Cialis) which have proven efficacy without the adverse effect of hypertrichosis or local irritation from an alcohol-based topical formulation.

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