Part VI: Summary of the risk management plan

Summary of risk management plan for Melatonin Tablets (melatonin)

This is a summary of the RMP for Melatonin Tablets. The RMP details important risks of these products, and how more information will be obtained about their risks and uncertainties (missing information).

The Summary of Product Characteristics (SmPC) and their package leaflets of Melatonin Tablets provide essential information to healthcare professionals and patients on how these products should be used.

I The medicine and what it is used for
Melatonin Tablets are used 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.

II Risks associated with the medicine and activities to minimise or further characterise the risks
Important risks of Melatonin Tablets, 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.

If important information that may affect the safe use of Melatonin Tablets is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information
Important risks of Melatonin Tablets are risks that need special risk management activities to further investigate or minimise the risk, so that these medicinal products 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 these products. Potential risks are concerns for which an association with the use of these medicines 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	• Long-term safety in children and adolescents • Effects on sexual maturation and development in children and adolescents
Missing information	None

II.B Summary of important risks

Effects on sexual maturation and development in children and adolescents	
Evidence for linking the risk to the medicine	Scientific literature including published clinical studies and results from studies of prenatal and postnatal development in rats indicate that melatonin administration affects the hormonal level and sexual maturation in the offspring.
Risk factors and risk groups	Children in prepuberty/puberty
Risk minimisation measures	Routine risk minimisation measures SmPC section 4.2 states that the patient should be monitored at regular intervals (at least every 6 months) to check that Melatonin Tablets is still the most appropriate treatment. 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
Additional pharmacovigilance activities	Additional pharmacovigilance activities: PASS AGB008: Retrospective registry study evaluating the safety of melatonin in children and adolescents with attention-deficit hyperactive disorder (ADHD) in Sweden. See section II.C of this summary for an overview of the post-authorisation development plan.

Long-term safety in children and adolescents	
Evidence for linking the risk to the medicine	Data for long-term safety in children in prepuberty/puberty for melatonin are not extensive
Risk factors and risk groups	Children in prepuberty/puberty
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. 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.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: PASS: AGB008. Retrospective registry study evaluating the safety of melatonin in children and adolescents with attention-deficit hyperactive disorder (ADHD) in Sweden. See section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-authorisation development plan
Not applicable

II.C.1 Studies which are conditions of the marketing authorisation
Not applicable

II.C.2 Other studies in post-authorisation development plan
Study short name: PASS AGB008
Purpose of the study:

In connection to the approval of Melatonin AGB® in Sweden (National procedure; Asp no.: 2017-0394, 2017-0395, 2017-0396, 2017-0397, 2017-0398), AGB-Pharma AB was requested to conduct a Category 3 -authorisation study on long-term safety in prepubertal and pubertal children: Insomnia in children and adolescents aged 6-17 years with ADHD, where sleep hygiene measures have been insufficient. The MPA specified specific aspects of the study design in the National procedure, Day 190 Overview, dated 07 Nov 2019 (V.3 Clinical Aspects, Risk Management Plan). The background for this request was the theoretical concern on the effect of melatonin on sexual maturation in children and adolescents with ADHD.

This PASS study aims to study the height development in children and adolescents with ADHD, which are prescribed melatonin. The primary objective is to determine whether long-term treatment of melatonin (>30 days) influences height development in children and adolescents with ADHD. The exploratory objective is to describe melatonin medicine adherence as defined by medicine possession ratio and proportion of days covered and to study the growth of children and adolescents with ADHD and prescribed melatonin compared to national Swedish growth charts[13].

Part VII: Annexes