National UK Risk Management Plan for Minoxidil 2.5mg, 5mg and 10mg Tablets (minoxidil)

RMP version to be assessed as part of this application:

RMP Version number: 0.4

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Summary of significant changes in this RMP: N/A

Other RMP versions under evaluation: N/A

Details of the currently approved RMP: N/A

QPPV name:

QPPV signature:

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Part I: Product(s) Overview

Table Part I.1 – Product Overview

Active substance(s) **(INN or common name)**	Minoxidil
Pharmacotherapeutic group(s) (ATC Code)	Pharmacotherapeutic group: Pyrimidine derivatives ATC Code: C02 DC01
Marketing Authorisation Applicant	
Medicinal products to which this RMP refers	3
Invented name(s) in the European Economic Area (EEA)	Minoxidil 2.5mg, 5mg and 10mg Tablets
Marketing authorisation procedure	National
Brief description of the product	Chemical class Piperidinopyrimidine
	Summary of mode of action Minoxidil lowers the elevated systolic and diastolic blood pressure by decreasing peripheral vascular resistance via vasodilation. The smooth musculature of the resistance vessels must be regarded as the site of action for the relaxant effect of minoxidil. The active metabolite of minoxidil activates the ATP-modulated potassium (K^+_{ATP}) channel causing K^+ efflux, hyperpolarization, and smooth muscle relaxation.
	Important information about its composition N/A
Hyperlink to the Product Information	Please refer to Module 1.3.1 SmPC, Labelling and Package Leaflet, common combined in Sequence 0002.
Indication(s) in the EEA	Current (if applicable): Minoxidil is indicated for the treatment of severe hypertension. It should not be used as the sole agent to initiate therapy. It is a peripheral vasodilator and should be given in conjunction with a diuretic, to control salt and water retention, and a beta-adrenergic blocking agent, or appropriate substitute, to control reflex tachycardia.

	Proposed (if applicable): N/A
Dosage in the EEA	Current (if applicable): <u>Patients over 12 years and adults</u> The recommended starting dose is 5 mg per day. If required, this dosage can later be increased up to 20 mg, and then to 40 mg daily (given as a single dose or in two divided doses). Dose increases should be made at increments of 5 mg to 10 mg minoxidil per day at intervals of three or more days. If a dose of 50 mg of minoxidil has been reached, the dose may be increased by 25 mg minoxidil per day to a maximum dose of 100 mg per day. If the desired decrease of diastolic blood pressure exceeds 30 mmHg, dosage should be divided to two daily doses to keep daily blood pressure fluctuations as low as possible. <u>Patients younger than 12 years of age</u> The use of minoxidil in children is restricted to children with severe hypertension associated with target organ damage where other treatment has failed. The data regarding the use of minoxidil in children is very limited, especially in infants. The dosage recommendations can only be considered as a rough guide to treatment at present as this is based on the publication of a few case reports and studies involving a small number of children. The starting dose used based on these reports is 0.2 mg/kg of minoxidil as a single or divided dose. Careful titration increasing in steps of 0.1 to 0.2 mg/kg/day at intervals of at least 3 days is essential. The effective dose range is 0.25 to 1.0 mg/kg/day. The maximum dose is 50 mg/day. Treatment of children with minoxidil should only be initiated under the close supervision of a specialist in hospital. <u>Elderly patients</u> At present there are no extensive clinical studies with minoxidil in patients over age 65. There is data indicating that elevated systolic and diastolic pressures are important risk factors for cardiovascular disease in individuals over age 65. However, elderly patients may be sensitive to the blood pressure lowering effect of minoxidil and thus caution is urged in initiating therapy as orthostatic hypotension may occur. It is suggested that 2.5 mg per day be used as the initial starting dose in patients over 65 years of age.
	Proposed (if applicable): N/A
	Current (if applicable): 2.5mg, 5mg and 10mg Tablets

Pharmaceutical form(s) and strengths	Proposed (if applicable):
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety specification

The market authorisation applications for Minoxidil 2.5mg, 5mg and 10mg Tablets are being submitted as an abridged application made under HMR, generic application – Regulation 51 (previously Article 10.1 of Directive 2001/83/EC).

In accordance with Section V.C.1.1 of the Guideline on Good Pharmacovigilance Practices (GVP) Module V – Risk management systems (EMA/838713/2011 Revision 2), Modules SI to SVI of this RMP have been omitted.

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

N/A – not required for generic medicinal products

Part II: Module SII - Non-clinical part of the safety specification

N/A – not required for generic medicinal products

Part II: Module SIII - Clinical trial exposure

N/A – not required for generic medicinal products

Part II: Module SIV - Populations not studied in clinical trials

N/A – not required for generic medicinal products

Part II: Module SV - Post-authorisation experience

N/A – not required for generic medicinal products

Part II: Module SVI - Additional EU requirements for the safety specification

N/A – not required for generic medicinal products

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

- **Hypertrichosis** – This occurs in most patients treated with minoxidil (listed in the SmPC at a very common frequency (≥1/10)) and all patients should be warned of this possibility before starting therapy. However, hypertrichosis was hardly or not at all tolerable in less than 10% of patients. Spontaneous reversal to the pre-treatment state can be expected one to six months after cessation of therapy.
- **ECG alterations** - Listed in the SmPC at a very common frequency (≥1/10). Soon after starting minoxidil therapy approximately 60% of patients exhibit ECG alterations in the direction and magnitude of their T waves. Large changes may encroach on the ST segment, unaccompanied by evidence of ischaemia. These asymptomatic changes usually disappear with continuing minoxidil treatment. The ECG reverts to the pre-treatment state when minoxidil is discontinued.
- **Infertility** - There are no fertility data from the use of minoxidil in humans. In a fertility study with male and female rats, a dose-dependent reduction of the conception rate was found. The dose corresponded to one to five times the maximum dose used in humans to treat hypertension. However, this is not considered important for inclusion in the list of safety concerns as minoxidil is usually a last-line treatment for severe hypertension, when other treatment options are limited.
- **Thrombocytopenia and leucopoenia** – These events have been rarely reported. Listed in the SmPC as rare (≥1/10,000 to <1/1,000). Based on the low frequency, this risk is considered to be acceptable in relation to the severity of the indication treated, as minoxidil is usually a last-line treatment for severe hypertension.
- **Stevens-Johnson syndrome, dermatitis bullous, rash** - These events have been rarely reported. Listed in the SmPC as rare (≥1/10,000 to <1/1,000). Based on the low frequency, this risk is considered to be acceptable in relation to the severity of the indication treated, as minoxidil is usually a last-line treatment for severe hypertension.
- **Use in elderly patients** - At present there are no extensive clinical studies with minoxidil in patients over age 65. There is data indicating that elevated systolic and diastolic pressures are important risk factors for cardiovascular disease in individuals over age 65. However, elderly patients may be sensitive to the blood pressure lowering effect of minoxidil and thus caution is urged in initiating therapy as orthostatic hypotension may occur. It is suggested that 2.5 mg per day be used as the initial starting dose in patients over 65 years of age. This is standard clinical practice in the UK, as per the British National Formulary (BNF).
- **Use in renal failure or dialysis patients** - Dosage requirements may be lower in dialysis patients. Minoxidil is removed from the blood by dialysis, but its pharmacological action, once established is not reversed. Therefore, haemodialysis patients should take minoxidil either after or at least two hours before dialysis. The product should be used with particular attention to maintenance of salt and water balance in patients with renal impairment, but who are not on dialysis.
- **Use in patients with a phaeochromocytoma** - Minoxidil is contra-indicated in patients with a phaeochromocytoma because it may stimulate secretion of catecholamines from the tumour through its antihypertensive action. No additional risk minimisation measures are considered necessary.

- **Use in patients with myocardial infarction** - Patients who have had myocardial infarction should only be treated with minoxidil after a stable post-infarction state has been established. No additional risk minimisation measures are considered necessary.
- **Pleural effusion, gastrointestinal disorder, breast tenderness, blood creatinine increased and blood urea increased** - The frequency of these events has not been established from the available data. However, the risk is considered to be acceptable in relation to the severity of the indication treated, as minoxidil is usually a last-line treatment for severe hypertension.
- **Hypotension due to interaction with peripheral vasodilators** - This interaction is listed in the SmPC which states that 'If possible guanethidine should be discontinued well before minoxidil is begun. If this is not feasible minoxidil therapy should be instituted in the hospital and the patient monitored carefully for orthostatic events.' However, given the patient population that may be expected to receive concurrent guanethidine and minoxidil, it is considered that these patients would likely be very closely monitored/in hospital already and therefore it is not necessary to include this risk within the RMP.

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

- Hypertrichosis
- ECG alterations
- Infertility

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

- Thrombocytopenia and leucopoenia
- Stevens-Johnson syndrome, dermatitis bullous, rash
- Hypotension due to interaction with peripheral vasodilators

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised):

- Use in elderly patients
- Use in renal failure or dialysis patients
- Use in patients with a phaeochromocytoma
- Use in patients with myocardial infarction

Known risks that do not impact the risk-benefit profile:

- Pleural effusion
- Gastrointestinal disorder
- Breast tenderness

- Blood creatinine increased, blood urea increased

Other reasons for considering the risks not important:

- None

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risk 1: Sodium and water retention

Risk-benefit impact: Fluid retention and oedema are listed in the SmPC at a frequency of common (≥1/100 to <1/10). If used alone, minoxidil can cause a significant retention of salt and water leading to physical signs such as oedema, and to clinical deterioration of some patients with heart failure. Diuretic treatment alone, or in combination with restricted salt intake is, therefore, necessary for all patients taking minoxidil. Haemodilution may occur leading to temporary decrease in haematocrit, haemoglobin, and erythrocyte count (by approximately 7% initially which then recovers to pre-treatment levels). The patient's bodyweight, fluid and electrolyte balance should be monitored for evidence of fluid retention. Salt and water retention in excess of 1 to 1.5 kg may diminish the effectiveness of minoxidil. Patients should, therefore, be carefully instructed about compliance with diuretic therapy and a detailed record of body weight should be maintained. The product should be used with particular attention to maintenance of salt and water balance in patients with renal impairment, but who are not on dialysis. These specific clinical measures are considered sufficient to reduce the risk of salt and water retention. No additional risk minimisation measures are considered necessary. This is standard clinical practice in the UK, as per the BNF.

Important Identified Risk 2: Cardiovascular disorders (including palpitations, heart rate increased and chest pain)

Risk-benefit impact: Tachycardia is listed in the SmPC at a very common frequency (≥1/10), the frequency of angina has not been established from the available data. Because minoxidil is a vasodilator, reflex tachycardia may occur and possibly angina pectoris may occur in patients at risk; it is recommended that minoxidil be used in combination with beta-adrenergic blocking agent or other sympathetic-nervous system suppressants to blunt or prevent such a response. These specific clinical measures are considered sufficient to reduce the risk of cardiovascular disorders (including palpitations, heart rate increased and chest pain). No additional risk minimisation measures are considered necessary. This is standard clinical practice in the UK, as per the BNF.

Important Identified Risk 3: Pericarditis, Pericardial Effusion and Tamponade

Risk-benefit impact: There have been multiple reports of pericarditis occurring in association with minoxidil.

Pericardial effusion and occasionally tamponade, has been observed in about 3% - 5% of treated patients not on dialysis. While in many cases, the pericardial effusion is associated with other potential aetiologies, there have been cases in which these potential causes of effusion were not present. Patients should be observed closely for any suggestion of a pericardial effusion. Pericardiocentesis, or surgery may be required. If the effusion persists, withdrawal of minoxidil should be considered in light of other means of controlling the hypertension and the patient's clinical status.

Post authorisation experience (of the reference medicinal product) has shown that, in a particular study, out of 50 patients on oral minoxidil, one case involved a two year old female with a history of chronic renal failure and peritoneal dialysis who developed pericardial effusion from which she recovered after treatment.

In addition, the estimated total exposure (based on only nine months of data) was about 17,000 patient-years with however no appreciable use in children.

Important Potential Risks:

None

Missing information 1: Safety and efficacy during pregnancy and lactation

Risk-benefit impact: There is limited data from the use of minoxidil in pregnant women. Studies in animals have shown reproductive toxicity. Neonatal hirsutism has been reported following exposure of minoxidil during pregnancy.

Minoxidil has been reported to be excreted in human milk. A risk to the suckling child cannot be excluded.

Missing information 2: Safety and efficacy in off-label use in treatment of alopecia

Risk-benefit impact: In light of the licensed use of topical formulations of minoxidil for the treatment of alopecia, and the off-label use of the tablet formulation (divided) in some dermatology departments, 'safety and efficacy in off-label use in treatment of alopecia' has been included as missing information.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

N/A – this is an initial RMP submission

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Important Identified Risks

Important Identified Risk 1: Sodium and water retention

Potential mechanisms:

The mechanism of the sodium and water retention with minoxidil is a varying combination of renal hemodynamic and/or neurohumoral changes as well as direct tubular effects.[2] The latter may relate to minoxidil's action as a potassium channel opener. Activation of the potassium channel in the thick ascending limb increases Na+/2Cl-/K+ co-transporter activity and thereby increases sodium and chloride reabsorption. This occurs without major changes in potassium or calcium excretion.[3]

Evidence source(s) and strength of evidence:

If used alone, minoxidil can cause a significant retention of salt and water leading to physical signs such as oedema, and to clinical deterioration of some patients with heart failure.

Characterisation of the risk:

Fluid retention and oedema are listed in the SmPC at a frequency of common (≥1/100 to <1/10). Haemodilution may occur leading to temporary decrease in haematocrit, haemoglobin, and erythrocyte count (by approximately 7% initially which then recovers to pre-treatment levels).

Risk factors and risk groups:

Patients with renal impairment, but who are not on dialysis.

Preventability:

Diuretic treatment alone, or in combination with restricted salt intake is necessary for all patients taking minoxidil. The patient's bodyweight, fluid and electrolyte balance should be monitored for evidence of fluid retention. Salt and water retention in excess of 1 to 1.5 kg may diminish the effectiveness of minoxidil. Patients should, therefore, be carefully instructed about compliance with diuretic therapy and a detailed record of body weight should be maintained. The product should be used with particular attention to maintenance of salt and water balance in patients with renal impairment, but who are not on dialysis.

Impact on the risk-benefit balance of the product:

Routine risk minimisation measures are currently considered sufficient.

Minoxidil is usually a last-line agent for treating severe hypertension.

Public health impact:

Fluid retention and oedema are listed in the SmPC at a frequency of common (≥1/100 to <1/10).

Important Identified Risk 2: Cardiovascular disorders (including palpitations, heart rate increased and chest pain)

Potential mechanisms:

The cardiac consequences of the baroreceptor-mediated activation of the sympathetic nervous system during minoxidil therapy are an increase in heart rate, myocardial contractility, and myocardial oxygen consumption.[4]

Evidence source(s) and strength of evidence:

Because minoxidil is a vasodilator, reflex tachycardia may occur and possibly angina pectoris may occur in patients at risk.

Characterisation of the risk:

Tachycardia is listed in the SmPC at a very common frequency (≥1/10), the frequency of angina has not been established from the available data.

Risk factors and risk groups:

Elderly patients and patients with renal failure.

Preventability:

Minoxidil should be given in conjunction with a beta-adrenergic blocking agent, or appropriate substitute, to control reflex tachycardia which may lead to angina pectoris.

Impact on the risk-benefit balance of the product:

Routine risk minimisation measures are currently considered sufficient.

Minoxidil is usually a last-line agent for treating severe hypertension.

If minoxidil is used in conjunction with a beta-adrenergic blocking agent, or appropriate substitute, to control reflex tachycardia which may lead to angina pectoris, the risk is minimised.

Public health impact:

Tachycardia is listed in the SmPC at a very common frequency (≥1/10), the frequency of angina has not been established from the available data.

Important Identified Risk 3: Pericarditis, Pericardial Effusion and Tamponade

Potential mechanisms:

The exact mechanism[1] of pericardial effusion in patients taking minoxidil is not clearly understood. It has been attributed to uraemia, pericarditis as well as salt/water retention secondary to peripheral arterial dilatation.

Evidence source(s) and strength of evidence:

Although there is no evidence of a causal relationship, there have been multiple reports of pericarditis (inflammation of the tissues that surround the heart) occurring in association with minoxidil.

Pericardial effusion (the build-up of extra fluid in the space around the heart) and occasionally tamponade (where the build-up in fluid places extreme pressure on the heart and stops it from function properly), has been observed in about 3% - 5% of treated patients not on dialysis. Pericardiocentesis (a procedure to remove fluid that has built up in the sac around the heart (pericardium)), or surgery may be required.

Characterisation of the risk:

The above adverse events have been reported in several clinical studies.

Pericarditis is listed in the RSI at a very common (≥1/10) frequency, whilst pericardial effusion and cardiac tamponade are listed at a common (≥1/100 to <1/10) frequency.

Post authorisation experience has shown that, in a particular study, out of 50 patients on oral minoxidil, one case involved a two year old female with a history of chronic renal failure and peritoneal dialysis who developed pericardial effusion from which she recovered after treatment.

In addition, the estimated total exposure (based on only nine months of data) was about 17,000 patient-years with however no appreciable use in children.

Risk factors and risk groups:

Patients with kidney problems.

Preventability:

Patients should be observed closely for any suggestion of a pericardial effusion and pericardiocentesis, or surgery may be required. If the effusion persists, withdrawal of minoxidil should be considered in light of other means of controlling the hypertension and the patient's clinical status.

Treatment of children with minoxidil should only be initiated under the close supervision of a specialist in hospital.

Impact on the risk-benefit balance of the product:

Routine risk minimisation measures are currently considered sufficient.

Minoxidil is usually a last-line agent for treating severe hypertension.

Further pharmacovigilance data is required to establish a causal relationship with minoxidil and understand the impact on the risk-benefit balance.

Public health impact:

Pericardial effusion and occasionally tamponade, has been observed in about 3% - 5% of treated patients not on dialysis.

Important Potential Risk:

None

SVII.3.2. Presentation of the missing information

Missing information 1: Safety and efficacy during pregnancy and lactation

Evidence source:

There is limited data from the use of minoxidil in pregnant women. Studies in animals have shown reproductive toxicity. Minoxidil has been reported to be excreted in human milk. A risk to the suckling child cannot be excluded.

Population in need of further characterisation:

Pregnant or breastfeeding women exposed to minoxidil.

Missing information 2: Safety and efficacy in off-label use in treatment of alopecia

Evidence source:

Topical formulations of minoxidil are licensed for the treatment of alopecia. The off-label use of the tablet formulation (divided) may occur in some dermatology departments.

Population in need of further characterisation:

Patients treated with minoxidil off-label for the indication of alopecia.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Sodium and water retention • Cardiovascular disorders (including palpitations, heart rate increased and chest pain) • Pericarditis, Pericardial Effusion and Tamponade
Important potential risks	• None
Missing information	• Safety and efficacy during pregnancy and lactation • Safety and efficacy in off-label use in treatment of alopecia

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for safety and efficacy during pregnancy and lactation and safety and efficacy in off-label use in treatment of alopecia:

are using specific adverse reaction follow up questionnaires for minoxidil to capture more information on the safety/efficacy in the populations considered to be missing information.

Targeted follow up will also be completed if any adverse event reports are received that warrant specific questioning to the reporter to clarify details within the report.

Other forms of routine pharmacovigilance activities for minoxidil:

will provide a cumulative update on use in pregnancy/lactation and off label use in treatment of alopecia to the Licensing Authority every time a further 10 case reports have been received.

III.2 Additional pharmacovigilance activities

Additional pharmacovigilance requirements are not considered necessary and routine pharmacovigilance activities are considered sufficient to monitor the benefit-risk profile of the product and detect any safety concerns.

III.3 Summary Table of additional Pharmacovigilance activities

N/

Part IV: Plans for post-authorisation efficacy studies

No PAES studies have been conducted and none are considered required.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

The safety information in the proposed product information is aligned to the reference medicinal product.

V.1. Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Sodium and water retention	Routine risk communication: SmPC section 4.1, 4.2, 4.4 and 4.8. PL section 2. Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC sections 4.1, 4.2 and 4.4 state that minoxidil is a peripheral vasodilator and should be given in conjunction with a diuretic, to control salt and water retention. There is also a recommendation in Section 4.2 that if excessive water retention results in a weight gain of more than 3 pounds when a thiazide or chlortalidone is being used, diuretic therapy should be changed to furosemide, the dose of which may be increased in accordance with the patient's requirements. Recommendation for patients to be carefully instructed about compliance with diuretic therapy and a detailed record of body weight to be maintained is included in Section 4.4. Information for patients in PL section 2 that to avoid the problems of salt and water retention, the doctor will prescribe two other medicines to take with Minoxidil tablets. One will be a water tablet (diuretic). If a low salt diet is recommended, it should be followed carefully. Patients should weigh themselves daily and keep an accurate record of their weight while taking this medicine. A patient should inform their doctor if they think they have gained weight – even though it may not be due to the medicine. The doctor will want to monitor fluid and salt (electrolyte) levels. Other routine risk minimisation measures beyond the Product Information: Legal status: This is a prescription only medicine

Cardiovascular disorders (including palpitations, heart rate increased and chest pain)	Routine risk communication: SmPC section 4.1, 4.4 and 4.8. PL section 2. Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC sections 4.1 and 4.4 state that it is recommended that minoxidil be used in combination with beta-adrenergic blocking agent or other sympathetic-nervous system suppressants to blunt or prevent reflex tachycardia. Information for patients in PL section 2 that to avoid the problems of increased heart rate, the doctor will prescribe two other medicines to take with Minoxidil tablets. One will be a beta-blocker or similar medicine to stop the heart beating too fast or angina pain in the chest. Other routine risk minimisation measures beyond the Product Information: Legal status: This is a prescription only medicine
Pericarditis, Pericardial Effusion and Tamponade	Routine risk communication: SmPC section 4.4 and 4.8. PL section 2. Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC section 4.4 states that patients should be observed closely for any suggestion of a pericardial effusion and pericardiocentesis, or surgery may be required. If the effusion persists, withdrawal of minoxidil should be considered in light of other means of controlling the hypertension and the patient's clinical status. Recommendation for doctors to monitor carefully and drain the fluid or consider stopping treatment with Minoxidil tablets in PL section 2. Other routine risk minimisation measures beyond the Product Information: Legal status: This is a prescription only medicine
Safety and efficacy during pregnancy and lactation	Routine risk communication: SmPC section 4.6. PL section 2. Routine risk minimisation activities recommending specific clinical measures to address the risk:

	SmPC section 4.6 states that minoxidil is not recommended during pregnancy and in women of childbearing potential not using contraception. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from minoxidil therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. Recommendation for patients to ask their doctor or pharmacist for advice before taking this medicine if they are pregnant or breast-feeding, think they may be pregnant or are planning to have baby, in PL section 2. Other routine risk minimisation measures beyond the Product Information: Legal status: This is a prescription only medicine
Safety and efficacy in off-label use in treatment of alopecia	Routine risk communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: Legal status: This is a prescription only medicine

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Sodium and water retention	Routine risk minimisation measures: SmPC section 4.1, 4.2, 4.4 and 4.8. SmPC sections 4.1, 4.2 and 4.4 state that minoxidil is a peripheral vasodilator and should be given in conjunction with a diuretic, to control salt and water retention. PL section 2. Legal status of the medicinal product.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures: No risk minimisation measures	
Cardiovascular disorders (including palpitations, heart rate increased and chest pain)	Routine risk minimisation measures: SmPC section 4.1, 4.4 and 4.8. SmPC sections 4.1 and 4.4 state that it is recommended that minoxidil be used in combination with beta-adrenergic blocking agent or other sympathetic-nervous system suppressants to blunt or prevent reflex tachycardia. PL section 2. Legal status of the medicinal product. Additional risk minimisation measures: No risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Pericarditis, Pericardial Effusion and Tamponade	Routine risk minimisation measures: SmPC section 4.4 and 4.8. SmPC section 4.4 where advice is given on monitoring the patient and that surgery or withdrawal of minoxidil may be required. PL section 2. Legal status of the medicinal product. Additional risk minimisation measures: No risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Safety and efficacy during pregnancy and lactation	Routine risk minimisation measures: SmPC section 4.6 where it is recommended minoxidil is not used during pregnancy or in women of childbearing potential not using contraception, and a decision should be made about breast-feeding, on an individual basis. PL section 3. Legal status of the medicinal product.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up forms A cumulative update will be provided to the Licensing Authority every time a further 10 case reports concerning use in pregnancy/lactation have been received. Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures: No risk minimisation measures	
Safety and efficacy in off-label use in treatment of alopecia	Routine risk minimisation measures: None Legal status of the medicinal product. Additional risk minimisation measures: No risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up forms A cumulative update will be provided to the Licensing Authority every time a further 10 case reports concerning off label use in treatment of alopecia have been received. Additional pharmacovigilance activities: None

Part VI: Summary of the risk management plan

Summary of risk management plan for Minoxidil 2.5mg, 5mg and 10mg Tablets (minoxidil)

This is a summary of the risk management plan (RMP) for Minoxidil 2.5mg, 5mg and 10mg Tablets. The RMP details important risks of Minoxidil 2.5mg, 5mg and 10mg Tablets, how these risks can be minimised, and how more information will be obtained about Minoxidil 2.5mg, 5mg and 10mg Tablet's risks and uncertainties (missing information).

Minoxidil 2.5mg, 5mg and 10mg Tablet's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Minoxidil 2.5mg, 5mg and 10mg Tablets should be used.

I. The medicine and what it is used for

Minoxidil 2.5mg, 5mg and 10mg Tablets are authorised for the treatment of severe hypertension (see SmPC for the full indication). It contains minoxidil as the active substance and it is given by oral tablets.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Minoxidil 2.5mg, 5mg and 10mg Tablets, together with measures to minimise such risks and the proposed studies for learning more about Minoxidil 2.5mg, 5mg and 10mg Tablet's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Minoxidil 2.5mg, 5mg and 10mg Tablets is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Minoxidil 2.5mg, 5mg and 10mg Tablets are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Minoxidil 2.5mg, 5mg and 10mg Tablets. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	• Sodium and water retention • Cardiovascular disorders (including palpitations, heart rate increased and chest pain) • Pericarditis, Pericardial Effusion and Tamponade
Important potential risks	• None
Missing information	• Safety and efficacy during pregnancy and lactation • Safety and efficacy in off-label use in treatment of alopecia

II.B Summary of important risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Minoxidil 2.5mg, 5mg and 10mg Tablets.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Minoxidil 2.5mg, 5mg and 10mg Tablets.

Part VII: Annexes

Table of contents

Annex 1 – EudraVigilance Interface

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

N/A

Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan

N/A

Annex 4 - Specific adverse drug reaction follow-up forms

Reference Number:

PREGNANCY AND LACTATION FOLLOW-UP FORM

Reporter Details

Name of Reporter:..... Position: .....

Contact Address: .....

.....

Telephone Number: .....

Patient Details

Patient ID (e.g. initials, Hospital no.): ..... DOB/Age: .....

Underlying Medical Conditions: .....

Risk Factors: Smoking □ Alcohol □ Drug Abuse □ Other .....

Part 1 *Only to be completed following drug use in pregnancy*

Pregnancy Details

Date of Last Menstrual Period: ..... Estimated Date of Delivery: .....

Previous pregnancy-related history:

Gravida (Number of Previous Pregnancies): Para (Number of Previous Live-births):

Abortus (Number of Previous Lost Pregnancies):

Other Comments: .....

.....

Drug Details

Please provide details of all drugs given during pregnancy or in the 6 months leading up to the pregnancy in the table below (please continue on separate page provided if needed).

Drug	Route	Dose	Start date	Stop date	Indication	Date of exposure

Were the treatments considered to be effective in the prescribed indications?

Yes ☐ No ☐

Please include any additional details, if necessary:

.....

.....

.....

Please describe any adverse event(s) experienced by the mother following drug exposure and any treatment given:

- Adverse event: .....
- Associated with other events? Yes ☐ No ☐
- If yes, please specify:.....

Date adverse event started:.....

Date adverse event stopped:.....

Please include the patient's description of symptoms and their duration:

.....

.....

.....

Do you consider the reaction to be serious? Yes / No

If *yes*, please indicate why the reaction is considered to be serious (please tick all that apply):

Patient died due to reaction ☐

Involved or prolonged inpatient hospitalisation ☐

Life threatening ☐

Involved persistent or significant disability or incapacity ☐

Congenital abnormality ☐

Medically significant; please give details:.....

Outcome: Recovered ☐ Recovering ☐ Not recovered ☐ Other:.....

Action taken with minoxidil tablets (including any recurrence of event):

Did the patient require any treatment? If so, please describe any treatment given.

.....

.....

.....

Were any investigations carried out during pregnancy? If so, please investigations completed and the results.

.....

.....

.....

Causality Assessment

Please provide your causality assessment of events experienced by the mother to the drug(s):

.....

Definitely Related □ Probably related □ Possibly related □ Definitely not related

Is this pregnancy ongoing? Yes / No

If **NO** please complete part 2 below

Part 2 *Only to be completed when the outcome of the pregnancy is known (following drug use in pregnancy)*

Outcome Details

Date of outcome: .....

Full term live birth □

Premature live birth □ Date/weeks: .....

Still birth □ Date/weeks: .....

Spontaneous abortion □ Date/weeks: .....

Elective abortion □ Date/weeks: .....

Delivery details: .....

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.....

Infant Details

Sex: Male / Female Birth Weight: ..... Gestational Age at Birth: .....

Apgar scores: 1 Minute ..... 5 Minutes ..... 10 Minutes .....

Does infant have any congenital abnormalities? Yes □ No □

Did infant develop any other adverse symptoms? Yes □ No □

If Yes for either question please give details:

.....

.....

Follow-up information

- **Status of child at 3 months after birth**

Date of information:……

Please complete table below:

Cognitive, motor and social development status (please detail any problems)	
Malformation/anomalies diagnosed since initial report	
Other medical problems since birth	

- **Status of child at 12 months after birth**

Date of information:……

Please complete table below:

Cognitive, motor and social development status (please detail any problems)	
Malformation/anomalies diagnosed since initial report	
Other medical problems since birth	

Causality Assessment

In cases of untoward outcome please provide your assessment of its relationship to the drug(s):

.....

Definitely Related □ Probably related □ Possibly related □ Definitely not related □

Lactation Information

Please provide details of all drugs given during breastfeeding in the table below

Drug	Route	Dose	Start date	Stop date	Indication	Date of exposure

Date that infant was breastfed……..

Age that infant was exposed to drugs in breast milk……

Did the infant develop any adverse symptoms (*If yes, please give detail*)……..

……..

Causality assessment

In cases of untoward outcome, please provide your assessment of its relationship to the drug(s):

……..

Definitely related □ Probably related □ Possibly related □ Definitely not related □

Additional Page if Required

Drug	Route	Dose	Start date	Stop date	Indication	Date of exposure

.....

.....

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.....

By completing this form you are consenting to the collection of sensitive data as defined under General Data Protection Regulation/Data Protection Act 2018

Specific adverse event targeted report form/follow-up questionnaire

The targeted follow-up checklist for cases is provided for the following adverse event:

- Safety and efficacy in off-label use in treatment of alopecia

ADVERSE EVENT REPORTING FORM FOR Minoxidil 2.5mg, 5mg and 10mg Tablets

Reference No: .....

1. PATIENT DETAILS

Please tell us more about the person who had the suspected side effect.

Patient Initials:		
Weight (kg):	Height (cm):	
Age (at time of reaction):	Male ☐	Female ☐
Identification (Your Practice/Hospital ref.):		

2. INFORMATION REGARDING Minoxidil 2.5mg, 5mg and 10mg Tablets

Brand name and batch number if known	Route	Dosage	Date started	Date stopped	Prescribed for
	Oral				
	Oral				

	Oral				

Action taken with minoxidil tablets (including any recurrence of event):

3. INFORMATION REGARDING THE ADVERSE EVENTS

Please provide all applicable medical information with this form. This may include, but is not limited to diagnostic test results, medical records, discharge summaries etc.

a. Details of the adverse event

Please describe the adverse event(s) and any treatment given:

- Adverse event: .....
- Associated with other events? Yes ☐ No ☐
- If yes, please specify:.....

Date adverse event started:.....

Date adverse event stopped:.....

Please describe the circumstances of the event:

.....

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Please include the patient's description of symptoms and their duration:
.....

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.....

What was the diagnosis made?

Please specify below:

.....

.....

.....

Do you consider the reaction to be serious? Yes / No

If *yes*, please indicate why the reaction is considered to be serious (please tick all that apply):

Patient died due to reaction ☐

Involved or prolonged inpatient hospitalisation ☐

Life threatening ☐

Involved persistent or significant disability or incapacity ☐

Congenital abnormality ☐

Medically significant; please give details:.....

Outcome: Recovered ☐ Recovering ☐ Not recovered ☐ Other:.....

Did the patient require any treatment? If so, please describe any treatment given?

.....

.....

.....

4. INFORMATION REGARDING THE EFFICACY IN THE OFF-LABEL INDICATION OF ALOPECIA

Was the treatment considered to be effective in the off-label indication of alopecia?

Yes ☐ No ☐

Please include any additional details, if necessary:

.....

.....

.....

5. CONCOMITANT DRUG(S)

Please list other drugs taken in the last 3 months prior to the reaction (including self-medication & herbal remedies)

Was the patient on any other medication? Yes / No

If *yes*, please give the following information if known:

Give brand name of drug and batch number if known	Route	Dosage	Date started	Date stopped	Prescribed for

Do you consider that a possible drug interaction has occurred? Yes/No

If *yes*, please provide details:

.....

.....

6. ADDITIONAL INFORMATION

Diagnostic test	Results		
	Before event	During event	After event
	Date	Date	Date

Were any other special investigations undertaken (e.g. chest X-ray, echocardiogram etc.) If so, please provide details below and include results.

.....

.....

.....

Did the patient have any relevant medical history:

.....

.....

.....

7. REPORTER DETAILS

Name and Professional Address:.....

.....

Post code: ..... Tel. No.: .....

Speciality: .....

Signature: _____ Date: _____

By completing this form you are consenting to the collection of sensitive data as defined under General Data Protection Regulation/Data Protection Act 2018

Annex 5 - Protocols for proposed and on-going studies in RMP part IV

N/A

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

N/A

Annex 7 - Other supporting data (including referenced material)

1. Shafter AM (2018) Understanding Minoxidil-Induced Pericardial Effusion. J Cardiovasc Dis Diagn 6: 323. doi: 10.4172/2329-9517.1000323. Available from: https://www.hilarispublisher.com/open-access/understanding-minoxidilinduced-pericardial-effusion-2329-9517-1000323.pdf (Accessed 27/04/2021)
2. Gilmore E, Weil J, Chidsey C. Treatment of essential hypertension with a new vasodilator in combination with beta-adrenergic blockade. N Engl J Med. 1970 Mar 5;282(10):521-7. doi: 10.1056/NEJM197003052821001. PMID: 4391708.
3. Tong Wang. The Effects of the Potassium Channel Opener Minoxidil on Renal Electrolytes Transport in the Loop of Henle. Journal of Pharmacology and Experimental Therapeutics February 1, 2003, 304 (2) 833-840; DOI: https://doi.org/10.1124/jpet.102.043380
4. Brunton LL, Chabner BA, Knollmann BC. Goodman & Gilman's the Pharmacological Basis of Therapeutics. 12th ed. New York: McGraw-Hill Companies, Inc; 2011. p. 781

Annex 8 – Summary of changes to the risk management plan over time

N/A – initial application