EU Risk Management Plan for Melatonin 1mg/mL oral solution (melatonin)

RMP version to be assessed as part of this application:

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Rationale for submitting an updated RMP: Revised indications and name during MA-registration

Summary of significant changes in this RMP: Updated to reflect the current indications and posology

QPPV name: [redacted]

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation applicant´s QPPV. The electronic signature is available on file.

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Part I: Product(s) Overview

Table Part I.1 – Product(s) Overview

Active substance(s) **(INN or common name)**	Melatonin
Pharmacotherapeutic group(s) (ATC Code)	N05CH
Marketing Authorisation Applicant	Consilient Health Ltd., 5th floor, Beaux Lane House, Mercer Street Lower, Dublin 2, Ireland
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Melatonin 1mg/mL oral solution
Marketing authorisation procedure	[redacted]
Brief description of the product	*Chemical class:* [redacted] Molecular structure: [redacted]
	Summary of mode of action: [redacted]

	[redacted]
	Important information about its composition: [redacted]
Hyperlink to the Product Information	*Include a link or reference to the proposed PI in the eCTD sequence.* *If no updated PI is submitted with the procedure, the link should direct to the latest approved PI.*
Indication(s) in the EEA	Current: -Short-term treatment to alleviate the subjective feelings of jet lag in adults. The medicinal product is recommended to adult travellers flying across ≥5 time zones, particularly in an easterly direction, and especially if they have experienced jet lag symptoms on previous journeys. Travellers crossing 2-4 time zones can also use it if need be. -Insomnia in children and adolescents aged 6-17 years with ADHD where sleep hygiene measures have been insufficient.
Dosage in the EEA	*Adults with jet lag* The recommended dose is 1-5 mg one hour before bedtime at destination. Recommended starting dose: 2 ml (equivalent to 2 mg) Due to the potential for incorrectly timed intake of melatonin to have no effect, or an adverse effect, on re-synchronisation following jet lag, Melatonin oral solution should not be taken before 20:00 hr or after 04:00 hr at destination. Maximal recommended daily dose: 5 ml (equivalent to 5 mg) for a maximum of 5 days. A maximum of 16 treatment cycles may occur per year. *Paediatric population with ADHD* Recommended starting dose: 1-2 ml (equivalent to 1-2 mg) 30 to 60 minutes before bedtime. The dose should be adjusted individually to a maximum of 5 ml (equivalent to 5 mg) daily regardless of age. The lowest effective dose should be sought. Maximal recommended daily dose: 5 ml (equivalent to 5 mg) Limited data are available for up to 3 years of treatment. After at least 3 months of treatment, the physician should evaluate the treatment effect and consider stopping 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 is still the most appropriate treatment. During ongoing treatment, especially if the treatment effect is uncertain, discontinuation attempts should be done regularly, e.g. once per year. If the sleep disorder has started during treatment with medicinal products for ADHD, dose adjustment or switching to another product should be considered.
Pharmaceutical form(s) and strengths	Oral solution 1mg/ml
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety specification

[redacted]

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

[redacted]

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

[redacted]

Part II: Module SIII - Clinical trial exposure

[redacted]

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

[redacted]

Part II: Module SV - Post-authorisation experience

[redacted]

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

[redacted]

Part II: Module SVII - Identified and potential risks

[redacted]

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

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

- [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

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

[redacted]

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

Important Identified Risk

[redacted]

Important Potential Risk

[redacted]

Missing information 1:

[redacted]

Missing information 2:

[redacted]

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

[redacted]

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 Potential Risk: [redacted]

Potential mechanisms:

[redacted]

Evidence source(s) and strength of evidence:

[redacted]

Characterisation of the risk:

[redacted]

Risk factors and risk groups:

[redacted]

Preventability:

[redacted]

Impact on the risk-benefit balance of the product:

[redacted]

Public health impact:

[redacted]

SVII.3.2. Presentation of the missing information

Missing information 1: [redacted]

Evidence source:

[redacted]

Population in need of further characterisation:

[redacted]

Missing information 2: [redacted]

Evidence source:

[redacted]

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Delay of sexual maturation and development
Missing information	Use in pregnancy and lactation Long-term safety

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

III.1 Routine pharmacovigilance activities

[redacted]

III.2 Additional pharmacovigilance activities

[redacted]

III.3 Summary Table of additional Pharmacovigilance activities

[redacted]

Part IV: Plans for post-authorisation efficacy studies

[redacted]

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

Risk Minimisation Plan

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
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

V.2. Additional Risk Minimisation Measures

[redacted]

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
[redacted]	[redacted]	[redacted]

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	[redacted]	
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Part VI: Summary of the risk management plan

Summary of risk management plan for Melatonin 1mg/mL oral solution

This is a summary of the risk management plan (RMP) for Melatonin 1mg/mL oral solution. The RMP details important risks of Melatonin 1mg/mL oral solution, how these risks can be minimised, and how more information will be obtained about Melatonin 1mg/mL oral solution risks and uncertainties (missing information).

Melatonin 1mg/mL oral solution summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Melatonin 1mg/mL oral solution should be used.

I. The medicine and what it is used for

Melatonin 1mg/mL oral solution is authorised for sleep disorders in children and adults (see SmPC for the full indication). It contains melatonin as the active substance and it is given orally.

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

Important risks of Melatonin 1mg/mL oral solution, together with measures to minimise such risks and the proposed studies for learning more about Melatonin 1mg/mL oral solution 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 the case of Melatonin 1mg/mL oral solution, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly 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 1mg/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 1mg/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 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 Melatonin 1mg/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);

List of important risks and missing information	
Important identified risks	None
Important potential risks	Delay of sexual maturation and development
Missing information	Use in pregnancy and lactation Long-term safety

II.B Summary of important risks

Delay of sexual maturation and development	
Evidence for linking the risk to the medicine	Melatonin delays sexual development in rats in a transient and reversible manner. No evidence for delay in human.
Risk factors and risk groups	Children and adolescents that are between pre-pubertal to pubertal stages.
Risk minimisation measures	Indication in Section 4.2 of SmPC that the patient should be monitored at regular intervals (at least every 6 months) to check that Melatonin 1mg/mL oral solution is still the most appropriate treatment. Inclusion in the package leaflet under section 3: "You or your child should be monitored by your doctor at regular intervals (recommended every 6 months) to check that Melatonin is still the right treatment for you/them."
Additional pharmacovigilance activities	Monitor any relevant post marketing safety reports. Reports describing sexual maturation and development would be specifically followed up.

Missing information: Long term safety	
Evidence for linking the risk to the medicine	Possible long-term effects of melatonin have been inadequately studied.
Risk factors and risk groups	The target population and children that will be treated off-

	label.
Risk minimisation measures	Indication in Section 4.4 of the SmPC that long-term effects have been inadequately studied.

Missing information: Use in pregnancy and lactation	
Evidence for linking the risk to the medicine	For melatonin there are no data from the treatment of pregnant women. Melatonin has been measured in breast milk and thus exogenous melatonin is probably secreted into breast milk.
Risk factors and risk groups	Pregnant and lactating women.
Risk minimisation measures	Routine risk minimisation measures. Indication in Section 4.6 of the SmPC that there is not sufficient data relating to the use of Melatonin 1mg/mL oral solution during breastfeeding and pregnancy. Inclusion of warning in the package leaflet.

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 Melatonin 1mg/mL oral solution.

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

There are no studies required for Melatonin 1mg/mL oral solution.

Part VII: Annexes

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Annex 1 – EudraVigilance Interface

[redacted]

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]

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]

Annex 7 - Other supporting data (including referenced material)

[redacted]

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

Version	Approval date/Procedure	Change
[redacted]	[redacted]	[redacted]