Risk Management Plan: UK specific annex

Active ingredient (INN)	Melatonin
Invented name(s) in UK	Adaflex 1 mg tablets Adaflex 2 mg tablets Adaflex 3 mg tablets Adaflex 4 mg tablets Adaflex 5 mg tablets
Marketing authorisation applicant or holder	AGB-Pharma AB
UK specific RMP annex version number and final sign-off date	Version number: 1.1 Final sign-off-date: 22 September 2025
EU RMP version number and final sign off-date	Version number: 5.1 Final sign-off-date: 22 September 2025
Data lock point (DLP)	UK specific RMP annex: 16 September 2025 EU RMP version 5.1: 16 September 2025

UK QPPV name, signature and date

UK QPPV oversight declaration: The content of this UK-specific RMP annex has been reviewed and approved by the marketing authorisation holder's AGB-Pharma AB UK QPPV.

UK QPPV name: [redacted]

UK QPPV date and signature: 2025-09-22 [redacted]

Table of contents

Summary of UK specific RMP annex

Safety specification

Summary of safety concerns	
Important identified risks	None Same as in the EU RMP v 5.1
Important potential risks	1. Off-label use in children under the age of 6 years The important potential risk is additional in the UK specific RMP annex upon request by the MHRA for harmonisation of melatonin GB/UK specific RMP:s.
Missing information	1. Long-term safety in children and adolescents 2. Fertility, pregnancy and lactation The missing information bullet number 1 is the same as in the updated EU RMP v 5.1. The missing information bullet number 2 is additional in the UK specific RMP annex [redacted]

Pharmacovigilance activities

The routine risk minimisation measures for the safety concerns in addition to the ones stated in the EU RMP v 5.1 is listed below.

1. Important potential risks - Off-label use in children under the age of 6 years
In the SmPC section 4.2, the following is stated:

Adaflex tablets are not recommended for children below 6 years with ADHD.

In the PL section 2, the following is stated:

'Adaflex should not be given to children below the age of 6 years.'

2. Missing information - Fertility, pregnancy and lactation
In the SmPC section 4.6, the following is stated:

'Fertility, pregnancy and lactation
Pregnancy
There are no data from the use of melatonin in pregnant women. Animal studies are incomplete regarding effects on pregnancy, embryonic / fetal development, childbirth and postnatal development (see section 5.3). Exogenous melatonin readily crosses the human placenta. Considering the lack of clinical data, treatment with Adaflex is not recommended during pregnancy or in women of childbearing potential not using contraceptives.

Breastfeeding
Data from animal studies indicate maternal transfer of melatonin to the foetus via the placenta or in the milk. Endogenous melatonin has also been measured in breast milk from breast-feeding women, and therefore exogenous melatonin is most likely also excreted in human milk. Melatonin is therefore not recommended to breastfeeding women.

Fertility
No adequate data on the effect of melatonin on human fertility are available. Animal studies are incomplete in terms of effects on fertility. High doses of melatonin and use for longer periods than indicated may compromise fertility in humans.'

In the PL section 2, the following is stated:

'Pregnancy, breast-feeding and fertility

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, you should not use Adaflex.

Pregnancy
Adaflex tablets are not recommended if you are pregnant. Melatonin crosses the placenta and there is insufficient information on the risk this may pose to the unborn child. If you are a woman of childbearing potential you have to use contraception.

Breast-feeding
Adaflex tablets are not recommended if you are breast-feeding. Melatonin is excreted in human milk, and a risk to the breast-fed child cannot be excluded.

Fertility
Adaflex tablets are not recommended in women and men planning to have a baby as there is insufficient information on the effects of melatonin on female and male fertility.'

Reasoning for differences between the routine risk minimisation measures in the UK specific RMP annex and the EU RMP

[redacted]

Post authorisation development plan (other mandatory studies)

Not applicable; there are no studies which are conditions of the marketing authorisations.

There are no differences in post-authorisation development plan for the UK as compared with the EU RMP v 5.1.

Additional risk minimisation activities

Not applicable; no additional risk minimisation activities.

There are no differences in post-authorisation development plan for the UK as compared with the EU RMP v 5.1.

UK Specific RMP annex overview

Part	Module/annex	Summary of UK specific content (if applicable)
Part I Product overview	---	See Part I below. Only invented names differ as compared with the EU RMP v 5.1.
Part II Safety specification	SI Epidemiology of the Indications(s) and Target Population(s)	Module not applicable, see EU RMP v 5.1; no UK specific content is provided.
	SII Non-clinical part of the safety specification	Module not applicable, see EU RMP v 5.1; no UK specific content is provided.
	SIII Clinical trial exposure	Module not applicable, see EU RMP v 5.1; no UK specific content is provided.
	SIV Populations not studied in clinical trials	Module not applicable, see EU RMP v 5.1; no UK specific content is provided.
	SV Post-authorisation experience	Module not applicable, see EU RMP v 5.1; no UK specific content is provided.
	SVI Additional EU/UK requirements for the Safety Specification	Module not applicable, see EU RMP v 5.1; no UK specific content is provided.
	SVII Identified and potential risks	One additional important potential risk: 1. Off-label use in children under the age of 6 years One additional missing information: 2. Fertility, pregnancy and lactation For the safety concerns that are the same in EU RMP v 5.1 and in UK specific RMP annex, see EU RMP v 5.1.
	SVIII Summary of the safety concerns	One additional important potential risk: 1. Off-label use in children under the age of 6 years One additional missing information: 2. Fertility, pregnancy and lactation For the safety concerns that are the same in EU RMP v 5.1 and in UK specific RMP annex, see EU RMP v 5.1.
Part III Pharmacovigilance plan (Including post-authorisation safety studies)	---	Not applicable, see EU RMP v 5.1; no UK specific content is provided.
Part IV Plan for post-authorisation efficacy studies	---	Not applicable, see EU RMP v 5.1; no UK specific content is provided.

Part	Module/annex	Summary of UK specific content (if applicable)
Part V Risk minimisation measures (Including evaluation of the effectiveness of risk minimisation activities)	---	For V.1. and V.3.: UK specific content is provided for routine risk minimisation measures for the two additional UK safety concerns. For V.2.: Not applicable, see EU RMP v 5.1; no UK specific content is provided.
Part VI Summary of risk management plan	---	Not applicable; Part VI is not included in the UK-MHRA template 'Guidance on the format and content of the UK-specific risk management plan annex, October 2021; Version 1.0'.
Part VII Annexes	Annex 2 Tabulated summary of planned, on-going, and completed pharmacovigilance study programme	Omitted (Not applicable, see EU RMP v 5.1; no UK specific content is provided.)
	Annex 3 Protocols for proposed, on-going and completed studies in the pharmacovigilance plan	Omitted (Not applicable, see EU RMP v 5.1; no UK specific content is provided.)
	Annex 4 Specific adverse drug reaction follow-up forms	Omitted (Not applicable, see EU RMP v 5.1; no UK specific content is provided.)
	Annex 5 Protocols for proposed and on-going studies in RMP Part IV	No UK specific content is provided, and reference is made to Annex 2 in EU RMP v 5.1 for a summary of the completed PAS study.
	Annex 6 Details of proposed additional risk minimisation activities	Omitted (Not applicable, see EU RMP v 5.1; no UK specific content is provided.)
	Annex 7 Other supporting data	Two references are provided in UK specific RMP annex v 1.1.
	Annex 8 Summary of changes to the EU Risk Management Plan and UK-specific RMP Annex over time	Two tables for summary of changes are included: • one table for EU RMP from v 5.1 and, • one table for UK specific RMP annex from v 1.1.

Part I: Product overview

Active ingredient(s) (INN):	Melatonin
Pharmacotherapeutic group(s) (ATC Code)	Hypnotics and sedatives, melatonin receptor agonists (ATC code: N05CH01)
Marketing Authorisation Holder/Applicant	AGB-Pharma AB
Medicinal products to which this RMP annex refers	1
Invented name(s) in UK	UK specific RMP annex v 1.1: Adaflex 1 mg tablets Adaflex 2 mg tablets Adaflex 3 mg tablets Adaflex 4 mg tablets Adaflex 5 mg tablets EU RMP v 5.1: Melatonin AGB 1 mg tablets Melatonin AGB 2 mg tablets Melatonin AGB 3 mg tablets Melatonin AGB 4 mg tablets Melatonin AGB 5 mg tablets
Brief description of the product	Chemical class: Hypnotics and sedatives, melatonin receptor agonists. Melatonin is a member of the class of acetamides that is acetamide in which one of the hydrogens attached to the nitrogen atom is replaced by a 2-(5-methoxy-1H-indol-3-yl) ethyl group.
	Summary of mode of action Melatonin is a hormone produced by the pineal gland. It is structurally related to serotonin. Melatonin secretion increases shortly after dark, reaching its peak between 2 am and 4 am and decreases during the latter half of the night. Melatonin is involved in controlling the circadian rhythm and adaptation to the light-dark cycle. Melatonin is also associated with a sedative effect and an increased propensity for sleep. Melatonin activity on MT1 and MT2 receptors is considered to contribute to its effect on sleep, as these receptors are involved in the regulation of circadian rhythm and sleep.
	Important information about its composition: The product contains the following excipients: microcrystalline cellulose, calcium hydrogen phosphate dihydrate and magnesium stearate.
Hyperlink to the Product Information	Link to the latest approved PI
Indication(s) in UK	Current: • Short-term treatment of jet lag in adults. • Insomnia in children and adolescents aged 6-17 years with ADHD, where sleep hygiene measures have been insufficient.

	There are no differences in the indications between the EU RMP v 5.1 and this UK specific RMP annex v 1.1.
	Proposed (if applicable): Not applicable. There are no differences in this regard between the EU RMP v 5.1 and this UK specific RMP annex v 1.1.
Dosage in UK	Current: <u>Adults with jet lag</u> The recommended dose is 1-5 mg for a maximum of 5 days. The dose should be taken at the time of destination bedtime for journeys of 5 time zones or longer, especially when traveling in an easterly direction. 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 AGB tablets should not be taken before 20:00 hr or after 04:00 hr at destination. As alcohol can impair sleep and potentially worsen certain symptoms of jet lag (e.g., headache, morning fatigue, concentration) it is recommended that alcohol is not consumed when taking Melatonin AGB tablets. A maximum of 16 treatment cycles may occur per year. <u>Insomnia in children and adolescents with ADHD</u> Treatment should be initiated by physicians experienced in ADHD and/or paediatric sleep medicine. Recommended starting dose of Melatonin AGB tablet: 1-2 mg 30-60 minutes before bedtime. The dose of melatonin can be increased by 1 mg every week until effect up to a maximum 5 mg per day, independent of age. The lowest effective dose should be sought. Limited data are available for up to 3 years of treatment. After about 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 AGB 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. There are no differences in the posology between the EU RMP v 5.1 and this UK specific RMP annex v 1.1.
	Proposed (if applicable): Not applicable.

	There are no differences in this regard between the EU RMP v 5.1 and this UK specific RMP annex v 1.1.
Pharmaceutical form(s) and strengths	Current (if applicable): Tablet All strengths: White, round, biconvex tablets, diameter 9.5 mm. Adaflex 1 mg: marked 1 Adaflex 2 mg: marked 2 Adaflex 3 mg: marked 3 Adaflex 4 mg: marked 4 Adaflex 5 mg: marked 5 There are no differences in this regard between the EU RMP v 5.1 and this UK specific RMP annex v 1.1, except for different invented names.
	Proposed (if applicable): Not applicable. There are no differences in this regard between the EU RMP v 5.1 and this UK specific RMP annex v 1.1.
Is/will the product be subject to additional monitoring in the UK?	No

Part II: Safety specification

The differences in the list of safety concerns between this UK specific RMP v 1.1 and the EU RMP v 5.1 are as follows:

Important potential risks:
One additional as compared with the EU RMP v 5.1:

- Off-label use in children under the age of 6 years

Missing information:
One additional missing information as compared with the EU RMP v 5.1:

- Fertility, pregnancy and lactation

In EU RMP v 5.1the following safety concerns has been re-evaluated [redacted]

- "Effects on sexual maturation and development in children and adolescents" previously classified as important potential risk is removed from the list of safety concerns.
- "Long-term safety in children and adolescents" previously classified as important potential risk is re-classified as Missing information.

The details of these UK specific additional safety concerns are provided below in sections SVII.3.1 and SVII.3.2.

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

Not applicable, see EU RMP v 5.1; no UK specific content is provided.

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

Not applicable, see EU RMP v 5.1; no UK specific content is provided.

Part II: Module SIII - Clinical trial exposure

Not applicable, see EU RMP v 5.1; no UK specific content is provided.

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

Not applicable, see EU RMP v 5.1; no UK specific content is provided.

Part II: Module SV - Post-authorisation experience

Not applicable, see EU RMP v 5.1; no UK specific content is provided.

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

Potential for misuse for illegal purposes

Not applicable, see EU RMP v 5.1; no UK specific content is provided.

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

Not applicable, see EU RMP v 5.1; no UK specific content is provided.

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

Important identified risks:

Not applicable, see EU RMP v 5.1; no UK specific content is provided.

Important potential risks:

One additional as compared with the EU RMP v 5.1:

1. Off-label use in children under the age of 6 years

Missing information:

One additional missing information as compared with the EU RMP v 5.1:

2. Fertility, pregnancy and lactation

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

The listed two additional safety concerns in section SVII.1.2 above are not new as such; they are listed in the SmPC for Adaflex tablets.

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:

Not applicable, see EU RMP v 5.1; no UK specific content is provided.

Important potential risk:

1. Off-label use in children under the age of 6 years

Potential mechanisms:

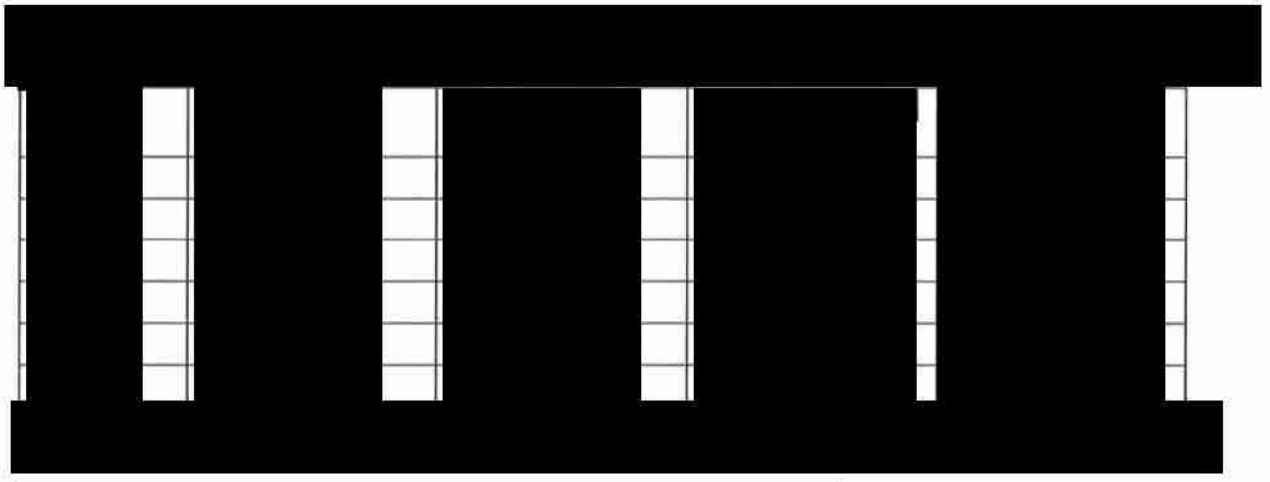
A plausible biological mechanism cannot be provided as the risk does not concern an actual adverse event/adverse reaction but reflects use outside the terms of the marketing authorisation (i.e. off-label use).

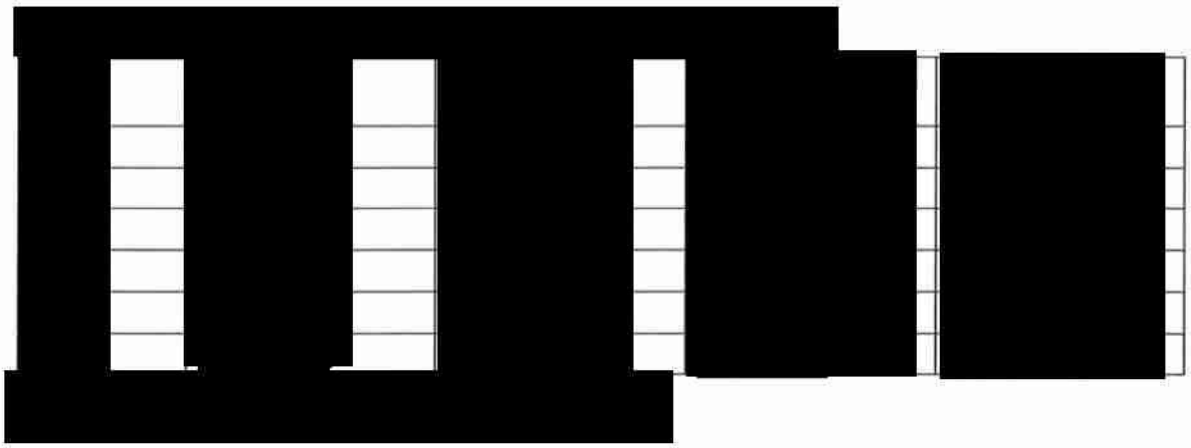
Evidence source(s) and strength of evidence:

See below under the heading 'Characterisation of the risk' for information on reporting rate and exposure data.

[redacted]

[redacted]





Risk factors and risk groups:
The risk groups are children under the age of 6 years who are prescribed Adaflex off-label.

Preventability:
The current routine risk minimisation measures in place for Adaflex are considered sufficient to prevent off-label use in children under the age of 6 years: [redacted]

Impact on the risk-benefit balance of the product:
The risk-benefit balance of Adaflex is considered to not be impacted, [redacted]

Public health impact:
The public health impact is considered low.

SVII.3.2 Presentation of missing information

Missing information:
2. Fertility, pregnancy and lactation

Evidence source:
Fertility
It is included in the SmPC that no adequate data on the effect of melatonin on human fertility are available and that animal studies are incomplete in terms of effects on fertility.

In a Cochrane review, it was assessed whether antioxidants, including melatonin, may improve fertility, since trials have explored this area with varied results (Showell et al. 2020). The main results of the review were: 63 trials involving 7760 women were included. Investigators compared oral antioxidants, including combinations of antioxidants, N-acetylcysteine, melatonin, L-arginine, myo-inositol, carnitine, selenium, vitamin E, vitamin B complex, vitamin C, vitamin D+calcium, CoQ10, and omega-3-polyunsaturated fatty acids versus placebo, no treatment/standard treatment or another antioxidant. The authors concluded that based on the review, there was low- to very low-quality evidence to show that taking an antioxidant may benefit subfertile women. Overall, there was no evidence of increased risk of miscarriage, multiple births, gastrointestinal effects or ectopic pregnancies, but evidence was of very low quality.

Pregnancy and breastfeeding
It is included in the SmPC of Adaflex that there are no data from the use of melatonin in pregnant women, and that animal studies are incomplete regarding effects on pregnancy, embryonic/fetal development, childbirth and postnatal development and that exogenous melatonin readily crosses the human placenta.

In a Canadian publication (Vine et al. 2022), a critical review of human studies related to exogenous melatonin use during pregnancy and lactation is provided. The electronic databases Ovid, MEDLINE, Embase, and the Cochrane Library were searched using terms and keywords related to melatonin, pregnancy, and breastfeeding. A summary of the review is as follows:

Fifteen studies were included in the review. Eight focused on melatonin use during pregnancy and seven focused on melatonin use during breastfeeding. There was a variety of study designs, including case reports, cohort studies, and clinical trials. There was a lack of randomised, controlled trials examining the efficacy and safety of melatonin as a treatment for sleep disorders during pregnancy and, notably, insomnia was not the primary outcome measure in any of the studies included in the review. The authors suggested that evidence from clinical studies to date indicate that melatonin use during pregnancy and

breastfeeding is probably safe in humans. However, the authors also stated that due to the scarcity of clinical trials of melatonin use during pregnancy and breastfeeding, especially trials with outcomes related to safety and efficacy in sleep disorders, no conclusions can be drawn from the available evidence.

Anticipated risk/consequence of the missing information:
As there is no or limited or inadequate data on whether the use of Adaflex may have an effect on fertility, pregnancy and lactation, treatment with Adaflex is not recommended for men and women planning pregnancy, pregnant women, women of childbearing potential not using contraceptives and breastfeeding women.

Part II: Module SVIII – Summary of the safety concerns

The list of safety concerns for Adaflex is presented in the table below. The differences between the list of safety concerns in the EU RMP v 5.1 and the UK specific RMP v 1.1 are also included in the table.

Summary of safety concerns	
Important identified risks	None Same as in EU RMP v 5.1
Important potential risks	1. Off-label use in children under the age of 6 years The important potential risk is additional to the EU RMP v 5.1. This additional important potential is included in this UK specific RMP annex [redacted]
Missing information	1. Long-term safety in children and adolescents 2. Fertility, pregnancy and lactation The missing information bullet number 1 is the same as in the updated EU RMP v 5.1. The missing information in bullet number 2, is additional to the EU RMP v 5.1 and it is included in this UK specific RMP annex [redacted]

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

III.1 Routine pharmacovigilance activities

Not applicable, see EU RMP v 5.1; no UK specific content is provided.

III.2 Additional pharmacovigilance activities

Not applicable, see EU RMP v 5.1; no UK specific content is provided. [redacted]

III.3 Summary table of additional pharmacovigilance activities

Not applicable, see EU RMP v 5.1; no UK specific content is provided [redacted]

Part IV: Plans for post-authorisation efficacy studies

Not applicable, see EU RMP v 5.1; no UK specific content is provided.

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

V.1. Routine risk minimisation measures

For the routine risk minimisation measures for the safety concerns that are the same in EU RMP v 5.1 and in this UK-specific RMP annex v 1.1, refer to section V.1 of EU RMP v 5.1 (covering the one missing information: long-term safety in children and adolescents).

Table Part V.1: Description of routine risk minimisation measures by safety concern for the additional UK specific safety concerns

Safety concern	Routine risk minimisation activities
Important potential risk - Off-label use in children under the age of 6 years	SmPC: In the SmPC section 4.2, the following is stated: 'Adaflex tablets are not recommended for children below 6 years with ADHD.' PL: In PL section 2, the following is stated: 'Adaflex should not be given to children below the age of 6 years.' Legal status: Prescription medicinal product only.
Missing information – Pregnancy, lactation and fertility	SmPC: In the SmPC, section 4.6 the following is stated: **'Fertility, pregnancy and lactation** Pregnancy There are no data from the use of melatonin in pregnant women. Animal studies are incomplete regarding effects on pregnancy, embryonic / fetal development, childbirth and postnatal development (see section 5.3). Exogenous melatonin readily crosses the human placenta. Considering the lack of clinical data, treatment with Adaflex is not recommended during pregnancy or in women of childbearing potential not using contraceptives. Breastfeeding Data from animal studies indicate maternal transfer of melatonin to the foetus via the placenta or in the milk. Endogenous melatonin has also been measured in breast milk from breast-feeding women, and therefore exogenous melatonin is most likely also excreted in human milk. Melatonin is therefore not recommended to breastfeeding women. Fertility No adequate data on the effect of melatonin on human fertility are available. Animal studies are incomplete in terms of effects on fertility. High doses of melatonin and use for longer periods than indicated may compromise fertility in humans.' PL: In the PL section 2 the following is stated: **'Pregnancy, breast-feeding and fertility** If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, you should not use Adaflex.

	Pregnancy Adaflex tablets are not recommended if you are pregnant. Melatonin crosses the placenta and there is insufficient information on the risk this may pose to the unborn child. If you are a woman of childbearing potential you have to use contraception. Breast-feeding Adaflex tablets are not recommended if you are breast-feeding. Melatonin is excreted in human milk, and a risk to the breast-fed child cannot be excluded. Fertility Adaflex tablets are not recommended in women and men planning to have a baby as there is insufficient information on the effects of melatonin on female and male fertility.' Legal status: Prescription medicinal product only.

V.2. Additional risk minimisation measures

Not applicable, see EU RMP v 5.1; no UK specific content is provided.

V.3 Summary of risk minimisation measures

For the summary of risk minimisation measures for the safety concerns that are the same in the EU RMP v 5.1 as in this UK specific RMP annex v 1.1, see section V.3. in EU RMP v 5.1 (for the one missing information, long-term safety in children).

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern for the additional UK specific safety concerns

Safety concern	Routine risk minimisation activities	Pharmacvigilance activities
Important potential risk - Off-label use in children under the age of 6 years	SmPC: In the SmPC, section 4.2 the following is stated: 'Adaflex tablets are not recommended for children below 6 years with ADHD.' PL: In the PL section 2 the following is stated: 'Adaflex should not be given to children below the age of 6 years.' Legal status: Prescription medicinal product only. Additional risk minimisation measures: No additional risk minimisation measures.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Missing information - Fertility, pregnancy and lactation	SmPC: In the SmPC, section 4.6 the following is stated: **'Fertility, pregnancy and lactation** Pregnancy There are no data from the use of melatonin in pregnant women. Animal studies are incomplete regarding effects on pregnancy, embryonic / fetal development, childbirth and postnatal development (see section 5.3). Exogenous melatonin readily crosses the human placenta. Considering the lack of clinical data, treatment with Adaflex is not recommended during pregnancy or in	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

	women of childbearing potential not using contraceptives. Breastfeeding Data from animal studies indicate maternal transfer of melatonin to the foetus via the placenta or in the milk. Endogenous melatonin has also been measured in breast milk from breast-feeding women, and therefore exogenous melatonin is most likely also excreted in human milk. Melatonin is therefore not recommended to breastfeeding women. Fertility No adequate data on the effect of melatonin on human fertility are available. Animal studies are incomplete in terms of effects on fertility. High doses of melatonin and use for longer periods than indicated may compromise fertility in humans.' PL: In the PL section 2 the following is stated: **'Pregnancy, breast-feeding and fertility** If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, you should not use Adaflex. Pregnancy Adaflex tablets are not recommended if you are pregnant. Melatonin crosses the placenta and there is insufficient information on the risk this may pose to the unborn child. If you are a woman of childbearing potential you have to use contraception. Breast-feeding Adaflex tablets are not recommended if you are breast-feeding. Melatonin is excreted in human milk, and a risk to the breast-fed child cannot be excluded. Fertility Adaflex tablets are not recommended in women and men planning to have a baby as there is insufficient information on the effects of melatonin on female and male fertility.' Legal status: Prescription medicinal product only. Additional risk minimisation measures: No additional risk minimisation measures.	

Part VI: Summary of the risk management plan

Part VI is not included in the UK-MHRA template 'Guidance on the format and content of the GB/UK-specific risk management plan annex, October 2021; Version 1.0'.

Part VII: Annexes

Annexes 2 to 6

Not applicable, see EU RMP v 5.1; no UK specific content is provided and thereby Annexes 2 to 6 are omitted. [redacted]

Annex 7 - Other supporting data (including referenced material)

Due to different safety concerns in UK and EU RMP:

1. WHO, ATC/DDD Index 2025, https://atcddd.fhi.no/atc_ddd_index/?code=N05CH01 (accessed on 14 August 2025)
2. Showell, M.G., R. Mackenzie-Proctor, V. Jordan, R.J. Hart. 2020. 'Antioxidants for female subfertility'. Cochrane Database Systematic Reviews, 27;8(8): CD007807, https://doi.org/10.1002/14651858.CD007807.pub4.
3. Vine, T., G.M. Brown, B.N. Frey. 2022. 'Melatonin use during pregnancy and lactation: A scoping review of human studies.' *Braz J Psychiatry*, 44(3):342-348. doi: 10.1590/1516-4446-2021-2156. PMID: 34730672; PMCID: PMC9169489.

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

Two tables for summary of changes are presented below: one table for the EU RMP and one for the UK specific RMP annex.

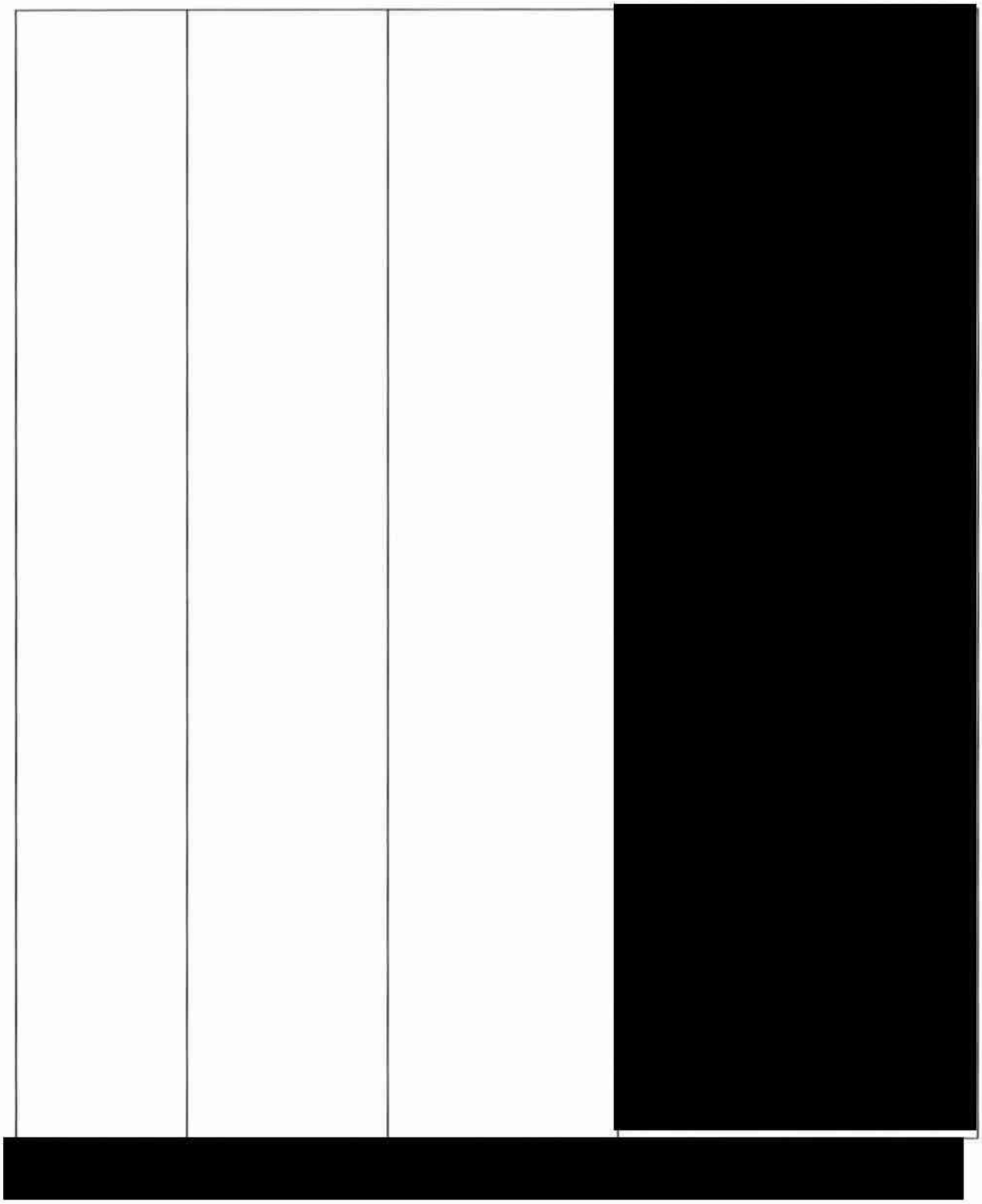
Summary of changes to EU RMP

Version (Initials of author and reviewer)	**Procedure and other references**	**Changes**
5 [redacted]	[redacted]	[redacted]
5.1 [redacted]		[redacted]

Summary of changes to UK specific RMP annex

Version (Initials of author and reviewer)	**Version of EU RMP the UK specific RMP annex is referring to**	**Procedure and other references**	**Changes**
1 [redacted]	5	[redacted]	[redacted]
1.1[a)] [redacted]	5.1		

			[redacted]



EU Risk Management Plan for Melatonin AGB (melatonin)

Risk Management Plan (RMP) version to be assessed as part of this application:

RMP Version number: 5.1

Data lock point for this RMP: 16 September 2025

Date of final sign-off: 22 September 2025

[redacted]

[redacted]

Other RMP versions under evaluation: None

[redacted]

QPPV name: [redacted]

QPPV signature [redacted]

Table of content

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)	Hypnotics and sedatives, melatonin receptor agonists (ATC code: N05CH01)
Marketing Authorisation Holder	AGB-Pharma AB
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Melatonin AGB 1, 2, 3, 4 and 5 mg tablets
Marketing authorisation procedure	[redacted]
Brief description of the product	Chemical class Hypnotics and sedatives, melatonin receptor agonists. Melatonin is a member of the class of acetamides that is acetamide in which one of the hydrogens attached to the nitrogen atom is replaced by a 2-(5-methoxy-1H-indol-3-yl) ethyl group.
	Summary of mode of action Melatonin is a hormone produced by the pineal gland. It is structurally related to serotonin. Melatonin secretion increases shortly after dark, reaching its peak between 2 am and 4 am and decreases during the latter half of the night. Melatonin is involved in controlling the circadian rhythm and adaptation to the light-dark cycle. Melatonin is also associated with a sedative effect and an increased propensity for sleep. Melatonin activity on MT1 and MT2 receptors is considered to contribute to its effect on sleep, as these receptors are involved in the regulation of circadian rhythm and sleep.
	Important information about its composition The product contains microcrystalline cellulose, calcium hydrogen phosphate dihydrate and magnesium stearate.
Hyperlink to the Product Information	Link to the latest approved PI
Indication(s) in the EEA	Current: • Short-term treatment of jet lag in adults. • Insomnia in children and adolescents aged 6-17 years with ADHD, where sleep hygiene measures have been insufficient.
	Proposed (if applicable): Not applicable
Dosage in the EEA	Current: Adults with jet lag The recommended dose is 1-5 mg for a maximum of 5 days. The dose should be taken at the time of destination bedtime for journeys of 5 time zones or longer, especially when traveling in an easterly direction. 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 AGB tablets should not be taken before 20:00 hr or after 04:00 hr at destination. As alcohol can impair sleep and potentially worsen certain symptoms of jet lag (e.g., headache, morning fatigue, concentration) it is recommended that alcohol is not consumed when taking Melatonin AGB tablets. A maximum of 16 treatment cycles may occur per year. <u>Insomnia in children and adolescents with ADHD</u> Treatment should be initiated by physicians experienced in ADHD and/or paediatric sleep medicine. Recommended starting dose of Melatonin AGB tablet: 1-2 mg 30-60 minutes before bedtime. The dose of melatonin can be increased by 1 mg every week until effect up to a maximum 5 mg per day, independent of age. The lowest effective dose should be sought. Limited data are available for up to 3 years of treatment. After about 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 AGB 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.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current (if applicable): Tablet All strengths: White, round, biconvex tablets, diameter 9.5 mm. Melatonin AGB 1 mg: marked 1 Melatonin AGB 2 mg: marked 2 Melatonin AGB 3 mg: marked 3 Melatonin AGB 4 mg: marked 4 Melatonin AGB 5 mg: marked 5
	Proposed (if applicable): Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety specification
Marketing authorisation has been obtained for Melatonin AGB under Article 10a of Directive 2001/83/EC, a 'well established use' application.

Part II: Module SI - Epidemiology of the indication(s) and target population(s)
Not applicable; marketing authorisation has been obtained under Article 10a of Directive 2001/83/EC, a 'well established use' application, and accordingly this section is omitted.

Part II: Module SII - Non-clinical part of the safety specification
Not applicable; marketing authorisation has been obtained under Article 10a of Directive 2001/83/EC, a 'well established use' application, and accordingly this section is omitted.

Part II: Module SIII - Clinical trial exposure
Not applicable; marketing authorisation has been achieved under Article 10a of Directive 2001/83/EC, a 'well established use' application, and accordingly this section is omitted.

Part II: Module SIV - Populations not studied in clinical trials
Not applicable; marketing authorisation has been achieved under Article 10a of Directive 2001/83/EC, a 'well established use' application, and accordingly this section is omitted.

Part II: Module SV - Post-authorisation experience
Not applicable; marketing authorisation has been obtained under Article 10a of Directive 2001/83/EC, a 'well established use' application, and accordingly this section is omitted.

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

Potential for misuse for illegal purposes
Not applicable; it is assessed that there is no potential for misuse for illegal purposes, linked to the safety specification for Melatonin Tablets.

Part II: Module SVII - Identified and potential risks
Only safety concerns that could affect the benefit-risk balance and warrants further investigation as part of the pharmacovigilance plan are included in this RMP.

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
Not applicable

Reasons 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):

- None.

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:

- None.

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:

- None.

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 risks:
None

Important potential risks:
None

Missing information:

Long-term safety in children and adolescents

[redacted]

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

-

- "Effects on sexual maturation and development in children and adolescents" previously classified as important potential risk is removed from the list of safety concerns.
- "Long-term safety in children and adolescents" previously classified as important potential risk is re-classified as Missing information.

Reasons for the removal to the list of safety concerns:

[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:
None

Important potential risk:
None

SVII.3.2 Presentation of the missing information
Missing Information: Long-term safety in children and adolescents

Evidence source
Long-term safety studies presented in 2.5 Clinical Overview suggests a benign AE profile. AGB-Pharma AB monitors any relevant post marketing safety reports.

Population in need of further characterisation:
Children and adolescents

Anticipated risk/consequence of the missing information:
The SmPC under section 4.2 indicates that" Limited data are available for up to 3 years of treatment". In addition, treatment should be initiated by physicians experienced in ADHD and/or paediatric sleep medicine.

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	None
Missing information	Long-term safety in children and adolescents

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

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance is conducted for Melatonin AGB as detailed in corresponding pharmacovigilance procedures that are in place at AGB-Pharma AB.

III.2 Additional pharmacovigilance activities

Not applicable[redacted]

III.3 Summary table of additional pharmacovigilance activities

Not applicable;[redacted]

Part IV: Plans for post-authorisation efficacy studies

No post-authorisation efficacy studies are ongoing, completed or planned. The available medical literature and routine pharmacovigilance activities are considered sufficient to evaluate and monitor the benefit-risk ratio of Melatonin tablets over time.

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

Risk minimisation plan

On basis of the safety specification the needed risk minimisation measures and additional pharmacovigilance activities for the safety concerns listed in part II module SVIII in the present RMP are presented here.

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
Missing Information	
Long-term safety in children and adolescents	In SmPC section 4.2 it is stated that 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 Tablets is still the most appropriate treatment. SmPC section 4.8: Melatonin causes few, and no serious, adverse reactions in the short term, up to three months. Long-term effects are poorly studied. Included in PL section 3: Treatment should be followed up regularly by a doctor (at least every 6 months is recommended) to see if it is still appropriate. Legal status: Prescription medicinal product only.

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
Missing Information		
Long-term safety in children and adolescents	Routine risk minimisation measures: In SmPC section 4.2 it is stated that 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 Tablets is still the most appropriate treatment. SmPC section 4.8: Melatonin causes few, and no serious, adverse reactions in the short term, up to three months. Long-term effects are poorly studied. Included in PL section 3: Treatment should be followed up regularly by a doctor (at least every 6 months is recommended) to see if it is still appropriate. Legal status: Prescription medicinal product only. Additional risk minimisation measures: No risk minimisation measures.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Part VI: Summary of the risk management plan

Summary of risk management plan for Melatonin AGB (melatonin)

This is a summary of the risk management plan (RMP) for Melatonin AGB. The RMP details important risks of the medicinal product Melatonin AGB, how these risks can be minimised, and how more information will be obtained about Melatonin AGB's risks and uncertainties (missing information).

The Summary of Product Characteristics (SmPC) and its package leaflet provide essential information to healthcare professionals and patients on how Melatonin AGB should be used.

Important new concerns or changes to the current ones will be included in updates of Melatonin AGB RMP.

I. The medicine and what it is used for

Melatonin AGB is authorised for short-term treatment of jet lag in adults and insomnia in children and adolescents aged 6-17 years with ADHD, where sleep hygiene measures have been insufficient (see SmPC for the full indication). It contains melatonin as the active substance, and it is administered orally (tablet).

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

Important risks of Melatonin AGB, together with measures to minimise such risks and the proposed studies for learning more about the 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 actions can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A List of important risks and missing information

Important risks of Melatonin AGB 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 AGB. 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).

Table VI.1: Summary of safety concerns

List of important risks and missing information	
Important identified risks	None
Important potential risks	None
Missing information	Long-term safety in children and adolescents

II.B Summary of important risks

Missing Information	
Long-term safety in children and adolescents	
Evidence for linking the risk to the medicine	Data for long-term safety Children and adolescents for treatment with melatonin are not extensive
Risk factors and risk groups	Children and adolescents
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.2 states that 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 Tablets is still the most appropriate treatment. SmPC section 4.8 Melatonin causes few, and no serious, adverse reactions in the short term, up to three months. Long-term effects are poorly studied. Included in PL section 3: Treatment should be followed up regularly by a doctor (at least every 6 months is recommended) to see if it is still appropriate. Additional risk minimisation measures: No additional risk minimisation measures.

II.C Post-authorisation development plan

Not applicable

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

Not applicable; there are no studies which are conditions of the marketing authorisation.

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

Not applicable

Part VII: Annexes

Annex 1 - EudraVigilance Interface

Not applicable

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

Table 1 Annex II: Planned and on-going studies

Not applicable

Table 2 Annex II: Completed studies

Study	Summary of objectives	Safety concerns addressed	Date of final study report and link to report
[redacted]	[redacted]	[redacted]	[redacted]

Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan
Not applicable

Annex 4 - Specific adverse drug reaction follow-up forms
Not applicable

Annex 5 - Protocols for proposed and on-going studies in RMP part IV
Not applicable

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)
Not applicable

Annex 7 - Other supporting data (including refereneed material)

1. Swedish growths charts; Albertsson-Wikland K, Niklasson A, Holmgren A, Gelander L, Nierop AFM. 'A new Swedish reference for total and prepubertal height.' Acta Paediatrica, 2020;109:754-763

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

Version	Procedure	Changes
1.0	[redacted]	[redacted]
1.1	[redacted]	[redacted]
1.2	[redacted]	[redacted]

Version	Procedure	Changes
1.3	[redacted]	[redacted]
2[a)]	[redacted]	[redacted]
3	[redacted]	[redacted]

Version	Procedure	Changes
4	[redacted]	[redacted]

Version	Procedure	Changes
5	[redacted]	[redacted]
5.1[b)]	[redacted]	[redacted]

Version	Procedure	Changes
		[redacted]