Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Minoxidil 5% cutaneous solution

(minoxidil)

PL 50640/0001

Careforsons Limited.

LAY SUMMARY

Minoxidil 5% cutaneous solution (minoxidil)

This is a summary of the Public Assessment Report (PAR) for Minoxidil 5% cutaneous solution. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

For practical information about using Minoxidil 5% cutaneous solution, patients should read the package leaflet or contact their doctor or pharmacist.

What is Minoxidil 5% cutaneous solution and what is it used for?
This application is for a medicine that has a well-established use. This means that the use of the active substance in this medicine has been well-established in the European Union for at least 10 years, with recognised efficacy and an acceptable level of safety.

Minoxidil 5% cutaneous solution is a medicine for topical application to the scalp that stimulates hair growth in men aged 18-65 years with male-pattern hair loss (androgenetic alopecia) when applied to the skin.

How does Minoxidil 5% cutaneous solution work?
This medicine contains the active ingredient minoxidil which is thought to work by aiding the blood flow to the hair follicles on the scalp.

How is Minoxidil 5% cutaneous solution used?
The pharmaceutical form of this medicine is a cutaneous solution and the route of administration is cutaneous (via the skin (scalp)).

The patient's doctor will determine the suitable dose and length of treatment with Minoxidil 5% cutaneous solution.

The recommended daily dose for adult men aged 18-65 years is 1 ml of solution twice daily (10 sprays from the dosage pump is equivalent to 1 ml of solution). The patient must respect the recommended daily dose regardless of the extent of their hair loss.

For further information on how Minoxidil 5% cutaneous solution is used, including method of application, refer to the package leaflet and Summary of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can be obtained without a prescription.

The patient should always use the medicine exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Minoxidil 5% cutaneous solution have been shown in studies?
As the active substance minoxidil has been in clinical use for over 10 years, data were provided in the form of literature references to show that minoxidil is a safe and efficacious treatment for male-pattern hair loss (androgenetic alopecia) when applied to the skin.

What are the possible side effects of Minoxidil 5% cutaneous solution?
The most common side effect with minoxidil (which may affect more than 1 in 10 people) is headache.

For the full list of all side effects reported with this medicine medicines, see Section 4 of the package leaflet or the Summary of Product Characteristics (SmPC) available on the MHRA website.

Why was Minoxidil 5% cutaneous solution approved?
It was concluded that the data provided from literature references had shown that Minoxidil 5% cutaneous solution is effective in the treatment for male-pattern hair loss (androgenetic alopecia) when applied to the skin. Furthermore, use of the active substance minoxidil in the European Union has shown that it has a recognised efficacy and an acceptable level of safety. Therefore, the MHRA decided that the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Minoxidil 5% cutaneous solution?
A Risk Management Plan (RMP) has been developed to ensure that Minoxidil 5% cutaneous solution is used as safely as possible. Based on this plan, safety information has been included in the SmPC and the package leaflet, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored and reviewed continuously.

Other information about Minoxidil 5% cutaneous solution
A Marketing Authorisation for Minoxidil 5% cutaneous solution was granted in the UK on 06 August 2020.

The full PAR for Minoxidil 5% cutaneous solution follows this summary.

This summary was last updated in September 2020.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Minoxidil 5% cutaneous solution (PL 50640/0001) could be approved.

The product is approved for the following indication:
Treatment of moderate androgenetic alopecia in adult male subjects.

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.

This application was submitted under Article 10a of Directive 2001/83/EC, as amended, as a well-established use application. No new non-clinical or clinical studies were submitted, as the data submitted for this application is in the form of literature references.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of this product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

A national marketing authorisation was granted in the UK on 06 August 2020.

II QUALITY ASPECTS

II.1 Introduction

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

In addition to minoxidil, this product also contain the excipients ethanol 96%, propylene glycol and purified water.

The finished product is packaged in plastic bottles 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.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

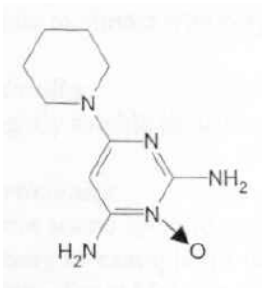
II.2 ACTIVE SUBSTANCE

rINN: Minoxidil

Chemical Name: 6-(Piperidin-1-yl) Pyrimidine-2,4-diamine 3 oxide 2,4-Diamino-6-piperidinopyrimidine 3-oxide

Molecular Formula: $C_9H_{15}N_5O$

Chemical Structure:



Molecular Weight: 209.25 g/mole

Appearance: White to almost white crystalline powder

Solubility: Soluble in methanol and in propylene glycol, slightly soluble in water and very slightly soluble in ether.

Minoxidil is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3 DRUG PRODUCT

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

No excipients of animal or human origin are used in the finished product.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product
A description and flow-chart of the manufacturing method has been provided.

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specification
The finished product specification is satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 3 years, with no special storage conditions, is acceptable.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a marketing authorisation is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
This application was submitted under Article 10a of Directive 2001/83/EC, as amended, a well-established use application. No new non-clinical studies were submitted, as the data submitted for this application is in the form of literature references. The literature review provided is satisfactory.

III.2 Pharmacology
Minoxidil is a potent vasodilator that reduces the systolic and diastolic pressure secondarily to the reduction of the peripheral vascular resistances, in a way similar to that observed with hydralazine or diazoxide. Due to this mechanism of action, the initial development for minoxidil was directed towards cardiovascular therapeutics, for its vasodilator properties.

The topical application of minoxidil acts as a stimulant on capillary growth. The mechanism by which the topical application of minoxidil and/or its metabolite stimulate capillary regrowth in androgenetic alopecia’s and other forms of alopecia has not been completely clarified. Since minoxidil stimulates capillary regrowth in various forms of alopecia, it seems to be that the drug acts on the hair follicle level, possibly involving the direct stimulation of the epithelial growth of hair follicles, prolonging the duration of anagen of the hair cycle and shortening the telogen. Limited evidence suggests that minoxidil induces changes such as hypertrophy and return to the normal diameter of the follicle and of the base of the small follicles (i.e., regrowth) rather than the stimulation of the formation of the new hair follicles. An increase of the capillary flow in the scalp resulting from the local vasodilation has been proposed as the principal mechanism, however, it has not been completely verified, and not all the vasodilators produce hypertrichosis.

Primary pharmacodynamics
Minoxidil seems to exercise a favourable effect of hair growth by acting preferably on the cellular cycle prolonging duration of anagen of the hair cycle and increases miniaturised hair follicle size in addition to its significant ability to maintain and thicken pre-existing hair although it also seems to increase the diameter of the hair.

In an attempt to understand the mechanism by which minoxidil exercises a beneficial effect on capillary growth, different studies were conducted *in vitro*. In human epidermal cell cultures, those treated with minoxidil, in relation to the control group, had greater survival and an extension over time in which the cells could be passed after achieving confluence.

In a culture model of mouse vibrissae follicles, the control follicles, cultivated without minoxidil, showed macroscopic changes, including twisting of the hair shaft and curving of the follicles; the necrosis in the differentiating elements of the epithelium that form the cuticles, cortex and the root of the internal sheath was evident. With minoxidil, on the contrary, these effects disappeared or were reduced significantly. The morphology of these follicles was consistent with the new hair production during the culture. The follicles treated with minoxidil grew significantly more than those of the control group throughout the 3 days of the culture, minoxidil increased the incorporations of radiolabelled cysteine and glycine compared with the control group. The dosage of minoxidil of up to 1 mM originated an increase in the incorporation of cysteine, while higher doses exercised an inhibiting effect. Experiments with labelled thymidine indicated that minoxidil induces the proliferation of the epithelial cells of the hair nears the base of the follicle. Autoradiographs also showed that the cysteine was accumulated in the keratogenous zone, above the dermal papilla.

Stump-tailed macaques are a primate species that exhibit baldness similar to that of humans with androgenic alopecia. In these animals, the administering of topical minoxidil induced an acceleration of cyclic change of the hair follicle and a simultaneous increase in the hair regrowth in the initial anagenic phases; it did not cause changes in the surface epithelium. In many cases, the transformed hair follicles in the bald areas were able to recover the ability to produce thick hair. This phenomenon was most notable in the macaques that more recently began to lose their hair.

Also, in the stump-tailed macaques in which the weight of a quantity of hair grown in a bald area of the scalp was determined, the results obtained showed that minoxidil stimulated the capillary growth in a dose-dependent way. The dosage of minoxidil used (100 and 250 mM) originated a significant increase in the capillary weight if we compare it to the control group and the average hair weights at intervals of 4 weeks showed a peak in the increase in week 8 for both dosages of minoxidil tested but, only with the greater dosage was the growth rate sustained throughout the entire study.

On the other hand, *in vivo* studies showed that topical minoxidil was associated to changes in the follicular, tissue, vascular perifollicular epithelium, of lymphocytaric populations of the blood and blastogenic lymphocytes response of mitogens. Minoxidil seems to induce a capillary regrowth in alopecia areata by a synergistic effect, on the one hand, stimulant on the follicular epithelium and, on the other hand, suppressor on the immunological phenomena measured by lymphocytes, as well as its vasodilator role.

In addition, the effects of minoxidil were shown in different *in vitro* studies with monocultures of various cellular types of skin and hair follicles, including the stimulation of cellular proliferation, the inhibition of the collagen synthesis, a stimulant of the growth factor

of the vascular endothelium and of the prostaglandin synthesis. Some of these effects can be relevant in capillary growth, but the application of the results obtained in cellular culture studies, given the biological complexity of the hair follicle, is uncertain.

Secondary pharmacodynamics
Minoxidil was considered one of the drugs of choice for the treatment of malignant renal hypertension and was widely used in the early 1970s. The antihypertensive activity of minoxidil is due to rapid relaxation of vascular smooth muscle by its sulphated metabolite, minoxidil sulphate.

One study. evaluated the effectiveness of topically applied of minoxidil (5% twice a day) in the pharmacological delay phenomenon to demonstrate the comparable microscopic and macroscopic changes between minoxidil-pre-treated flaps and surgically delayed flaps in male Wistar rats. The results showed that minoxidil, as an effective vasoactive agent, not only causing vasodilation but also stimulating angiogenesis in rat cutaneous flaps. However, it requires sufficient time and a suitable dose to act as an angiogenetic factor for increasing flap vascularity and viability before flap elevation.

Effect of minoxidil on stress-induced hair growth
Although the association between stress and hair loss is well accepted, no specific pharmacological intervention was available to manage stress-induced hair loss. A study exposed mice to a psycho-emotional stressor resulted in a premature catagen development in cycling hair follicles (HFs) and a significantly increased keratinocyte apoptosis and decreased keratinocyte proliferation in resting (telogen) HFs. Furthermore, activated perifollicular macrophages and mast cells appeared to be involved in the pathways of stress induced hair follicle apoptosis. Interestingly, the neuropeptide Substance P (SP) could be identified as a potential mediator by which stress exerts its inhibitory influence on hair growth. These novel data indicated the existence of a ‘brain-hair follicle axis (BHA). All of these stress-induced hair growth inhibitory changes along the BHA were down-regulated by topical minoxidil application. Minoxidil treatment had been demonstrated to cause an early initiation of anagen encouraging to explore clinically whether topical minoxidil is a safe and effective pharmacologic tool for the management of stress-associated telogen effluvium in humans.

Effect of minoxidil on alopecia areata
One author stated that minoxidil may induce hair regrowth in alopecia areata by a synergistic stimulatory effect on follicular epithelium and suppressive effect on lymphocyte-mediated immunologic phenomena. A contributing role for its vasodilatory properties must also be considered.

Safety pharmacology
Studies of topically applied minoxidil in the stump-tailed macaques do not appear to affect systemic parameters, including electrocardiograms, blood pressure or any complete blood count measurement. Moreover, these studies demonstrated fairly constant serum concentration of minoxidil at 2, 4, 6, 15, and 24 hours (15 ng/ml) after a single application of minoxidil of 10 mg in a propylene glycol/alcohol vehicle. During 4 years of experience with topical minoxidil, one author did not see any pathologic changes of the skin except for occasional nonspecific mild inflammatory changes, which have occurred sporadically in both vehicle- and minoxidil treated animals.

The most common adverse reactions of the topical formulation are limited to irritant and allergic contact dermatitis on the scalp. There have been cases of allergic reactions to the nonactive ingredient propylene glycol, which is found in some topical solution.

Pharmacodynamic drug interactions
While knowledge about effects of multiple sulfotransferases is presently limited and the clinical consequences for many drugs are still being examined, it may be prudent to exercise care when administering etoricoxib concurrently with other drugs primarily metabolised by human sulfotransferases as minoxidil.

Adenosine triphosphate (ATP)-sensitive potassium (K^+) channels are modulated by drugs, so that they are opened by vasodilators such as minoxidil but are closed by hypoglycaemic agents such as glibenclamide. Animal studies and *in vitro* evidence suggests that the coadministration of drugs with opposing effects on K+ channels attenuates their pharmacodynamic effects.

The effect of oral minoxidil may be additive to concurrent antihypertensive agents and other agents with blood pressure lowering effects. The interaction of minoxidil with sympathetic blocking agents such as guanethidine or betanidine may produce excessive blood pressure reduction and/or orthostatic hypotension.

In a three-way, randomised, crossover study carried out by one research group to determine the effect of the tretinoin (synthetic retinoid), on percutaneous absorption of minoxidil was reported that minoxidil absorption is enhanced by tretinoin as a consequence of increased stratum corneum permeability.

III.3 Pharmacokinetics

Absorption
The percutaneous absorption of minoxidil seems to be minimal after topical application in intact skin. However, the systemic absorption of topical minoxidil is variable and depends on several factors, including the vehicle used in the formulation, the area of application, the condition of the skin and the interindividual variability of the amount of absorption. For an application of 2% minoxidil, percutaneous absorption varies between 0.3 and 4.5%. Studies in animals show a systemic absorption of 5-36%. With respect to the serum concentrations reached after topical administration, they are variable and no correlation between them and capillary growth has been shown. In monkeys, the plasmatic concentrations of minoxidil obtained at 2, 4, 6, 15 and 24 hours after the application of the drug at 1 or 5% were constant, around 15 ng/ml.

Minoxidil cutaneous solution contains ethanol, water, and propylene glycol as vehicle. Both alcohol and propylene glycol induce the drug’s uptake. Experimental studies show that the increase in the alcohol percentage increases better minoxidil uptake. This means that propylene glycol is important for minoxidil uptake in the tissues.

Different dose-response studies show that 2% minoxidil is more effective in favouring hair growth than other formulations with lesser concentrations.

Recent results on follicular penetration emphasise that the hair follicles represent a highly relevant and efficient penetration pathway (through passive transport) and reservoir for topically applied substances.

Although the limited *in vitro* evidence indicates a comparable release of minoxidil from solutions with different propylene-glycol, alcohol and water levels, its release from pharmaceutical presentations such as creams is substantially different, as it is from oily solutions compared with the watery ones or ointments regarding dermal penetration. Minoxidil's absorption from extemporaneously prepared solutions, ointments, creams and other forms of topical application might not be comparable to that from the marketed topical forms.

In a study conducted to learn about the absorption, distribution and excretion of minoxidil after oral administration of a single dose (5 mg/kg) and repeated doses (10 mg/kg/day for 30 days) in rats, dogs and monkeys, the results were the following: the absorption after a single dose is rapid and complete and its elimination is also rapid in the three animal species.

A study with Minoxidil topical foam in the hamster ear model showed that 5% of minoxidil topical foam increased uptake of minoxidil by five times over 5% minoxidil topical solution at 2 hours of application.

There are also published studies related to the penetration improvement of minoxidil solution free of propylene glycol (composed particularly by water, ethanol and PEG 400) when it is supplemented with Tocopheryl Polyethylene Glycol Succinate (TPGS). This co-solvent improved the local effect and reduced the systemic effect (which would produce side effects) compared to the reference solution composed by water, ethanol and propylene glycol but must be mentioned that the TPGS was only able to improve the solubility of minoxidil in those solvent systems with higher proportions of PEG 400 and water and an increase in the amount of TGPS to 2% led to deterioration in the enhancement of hair wroth.

Distribution

The distribution of minoxidil after topical administration is not well determined. There seems to exist a barrier formed by the stratum corneum of intact skin to the passing to the systemic circulation of minoxidil. Studies in humans with skin biopsies after application of radiolabelled 1% or 5% topical minoxidil show that, at 24 hours, less than 2.6% of the dose was still retained in the skin. The elimination of the absorbed minoxidil from its topical application was primarily through the urinary passage, approximately 95% before 4 days after the end of the topical application of the product. A significant portion of the topical dose seemed to be eliminated unnoticed from the surface of the hair through contact with hands or clothing, volatilisation, displacement by air currents and other non-systemic forms.

The minoxidil excretion in the breast milk of women is not known, although it has been detected in the breast milk of nursing mothers.

The minoxidil distribution followed similar patterns in all the species after oral, SC and topical administration; it is rapid and includes the liver, kidneys, intestine, bladder and aorta. The absorption patterns and distribution after administering minoxidil by SC route during 21 days did not show bioaccumulation of radioactivity in rats. The distribution patterns after multiple doses were similar to those of a single dose but the levels of radioactivity were much higher (in general, 2-9 times higher and 17 times in the skin). Without cerebral radioactivity and presence of radioactivity in the foetus. In the case of topical administration, the majority of the radioactivity was observed in the site of the application. The levels of radioactivity in females compared to males were doubled.

Metabolism
There exists a first-step phenomenon evident in all the tested species. Eight metabolites were characterised 3 minutes after the SC administration of 0.9 mg/kg in rats. The majority of radioactivity remained unaltered (50%), followed by the carboxy-minoxidil minoxidil. In the monkey, a glucuronide conjugate represented 50% of the radioactivity followed the unaltered drug. The majority of the minoxidil metabolites were also identified in other organs of the rat. In the case of topical administration, in the application site, 70-80% of the radioactivity corresponded to the drug without modification and there were qualitative differences in the metabolic profile observed with respect to that obtained after oral administration.

Excretion
The excretion characteristics and metabolic rate of the minoxidil topical form have not been entirely determined to date.

A study on healthy subjects who received the radiomarked agent indicated that following topical administration the systemically absorbed minoxidil is mainly excreted in the urine; no faecal radioactivity was detected. Once the treatment was stopped approximately 95% drug was systemically eliminated within 4 days.

After SC and topical administration of minoxidil in rats and monkeys, the radioactivity was almost exclusively excreted by the urine. There were no differences in the excretion rates with repeated SC administration up to 21 days with respect to the single dose; however, the excretion rates of radioactivity in the urine and faeces observed in rats treated with 1% topical minoxidil during 7 days decreased with the number of administrations. This decrease can be caused by a reduction in the percutaneous absorption as a result of repeated application and drying of the test material.

After chronic administration, a slight increase is produced in the plasmatic clearance rate, of minoxidil as well as its metabolites. After aqueous diuresis by water load to dogs, an even greater increase was produced in the elimination rate of the drug and its metabolites. The autoradiographic study of rats showed that minoxidil is rapidly distributed after both oral and IV administration and it is concentrated, principally, in the excretory system.

The biotransformation of minoxidil was studied in rats, dogs and monkeys and compared to the results obtained in humans. The chromatographic profiles of the urinary metabolites indicated that each species excreted substantially the same metabolites but in relatively different amounts. Monkeys and humans exhibited a similar metabolic profile, while dogs and rats were quantitatively different from each other and with respect to monkeys and humans. The principal component excreted by monkeys and humans was the glucuronide conjugate of minoxidil. Significantly smaller amounts of unaltered minoxidil, 4'-hydroxyminoxidil and more polar metabolites were excreted in both species.

In the rat, the principal component excreted was the unaltered minoxidil: also the two carboxylated metabolites and, in small amounts, the glucuronate minoxidil, 4'-hydroxyminoxidil, 3'-hydroxyminoxidil and reduced minoxidil. In the dog, the principal metabolite excreted was the 4'-hydroxyminoxidil, small amounts of unaltered minoxidil and polar metabolites and, in a much lesser amount, glucuronate minoxidil, 3'-hydroxyminoxidil and reduced minoxidil. In this species, another metabolite was observed, the glucuronide conjugate of 4'-hydroxyminoxidil.

In addition, it must be recalled that minoxidil has an active metabolite, the minoxidil sulphate, that participates in the stimulating effect of the capillary growth by acting as an activator of the potassium channels. The conversion of minoxidil in minoxidil sulphate is measured by the enzyme sulfotransferase whose activity has been shown in human and rat liver, platelets, epidermal keratinocytes, mouse vibrissae, rat fur and rat vibrissae and epidermal keratinocytes. The activity of the sulfotransferase was localised in the hair follicle in the skin of the macaques' scalp.

Biochemical evidence for minoxidil sulphation by two phenol sulphotransferases has been found in human scalp skin and one author reported finding mRNA expression for four sulphotransferases in human epidermal keratinocytes. There are interindividual variations in scalp sulphotransferase activity and this correlates with the level in platelets. In a clinical setting, scalp sulphotransferase activity was variable due to the availability of this enzyme in the follicle was higher in men who responded to minoxidil compared with those who did not respond.

III.4 Toxicology

Single dose toxicity

The systemic absorption and typical overdose risk might increase in case of excessive dosage or frequency of treatment, as well as after application on large, wounded or swollen skin areas. Yet no adverse effect was observed nor condition resulting from the ingestion of 1–2 ml solution by a 3 years old child who, albeit vomiting, reached systemic levels of total minoxidil of approximately 320 ng/ml. The toxic potential of the minoxidil preparations lies in their accidental ingestion.

There is a toxicity study of minoxidil conducted by the laboratory that developed the active ingredient, that, in the case of acute toxicity, consisted of determining the lethal dose fifty (LD_{50}) of minoxidil in mice (through IV and intraperiotoneal-IP) and rats (oral, IV and IP) and in combination with hydrochlorothiazide, propranolol, azathiopirine, prednisone and anti-thymocyte globulin (ATG). The calculation of the LD_{50} was based on the mortality data on the 7th day. By IP, the LD_{50} was 1001 mg/kg and 759 mg/kg in mice and rats, respectively. Orally, the LD_{50} for rats was 1321 mg/kg. By IV, the LD_{50} were 51 mg/kg and 49 mg/kg in mice and rats, respectively.

In a paper on the pharmacology and toxicity of an analogue of minoxidil (2,4-diamino- 6-piperidino-pyrimidine-3-oxide), minoxidil was used as comparator. The LD_{50} obtained in the spontaneously hypertensive mouse administered orally and by IP was >1 g/kg and 560 mg/kg, respectively.

In the RTECS (Registry of Toxic Effects of Chemical Substances) database, the following data appear in relation to the toxicity by single dose of minoxidil**.**

Table:

TOXICITY THROUGH SINGLE DOSE					
Test	Route	Species	Dose	Toxic effects	Reference
LD50	Oral	Rat	1321 mg/kg	Not reported	Toxicology and Applied Pharmacology: 39,1,1977
LD50	IP	Rat	759 mg/kg	Not reported	
LD50	IV	Rat	49 mg/kg	Not reported	
LD50	IV	Mouse	51 mg/kg	Not reported	
LD50	Oral	Mouse	>1 mg/kg	Not reported	Bollettino Chimico Farmaceutico: 121,16,1982
LD50	IP	Mouse	560 mg/kg	Not reported	
TLDo	IV	Rat	1.5 mg/kg	- Arterial hypotension - Changes in urine composition - Decline in urine volume - Changes in sodium	Journal of Pharmacology and Experimental Therapeutics: 304,833,2003

TLDo = Lowest toxic dose reported

Table 1. Toxicity data for single dose of minoxidil taken from RTECS

Assessor's conclusion

Acute toxicity has been suitably characterised from the literature.

Repeat-dose toxicity

In a study conducted with dogs that were infused with minoxidil (0.05-4.3 mg/kg/day) through IV during 3 days and that measured the plasma levels of minoxidil, heart rate, arterial pressure and macro and microscopic changes, the obtained results showed an increase in the minimum heart rate and a decrease in arterial pressure with serum levels of 2 ng/ml after 3 days of infusions. With these plasmatic levels, no cardiac lesions were observed. With plasma levels of 6-7 ng/ml, the heart rate increased by 45% without concomitant decrease in the arterial pressure; absence of cardiac lesions. When the plasma levels were 14 ng/ml (4.3 mg/kg/day), cardiac lesions were observed with an increase in the heart rate over 50% and a decrease in arterial pressure of more than 20%. Therefore, there is a difference of 7-10 times between the plasma levels that caused a detectable increase in the heart rate (2 ng/ml) and those that caused hypotension and cardiac lesions (14-22 ng/ml).

The atrophy and degeneration of the atrial septum when minoxidil was chronically administered to dogs or humans suggested limiting oral minoxidil use only to malignant renal hypertension patients who did not respond to other therapeutic regimens.

The following data were gathered in relation to the toxicity for repeated doses of minoxidil from the RTECS (Registry of Toxic Effects of Chemical Substances) database.

Table:

TOXICITY THROUGH REPEATED DOSES					
Test	Route	Animal	Dose/ Duration	Toxic effects	Reference
TLDo	Oral	Rat	19950 mg/kg 95 weeks-C	Changes in heart weight	Toxicology and Applied Pharmacology: 39(1),1,1977
TLDo	Oral	Dog	1600 mg/kg 16 Days-I	Cardiac changes Weight loss or gain Death	
TLDo	Oral	Dog	21840 mg/kg 2 years-C	Cardiac changes	
TLDo	Oral	Pig	640 mg/kg 32 Days-I	Weight loss or gain Changes in sodium	
TLDo	Intracutaneous	Rat	13500 mg/kg 90 Days-I	Tubular and glomerular changes Changes in spleen weight Changes in erythrocyte count	Iyakuhin Kenkyu. Study of Medical Supplies: 23,59,1992
TLDo	Intracutaneous	Rat	1638 mg/kg 52 weeks-I	Changes in heart weight Changes in lung weight Changes in spleen weight	
TLDo	Oral	Dog	3190 mg/kg 1 year-I	Cardiac changes	Toxicologic Pathology: 17,164,1989
TLDo	Oral	Pig	20 mg/kg 2 Days-I	Cardiomyopathy, including infarction Vascular changes Haemorrhage	Experimental and Molecular Pathology: 41,10,1984
TLDo = Lowest toxic dose published					

Table 2. Toxicity data for multiple doses of minoxidil taken from RTECS

One research group conducted a battery of toxicity studies for multiple doses that, in general lines, did not show toxicity. The appearance of a lesion in the right auricle of dogs with doses of 1-20 mg/kg during 1 month stands out; this lesion also appeared in dogs (not in all) subject to daily doses of 3, 10 or 30 mg/kg for 1 year, with a physiological rather than a toxicological origin being possible.

Assessor's conclusion

Sub-chronic and chronic toxicity has been suitably characterised from the literature.

Genotoxicity

Minoxidil does not show mutagen in the Ames test, DNA lesion, non-programmed DNA synthesis test, text of chromosomal aberrations, text of micronuclei in bone marrow.

A genotoxicity study with minoxidil administered topically for 8 days showed that this drug does not increase the nuclear aberrations in the hair follicle or in the micronuclei in the bone marrow, from which it is deduced that used topically it is not genotoxic.

Assessor's conclusion

There are limited data from the public domain to support the conclusion that minoxidil is non-genotoxic. Topical use *in vitro* data in murine hair follicles suggest a non-mutagenic effect following treatment over 8 days. Although not fully conclusive, given the established use of this active substance this can be considered to be suitably addressed.

Carcinogenicity

In one dermal carcinogenicity study in mice, with a duration of 2 years, an increase was observed in the incidence of mammary adenomas and adenocarcinomas in females at all the dosages used (8, 25 and 80 mg/kg/day) that was attributed to the increase of the prolactin activity. The hyperprolactinemia is a well-known mechanism for increasing mammary tumours in mice but that has not been associated with mammary tumorigenesis in women.

Another dermal carcinogenicity study in rats, with duration of 2 years, showed a significant increase in the incidence of pheochromocytomas in males and females and of adenomas of the preputial gland in males. This higher incidence seems to correspond to that observed with other antihypertensives in the case of pheochromocytoma, to hormonal disorders related to the treatment for the mammary adenocarcinoma of female mice and the adenoma of the preputial gland in males or to represent the normal variation in the historical incidence range of neoplasias in rodents (malignant lymphoma, hepatic nodule/adenoma in mice). Based on the absorption differences of minoxidil and the carcinogenicity mechanism of these rodents, none of these changes are considered relevant for the safety of those patients that receive topical minoxidil.

There is no evidence of epithelial hyperplasia or carcinogenicity in the application sites of minoxidil of mice or rats in the dermal carcinogenicity studies of a 2-year duration. Neither was there evidence of carcinogenicity in rats or rabbits treated topically with minoxidil for 1 year. In a photocarcinogenicity study lasting 12 months, (2% and 5%) topical minoxidil did not significantly reduce the latency period of the skin tumours by ultraviolet light (UV) in bald mice, compared to the control group.

Assessor's conclusion

A number of long-term studies have been completed with minoxidil, both orally and dermally. The dermal studies are quoted from a drug reference source. No evidence of neoplasia following long term exposure in rodent carcinogenicity studies is presented. Rabbit long term data also do not reveal positive tumorigenic findings.

Reproductive and developmental toxicity

Although there are not controlled and suitable studies at present in humans orally or topically treated with minoxidil, its oral administration has been associated with a higher fetal absorption in rabbits, not in rats though, when administered a doses five times the highest antihypertensive recommended oral dose. No evidence of teratogenic effect has been found after oral administration to rabbits and rats, neither in rats subcutaneously treated with minoxidil 80 mg/kg per day (2000 times the human systemic exposure reached with minoxidil topical). Yet, with dose maternal toxicity was observed.

Minoxidil lowers the conception rate when orally administered to male and female rats at doses 1 to 5 times the highest anti-hypertensive dose recommended for human treatment.

The teratogenicity studies conducted by a research group with pregnant rats and rabbits receiving minoxidil doses one- to five-fold those administered to humans did not show a significant increase in offspring malformation rate were negative. Larger doses, however, may cause abnormal fetal growth, skeletal abnormalities, and an increase in the offspring death rate.

Based on the RTECS (Registry of Toxic Effects of Chemical Substances) database, the following data were taken in relation to the reproductive toxicity of minoxidil (Table 13).

REPRODUCTIVE TOXICITY						
Test	Route	Animal	Dose	Sex/Duration	Toxic Effects	Reference
TLDo	SC	Rat	2080 mg/kg	♀/17-21 days post conception ♀ nursing 21 days post-parturition	- Parturition - Stillborn - Effect on index of live births	
TLDo	SC	Rat	2080 mg/kg	♀/17-21 days post conception ♀ nursing 21 days post-parturition	- Musculoskeletal abnormalities - Physical effects on the newborn	Iyakuhin Kenkyu. Study of Medical Supplies: 23,774,1992
TLDo	SC	Rat	1320 mg/kg	♀/7-17 days post conception	- Fetotoxicity - Musculoskeletal abnormalities - Stillborn	
TLDo	SC	Rat	1320 mg/kg	♀/7-17 days post conception	- Musculoskeletal abnormalities - Behavioural effects on newborn	
TLDo = Lowest toxic dose published						

Table 13. Reproductive toxicity data of minoxidil taken from RTECS.

Assessor's conclusion

There is no clear evidence of teratogenicity following exposure of high levels of oral minoxidil to rats and rabbits. Given the proposed route of administration, safety margins would be inherently increased, so the likelihood of exposure to minoxidil is highly limited.

Local tolerance

The studies with stump-tailed macaques with topical minoxidil during 4 years, have not seen pathologic changes of the skin except for occasional nonspecific mild inflammatory changes, which have occurred sporadically in both vehicle and minoxidil treated macaques.

In humans, the most frequent side events of these topical solutions are topical dermatological reactions such as pruritus, dryness and exfoliation as well as local irritation and burning including irritating dermatitis. In rare cases it could be sufficiently severe to force abandoning the treatment.

Assessor's conclusion

Local tolerance has been suitably described.

Other toxicity studies

Studies on impurities

A brief section discussing impurities is included in the non-clinical overview/summary, stating that

"the only impurities and degradation products associated with the proposed drug product are those characterised and controlled (Ph. Eur 2.2.46 method, current Edition) for the active constituents/excipients."

Assessor's conclusion (also making reference to the quality overall summary [module 2.3] and quality module 3 [quality])

The drug substance manufacturer of the active substance states that it is in accordance with the EP monograph for minoxidil, this is acceptable.

The drug product is presented in a colourless solution, formulated with ethanol (96%), propylene glycol and purified water. Given the topical and external use of this product, the

concerns for safety of these excipients is limited. The justification is acceptable. Drug product impurities are adequately characterised, and limits are justified in line with the drug substance monograph.

An extractables study of the container closure system (CCS) is provided. This is acceptable and does not identify compounds of interest for further toxicological review.

III.5 Ecotoxicity/Environmental Risk Assessment

A full Environmental Risk Assessment (ERA) has been provided. This contains a Phase I and Phase II Tier A assessment. The results of the ERA show that there is no significant environmental risk with the use of this product.

Assessor's conclusion

The submitted ERA is acceptable.

III.6 Discussion on the non-clinical aspects

The pharmacodynamic, pharmacokinetic and toxicological properties of minoxidil are well known. As this is a well-known active substance, the applicant has not provided additional studies and further studies are not required. An overview based on literature review is, thus, appropriate.

The non-clinical overview is acceptable.

Limits for impurities in the drug substance/product are acceptable. An acceptable elemental impurity risk assessment has been provided.

Suitability of the use of excipients in the final drug product is agreed, and there are no ongoing concerns for potential leachables in the drug product originating from the CCS.

An acceptable ERA has been submitted.

The grant of a marketing authorisation is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

No new clinical studies were submitted, as the data submitted for this application is in the form of literature references. The literature review provided is satisfactory.

IV. 2 Pharmacokinetics

Absorption:

After cutaneous application, minoxidil shows minimum absorption, only a mean amount of 1.7% (0.3-4.5%) of the dose applied of minoxidil 20 mg/ml and minoxidil 50 mg/ml, respectively, would pass to general circulation. Therefore, for a dose of 1 ml in solution form at 2% (i.e. application of 20 mg of minoxidil) or 5% (i.e. application of 50 mg of minoxidil), the amount of minoxidil absorbed corresponds to 0.28 mg and 0.85 mg, respectively.

Systemic effects may occur above the doses between 2.4-5.4 mg/daily. This dose could be reached with application of minoxidil 50 mg/ml on the entire scalp without limitation to the alopecic area.

By way of comparison, oral administration of minoxidil tablets, for treatment of certain types of hypertension determines its complete absorption at gastrointestinal tract level. Modification of its absorption in concomitant dermal disorders has not been determined.

Biotransformation and distribution:
The serum concentration of minoxidil after cutaneous application is according to its degree of percutaneous absorption.

Elimination:
The elimination half-life of 95% of minoxidil absorbed, after cutaneous application is 96 h (four days). Both minoxidil and its metabolite are excreted mainly in urine.

In a study on healthy volunteers in which minoxidil 50 mg/ml (5%) was radioactively labelled, low levels were observed in urine, with mean values between 1.6-3.9% of the dose applied. No levels of minoxidil were observed in faeces.

The quantity of minoxidil recovered on the skin surface of the scalp fluctuated between 41%-45% of the dose applied.

In a study in which serum samples were obtained from 1885 patients treated with 5% topical minoxidil, the mean serum concentrations of the agent were 2.6 ng/ml. No tendency for these levels to increase over time was noted (32-96 weeks). No patient showed minoxidil levels of above 20 ng/ml nor any evidence of systemic toxicity. In the majority of samples, serum levels of 0.1-2.0 ng/ml were detected. It can be concluded that minoxidil is only weakly absorbed by the skin, which keeps levels below those necessary for any toxic reaction to occur.

Following its topical application, minoxidil accumulates in the cornified layer and is later distributed, though very slowly. Approximately 45% of the dose applied can be recovered in the urine and scalp.

Minoxidil and its metabolites are excreted principally in the urine by glomerular filtration (about 97%); only insignificant amount is excreted in faeces (1-3%). Following cessation of topical dosing of minoxidil, approximately 95% of systemically absorbed drug is eliminated within four days. Renal clearance is 73.9 ml/min. No faecal excretion has been detected. With chronic therapy in patients with renal impairment, minoxidil's glucuronide metabolites accumulate in plasma but the unchanged drug does not. Minoxidil and its metabolites can be removed by haemodialysis or peritoneal dialysis. In one study in patients with various degrees of renal function (e.g., normal to uremic), the mean plasma half-life of minoxidil and its metabolites was 4.2 hours.

Assessor's conclusion
The pharmacokinetics of minoxidil are well known.

IV.3 Pharmacodynamics

Minoxidil (2,4 - diamino-6-piperidinopyrimidine-3-oxide) when administered orally is a vasodilator that acts directly on the smooth vascular muscle cells, causing a reduction in peripheral vascular resistance and reducing both systolic and diastolic blood pressure, even in patients with severe or refractory hypertension. Its hypotensive effect is associated with increased heart rate.

Cutaneous application of minoxidil has an anti-alopecic effect. The mechanism by which minoxidil stimulates hair growth, however, is not fully understood. Nonetheless, it has been shown that the agent has no hormonal or immunosuppressant activity.

Literature references highlight that minoxidil stimulates the growth of keratinocytes *in vitro* and *in vivo* together with hair growth in some patients with androgenic alopecia. The appearance of this phenomenon occurs after use of this medicine for a minimum period of 4 months, and varies according to each patient, although its mechanism of action remains unclear. When treatment with minoxidil is stopped, hair growth may stop and return to the initial state of alopecia within 3-4 months.

Assessor's conclusion
The pharmacodynamics and the precise mechanisms of action of minoxidil as an anti-alopecic remain largely unknown.

IV.4 Clinical efficacy

The applicant has submitted a substantial number of publications involving 2% and to some extent 1% and 3% dose strengths which demonstrated the efficacy on minoxidil in patients with alopecia. However, only the relevant publications using 5% dose strength which the applicant has applied for are summarised and discussed in this assessment report.

The efficacy and tolerability of 5% minoxidil solution in male and female androgenetic alopecia was determined in a 6-month open multicentric study. The aim of the study was to evaluate the efficacy and safety of minoxidil 5% applied twice daily on the scalp, on male and female androgenetic alopecia. Evaluation of efficacy was performed with subjective and objective methods, including operator and patient assessments, global photography and videodermoscopy. After 6 months of treatment with minoxidil 5%, androgenetic alopecia was improved in all 32 females and 16 males. The study confirmed that the data of the literature and the evidence coming from years of clinical experience, twice daily minoxidil 5% topical application is effective in the treatment of male and female androgenetic alopecia, with evident efficacy already after 6 months. Clinical improvement of androgenetic alopecia is evident in 100% of female patients, including those with severe forms. It should however be noticed that mild forms of androgenetic alopecia respond better to treatment, with improvement already visible both clinically and by videodermoscopy after a few months of minoxidil solution application. Minoxidil solution was effective also in males, with efficacy evident in 100% of the patients: after 6 months of treatment 2/3 of the patients showed improvement of androgenetic alopecia and 1/3 showed an arrest in the progression of the disease. Androgenetic alopecia with prevalent vertex involvement responds better to treatment than the other forms, followed by the anterior type.

In a search for greater effectiveness while conserving the safety profile of the 2% concentration, a double-blind study showed 5% minoxidil to be significantly more effective than either the 2% concentration or a placebo ($p<0.05$). In this study, which involved 345 patients (follow-up was completed in 321), objective assessment via the counting of the number of hairs per cm^2 in the vertex area gave the following results after 32 weeks of treatment.

This study was reported in Minoxidil topical solution monograph, was the first randomised, placebo-controlled, double-blind study in which the efficacy of 5% minoxidil solution was investigated, continued for 32 weeks. In this study (345 patients were randomised). Details on the study can be found in following table:

Table IV

	5% Minoxidil (n=163)	2% Minoxidil (n=79)	Placebo (n=79)
Objective assessment			
Increase in n° hairs/ cm²			
16 weeks	36 (34%)	25 (24%)	4 (3.8%)
32 weeks	39 (37%)*	30 (29%)*	5 (4.7%)*

*Significant difference between treatments ($p<0.05$)

It could be demonstrated that in the group of patients treated with 5% minoxidil the baseline count for 106 hairs on the evaluation site of 1 cm^2 was increased after 16 weeks by 36 hairs (34%) and after 32 weeks by 39 hairs (37%). In the group of patients treated with 2% minoxidil, the baseline count of 103 hairs was increased by 25 hairs after 16 weeks and by 30 hairs after 32 weeks. In the placebo group, the baseline count was 105 hairs, which was increased by 4 and 5 hairs after 16 and 32 weeks of treatment, respectively.

One study by that has been reported in Minoxidil topical solution monograph, was the first randomised, placebo-controlled, double-blind study in which the efficacy of 5% minoxidil solution was investigated, continued for 32 weeks. In this study (345 patients were randomised).

The difference observed between the effectiveness of the two treatment regimens (9 hairs/cm^2 in 8 months) is significant (especially given that 4 hairs/cm^2 are expected to be lost in 10 months in androgenetic alopecia).

No significant differences were seen between the results obtained for the subjective variables evaluated. Therefore, a further study was undertaken in which these variables were analysed using a detailed questionnaire developed by specialists in dermatology, statistics and the social sciences. This questionnaire collected information (from both researcher and patient) on the coverage of the scalp and the benefits of treatment. In this double-blind study (5% minoxidil vs. placebo), 62 patients were monitored over 48 weeks of treatment and both subjective and objective variables were taken into account.

With respect to the objective variables, 5% minoxidil was found to increase the number of hairs significantly more than the placebo. At the end of the experimental period, an increase of 36 hairs per cm^2 was recorded among the treated patients but of only five in the placebo group ($p< 0.05$).

With respect to all the subjective variables studied (change in scalp coverage, improvement in hair loss, satisfaction/expectation ratio, current hair loss situation), the 5% minoxidil produced significantly better results than the placebo**.**

The satisfaction/expectation ratio was 0.69 in the minoxidil group and 0.29 in the placebo group. The percentage of patients who experienced improvement was 56% in the 5% minoxidil group but only 11.5% in the placebo group ($p < 0.05$) as shown in the table below:.

	5% Minoxidil (n=25)	Placebo (n=26)
Objective evaluation **Increase in n° hairs/cm²**		
16 weeks	47	12
48 weeks	36	5*
Subjective evaluation		
Patient evaluation	53.8	45.7*
Satisfaction/expectation ratio	0.69	0.29*
Improvement over baseline	56%	11.5%*
Photographic evaluation	3.8% increase	7.8% loss

*Significant difference between treatments ($p<0.05$).

Several studies have shown the superiority of 5% minoxidil over the 2% concentration. One multicentre, double-blind, placebo-controlled study involving 393 male patients randomly assigned to three groups (2:2:1), tested the efficacy of 2% and 5% minoxidil and placebo in the treatment of androgenetic alopecia over 48 weeks. The placebo used in this study was the vehicle of the 5% solution; this had more propylene glycol (50%) and less ethanol (30%) than the 2% minoxidil vehicle (20% propylene glycol and 60% ethanol). The dose for both treatments and the placebo was 1 ml every 12 h.

The 5% minoxidil had significantly the greatest positive effect on hair count by the end of the experiment. Even on a weekly basis the 5% concentration was significantly superior to the 2% concentration: since week 8 the differences were significant, becoming very significant by week 32 ($p=0.005$). This result is very important in the treatment of hair**.**

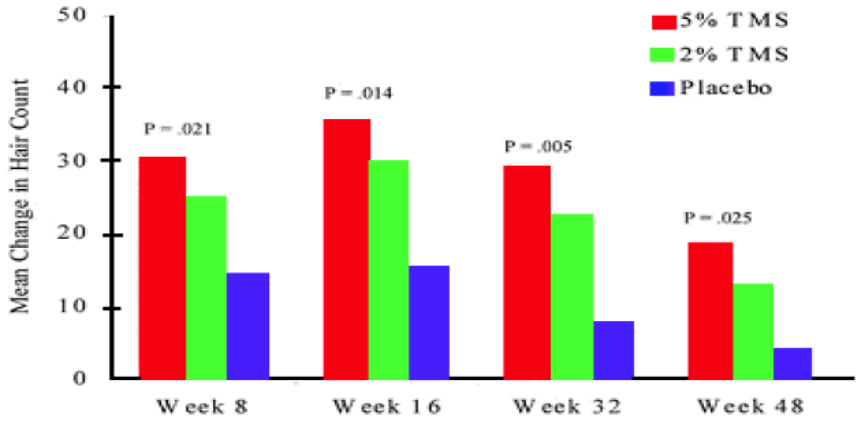


Figure: Changes in hair count between baseline and the end of the experimental period. The p values show significant differences between the 5% and 2% minoxidil concentrations.

This study not only confirms the rapid response obtained with the 5% concentration but also shows its significant superiority over the 2% concentration.
In addition, responses were seen earlier in the 5% group and improvements were seen in terms of the patients' psychosocial perception of their hair loss. The authors underline the clear superiority of 5% minoxidil in the treatment of androgenetic alopecia in men.

As mentioned earlier, the main variable in all studies that test the efficacy of hair growth promotion agents is the hair count. Studies performed on finasteride, which is authorised as an oral treatment for androgenetic alopecia, also make use of this variable. The results obtained with this agent are similar to those achieved with the 5% minoxidil concentration.

In one study involving 1553 men (779 treated with finasteride and 774 treated with a placebo), an increase was seen in the hair count of 86±3.4 per inch diameter circle [vertex area] (approximately 17 hairs per cm^2) after one year of treatment. Both patient and researcher evaluations of the agent were significantly better than those of the placebo. Photographic evaluation revealed a 48% improvement in the finasteride-treated group but only a 7% improvement in the placebo group.

The experimental period was then extended to 5 years. After 60 months of finasteride treatment, a mean increase of 38 hairs per inch diameter circle was observed (approximately 7.5 hairs per cm^2). The placebo group showed a loss of 239 hairs per inch diameter circle (-46.9 hairs cm2) ($p<0.001$).

A multi-centre, double-blind, placebo-controlled study, in which 326 patients with androgenetic alopecia were administered either finasteride (1 mg/day) or placebo, showed that after one year the number of hairs per cm^2 in the anterior and mid scalp had increased by 9.6±1.5. The placebo-treated patients, however, showed a reduction of 2.0±1.5 hairs/cm^2 ($p<0.001$). The objective benefit from treatment after one year of finasteride therapy was similar to that obtained in studies with 5% minoxidil.

One trial involving 382 patients, the aim of which was to determine the effective dose of finasteride in the treatment of androgenetic alopecia, showed a 69.8±8.9 increase in the number of hairs in a one inch diameter circle (13.5/cm^2) with the finally accepted dose of 1 mg/day. At 12 months, 278 finasteride-treated patients showed an increase of 85±11 hairs per inch diameter circle (16.66 hairs/cm^2).

The hair count results of the above finasteride and 5% minoxidil studies are therefore similar, and both treatments are significantly superior to placebo.

In another double-blind, randomised trial involving 36 men with androgenetic alopecia, changes in hair mass (another objective variable) were evaluated after 2% minoxidil treatment, 5% minoxidil treatment, treatment with the vehicle used for the 5% solution, and no treatment. This study showed the efficacy of minoxidil in promoting hair growth and delaying hair loss after 96 weeks of treatment (and 24 additional weeks of follow-up). Percentage hair growth was determined by the hair count and by estimating the mass of the hair in a pre-established area. This was determined every six weeks. The excess weight of hair induced by the treatment (excess accumulated weight) was also determined.

One research group performed an open, randomised comparative study to evaluate the efficacy of oral finasteride and 5% topical minoxidil treatment for 12 months in 65 male patients with male to severe AGA (vertex and frontal pattern type II, II, IV or V according to the modified Norwood-Hamilton scale). 40 patients (61.53%) were randomly assigned to receive 1 mg/day oral finasteride for 12 months and 25 patients (38.47%) applied 5% topical minoxidil solution twice daily for 12 months. There were no significant differences between the 2 groups considering age, age of onset of hair loss, family history and type of hair loss ($p>0.05$). In the clinical evaluation at the endpoint of treatment, the clinical cure rates (i.e. increased intensity of hair evaluated by standardised global photographs and clinical view in a 7-point scale every three months) were 80% (32/40) for the oral finasteride group and 52% (13/25) for the 5% topical minoxidil group

Evaluation was made on a 7-point scale by analysing photographs taken every three months:

1. 71 - 100% increase in scalp coverage over baseline
2. 41 - 70% increase in scalp coverage over baseline
3. 1 - 40% increase in scalp coverage over baseline
4. No change
5. 71 - 100% fall in scalp coverage from baseline
6. 41 - 70% fall in scalp coverage from baseline
7. 1 - 40% fall in scalp coverage from baseline

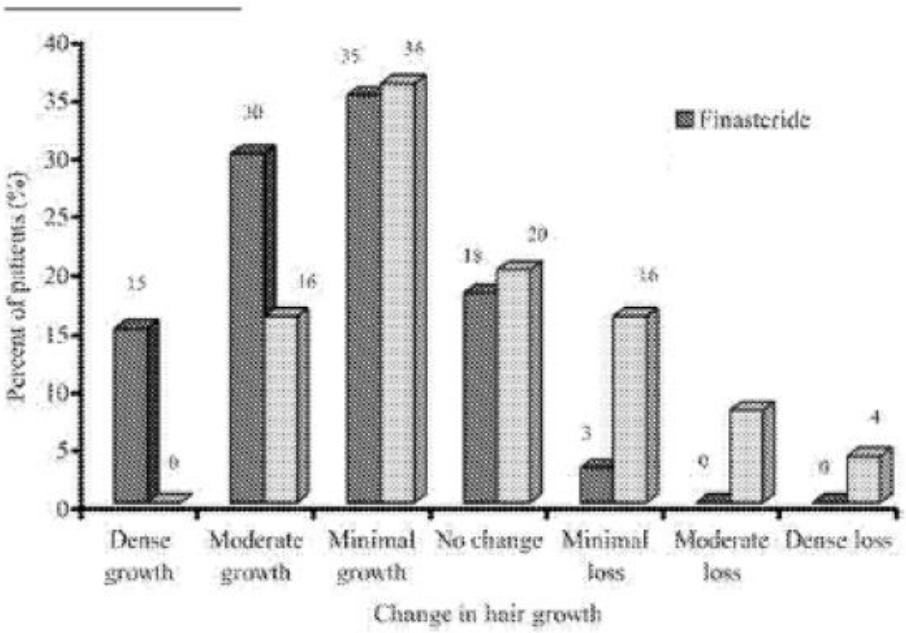


Figure: Clinical assessment at the end of treatment (percentage of men with change in hair growth)

The patients of both groups showed similar demographic characteristics. The results showed a subjective response in hair growth (1-100% increase over baseline) in 52% of the 5% minoxidil-treated patients, and in 80% of the finasteride-treated group. The adverse effects recorded (experienced by 17.5% of patients in the finasteride group and 4% in the 5% minoxidil group [this single patient developed a scalp irritation]) did not lead to the suspension of treatment. Blood analysis showed a slight increase in testosterone levels in the finasteride-treated patients; no such changes were seen in the 5% minoxidil-treated group.

Assessor's Comment
The hair count and hair mass are two of the main objective variables determined when testing the efficacy of agents that promote hair growth. Minoxidil has been effective in terms of both these variables. The 5% concentration has been found more effective both at promoting hair growth and stabilising hair loss. The results obtained with finasteride are similar to those obtained with 5% minoxidil. The studies were performed predominantly in adult male subjects. Those studies that have examined the psychological aspects of hair loss report the associated improvement of treatment with 5% minoxidil.

Assessor's conclusion on Efficacy:
Adequate literature review confirming the efficacy of minoxidil cutaneous solution in male patients androgenetic alopecia has been provided.

The applicant has provided a satisfactory discussion regarding the comparability of the proposed formulation to similar currently marketed products (in accordance with Annex 1, Part II of Directive 2001/83/EC, as amended).

IV.5 Clinical safety

The safety of 5% minoxidil has been well established by clinical trials and by post-marketing data gathered in many countries around the world.

The most common adverse effects associated with this concentration of the agent are dermatological and occur at the site of application (pruritus, irritation, erythema, contact dermatitis, plus hypertrichosis in non-treated areas due to accidental application).

Adverse systemic reactions involving the cardiovascular system (oedema, hypertension, palpitations) and nervous system (headaches, worse migraines) have been reported, but only very rarely.

Adverse effects
The following summarises the adverse effects reported with the topical use of minoxidil.

Adverse dermatological effects
At the beginning of treatment with minoxidil, an increase in hair loss may actually be noticed. This occurs because some hairs are in the telogen phase while others are in anagen (the growth phase). The oldest hairs fall and are replaced by new ones. This 'negative' effect on hair loss is only temporary and usually starts about 2-6 weeks after the start of treatment; it only lasts about two weeks.

Other possible problems include contact reactions at the application site, changes in hair colour, and the appearance of vellous hair outside the application area (hypertrichosis). Yellowing of the hair has been reported with the oral use of minoxidil and with pharmaceutical preparations containing the agent.

Severe, diffuse hypertrichosis is more frequently reported with the oral than the topical use of minoxidil, and especially in women. In men, hair generally appears on the neck, chest, back and extremities. In women it is generally seen on the face as well. Hypertrichosis may occur in 0.5- 1% of patients. The probable reason for this is the inadvertent transfer of the agent to other areas of the body, perhaps by the hands or via pillows. Some hair follicles may show atypical sensitivity to the product at very low systemic concentrations. Although this has provoked the interruption of treatment, it is a cosmetic problem and poses no risk to patients,

who usually improve with continued use and by applying the product more carefully to the scalp one hour before going to bed. Washing the hands after use also helps. This adverse effect is therefore reversible whether the agent is used topically or administered orally

Eight clinical studies on minoxidil, involving more than 1300 women, show hypertrichosis to be a rare problem; only 7 patients treated with 5% minoxidil and 2 treated with the 2% solution discontinued treatment for this reason. This safety clinical study was a randomised, double blind, placebo controlled study on women ≤ 18 years old. Total of 979 patients (similar demographically in age, weigh, height, race and hair loss), show local intolerance as mild, transient and generally resolved upon treatment discontinuation. Treatment related events were not serious, required minimal medical attention. Premature study withdraw due to hypertrichosis was rare. Clinical data demonstrated that minoxidil is safe and effective in woman with AGA.

Several reports mention allergic reactions at the site of application. No dose-effect relationship has been described. Propylene glycol can cause allergic contact dermatitis, known as vehicle-dependent allergic contact dermatitis.

On study group conclude that the maximum percentage of patients who show contact sensitisation is only 4% (observed both in human and animal studies). In their study of 60 patients with androgenetic alopecia, only two showed contact sensitisation, and of 25 experimental animals only one showed a positive patch test with minoxidil. One paper reports a case of pigmented contact dermatitis.

In a review, the authors state that after 10 years of the topical use of minoxidil, this agent has been shown safe and effective in the treatment of androgenetic alopecia. The most common adverse effects observed have been contact, irritant or allergic dermatitis, and an exacerbation of seborrheic dermatitis. These authors also point out that the most common irritant is the product's propylene glycol vehicle, rather than the minoxidil itself. Although the safety profile of minoxidil is favourable, its continued use over time could lead to contact dermatitis caused by some ingredient used in the preparation. On study group found that propylene glycol was the agent most commonly involved in this type of problem. Of 11 patients in whom the solution provoked contact dermatitis, 4 patch tests were positive for minoxidil, 1 for butylene glycol and 9 for propylene glycol.

One study of 381 women, indicates the most common adverse effects to be dermatological in nature. These were more common in the group treated with 5% minoxidil (14% of patients) and in the group treated with the vehicle used for this 5% solution. The occurrence of such problems may therefore be more due to the propylene glycol in the preparation than to minoxidil itself.

Few reports cite phototoxic or photoallergic reactions. One author concluded that the concomitant use of minoxidil and UV light (UVB-PUVA therapy) had neither beneficial nor adverse effects in the treatment of alopecia. A trial with a 1562 patients reported no evidence of photosensitivity or phototoxic reactions, nor of contact sensitisation in patients treated with 5% minoxidil.

Neurological effects
Headaches and migraines have occasionally been reported with minoxidil use. However, the cause of headaches, migraines and dizziness are multiple, and no causal relationship with minoxidil has been established.

Cardiovascular effects
Minoxidil may cause hydrosaline retention, an increase in heart rate (3-5 beats per minute), and a reduction in blood pressure. Rarely has it been associated with heart disease, myocardial infarction or death, and the evidence suggests that any such deaths have been due to causes unrelated to minoxidil use. However, it has been suggested that the use of minoxidil be more carefully monitored in patients with a history of cardiovascular disease.

Recently, a multicentre study has indicated that the cardiovascular problems that appeared during a clinical trial (angina, chest pain, changes in the electrocardiogram, palpitations and increased blood pressure) were not associated with the use of minoxidil. Only 1% of patients treated with 5% minoxidil and 6% of patients treated with 2% minoxidil developed such problems, as did 2-4% of subjects in the placebo group.

One research group reported no differences in the systemic pharmacological effects seen in hypertensive patients treated with 1%, 2%, 3%, 4% or 5% minoxidil or a placebo. Patients at known cardiovascular risk or with cardiovascular disease who were treated with topical minoxidil showed no greater risk of being admitted to hospital than similar patients who did not receive the agent. No fall in blood pressure caused by topical minoxidil use has ever been recorded in normotensive patients.

Interactions with other medications
The absorption of topically applied minoxidil is controlled and rate-limited by the stratum corneum.

Topical minoxidil has been used concomitantly with topical tretinoin in a limited number of individuals for potential additive or synergistic effects on hair regrowth. The percutaneous minoxidil absorption is enhanced by tretinoin as a result of increased stratum corneum permeability. There are references to a threefold increase in percutaneous absorption of minoxidil when applied in conjunction with tretinoin. In a recent published study in a limited number of individuals with androgenetic alopecia, combined topical therapy with tretinoin and low-dose of minoxidil suggested a possible synergism in hair growth response for the combination, compared with either of the agents administered alone and appeared to be more effective than tretinoin alone in stimulating hair regrowth. Tretinoin increased the rate and extent of percutaneous minoxidil absorption without changing apparent steady-state accumulation in the skin. This increase occurred as a result of a decrease in the barrier function of the stratum corneum unrelated to changes in stratum corneum thickness. The penetration enhancement of minoxidil elicited by tretinoin may explain, in part, the synergism in hair growth response reported for tretinoin applied topically in combination with minoxidil.

Simultaneous application of topically administered drugs that alter the stratum corneum barrier, e.g. topical corticosteroids, retinoids (tretinoin), anthralin, dithranol or agents that increase the percutaneous absorption of minoxidil, is not recommended. Individuals receiving topical minoxidil therapy should be advised to not use the drug concurrently with other topical therapy for the scalp.

Betamethasone dipropionate has been shown to increase local tissue concentrations of minoxidil and reduces its systemic absorption. However, the effect of betamethasone dipropionate on minoxidil absorption with an inflamed scalp is not known.

No interactions have been reported during the concomitant use of topical minoxidil and any

systemically administered drugs. In a group of 98 patients who applied minoxidil at the same time they were receiving medication for high blood pressure (such as beta-blockers and or diuretics), no interactions between these medications were seen.

Assessor's conclusion

Sufficient review of literature regarding the clinical safety of minoxidil cutaneous solution has been provided. Although adverse reactions may appear slightly more often with 5% minoxidil than with the 2% concentration, this increase does not appear to be clinically important. It is estimated that the product has been used by more than 2 million people since 1996 and only a very few adverse reactions have been reported in the literature, none of which were serious and all of which had been previously documented.

IV.6 Risk Management Plan (RMP)

The Applicant has submitted a RMP, in accordance with the requirements of Directive 2001/83/EC, as amended. The Applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects

Overall the application complies with the Committee for Medicinal Products for Human Use (CHMP) guidance documents and contains an adequate published clinical data. Minoxidil is a widely used and well-known active substance which has a long history of established favourable risk-benefit profile.

A satisfactory discussion regarding the comparability of the proposed formulation to similar currently marketed products described in the publications have been submitted.

The grant of a marketing authorisation is recommended for this application.

V USER CONSULTATION

The Patient Information Leaflet (PIL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The results show that the PIL meets the criteria for readability as set out in the guideline on the readability of the label and package leaflet of medicinal products for human use.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified from the literature. Extensive clinical experience with minoxidil is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.

The Summary of Product Characteristics (SmPC), PIL and labelling are satisfactory, and in line with current guidelines.

In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPC and PIL for this product are available on the MHRA website.

Representative copies of the labels at the time of UK licensing are provided below.


Minoxidil 5%
Cutaneous solution
60 ml
Marketing Authorisation Holder
Careforsons Limited, 2 Upper Wimpole Street, London, W1G 6LD, United Kingdom.
PL 50640/0001
Sons
Minoxidil 5%
Cutaneous solution
60 ml
Minoxidil 5% cutaneous solution
For the treatment of moderate male-pattern hair loss in adult males.
Each ml of solution contains 50 mg of minoxidil.
Also contains ethanol 96%, propylene glycol and purified water. See leaflet for further information.
For cutaneous use.
The recommended dose is 1 ml of solution every 12 hours. The hair and scalp must be completely dry when applying the product. Apply 1 ml of solution (equivalent to 10 metered sprays). Spread the solution using your fingertips on the treatment area, starting from the centre. To be applied to the hair only. For external use only. Read the package leaflet before use.
Do not exceed 2 ml of solution in one day and do not use more than twice a day. Wash hands after use.
This product should not be used by women.
Talk to your doctor before using this medicine if you have heart disease or a circulation disorder.
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.
Keep out of the sight and reach of children.
5 060678 930011
Batch No.
EXP

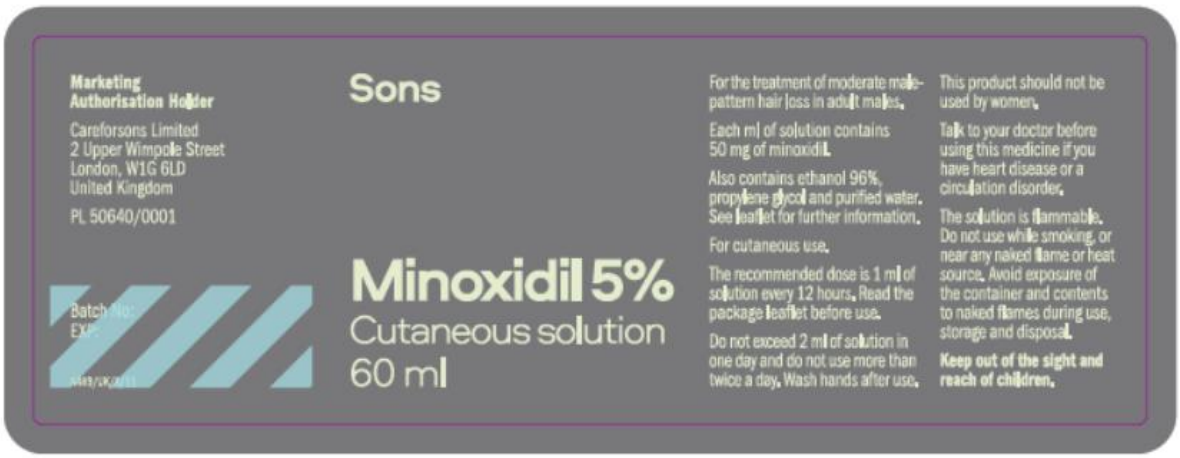

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TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**