SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Minoxi 2

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Minoxidil 2% w/v.

Contains propylene glycol 207 mg/ml and alcohol 488 mg/ml.

For full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Cutaneous Solution (to be applied to the scalp)

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Minoxi 2i s indicated for the treatment of alopecia androgenetica in women aged between 18 and 65.

Onset and degree of hair regrowth may be variable among users. Although trends in the data suggest that those users who are younger, whose hair has been thinning for a shorter period of time or who have a smaller area of thinning on the vertex are more likely to respond to Minoxi 2, individual responses cannot be predicted.

4.2 Posology and method of administration

Women aged 18-65:

Hair and scalp should be thoroughly dry prior to topical application of Minoxi 2. A dose of 1 ml Minoxi 2 cutaneous solution should be applied to the total affected areas of the scalp twice daily. The total dosage should not exceed 2 ml. If fingertips are used to facilitate drug application, hands should be washed afterwards.

It may take twice daily applications for four months or more before evidence of hair growth can be expected.

If hair re-growth occurs, twice daily applications of Minoxi 2 are necessary for continued hair growth. Anecdotal reports indicate that re- grown hair may disappear three to four months after stopping minoxidil application and the balding process will continue.

Users should discontinue treatment if there is no improvement after one year.

Special Populations

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

Paediatric and Elderly Populations

Not recommended. The safety and effectiveness of minoxidil in children and adolescents below the age of 18 years or adults over the age of 65 years has not been established.

Method of administration

For topical use only.

The method of application varies according to the disposable applicator used:

Aim the pump at the centre of the bald area, press once and spread with fingertips over the entire bald area. Repeat for a total of 7 times to apply a dose of 1 ml. Avoid breathing spray mist.

4.3. Contraindications

Minoxi 2 is contra-indicated:
- in users with a history of sensitivity to minoxidil, ethanol, or propylene glycol
- in users with treated or untreated hypertension
- in users with any scalp abnormality (including psoriasis and sunburn)
- in users with a shaved scalp
- if occlusive dressings or other topical medical preparations are being used.

4.4 Special warnings and precautions

Before using Minoxi 2, the user should determine that the scalp is normal and healthy. Topical minoxidil should not be applied to inflamed, infected, irritated or painful scalp skin (see section 4.3).

Topical minoxidil is only indicated for the treatment of alopecia androgenetica and should not be used in other types of hair loss for example when there is no family history of hair loss, hair loss is sudden and/or patchy, hair loss is due to childbirth or the reason for hair loss is unknown.

The patient should stop using Minoxi 2 and see a doctor if hypotension is detected or if the patient is experiencing chest pain, rapid heart beat, faintness or dizziness, sudden unexplained weight gain, swollen hands or feet or persistent redness or irritation of the scalp or other unexpected new symptoms occur (see section 4.8).

Patients with known cardiovascular disease or cardiac arrhythmia should contact a physician before using Minoxi 2.

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

Minoxi 2 is for external use only. Do not apply to areas of the body other than the scalp.

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

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

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

Some consumers reported increased hair shedding upon initiation of therapy with minoxidil. This is most likely due to minoxidil's action of shifting hairs from the resting telogen phase to the growing anagen phase (old hairs fall out as new hairs grow in their place).
This temporary increase in hair shedding generally occurs two to six weeks after beginning treatment and subsides within a couple of weeks. If shedding persists (>2 weeks), users should stop Minoxi 2 and consult their doctor.
Users should be aware that, whilst extensive use of minoxidil has not revealed

evidence that sufficient minoxidil is absorbed to have systemic effects, greater absorption because of misuse, individual variability, unusual sensitivity or decreased integrity of the epidermal barrier caused by inflammation or disease processes in the skin (e.g. excoriations of the scalp, or scalp psoriasis) could lead, at least theoretically, to systemic effects.

Accidental ingestion may cause serious cardiac adverse events. Therefore, this product has to be kept out of the reach of children.

This medicine contains 488 mg of alcohol (ethanol) in each 1 ml. It may cause burning sensation on damaged skin. Ethanol may cause burning and irritation of the eye. In the event of accidental contact with sensitive surfaces (eye, abraded skin and mucous membranes) the area should be bathed with large amounts of cool tap water.

This medicine contains 207 mg of propylene glycol in each 1 ml and may cause skin irritation. Because this medicine contains propylene glycol, do not use it on open wounds or large areas of broken or damaged skin (such as burns) without checking with your doctor or pharmacist.

Patients should be advised to consult their doctor or pharmacist if they are concerned at any time during treatment with Minoxi 2.

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

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

4.6 Fertility, pregnancy and lactation

This product should not be used during pregnancy or lactation.

Pregnancy

There are no adequate and well controlled studies in pregnant women. Studies in animals have shown a risk to the foetus at exposure levels that are very high compared to those intended for human exposure. There is potentially a risk of foetal harm in humans (see section 5.3).

Lactation

Systemically absorbed minoxidil is secreted in human milk. The effect of minoxidil on newborns/infants is unknown.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The safety of topical minoxidil from clinical trial data is based on data from 7 placebo-controlled randomised clinical trials in adults evaluating either 2% or 5% minoxidil solution, and two placebo-controlled randomised clinical trials in adults evaluating a 5% foam formulation.
Adverse drug reactions (ADRs) identified during clinical trials and post-marketing experience with minoxidil are included in the table below by System Organ Class (SOC).

The frequencies are provided according to the following convention:
Very common ≥1/10
Common ≥1/100 and < 1/10
Uncommon ≥1/1,000 and <1/100
Rare ≥1/10,000 and <1/1,000
Very rare <1/10,000, including isolated reports
Not known (cannot be estimated from the available data)

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

Body System (SOC)	**Frequency**	**Adverse Drug Reaction (Preferred Term)**
Immune System Disorders	Common	Hypersensitivity reactions (including face oedema, generalised erythema, pruritus generalised, swelling face, and throat tightness)
	Not known	Angioedema (including lip oedema, lip swelling, oedema mouth, oropharyngeal swelling, pharyngeal oedema, swollen tongue and tongue oedema)

Psychiatric Disorders	Not known	Depressed mood
Nervous System Disorders	Very common	Headache
	Uncommon	Dizziness
Eye disorders	Not known	Eye irritation
Cardiac disorders	Common	Chest pain
	Uncommon	Palpitations
	Not known	Heart rate increased
Vascular disorders	Not known	Hypotension
Respiratory, thoracic and mediastinal disorders	Uncommon	Dyspnoea
Gastrointestinal Disorders	Uncommon	Nausea
	Not known	Vomiting
Skin and subcutaneous tissue disorders	Common	Hypertrichosis (unwanted non-scalp hair including facial hair growth in women) Pruritus (including rash pruritic generalised and eye pruritus) Rash (including pustular, papular, generalised, vestibular and macular rash) Dermatitis (including contact, allergic, atopic and seborrhoeic dermatitis)
	Rare	Changes in hair texture
	Not known	Dry skin Skin exfoliation (including exfoliative rash and dermatitis exfoliative) Acne (acneiform rash) Temporary hair loss (see section 4.4) Changes in hair colour

General disorders and administration site conditions	Common	Oedema peripheral
	Not known	Application site reactions (These sometimes involve nearby structures like the ears and face and typically consist of pruritus, irritation, pain, rash, oedema, dry skin, erythema and rash erythematous but can sometimes be more severe and include exfoliation, dermatitis, blistering, bleeding and ulceration)
Investigations	Common	Weight increased

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il
Side effects can also be reported to the following email: safety@trima.co.il

4.9 Overdose

Increased systemic absorption of minoxidil may potentially occur if higher-than-recommended doses of Minoxi 2 are applied to larger surface areas of the body or areas other than the scalp.

Because of the concentration of minoxidil in Minoxi 2, accidental ingestion has the potential of producing systemic effects related to the pharmacological action of the drug (5 ml of Minoxi 2 contains 100 mg minoxidil; the maximum recommended adult dose for oral minoxidil administration in the treatment of hypertension). Signs and symptoms of minoxidil overdosage would primarily be cardiovascular effects associated with sodium and water retention.
Tachycardia, hypotension, dizziness and lethargy can also occur.

Treatment
Treatment of minoxidil overdosage should be symptomatic and supportive.
Fluid retention can be managed with appropriate diuretic therapy.
Clinically significant tachycardia can be controlled by administration of a beta- adrenergic blocking agent.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other dermatologicals, ATC code: D11AX

Individual responses to minoxidil 2% are variable and unpredictable.

The effect of minoxidil 2% has been assessed in phase III clinical trials in women conducted over a 48 week treatment period.

In these studies minoxidil 2% was compared to the product vehicle without the minoxidil active ingredient. The primary efficacy criterion was non-vellus hair count in a 1.0 cm^2 reference area of affected scalp. The mean changes observed in this parameter in these studies were significantly in favour of minoxidil 2% and were as follows:

Mean change in non-vellus hair count in reference 1 cm^2 area of scalp compared with baseline			
	minoxidil 2%	**Vehicle**	**Pairwise comparison**
Baseline	150.4	138.4	
	Mean change from baseline	Mean change from baseline	
16 weeks	+35.9	+20.0	2%>vehicle
32 weeks	+26.7	+15.2	2%>vehicle
48 weeks	+20.7	+9.4	2%>vehicle

Using non-vellus hair count as an efficacy criteria, minoxidil 2% has also been shown to stabilise hair loss (defined as re- growth or no loss) in 88% of patients compared with 69% of patients who received vehicle in one trial following 48 weeks treatment and in 87% of patients compared with 73% of patients who received vehicle in a further trial following 32 weeks treatment.

Female patients' own evaluations in clinical studies have shown that hair growth was reported by approximately 60% of females after 8 months of minoxidil 2% usage.

Patient evaluation of visible hair growth		
	% of Females reporting regrowth after 8 months minoxidil 2% usage	**% of Females reporting regrowth after 4 months Product vehicle usage**
Minimal re-growth	30-40	29-33
Moderate to dense re-growth	20-25	7-12
Total	55-59	40-41

In addition, minoxidil 2% has been shown to stabilise hair loss (shown as re-growth or no loss) in 4 out of 5 females as calculated from two clinical studies that showed stabilisation with 88 and 87% respectively while corresponding figures for vehicle were 69 and 74%.

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:

- increase the diameter of the hair shaft
- stimulate anagen growth
- prolong the anagen phase
- stimulate anagen recovery from the telogen phase

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

5.2 Pharmacokinetic properties

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

In a study in males, the minoxidil serum concentration time curve (AUC) for the 2% solution averaged 7.54 ng·h/ml compared to a mean AUC of 35.1 ng·h/ml for the 2.5 mg oral formulation. The mean peak plasma concentration (C_{max}) for the topical solution was 1.25 ng/ml, compared to18.5 ng/ml following the 2.5 mg oral dose.

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

Approximately 60% minoxidil absorbed after topical application is metabolised to minoxidil glucuronide, primarily in the liver. Minoxidil and its metabolites are excreted almost entirely in the urine, with a very minor degree of elimination via the faeces. Following cessation of dosing, approximately 95% of topically applied minoxidil will be eliminated within four days.

5.3 Preclinical safety data

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

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

Teratogenicity

Animal reproduction toxicity studies in rats and rabbits have shown signs of maternal toxicity and a risk to the foetus at exposure levels that are very high compared to those intended for human exposure (from 19 to 570-fold human exposure). A low, albeit remote, risk of foetal harm is possible in humans.

Fertility

Preclinical fertility studies in rats have shown minoxidil doses equal to or greater than 3 mg/kg/day (at least 21-fold human exposure) when administered orally and greater than 9 mg/kg/day (at least 64-fold human exposure) when administered subcutaneously were associated with reduced conception and implantation rates as well as a reduction in the number of live pups.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

Alcohol, purified water, propylene glycol, dexpanthenol.

6.2 Incompatibilities

Not applicable.

6.3. Shelf-Life

The expiry date of the product is indicated on the packaging materials.

6.4. Special Precautions for Storage

Minoxi 2 is flammable. Store in a cool place, below 25°C.

6.5 Nature and contents of container

HDPE bottle with a spray pump containing 80 ml of solution.
Packs contain either one or two bottles.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7 MANUFACTURER AND LICENSE HOLDER

Trima, Israel Pharmaceutical Products Maabarot Ltd., Maabarot 4023000, Israel.

8. MARKETING AUTHORISATION NUMBER(S)

049.97.26155.00

Revised in July 2022 according to MOHs guidelines.