Part VI: Summary of the risk management plan for Melatonin Orifarm

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

Melatonin Orifarm's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Melatonin Orifarm should be used.

I. The medicine and what it is used for

Melatonin Orifarm is authorised for 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 substances and it is given orally as film-coated tablets.

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

Important risks of Melatonin Orifarm, together with measures to minimise such risks and the proposed studies for learning more about Melatonin Orifarm's risks, are outlined below.

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

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

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

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

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

II.A List of important risks and missing information

Important risks of Melatonin Orifarm 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 Orifarm. 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	None
Important potential risks	Effects on sexual maturation and development in children and adolescents

Summary of safety concerns	
Missing information	Long-term safety in children and adolescent is a new important potential risk

II.B Summary of important risks

Important potential risk: Effects on sexual maturation and development in children and adolescents	
Evidence for linking the risk to the medicine	The active substance is the hormone melatonin which regulates the reproductive process in seasonal but not in continuous breeders: however, it delays sexual development in the rat in a transient and reversible manner (Lang, 1986; Lang et al, 1984) Evidence indicating that endogenous melatonin levels in humans show a sharp decline just before the onset of puberty has raised some concern of a potential risk of delayed sexual maturity in pre-pubertal children taking melatonin over extended periods (Besag et al., 2019). The available studies investigating possible alteration in puberty timing of children taking melatonin are not conclusive (Boafo et al., 2019; van Geijlswijk et al., 2011; Zwart et al., 2018).
Risk factors and risk groups	Children and adolescents that are between pre-pubertal to pubertal stages.
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.2 / PL section 3 where advice is given on monitoring the patient at regular intervals (at least every 6 months).*

Missing information: Long-term safety in children and adolescent	
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.2 and 5.1.* *SmPC section 4.2 / PL section 3 where advice is given on monitoring the patient at regular intervals (at least every 6 months), also during ongoing treatment.*

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 Orifarm.

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

There are no studies required for Melatonin Orifarm.