SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Minox 5, 50 mg/ml, cutaneous solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each milliliter of the cutaneous solution contains 50 mg of minoxidil.

Excipient(s) with known effect:
Propylene glycol - 100 mg/ml

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Cutaneous solution.
Minox 5 is a clear, colourless or lightly yellow cutaneous solution with an alcoholic odour.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of male and female baldness, known as androgenic alopecia.
Treatment of alopecia areata, also known as spot baldness.

4.2 Posology and method of administration

Minox 5 is intended for external use only, with an application on the scalp, twice daily (12/12h), on completely dry hair.

The dose for each application is 1 ml of solution (corresponding to 30 drops), regardless of the size of the area to be treated, spreading the product from the centre out to the edge of the scalp with the fingers.

The recommended daily dose is 2 ml and should not be exceeded, causing the risk of inducing systemic effects.

In case of a forgotten dose, continue the applications, without doubling the dose.

The treatment period is of approximately one year; the best results are observed at the end of this period. The use of minoxidil 5% should be interrupted if capillary growth is not verified after 4 months of use.
In order to maintain and to improve the benefits achieved, the applications should continue twice daily after the attack phase, which can last about 6 months.

The treatment with Minox 5 can be initiated, according to the criteria and clinical assessment of alopecia.
Interruption of treatment may induce the return to the initial alopecia state after 3 to 4 months.

Experience has shown that the sooner the treatment starts, the better the results are due to the fact that there are more hair follicles capable of responding to the effect of the medicine. On the other hand, hair condition, alopecia duration and the treating area appears to also have a relevant role in the achievement of cosmetic acceptable results.

Paediatric population
Minox 5 should not be used in children.

4.3 Contraindications

Minox 5 is contraindicated in:

- Individuals with hypersensitivity to the active substance (minoxidil) or to any of the excipients listed in section 6.1.

- Patients with arterial hypertension or cardiovascular disease, namely coronary insufficiency (possible systemic effects may happen if significant absorption occurs).

- Individuals with scalp psoriasis, seborrheic dermatitis, sun burn, irritation or abrasion of the scalp.

- Pregnancy and breast-feeding (see section 4.6 and section 5.3).

Paediatric population
Minox 5 should not be used in children and individuals aged under 18 years.

4.4 Special warnings and precautions for use

Whenever a reaction is observed on the application site, for example irritation or itching, folliculitis or peeling, a dermatologist must be consulted.
In case of a serious reaction, the scalp must be immediately washed and the product must not be applied until consulting the doctor.

If Minox 5 accidently contacts with sensitive areas (eyes), these must be immediately washed with abundant and running cold water. If irritation persists, the doctor should be consulted.

Because the treatment with minoxidil may cause liquid retention, precaution is advised in patients with history of heart failure, ventricular dysfunction or hypertension and in patients with pre-existing edema due to another etiology.

If palpitation, chest pain, dizziness or cephalgia occurs, the use of cutaneous solution of minoxidil must be interrupted until contact with the doctor.

Adequate clinical surveillance must be kept in elderly patients and in patients with renal, liver or cardiac dysfunction who are using minoxidil.
Ischemic symptoms may be aggravated with the use of minoxidil in individuals with arterial coronary disease.

In clinical studies, during treatment with topical minoxidil vs placebo (6 months), systemic cardiovascular effects were evaluated and blood pressure did not suffer any variations. However, there was an increase in heart rate and in cardiac output.

Some long term clinical studies reported a development of diffuse hypertrichosis in some women. This should be evaluated to confirm its persistence. The treatment should be interrupted if persistent abnormal results are detected.

The risks of systemic symptoms are increased with the frequency of the doses. So, the application of doses beyond the recommended may cause systemic symptoms.

The use of topical minoxidil is not recommended in women who plan to get pregnant, because there is the risk of hypertrichosis development in the newborn.

Propylene glycol may cause skin irritation.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions:

Concomitant use of minoxidil and topical corticosteroids may increase the effect of minoxidil.
Vaseline may increase minoxidil absorption, because of its occlusive property.
Topical retinoids, for example tretinoin and isotretinoin, increase the cutaneous absorption due to the increase of the *stratum corneum* permeability. Minoxidil percutaneous absorption is threefold increased when used along with tretinoin, which may cause a synergic effect. However, the safety and efficacy of combined therapy with minoxidil and retinoids require further study.

Administration of topical minoxidil and anthralin, with irritative properties, causes a synergic effect that may be useful in the treatment of extensive and resistant alopecia areata.
Systemic minoxidil may increase the risk of toxicity of topical minoxidil if used at the same time, so, individuals receiving concomitant treatment must be monitored.

4.6 Pharmacokinetic interactions:

- Effect of minoxidil in other drugs pharmacokinetics:
In studies about drug interactions, topical minoxidil does not seem to have clinically important effects in the pharmacokinetics of other drugs. However, taking into account the possibility of systemic absorption, the potentiation of orthostatic hypotension in patients receiving guanethidine and bethanidine therapy, may occur.

- Effect of other drugs in minoxidil pharmacokinetics:
The pharmacokinetic of topical minoxidil, given its low absorption, does not seem to be affected in a clinically relevant way by other drugs. However, the presence of anthralin may enhance minoxidil systemic absorption, taking into account that anthralin changes the permeability of the skin, due to its irritative properties.

4.7 Fertility, pregnancy and lactation

Pregnancy
In women who plan on getting pregnant, it is recommended to interrupt the treatment with minoxidil at least one month before.
The use of minoxidil has not been studied in pregnant women in adequate and controlled clinical studies. Therefore, minoxidil should not be used during pregnancy.

Breast-feeding
It is not known whether topical minoxidil is excreted in human milk.
Although it is not known whether topical minoxidil excreted in breast milk, it is not recommended its use during breast-feeding (see sections 4.3, 4.4 and 5.3).

4.8 Effects on ability to drive and use machines

Not relevant.
There are no known effects on the ability to drive and use machines.

4.9 Undesirable effects

The following undesirable effects, related to the drug minoxidil, were reported:

Common (≥1/100, <1/10):

The most common adverse reactions observed in clinical studies were minor dermatological reactions.

Skin – scalp:	Itching, dry skin, peeling; Irritation and irritative dermatitis; Burn sensation; Reversible diffuse hypertrichosis (face, eyebrows, ears, arms).

Uncommon (≥1/1.000, <1/100):

Skin – scalp:	Eczema, folliculitis, local erythema; Seborrheic dermatitis exacerbation; Allergic contact dermatitis.
Body:	Edema (salt and liquids retention).
Cardiovascular system:	Palpitation, chest pain (angina), tachycardia; Electrocardiogram (ECG) alteration; Heart rate increase; Cardiac output increase.

(Note: it has not been established a causal relation between the cardiovascular effects and minoxidil topical use.)

Rare (≥1/10.000, <1/1.000):

Skin – scalp:	Allergic contact dermatitis; Baldness, capillary alterations.
Nervous system:	Cephalgia, weakness, dizziness, vertigo, asthenia; Delusions, anxiety.
Reproductive/urinary system	Urinary infections, renal calculus; Sexual dysfunction.
Eyes:	Visual disturbance (visual acuracy decrease); Conjunctivitis.
Ears:	Buzz sensation, external otitis.

(Note: it has not been established a causal relation between the effects in the nervous, reproductive and urinary systems and in the eyes and minoxidil topical use.)

Frequency not known:

Immune system disorders	Allergic reactions including angioedema

Signs and symptoms of systemic absorption
Chest pain (angina), irregular and accelerated heart rate, hypotension, neuritis, edema, vasodilatation.
If collateral systemic effects occur, it is recommended the suspension of the drug.

Overdose

No cases of overdosage were reported.
There are no known cases of overdosage resulting from topical application.
Systemic absorption and the risk of overdosage is increased if the dose and frequency of topical administration is exceeded or if the medicinal products applied to larger surface areas of the body or areas other than the scalp.

If systemic toxicity occurs (edema, tachycardia and hypotension) as a result of accidental or deliberate ingestion, therapeutic measures are recommended which may include intravenous administration of sodium chloride to maintain blood pressure and facilitate urine formation or the administration of a diuretic.
Tachycardia and angina crisis may be controlled with beta-blockers or other sympathetic nervous system inhibitors.
Hypotension should be treated with the intravenous administration of a saline solution. It can be also treated with phenylephrine, angiotensin II, vasopressin or dopamine, but only in case of vital organs perfusion failure.
Sympathomimetic drugs, as noradrenaline or adrenaline, must be avoided due to the risk of excessive cardiac stimulation.

Minoxidil and its metabolites are dialyzed by hemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: 13.8.4 – Dermatologicals. Other dermatological preparations. Androgenic alopecia preparations.

ATC code: D11AX01

Topical minoxidil was the first drug approved by the FDA for hair growth stimulation. Interest arose when it was observed, in clinical studies, that the oral administration of minoxidil for more than one month caused hypertrichosis.

Minoxidil is a potent peripheral vasodilator used topically to induce the dilatation of the scalp microcirculation. A dose-response relation was demonstrated.
On the other hand, it appears to induce proliferation of epithelial cells near the base of the hair follicle. It increases cysteine and glycine incorporation into the follicle. Presumably it stimulates hair growth because it favors and promotes anagen phase in epithelial cells culture, with mitogenic and morphological direct effects in neonatal epithelial cells.

Therapeutic maintenance seems necessary to keep hair growth within cosmetic acceptable parameters. The beginning and degree of capillary growth stimulation may vary between individuals.

Minoxidil was studied in the treatment of androgenic alopecia and alopecia areata.

Minoxidil effects were demonstrated in conventional animal models (rats, mice, white rabbits, *beagle* dogs, monkeys with hereditary alopecia) used to assess the treatment efficacy.

The response to the treatment with topical minoxidil was favorable in men aged under 40 years, men who were bald for less than 10 years and in men with a bald area with less than 10 cm diameter.
Women seem to respond better. After 32 weeks of treatment with minoxidil 2% solution, 63 % of the treated women showed a minimum to moderate hair growth.

In case of women with androgenic alopecia (Ludwig phase I and II), the best treatment option seems to be minoxidil 5% solution, at a first stage.

Interruptions of treatment due to adverse experiences caused by minoxidil were uncommon.

The main evaluations of efficacy were conducted. Minoxidil cutaneous solution proved to be safe and effective in the treatment of progressive androgenic alopecia.

Progressive androgenic alopecia affects about 50% of caucasian men and women aged under 40 years. In case of asian and afro-american men, the prevalence is inferior and the alopecia is less severe.
In alopecia areata, topical minoxidil appears to have some clinical efficacy. However, it is not of universal use; it depends on individual response.

In vitro studies show different minoxidil effects in epithelial and lymphocytic cells which may lead to synergic effects in hair growth in individuals with alopecia areata.
In histopathological studies, minoxidil promoted the return of follicular structure and size, with an increase in the diameter (0.029 mm to 0.043 mm).
In murine epithelial cells culture, minoxidil increased cellular proliferation and changed cellular morphology.

5.2 Pharmacokinetic properties

Minoxidil is a peripheral vasodilator used topically for hair growth stimulation.
Information on topical minoxidil pharmacokinetics is scarce.

<u>Absorption</u>
Percutaneous absorption appears to be minimal following topical application of minoxidil.
Topical use of the medicinal product practically does not imply a systemic absorption of its active substances. In clinical studies, in individuals with alopecia areata and

androgenic alopecia, treated with topical minoxidil 5% solution once to twice a day, blood concentrations did not exceed 5 micrograms/L.
After topical use of minoxidil 2% cutaneous solution, only 0.3% to 4.5% of the total applied dose was absorbed by the scalp.

Distribution
Topical minoxidil distribution is not clear.

Biotransformation
In man, the major metabolic pathway is hepatic reduction, which originatesminoxidil-N-O-sulfate metabolite (85%).

Elimination
Minoxidil elimination occurs almost exclusively through metabolization, followed by renal excretion; 15% in its unchanged form and 85% in its metabolite form. Metabolites did not show measurable activity.
After the application of a radiolabeled minoxidil 5% cutaneous solution, in healthy individuals, for 9 days, only a quantity of <5% was recovered in urine and none in the stool. Overall, 43 to 47% of the administered dose was recovered in urine or collected in the scalp surface by washing.

Patients' special characteristics

Elderly: there are no studies that relate age with certain effects of this medication in the elderly.
Patients who suffer from heart failure: the pharmacokinetics of a minoxidil dose has not been evaluated.
Paediatric patients: minoxidil pharmacokinetics has not been studied in pediatric patients.

5.3 Preclinical safety data

In pre-clinical studies, minoxidil has not shown to be genotoxic, mutagenic (Ames test, DNA damage assay or rat micronucleus assay) or carcinogenic, in rats nor in rabbits.

No teratogenic effects were observed in rats and rabbits after minoxidil oral administration, but there is evidence of fetal absorption in rabbits and not in rats up to 5 times its recommended dose as an antihypertensive agent.

Reproduction toxicity studies showed that minoxidil did not originate teratogenic effects in rats receiving subcutaneous minoxidil doses of 80 mg/kg daily (about 2000 times the maximal exposure achieved with topical minoxidil administration).

Developmental toxicity was observed in rats receiving subcutaneous doses exceeding 80 mg/kg.
Minoxidil produced a dose-dependent reduction in conception rate when administered orally to male and female rats, in doses 1 to 5 times the maximum recommended dose as an antihypertensive agent.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Isopropyl alcohol
Propylene glycol Salicylic acid
Ethanol 96%
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30ºC. Keep the bottle in the outer carton, in order to protect from light.

6.5 Nature and contents of container

Minox 5, cutaneous solution, is supplied in a 100 ml low density polyethylene white bottles , with seal dropper and high density polyethylene cap, containing 60 ml or 100 ml of solution.
After filled, bottles are packaged in properly printed cartons, with the package leaflet and according to the legislation in force.

Package of 1 bottle containing 60 ml of solution and packages of 1, 2 and 3 bottles containing 100 ml of solution.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handlingAdministration technique:
Carefully wash the head every morning and dry it.

Minox 5 – the dose for each application is 1 ml of solution (corresponding to 30 drops and to 50 mg/ml of minoxidil), regardless of the treating area and it should be spread from the centre out to the edge.

Hand wash after each cutaneous solution application to remove any trace of the medicinal product.

Avoid the inhalation of the medicinal product.
Avoid the contact of the medicinal product with the eyes, mucosae and damaged skin areas.

Do not use hairdryer to accelerate the medicinal product drying.
Do not use other product on the treating area.

If Minox 5 is used at night, wait 30 minutes before lying down, to minimize medicine loss on the pillow.

7. MARKETING AUTHORISATION HOLDER

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