

UK Risk Management Plan for Melatonin 1 mg/ml Oral Solution

RMP version to be assessed as part of this application:

RMP Version number: 0.5
Data lock point for this RMP: 28 June 2021
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Rationale for submitting an updated RMP:

- The RMP has been updated following on from the MHRA's request for further information

[REDACTED]

Summary of significant changes in this RMP:

- RMP updated to remove the following safety concerns: Drug interactions, Drug withdrawal, Infections, Visual disturbances, Use in individuals with autoimmune diseases, Use in patients with renal or hepatic impairment and Use in epileptic patients.
- RMP updated to include the following important potential risks: Off-label use in children under the age of 6, Long-term safety in children and adolescents & Effects on sexual maturation and development in children and adolescents.
- All reports describing sexual maturation and development are followed up via the use of a targeted follow-up questionnaire. The targeted follow-up questionnaire is presented in Annex 4 of the RMP.
- All relevant sections updated to address the points above.

[REDACTED]

[REDACTED]

[REDACTED]

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UK QPPV name: [REDACTED]

UK QPPV signature: [REDACTED]

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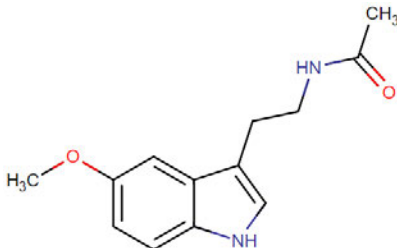
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Part I: Product(s) Overview

Table Part I.1 – Product Overview

Active substance(s) (INN or common name)	Melatonin
Pharmacotherapeutic group(s) (ATC Code)	Hypnotics and sedatives, melatonin receptor agonists (N05CH01)
Marketing Authorisation Holder	Colonis Pharma Limited, part of Clinigen Ltd.
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Melatonin 1 mg/ml Oral Solution
Marketing authorisation procedure	National UK
Brief description of the product	<p><u>Chemical class</u></p> <p>Melatonin is a naturally occurring hormone produced by the pineal gland and is structurally related to serotonin.</p> <p>Chemical name: N-[2-(5-Methoxy-1H-indol-3-yl)ethyl]acetamide</p> <p>CAS: 73-31-4</p> <p>Molecular formula: C₁₃H₁₆N₂O₂</p> <p>Molecular mass: 232.28</p>  <p>Chemical Structure of Melatonin</p>
	<p><u>Summary of mode of action</u></p> <p>Physiologically, melatonin secretion increases soon after the onset of darkness, peaks at 2-4 am and diminishes during the second half of the night. Melatonin is associated with the control of circadian rhythms and entrainment to the light-dark cycle. It is also associated with a hypnotic effect and increased propensity for sleep.</p> <p>The activity of melatonin at the MT₁, MT₂ and MT₃ receptors are believed to contribute to its sleep-promoting properties, as these</p>

	receptors (mainly MT1 and MT2) are involved in the regulation of circadian rhythms and sleep regulation.
	<u>Important information about its composition</u> Chemically active substance
Hyperlink to the Product Information	Proposed SmPC and PIL are hyperlinked
Indication(s) in the EEA	Current (if applicable): Melatonin 1mg/ml oral solution is indicated for short-term treatment of jet-lag in adults.
	Proposed (if applicable): Sleep onset insomnia in children and adolescents aged 6-17 years with attention-deficit hyperactivity disorder (ADHD) where sleep hygiene measures have been inadequate.
Dosage in the EEA	Current (if applicable): For the short-term treatment of jet lag in adults: The standard dose is 3 mg daily for a maximum of 5 days. The dose may be increased to 6 mg if the standard dose does not adequately alleviate symptoms. The dose that adequately alleviates symptoms should be taken for the shortest period. The first dose should be taken on arrival at destination at the habitual bed-time.
	Proposed (if applicable): Sleep onset insomnia in children and adolescents with ADHD: Treatment should be initiated by physicians experienced in ADHD and/or paediatric sleep medicine. Recommended starting dose is 1-2 mg (1.0-2.0 ml) 30-60 minutes before bedtime. The dose of melatonin can be increased by 1 mg (1.0ml) every week until effect up to a maximum 5 mg (5 ml) per day, independent of age. The lowest effective dose that controls symptoms should be given.
Pharmaceutical form(s) and strengths	Current (if applicable): Oral solution. Each 1 ml of oral solution contains 1 mg of melatonin (1mg/ml).
	Proposed (if applicable): Not applicable

Is/will the product be subject to additional monitoring in the EU?	No
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Part II: Safety specification

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

According to section V.C.1.1 of the GVP – Module V, this section is not applicable for “Well established medicinal use” medicinal products.

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

According to section V.C.1.1 of the GVP – Module V, this section is not applicable for “Well established medicinal use” medicinal products.

Part II: Module SIII - Clinical trial exposure

According to section V.C.1.1 of the GVP – Module V, this section is not applicable for “Well established medicinal use” medicinal products.

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

According to section V.C.1.1 of the GVP – Module V, this section is not applicable for “Well established medicinal use” medicinal products.

Part II: Module SV - Post-authorisation experience

According to section V.C.1.1 of the GVP – Module V, this section is not applicable for “Well established medicinal use” medicinal products.

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

According to section V.C.1.1 of the GVP – Module V, this section is not applicable for “Well established medicinal use” medicinal products.

Part II: Module SVII - Identified and potential risks

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

The following list of safety concerns was included in the initial RMP submission (v0.2 dated: 25 February 2019):

Important identified risks	<ul style="list-style-type: none">• Drug interactions
Important potential risks	<ul style="list-style-type: none">• Infections• Drug withdrawal• Visual disturbances

Missing information	<ul style="list-style-type: none"> • Use in individuals with autoimmune diseases • Use in patients with renal or hepatic impairment • Use in paediatric patients • Fertility, pregnancy and lactation
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SVII.1.1. Risks not considered important for inclusion 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):

- Irritability, nervousness, restlessness, insomnia, abnormal dreams, nightmares, anxiety
- Migraine, headache, lethargy, psychomotor hyperactivity, dizziness, somnolence
- Hot flush
- Abdominal pain, abdominal pain upper, dyspepsia, mouth ulceration, dry mouth, nausea
- Dermatitis, night sweats, pruritus, rash, pruritus generalised, dry skin
- Eczema, erythema, hand dermatitis, rash generalised, rash pruritic, nail disorder
- Angioedema, oedema of mouth, tongue oedema
- Pain in extremity
- Arthritis, muscle spasms, neck pain, night cramps
- Menopausal symptoms
- Asthenia
- Fatigue, pain, thirst
- Liver function test abnormal, weight increased
- Hypertriglyceridaemia, hypocalcaemia, hyponatraemia
- Mood altered, aggression, agitation, crying, stress symptoms, , early morning awakening, libido increased, depressed mood, depression
- Memory impairment, disturbance in attention, dreamy state, restless legs syndrome, poor quality sleep, paraesthesia
- Hypertension
- Gastro-oesophageal reflux disease, gastrointestinal disorder, oral mucosal blistering, tongue ulceration, gastrointestinal upset, vomiting, bowel sounds abnormal, flatulence, salivary hypersecretion, halitosis, abdominal discomfort, gastric disorder, gastritis
- Glycosuria, proteinuria
- Polyuria, nocturia
- Priapism, prostatitis
- Galactorrhoea
- Hepatic enzyme increased, blood electrolytes abnormal, laboratory test abnormal

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:

- Chest Pain
- Angina pectoris
- Palpitations
- Depression
- Disorientation
- Vertigo
- Haematuria
- Leukopenia
- Thrombocytopenia
- Psoriasis
- Hypersensitivity to the active substance

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):

- None

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

- Drowsiness/ somnolence

Drowsiness has been excluded from the list of the important risks since it represents the desired therapeutic outcome of the product, rather than an undesirable effect. The therapeutic effect of the product and the effect of drowsiness in case of overdose or driving and using machines has been captured in the relevant sections of the SmPC (4.1, 4.4, 4.7, 4.8 and 4.9).

Other risks, which are considered not important:

- Thyroid follicular cell hypertrophy

Thyroid follicular cell hypertrophy has been included as a safety concern in the RMP of Circadin. This was based on a rat carcinogenicity study, where an increased incidence of benign tumours of the thyroid was observed at the high dose level. Further evaluation showed that the carcinogenicity study in the rat did not reveal any effect, which may be relevant for humans. Subsequently, the risk was removed from the SmPC of Circadin.

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

Important Identified Risk 1: Drug interactions

Risk-benefit impact:

Melatonin has been observed in vitro, to induce CYP3A, which is responsible for the metabolism of many drugs. If induction occurs, this can give rise to reduced plasma concentrations of concomitantly administered medicinal products, which are metabolised by this enzyme family.

Melatonin's metabolism is mainly mediated by CYP1A enzymes. Interactions between melatonin and other active substances as a consequence of their effect on CYP1A isoenzymes are possible. Melatonin does not induce CYP1A enzymes at supra-therapeutic concentrations in vitro, it is therefore unlikely that these interactions would be clinically significant.

Caution due to the increased melatonin levels is recommended in patients on the following medications, which are known CYP1A2 inhibitors:

- fluvoxamine
- 5- or 8- methoxypsoralen
- Cimetidine
- Oestrogens (e.g., contraceptive or hormone replacement therapy)
- Quinolones

Caution due to decrease in melatonin level is recommended in patients on the following medications which are known CYP1A2 inducers:

- Carbamazepine
- Rifampicin
- Cigarette smoking

This is in accordance with Melatonin's (Circadin) modified release RMP, where drug interactions have been identified as a safety concern.

Important Potential Risk 1: Infections

Risk-benefit impact:

Infections may lead to a serious outcome, discontinuing the treatment and/or reducing the efficacy of the medicinal product, if not managed appropriately.

In the initial RMP of Melatonin (Circadin) modified release, an increase of the frequency of infections (of all kinds) in melatonin treated subjects was recorded during the trial programme. This was attributed to the inclusion of long-term data from a study protocol and was corrected by adjusting the rates of the adverse events for the extent of the exposure. After correction, the frequencies between the treated and the placebo groups appeared to be comparable. Nevertheless, infections were included a safety concern.

Additionally, herpes zoster and leukopenia have been identified as rare undesirable effects. Leukopenia may place individuals at an increased risk of infection.

Since the current data does not suggest a strong connection between melatonin and infections, the risk has been classified as an important potential risk.

Important Potential Risk 2: Drug withdrawal

Risk-benefit impact:

Drug withdrawal symptoms could have a severe impact on the patient.

In the initial RMP of Melatonin (Circadin) modified release, drug withdrawal has been identified as a safety concern, although no evidence was found for withdrawal dependence or rebound insomnia with melatonin during early and late withdrawal, beside the re-emergence of insomnia. A post-marketing study has been performed to evaluate the risk of withdrawal symptoms.

Since the current knowledge does not indicate a strong correlation between melatonin and drug withdrawal, it has been classified as an important potential risk.

Important Potential Risk 3: Visual disturbances

Risk-benefit impact:

In one literature report, evidence of retinal toxicity after exposure to melatonin in a rat strain (albino rats) was described. It is clear that melatonin has influence over many different visual functions although the precise mechanisms by which this hormone mediates these functions are likely to vary in a species-dependent manner. No such finding was observed in clinical trials.

Since there are animal data to show retinal toxicity, the risk has been categorised as potential.

Missing information 1: Use in individuals with autoimmune diseases

Risk-benefit impact:

A number of published literature articles suggest that melatonin has immune enhancing effect. No clinical data exists concerning the use of melatonin in individuals with autoimmune diseases.

Use in individuals with autoimmune diseases is a safety concern in the RMP of Melatonin (Circadin) modified release and is included in the SmPC of the product.

Missing information 2: Use in patients with renal or hepatic impairment

Risk-benefit impact:

The effect of any stage of renal impairment on melatonin pharmacokinetics has not been studied.

There is no experience in the use of melatonin in patients with liver impairment. In vitro studies using liver microsomes have identified that hydroxylation is the primary route of metabolism and published data also demonstrates markedly elevated endogenous melatonin levels during daytime hours due to decreased clearance in patients with hepatic impairment.

Missing information 3: Use in paediatric patients

Risk-benefit impact:

The safety and efficacy of melatonin in children aged 0 to 18 years has not yet been established.

Missing information 4: Fertility, pregnancy and lactation

Risk-benefit impact:

For melatonin, no clinical data on fertility are available.

In a similar manner, no clinical data on exposed pregnancies are available.

In reproductive studies in rodents, melatonin induced some toxicological effects on fertility, embryo-foetal development and postnatal development, but these were all in large excess of the anticipated clinical doses. Largely though animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development.

Endogenous melatonin was measured in human breast milk thus exogenous melatonin is probably secreted into human milk. There are data in animal models including rodents, sheep, bovine and primates that indicate maternal transfer of melatonin to the foetus via the placenta or in the milk.

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

- **Important Identified Risks:**

The important identified risk of Drug Interactions was removed from the list of safety concerns. There are no specific clinical measures or additional PV activities/additional risk minimisation measures in place to manage this risk. Therefore, this risk is not considered as an important risk.

- **Important Potential Risks:**

The risks of Drug withdrawal; Infections; Visual disturbances and Use in epileptic patients were removed from the list of safety concerns. There are no specific clinical measures or additional PV activities/additional risk minimisation measures in place to manage these risks. Therefore, these risks are not considered as important risks.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

- Long term safety in children and adolescents

The safety and efficacy of melatonin in children aged 0 to 18 years has not yet been established, therefore long-term safety in children and adolescents remains an important potential risk. This is also in line with products with a similar indication.

- Effects on sexual maturation and development in children and adolescents

The safety and efficacy of melatonin in children aged 0 to 18 years has not yet been established, therefore effects on sexual maturation and development in children and adolescents remains as an important potential risk. This is also in line with products with a similar indication.

- **Missing Information:**

The risks of Use in individuals with autoimmune diseases; Use in patients with renal or hepatic impairment and Use in paediatric patients under the age of 6 years were removed from the list of safety concerns.

The risk of Use in paediatric patients under the age of 6 years was reclassified as an important potential risk.

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

Off-label use in children under the age of 6

Potential mechanisms:

Melatonin is mainly metabolised by the liver. Experimental data suggest that the cytochrome P450 enzymes CYP1A1 and CYP1A2 are primarily responsible for melatonin metabolism, with CYP2C19 of minor importance. Melatonin is primarily metabolised to 6-hydroxymelatonin (constituting ~ 80 – 90% of melatonin metabolites recovered in the urine). N-acetylserotonin appears to be the primary minor metabolite (constituting ~ 10% of melatonin metabolites recovered in the urine). Melatonin metabolism is very rapid, with plasma 6-hydroxymelatonin level rising within minutes of exogenous melatonin entering the systemic circulation. The 6-hydroxymelatonin undergoes sulphate conjugation (~ 70%) and glucuronide conjugation (~ 30%) prior to excretion.

Prepubertal children metabolise melatonin faster than adults and the average $t_{1/2}$ is comparable or slightly shorter in children than adults.

Evidence source(s) and strength of evidence:

Cavallo and Ritschel, 1996, infused melatonin IV in 9 prepubertal, 8 pubertal, and 16 adult subjects and measured melatonin in serum and saliva, and 6-hydroxymelatonin sulphate in urine. It was found that melatonin levels were higher in serum than in saliva, and the ratio between serum and salivary melatonin varied up to 55-fold within and between individuals. The results based on salivary melatonin showed significant differences between prepubertal children and adults for the terminal elimination rate constant ($1.90 \pm 0.95/h$ vs $1.06 \pm 0.28/h$). [REDACTED] concluded that the prepubertal children metabolise melatonin faster than adults.

Characterisation of the risk:

The use of melatonin in both the UK / EU is increasing and despite the availability of licensed melatonin products for paediatrics, a large amount of off label and unlicensed use is not uncommon. It is also not uncommon for prescribers to recommend crushing of immediate and prolonged release formulations to aid administration in younger children and so the availability of the oral formulation could lead to regular off-label use in children under the age of 6 years.

[REDACTED]

[REDACTED]

Risk factors and risk groups:

The risk factors are children under the age of 6 who have been prescribed melatonin off-label.

Preventability:

No additional preventative measures or risk minimisation measures are proposed for this risk.

Public health impact:

The public health impact is considered to be low.

Long term safety in children and adolescents

Potential mechanisms:

The potential mechanism by which melatonin may cause long term effects in children and adolescents is unknown.

Evidence source(s) and strength of evidence:

The safety and efficacy of melatonin in children aged 0 to 18 years has not yet been established.

Some studies suggested that melatonin could inhibit reproductive function and delay the timing of puberty [REDACTED] and there has been an increasing concern around possible serious side effects of melatonin in children based on data from animal models (rodents, sheep and primates) suggesting putative effects on the reproductive, cardiovascular, immune and metabolic systems. However, so far, data in children with neurodevelopmental disorders from short-term [REDACTED]; [REDACTED]; [REDACTED]; [REDACTED]) and available long-term follow-up studies ([REDACTED], effects of long-term use of melatonin on pubertal development and fertility could not be properly assessed by the study design) failed to point to serious AEs associated with the use of melatonin, although clearly further evidence is needed and robust data on the long-term safety of treatment with melatonin in children and adolescents is still lacking [REDACTED]).

Characterisation of the risk:

The safety and efficacy of melatonin in children aged 0 to 18 years has not yet been established, therefore long-term safety in children and adolescents remains an important potential risk. This is also in line with products with a similar indication.

Risk factors and risk groups:

The risk groups are children and adolescents.

Preventability:

There is limited data available for up to 3 years of treatment. After at least 3 months of treatment, the physician should evaluate the treatment effect and consider discontinuing the treatment if no clinically relevant treatment effect is seen. The patient should be monitored at regular intervals (at least every 6 months) to check that Melatonin 1 mg/ ml oral solution is still the most appropriate treatment. During ongoing treatment, especially if the treatment effect is uncertain, discontinuation attempts should be done regularly, at least once per year.

Close and more frequent monitoring and assessment of any relevant post-marketing safety reports including scientific publications to enhance the routine PV activities. No additional preventative measures or risk minimisation measures are proposed for this risk.

Public health impact:

The expected incidence rate is expected to be minimal. The public health impact is considered to be low.

Effects on sexual maturation and development in children and adolescents

Potential mechanisms:

With age, nocturnal melatonin levels appear to decrease with the most striking falls appearing to occur around puberty. Nocturnal melatonin levels have been assessed in children at various pubertal stages and it is observed that they are higher in the earlier than in the later stages. Whether this is cause or effect is not known but there is a potential risk that exogenous melatonin may delay sexual maturity [REDACTED]. The exact mechanism by which melatonin may affect sexual maturation and development in children and adolescents is still unknown.

Evidence source(s) and strength of evidence:

Some studies suggested that melatonin could inhibit reproductive function and delay the timing of puberty (Wei et al, 2020) and there has been an increasing concern around possible serious side effects of melatonin in children based on data from animal models (rodents, sheep and primates) suggesting putative effects on the reproductive cardiovascular, immune and metabolic systems. However, so far, data in children with neurodevelopmental disorders from short-term [REDACTED] and available long-term follow-up studies [REDACTED] effects of long-term use of melatonin on pubertal development and fertility could not be properly assessed by the study design) failed to point to serious AEs associated with the use of melatonin, although clearly further evidence is needed and robust data on the long-term safety of treatment with melatonin in children and adolescents is still lacking [REDACTED].

From non-clinical data on seasonal breeders and the observation that plasma concentrations of melatonin rapidly decline around puberty, there is a theoretical concern that long-term treatment with melatonin may affect sexual hormones, sexual maturation/pubertal development and final height in children and adolescents. It would also appear that melatonin has effects on several hormones involved in the sexual maturation of pubertal female and male rats.

Characterisation of the risk:

The safety and efficacy of melatonin in children aged 0 to 18 years has not yet been established, therefore effects on sexual maturation and development in children and adolescents remains as an important potential risk. This is also in line with products with a similar indication.

Risk factors and risk groups:

The risk groups are children and adolescents who have existing genetic disorder affecting production of hormones or congenital abnormality and/or other relevant medical history, which has an impact on sexual maturation and development.

Preventability:

All reports describing effects on sexual maturation and development will be specifically followed up via the use of a targeted follow-up questionnaire to obtain further information.

Close and more frequent monitoring and assessment of any relevant post-marketing safety reports including scientific publications to enhance the routine PV activities.

Public health impact:

The expected incidence rate is expected to be minimal. The public health impact is considered to be low.

SVII.3.2. Presentation of the missing information

Fertility, pregnancy and lactation

Evidence source:

For melatonin, no adequate clinical data on fertility are available. Literature data indicate that melatonin shows promise as an adjunctive therapy in the treatment of infertility; however, more clinical data is needed to confirm this hypothesis [REDACTED]

For melatonin, no adequate clinical data on exposed pregnancies are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. In view of the lack of clinical data, use of melatonin in pregnant women is not recommended.

Endogenous melatonin has been measured in human breast milk, thus exogenously administered melatonin can be expected to be secreted into breast milk. Data from animal models including rodents, sheep, bovine and primates indicates placental transfer of melatonin and in the milk.

Therefore, breast-feeding is not recommended in lactating women receiving melatonin.

Fertility, pregnancy and lactation is a safety concern of Melatonin (Circadin) modified release and is included in the SmPC of the product.

Population in need of further characterisation:

Pregnant women and breastfeeding mothers.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	<ul style="list-style-type: none">• None
Important potential risks	<ul style="list-style-type: none">• Off-label use in children under the age of 6• Long term safety in children and adolescents• Effects on sexual maturation and development in children and adolescents
Missing information	<ul style="list-style-type: none">• Fertility, pregnancy and lactation

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

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection include use of a targeted follow-up questionnaire for all reports of 'Effects on sexual maturation and development in children and adolescents'.

Close and more frequent monitoring and assessment of any relevant post-marketing safety reports including scientific publications to enhance the routine PV activities for 'Long term safety in children and adolescents' and 'Effects on sexual maturation and development in children and adolescents'.

III.2 Additional pharmacovigilance activities

Not applicable. There are no additional pharmacovigilance activities.

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable. There are no additional pharmacovigilance activities.

Part IV: Plans for post-authorisation efficacy studies

Not applicable, there are no plans for post-authorisation efficacy clinical studies.

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

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
Off-label use in children under the age of 6	<p>Routine risk communication:</p> <ul style="list-style-type: none"> SmPC section 4.2 PL section 2 <p>Routine risk minimisation activities recommending specific clinical measures to address the risk: None</p> <p>Other routine risk minimisation measures beyond the Product Information: None</p>
Long term safety in children and adolescents	<p>Routine risk communication:</p> <ul style="list-style-type: none"> SmPC sections 4.2 <p>Routine risk minimisation activities recommending specific clinical measures to address the risk: None</p> <p>Other routine risk minimisation measures beyond the Product Information: None</p>
Effects on sexual maturation and development in children and adolescents	<p>Routine risk communication:</p> <ul style="list-style-type: none"> SmPC sections 5.3 <p>Routine risk minimisation activities recommending specific clinical measures to address the risk: None</p> <p>Other routine risk minimisation measures beyond the Product Information: None</p>
Fertility, pregnancy and lactation	<p>Routine risk communication:</p> <ul style="list-style-type: none"> SmPC sections 4.6 PL section 2 <p>Routine risk minimisation activities recommending specific clinical measures to address the risk: None</p> <p>Other routine risk minimisation measures beyond the Product Information: None</p>

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
Off-label use in children under the age of 6	Routine risk minimisation measures: <ul style="list-style-type: none">• SmPC sections 4.2• PL section 2 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Long term safety in children and adolescents	Routine risk minimisation measures: <ul style="list-style-type: none">• SmPC sections 4.2 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Close and more frequent monitoring and assessment of any relevant post-marketing safety reports including scientific publications to enhance the routine PV activities. Additional pharmacovigilance activities: None
Effects on sexual maturation and development in children and adolescents	Routine risk minimisation measures: <ul style="list-style-type: none">• SmPC sections 5.3 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up questionnaire Close and more frequent monitoring and assessment of any relevant post-marketing safety reports including scientific publications to enhance the routine PV activities. Additional pharmacovigilance activities: None
Fertility, pregnancy and lactation	Routine risk minimisation measures:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None

	<ul style="list-style-type: none"> • SmPC sections 4.6 • PL section 2 <p>Additional risk minimisation measures: None</p>	<p>Additional pharmacovigilance activities: None</p>
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Part VI: Summary of the risk management plan

Summary of risk management plan for Melatonin 1 mg/ml Oral Solution (Melatonin 1 mg/ml Oral Solution)

This is a summary of the risk management plan (RMP) for Melatonin 1 mg/ml Oral Solution. The RMP details important risks of Melatonin 1 mg/ml Oral Solution, how these risks can be minimised, and how additional information will be obtained about Melatonin 1 mg/ml Oral Solution's risks and uncertainties (missing information).

Melatonin 1 mg/ml Oral Solution's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Melatonin 1 mg/ml Oral Solution should be used.

Important new concerns or changes to the current ones will be included in updates of Melatonin 1 mg/ml Oral Solution RMP.

I. The medicine and what it is used for

Melatonin 1 mg/ml Oral Solution is authorised for sleep disorders resulting from disturbances of the normal sleep-wake cycle for adults and in children aged 6-17 years with attention-deficit hyperactivity disorder (ADHD) (see SmPC for the full indication). It contains melatonin as the active substance, and it is given by mouth.

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

Important risks of Melatonin 1 mg/ml Oral Solution, together with measures to minimise such risks and the proposed studies for learning more about Melatonin 1 mg/ml Oral Solution'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, including PSUR assessment 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 Melatonin 1 mg/ml Oral Solution is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Melatonin 1 mg/ml Oral Solution are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. 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 Melatonin 1 mg/ml Oral Solution. 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).

Summary of safety concerns	
Important identified risks	<ul style="list-style-type: none"> • None
Important potential risks	<ul style="list-style-type: none"> • Off-label use in children under the age of 6 • Long term safety in children and adolescents • Effects on sexual maturation and development in children and adolescents
Missing information	<ul style="list-style-type: none"> • Fertility, pregnancy and lactation

II.B Summary of important risks

Off-label use in children under the age of 6	
Evidence for linking the risk to the medicine	<p>██████████, infused melatonin IV in 9 prepubertal, 8 pubertal, and 16 adult subjects and measured melatonin in serum and saliva, and 6-hydroxymelatonin sulphate in urine. It was found that melatonin levels were higher in serum than in saliva, and the ratio between serum and salivary melatonin varied up to 55-fold within and between individuals. The results based on salivary melatonin showed significant differences between prepubertal children and adults for the terminal elimination rate constant ($1.90 \pm 0.95/h$ vs $1.06 \pm 0.28/h$). ██████████ concluded that the prepubertal children metabolise melatonin faster than adults.</p>
Risk factors and risk groups	<p>The risk factors are children under the age of 6 who have been prescribed melatonin off-label.</p>
Risk minimisation measures	<p>Routine risk minimisation measures:</p> <p><i>SmPC section 4.2</i></p> <p><i>PL section 4</i></p> <p>Additional risk minimisation measures:</p> <p><i>None</i></p>

Long term safety in children and adolescents	
Evidence for linking the risk to the medicine	<p>The safety and efficacy of melatonin in children aged 0 to 18 years has not yet been established.</p> <p>Some studies suggested that melatonin could inhibit reproductive function and delay the timing of puberty [REDACTED] and there has been an increasing concern around possible serious side effects of melatonin in children based on data from animal models (rodents, sheep and primates) suggesting putative effects on the reproductive, cardiovascular, immune and metabolic systems. However, so far, data in children with neurodevelopmental disorders from short-term ([REDACTED] [REDACTED]) and available long-term follow-up studies [REDACTED], effects of long-term use of melatonin on pubertal development and fertility could not be properly assessed by the study design) failed to point to serious AEs associated with the use of melatonin, although clearly further evidence is needed and robust data on the long-term safety of treatment with melatonin in children and adolescents is still lacking [REDACTED]</p>
Risk factors and risk groups	The risk groups are children and adolescents.
Risk minimisation measures	<p>Routine risk minimisation measures:</p> <p><i>SmPC sections 4.2</i></p> <p>Additional risk minimisation measures:</p> <p><i>None</i></p>
Effects on sexual maturation and development in children and adolescents	

Evidence for linking the risk to the medicine	<p>Some studies suggested that melatonin could inhibit reproductive function and delay the timing of puberty [REDACTED] and there has been an increasing concern around possible serious side effects of melatonin in children based on data from animal models (rodents, sheep and primates) suggesting putative effects on the reproductive, cardiovascular, immune and metabolic systems. However, so far, data in children with neurodevelopmental disorders from short-term [REDACTED] and available long-term follow-up studies [REDACTED], effects of long-term use of melatonin on pubertal development and fertility could not be properly assessed by the study design) failed to point to serious AEs associated with the use of melatonin, although clearly further evidence is needed and robust data on the long-term safety of treatment with melatonin in children and adolescents is still lacking ([REDACTED]).</p> <p>From non-clinical data on seasonal breeders and the observation that plasma concentrations of melatonin rapidly decline around puberty, there is a theoretical concern that long-term treatment with melatonin may affect sexual hormones, sexual maturation/pubertal development and final height in children and adolescents. It would also appear that melatonin has effects on several hormones involved in the sexual maturation of pubertal female and male rats.</p>
Risk factors and risk groups	The risk groups are children and adolescents who have existing genetic disorder affecting production of hormones or congenital abnormality and/or other relevant medical history, which has an impact on sexual maturation and development.
Risk minimisation measures	<p>Routine risk minimisation measures:</p> <p><i>SmPC sections 5.3</i></p> <p>Additional risk minimisation measures:</p> <p><i>None</i></p>
Fertility, pregnancy and lactation	
Risk minimisation measures	<p>Routine risk minimisation measures:</p> <p><i>SmPC sections 4.6</i></p> <p><i>PL section 2</i></p> <p>Additional risk minimisation measures:</p> <p><i>None</i></p>

II.C Post-authorisation development plan

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

[REDACTED]

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

[REDACTED]

Part VII: Annexes

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Annex 1 – EudraVigilance Interface



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

[REDACTED]

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

[REDACTED]

Annex 4 - Specific adverse drug reaction follow-up forms



[REDACTED]

[REDACTED]

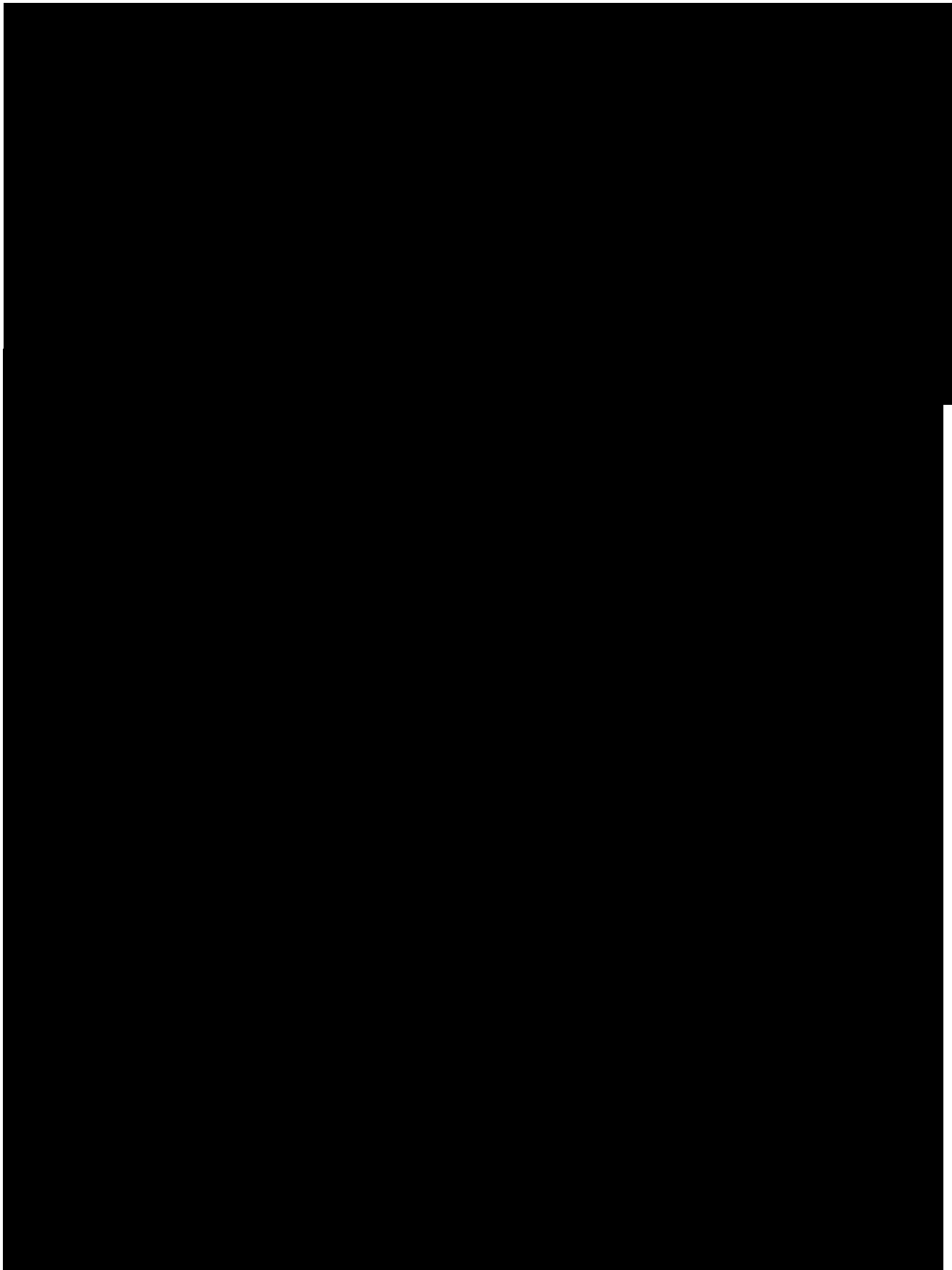
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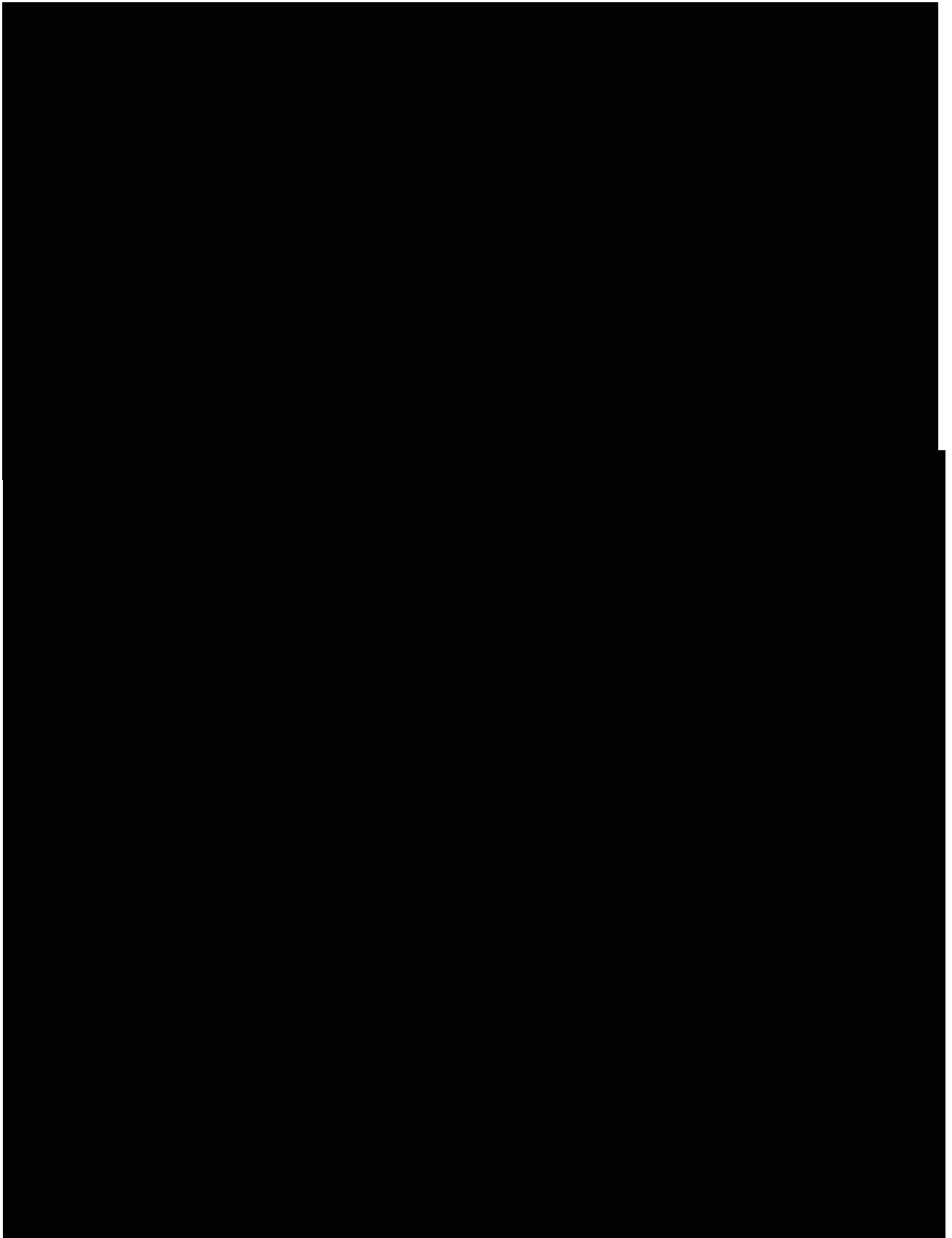
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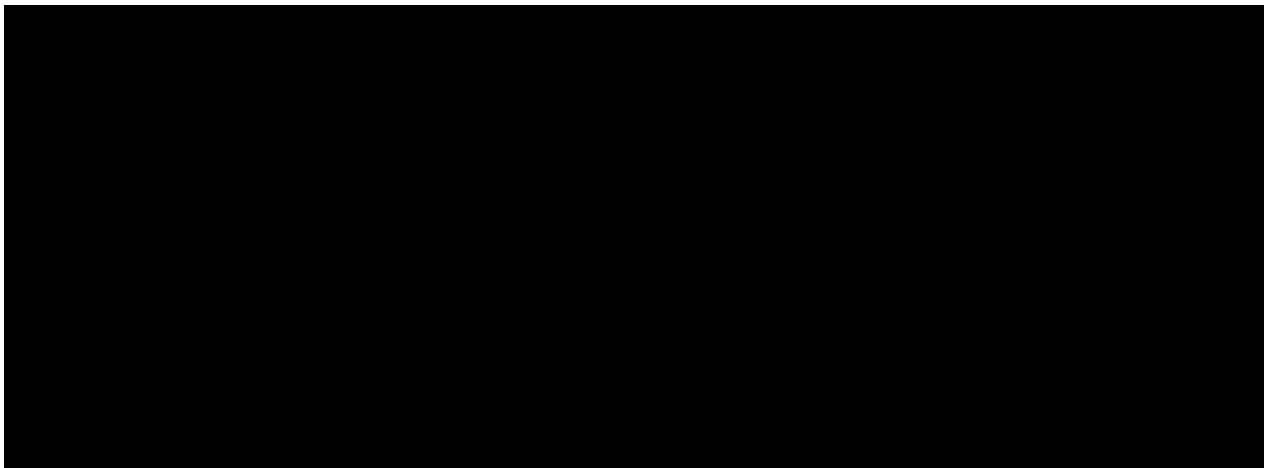
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[REDACTED]	[REDACTED] [REDACTED]	[REDACTED] [REDACTED] [REDACTED] [REDACTED]	[REDACTED] [REDACTED] text.







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

[REDACTED]

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

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[illegible]

