SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Minoxidil 5% cutaneous solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains 50 mg of minoxidil. One ml is equivalent to 10 sprays (if using the pump).

Excipient(s) with known effect

Each ml contains 520 mg of propylene glycol.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Cutaneous solution.

The solution is transparent and colourless to slightly yellowish with an alcohol aroma.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of moderate androgenetic alopecia in adult male subjects.

4.2 Posology and method of administration

Posology

Men aged 18 – 65 years

The recommended daily dose is 1 ml applied to the total affected areas of the scalp twice daily. 1 ml is equivalent to 10 sprays using the dosage pump. The total dosage should not exceed 2 ml. If fingertips are used to facilitate drug application, hands should be washed afterwards.

Special populations *Elderly patients*

Not recommended. The safety and effectiveness of Minoxidil solution in adults over 65 years has not been established.

Paediatric population (< 18 years old)

Not recommended. The safety and effectiveness of Minoxidil solution in children and adolescents below the age of 18 years has not been established.

Patients with renal or hepatic impairment

There are no specific recommendations for use in patients with renal or hepatic impairment.

Method of administration

For cutaneous use only.

Apply to a completely dry scalp, starting from the centre of the area to treat. Spread the solution using your fingertips to the treatment area. Do not ingest.

Do not apply Minoxidil solution to other parts of the body. Response to treatment with minoxidil is on an individual basis for each patient, therefore a 4-month course of treatment may be necessary before any signs of hair growth appear.

Hair growth may stop when treatment with Minoxidil solution is interrupted, returning to the initial state of alopecia within 3-4 months. (see section 5.1).

It is recommended to wash hands thoroughly with water before and after application of Minoxidil solution.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- In women.
- In users with treated or untreated hypertension.
- In users with any scalp abnormality (including psoriasis and sunburn).
- In users with a shaved scalp.
- If occlusive dressings or other topical medical preparations are being used.

4.4 Special warnings and precautions for use

Before using Minoxidil solution, the user should determine that the scalp is normal and healthy. Topical minoxidil should not be applied to inflamed, infected, irritated or painful scalp skin (see section 4.3).

Minoxidil solution is only indicated for the treatment of alopecia androgenetica in adult male subjects and should not be used in other types of

hair loss, for example when there is no family history of hair loss, hair loss is sudden and/or patchy or the reason for hair loss is unknown.

The patient should stop using Minoxidil solution and see a doctor if hypotension is detected or if the patient is experiencing chest pain, rapid heartbeat, faintness or dizziness, sudden unexplained weight gain, swollen hands or feet or persistent redness or irritation of the scalp or other unexpected new symptoms occur (see section 4.8).

Patients with known cardiovascular disease or cardiac arrhythmia should contact a physician before using Minoxidil solution.

Some patients have experienced changes in hair colour and/or texture with use of Minoxidil solution.

Minoxidil solution is for external use only. Do not apply to areas of the body other than the scalp.

Using more than the recommended dose or more often will not improve results.

Unwanted hair growth may be caused by the transfer of the product to areas other than the scalp.

Hands should be washed thoroughly after applying the solution. Inhalation of the spray mist should be avoided.

Some consumers reported increased hair shedding upon initiation of therapy with topical minoxidil products. This is most likely due to minoxidil's action of shifting hairs from the resting telogen phase to the growing anagen phase (old hairs fall out as new hairs grow in their place). This temporary increase in hair shedding generally occurs two to six weeks after beginning treatment and subsides within a couple of weeks. If shedding persists (> 2 weeks), users should stop using Minoxidil solution and consult their doctor.

Users should be aware that, whilst extensive use of Minoxidil solution has not revealed evidence that sufficient minoxidil is absorbed to have systemic effects, greater absorption because of misuse, individual variability, unusual sensitivity or decreased integrity of the epidermal barrier caused by inflammation or disease processes in the skin (e.g. excoriations of the scalp, or scalp psoriasis) could lead, at least theoretically, to systemic effects.

Accidental ingestion may cause serious cardiac adverse events, in particular in children under 18 years old. Therefore, this product has to be kept out of the reach of children.

Hypertrichosis in children following inadvertent topical exposure to minoxidil:

Cases of hypertrichosis have been reported in infants following skin contact with minoxidil application sites of patients (caregivers) using topical minoxidil. Hypertrichosis was reversible, within months, when infants were no longer exposed to minoxidil. Contact between children and minoxidil application sites should therefore be avoided.

Warnings on excipients

This medicine contains 243 mg alcohol (ethanol) in each 1 ml of cutaneous solution. It may cause burning sensation on damaged skin. Ethanol can also cause burning and irritation of the eye. In the event of accidental contact with sensitive surfaces (eye, abraded skin and mucous membranes) the area should be bathed with large amounts of cool tap water.

This medicine contains 520 mg propylene glycol in each 1 ml of cutaneous solution. Propylene glycol may cause skin irritation. Because this medicine contains propylene glycol, do not use it on open wounds or large areas of broken or damaged skin (such as burns) without checking with your doctor or pharmacist.

4.5 Interaction with other medicinal products and other forms of interaction

This product should not be used concomitantly with other medications applied topically on the scalp (see section 4.3).

Topical drugs, such as corticosteroids, tretinoin, dithranol or petrolatum, which alter the stratum corneum barrier, could result in increased absorption of minoxidil if applied concurrently. Although it has not been demonstrated clinically, there exists the theoretical possibility of absorbed minoxidil potentiating orthostatic hypotension caused by peripheral vasodilators.

Guanethidine has been reported to interact with oral formulations of minoxidil resulting in rapid and pronounced lowering of blood pressure.

There is a theoretical possibility that topical minoxidil may also interact with guanethidine.

4.6 Fertility, pregnancy and lactation

This product should not be used during pregnancy or breast-feeding.

Pregnancy

There is limited data from the use of minoxidil in pregnant women. Studies in animals have shown a risk to the foetus at exposure levels that are very high compared to those intended for human exposure. There is potentially a risk of foetal harm in humans (see section 5.3).

Breast-feeding

Minoxidil has been reported to be excreted in human milk. A risk to the suckling child cannot be excluded if minoxidil is administered to nursing women.

Fertility

There is no evidence of effects of minoxidil treatment on human fertility. Animal studies have shown evidence of reduced conception and implantation in female rats (see section 5.3).

4.7 Effects on ability to drive and use machines

This product may cause dizziness or hypotension (see section 4.8). If affected, patients should not drive or operate machinery.

4.8 Undesirable effects

The safety of topical minoxidil from clinical trial data is based on data from 7 placebocontrolled randomised clinical trials in adults evaluating either 2% or 5% minoxidil solution, and two placebo-controlled randomised clinical trials in adults evaluating a 5% foam formulation.

Adverse drug reactions (ADRs) identified during clinical trials and post-marketing experience with minoxidil are included in the table below by System Organ Class (SOC).

The frequencies are provided according to the following convention:

Very common (≥1/10)

Common (≥ 1/100 to < 1/10)

Uncommon (≥ 1/1,000 to < 1/100)

Rare (≥ 1/10,000 to < 1/1,000) Very rare (< 1/10,000)

Not known (cannot be estimated from the available data)

ADRs are presented by frequency category based on 1) incidence in adequately designed clinical trials or epidemiology studies, if available, or 2) when incidence cannot be estimated, frequency category is listed as 'Not known'.

Body system (SOC)	**Frequency**	**Adverse drug reaction**
Immune system disorders	Common	Hypersensitivity reactions (including face oedema, generalised erythema, pruritus generalised, swelling face, and throat tightness)
	Not known	Angioedema (including lip oedema, lip swelling, oedema mouth, oropharyngeal swelling, pharyngeal oedema, swollen tongue and tongue oedema)
Psychiatric disorders	Not known	Depressed mood
Nervous system disorders	Very common	Headache
	Uncommon	Dizziness
Eye disorders	Not known	Eye irritation
Cardiac disorders	Common	Chest pain
	Uncommon	Palpitations
	Not known	Heart rate increased
Vascular disorders	Not known	Hypotension
Respiratory, thoracic and mediastinal disorders	Uncommon	Dyspnoea
Gastrointestinal disorders	Uncommon	Nausea
	Not known	Vomiting
Skin and subcutaneous tissue disorders	Common	Hypertrichosis (unwanted non-scalp hair including facial hair growth in women)

		Pruritus (including rash pruritic generalised and eye pruritus) Rash (including pustular, popular, generalised, vestibular and macular rash) Dermatitis (including contact, allergic, atopic and seborrhoeic dermatitis)
	Rare	Changes in hair texture
	Not known	Dry skin Skin exfoliation (including exfoliative rash and dermatitis exfoliative) Acne (acneiform rash) Temporary hair loss (see section 4.4) Changes in hair colour
General disorders and administration site conditions	Common	Oedema peripheral
	Not known	Application site reactions (these sometimes involve nearby structures like the ears and face and typically consist of pruritus, irritation, pain, rash, oedema, dry skin, erythema and rash erythematous but can sometimes be more severe and include exfoliation, dermatitis, blistering, bleeding and ulceration)
Investigations	Common	Weight increased

Reporting of suspected adverse reactions Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App.

4.9 Overdose

Increased systemic absorption of minoxidil may potentially occur if higher-thanrecommended doses of Minoxidil solution are applied to larger surface areas of the body or areas other than the scalp.

Symptoms

Because of the concentration of minoxidil in Minoxidil solution, accidental ingestion has the potential of producing systemic effects related to the pharmacological action of the drug (2 ml of Minoxidil solution contains 100 mg minoxidil; the maximum recommended adult dose for oral minoxidil administration in the treatment of hypertension). Signs and symptoms of minoxidil overdosage would primarily be cardiovascular effects associated with sodium and water retention. Tachycardia, hypotension, dizziness and lethargy can also occur.

Treatment

Treatment of minoxidil overdosage should be symptomatic and supportive.

Fluid retention can be managed with appropriate diuretic therapy. Clinically significant tachycardia can be controlled by administration of a beta-adrenergic blocking agent.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other dermatological preparations, ATC Code: D11AX01.

The effect of a minoxidil 5% solution has been assessed in a phase III clinical trial conducted over a 48-week treatment period.

In this study a minoxidil 5% solution was compared to the product vehicle without the minoxidil active ingredient and also to 2% minoxidil solution.

The primary efficacy criterion was non-vellus hair count in a 1.0cm^2 reference area of affected scalp. The mean changes observed in this parameter in these studies were significantly in favour of active treatment. A significant dose effect was also demonstrated. The results are summarized in the following table:

Mean change in non-vellus hair count in reference 1cm^2 area of scalp compared with baseline

	(n=139) Minoxidil 5%	**(n=142) Minoxidil 2%**	**(n=71) Vehicle**	**Pair wise comparison**
Baseline	151.1	143.6	152.4	
	Mean change from baseline			
8 weeks	+29.7	+24.9	+14.3	5%>2%>vehicle
16 weeks	+35.3	+29.8	+15.3	5%>2%>vehicle
32 weeks	+29.0	+22.2	+7.7	5%>2%>vehicle
48 weeks	+18.6	+12.7	+3.9	5%>2%>vehicle

Efficacy was further assessed by comparing photographs taken at various time-points with baseline.

Assessment was undertaken by patients using a 100mm visual analogue scale and assessing scalp coverage where point 0 represented much less scalp coverage, 50mm no difference and 100mm much more scalp coverage. In addition, an assessment was undertaken by 2 blinded reviewers who compared photographs taken at baseline and after 48 weeks. Differences were assessed using a 7-point categorical scale viz:

- Dense growth
- Moderate growth
- Minimal growth
- No change
- Minimal loss
- Moderate loss
- Dense loss

The results of these analyses were as follows:

Patient evaluation of change in scalp coverage

	(n=139) Minoxidil 5%	**(n=142) Minoxidil 2%**	**(n=71) Vehicle**	**Pair wise comparison**
	mm	**mm**	**mm**	
16 weeks	63.5	58.2	51.4	5%>2%>vehicle

32 weeks	63.4	58.0	52.0	5%>2%>vehicle
48 weeks	62	56.9	51.0	5%>2%>vehicle

Photographic Evaluation of Clinical Response (Reviewer 1)

	Dense Growth %	**Moderate Growth %**	**Minimal Growth %**	**No change %**	**Hair Loss %**	**Unable to rate**
Minoxidil 5%	2.2	37.4	22.3	31.7	5.0	1.4
Minoxidil 2%	2.8	19.7	21.1	50.0	2.8	3.5
Vehicle	0	7.0	22.5	60.0	9.9	0

Photographic Evaluation of Clinical Response (Reviewer 2)

	Dense Growth %	**Moderate Growth %**	**Minimal Growth %**	**No change %**	**Hair Loss %**	**Unable to rate**
Minoxidil 5%	10.1	20.1	23.7	28.8	6.5	10.8
Minoxidil 2%	3.5	12.0	22.5	47.2	1.4	13.4
Vehicle	0	7.0	9.9	60.6	14.1	8.5

Based upon these photographic data, around 60% of the patients experienced an increased scalp coverage after 48 weeks treatment with Minoxidil 5% solution as defined by re-growth of hair; compared with around 23% at an average for those who received vehicle alone. Of these, around 35% treated with Minoxidil 5% solution experienced dense or moderate regrowth compared with around 7% who received vehicle alone. In addition, 30% of patients who received Minoxidil 5% solution were adjudged to have no change between the photographic assessments of hair growth compared with 60% who received vehicle alone. Stabilisation of hair loss (expressed both as regrowth of hair and no continuation of hair loss) can therefore be expected in about 4 out of 5 of patients using Minoxidil 5% solution compared with 3 out of 4 patients using vehicle alone.

Minoxidil 5% solution may therefore be considered by men who wish to achieve a faster onset and greater degree of hair regrowth than would be expected through the use of Minoxidil 2% solution.

The mechanism by which minoxidil stimulates hair growth is not fully understood, but minoxidil can reverse the hair loss process of androgenetic alopecia by the following means:

- increasing the diameter of the hair shaft
- stimulating anagen growth

- prolonging the anagen phase
- stimulating anagen recovery from the telogen phase

As a peripheral vasodilator, minoxidil enhances microcirculation to hair follicles. The Vascular Endothelial Growth Factor (VEGF) is stimulated by minoxidil and VEGF is presumably responsible for the increased capillary fenestration, indicative of a high metabolic activity, observed during the anagen phase.

5.2 Pharmacokinetic properties

Absorption

The failure to detect evidence of systemic effects during treatment with Minoxidil solution reflects the poor absorption of topically applied minoxidil from normal intact skin. Systemic absorption of minoxidil from topically applied solution ranges between 1% and 2% of the total applied dose.

The systemic absorption of minoxidil from a 5% solution formulation has been estimated in a pharmacokinetic study in subjects with androgenetic alopecia, which included 5% topical foam as a comparator. This demonstrated that in men, the systemic absorption of minoxidil from twice daily application of 5% minoxidil solution was about twice that, as observed with 5% minoxidil foam. The mean steady state AUC (0-12 hr) and Cmax for 5% minoxidil foam, 8.81 ng·hr/mL and 1.11 ng/mL, respectively, were both approximately 50 % of AUC (0-12 hr) and Cmax of the 5% solution, 18.71 ng·hr/mL and 2.13 ng/mL, respectively. The time to maximum minoxidil concentration (Tmax) for the 5% solution, 5.79 hr, was similar to Tmax for the 5% foam, 5.42 hr.

Distribution

There is some evidence from *in vitro* studies that minoxidil reversibly binds to human plasma proteins. However, since only 1 – 2% of topically applied minoxidil is absorbed, the extent of plasma protein binding occurring *in vivo* after topical application would be clinically insignificant. The volume of distribution of minoxidil after intravenous administration has been estimated at 70 litres.

Biotransformation

Approximately 60% minoxidil absorbed after topical application is metabolised to minoxidil glucuronide, primarily in the liver.

Elimination

Minoxidil and its metabolites are excreted almost entirely in the urine, with a very minor degree of elimination via the faeces. Following cessation of dosing, approximately 95% of topically applied minoxidil will be eliminated within four days.

5.3 Preclinical safety data

Preclinical data reveal no special hazards for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity or carcinogenic potential.

Cardiac effects of minoxidil in dogs are species-specific in terms of low doses that cause profound haemodynamic effects and associated changes in the heart. Available data indicate that similar cardiac effects do not occur in humans treated topically or orally with minoxidil.

Mutagenicity

Minoxidil showed no evidence of mutagenic/genotoxic potential in a number of *in vitro* and *in vivo* assays.

Carcinogenicity

A high incidence of hormone-mediated tumours was observed in mice and rats. These tumours are due to the secondary hormonal (hyperprolactinemia) effects observed only in the rodents at extremely high doses by a mechanism similar to that seen with reserpine. Application of topical minoxidil has not demonstrated any effect on hormonal status in women. Therefore, hormonally mediated tumour promotion by minoxidil does not represent a carcinogenic risk to humans.

Teratogenicity

Animal reproduction toxicity studies in rats and rabbits have shown signs of maternal toxicity and a risk to the foetus at exposure levels that are very high compared to those intended for human exposure. A low, albeit remote, risk of foetal harm is possible in humans.

Fertility

Preclinical fertility studies in rats have shown minoxidil doses equal or greater than 3 mg/kg/day (at least 8 fold human exposure) when administered orally and greater than 9 mg/kg (at least 25-fold human exposure) administered subcutaneously in rats were associated with reduced conception and implantation rates as well as reduction in the number of live pups.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol 96%, propylene glycol and purified water

6.2 Incompatibilities

The solution is flammable. Do not use while smoking, or near any naked flame or heat source. Avoid exposure of the container and contents to naked flames during use, storage and disposal. Any unused product or waste material should be disposed of in accordance with local requirements.

6.3 Shelf life

3 years

6.4 Special precautions for storage

No special storage conditions are required.

6.5 Nature and contents of container

Plastic bottle with dosage pump and lid, which contains 60 ml, 120 ml (2 bottles of 60 ml) or 180 ml (3 bottles of 60 ml) of cutaneous solution.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local regulations.

7 MARKETING AUTHORISATION HOLDER

Careforsons Limited,

Tintagel House,

92 Albert Embankment,

London

SE1 7TY,

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 50640/0001

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