Summary of risk management plan for Circadin / Melatonin Neurim (melatonin)

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

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

This summary of the RMP for Circadin/Melatonin Neurim should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Circadin's/Melatonin Neurim's RMP.

I. The medicine and what it is used for

Circadin/Melatonin Neurim is authorised for primary insomnia in patients aged 55 years or above (see SmPC for the full indication). It contains melatonin as the active substance and it is given by oral tablet.

Further information about the evaluation of Circadin's/Melatonin Neurim's benefits can be found in Circadin's/Melatonin Neurim's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/circadin

https://www.ema.europa.eu/en/medicines/human/EPAR/melatonin-neurim

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

Important risks of Circadin/Melatonin Neurim, together with measures to minimise such risks and the proposed studies for learning more about Circadin's/Melatonin Neurim'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 Circadin/Melatonin Neurim is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Circadin/Melatonin Neurim 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 Circadin/Melatonin Neurim. 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	Confusion Hallucinations Dyspnoea
Missing information	Use in pregnancy/lactation

II.B Summary of important risks

Important potential risk: Confusion	
Evidence for linking the risk to the medicine	Clinical trial and post-marketing case reports; published studies in the scientific and medical literature.
Risk factors and risk groups	Confusion is a possible consequence of lack of sleep which would be an underlying risk for any patient receiving Circadin/Melatonin Neurim. Additionally, any pre-existing condition that would pre-dispose a patient to confusion would be a strong predictor for confusion associated with Circadin/Melatonin Neurim. Case NEU-001063-2017 contained a specific history of confusion, and case NEU-0062-2010 contained a history of hallucinations. In 2 of the 27 reports of confusion the patients had Alzheimer's disease which is a very clear confounding factor (NEU-0062-2010 and NEU-0147-2011). Two cases included histories of drug abuse. Case NEU-0264-2010 involved abuse of lorazepam and alprazolam, and Circadin/Melatonin Neurim was being taken to facilitate their withdrawal. Case NEU-001202-2017 involved cannabis abuse and benzodiazepine withdrawal. A further 6 cases contained histories of anxiety or depression: NEU-0062-2010, NEU-0304-2010, NEU-0035-2013, NEU-0105-2014, NEU-0249-2014 and NEU-001037-2015. In case NEU-0277-2010 it was reported that the patient had not experienced any similar adverse events in the past and none of

	their concomitant medications would be implicated (anastrozole, caffeine / magnesium salicylate, calcium / vitamin D, estriol, felodipine, simvastatin, thyroxine, zolpidem). Therefore, it can be concluded that while a pre-disposing psychiatric history may increase the risk of confusion associated with Circadin/Melatonin Neurim it is not a necessary factor. However, there is no clear dose relationship. In 8 of the reports (8 / 27, 29.6%), the patients were receiving 2 mg daily of Circadin/Melatonin Neurim which is the approved daily dose. In case NEU-0105-2014, the patient was in a double-blind clinical trial, but the SAEs were not considered to be related as the patient was receiving placebo. However, in report NEU-0105-2014 the patient reported that the 2 mg dose was accompanied by poor sleep and an out-of-body experience, but when the dose was increased to 4 mg the patient experienced "the worst night of my life" alongside confusion, anxiety, sweating, nightmares and restlessness. In cases NEU-001151-2015 and NEU-001411-2019 the patients were receiving a melatonin daily dose of 3 mg, but it is not confirmed that these patients were actually receiving Circadin/Melatonin Neurim. In cases NEU-001557-2019 and NEU-001765-2019, the patients took overdoses of melatonin, but they also took at least one other medication in overdose.
Risk minimisation measures	Routine risk minimisation measures: Pack size of 7, 20, 21 or 30 tablets Prescription-only medicine

Important potential risk: Dyspnoea	
Evidence for linking the risk to the medicine	Clinical trial and post-marketing case reports; published studies in the scientific and medical literature.
Risk factors and risk groups	There were no common risk factors to any of the 20 patients experiencing dyspnoea associated with Circadin/Melatonin Neurim. Only 3 cases involved underlying respiratory disorders: NEU-0145-2010 chronic obstructive pulmonary disease; NEU-001533-2019 asthma and bronchiectasis; NEU-001890-2019 asthma and non-productive cough. Case NEU-0015-2013 involved an 85 year old obese patient with a history of cardiac failure and Parkinson's disease. In case NEU-001009-2015, amisulpride and clomipramine were started at exactly the same time as Circadin/Melatonin Neurim and the time to onset of the dyspnoea was 2 days later. Also, all 3 drugs were stopped at the same time and the dyspnoea resolved. However, dyspnoea is not a recognized undesirable effect of amisulpride or clomipramine. In case NEU-001005-2016, the patient was receiving amoxicillin presumably for an infection. If the infection was respiratory in nature then this would be a confounding factor. Also, the patient was receiving an unspecified brand of melatonin and so the possibility of a reaction to a different excipient cannot be ruled out. In the discussion on mechanism above, it is hypothesized that dyspnoea associated with Circadin/Melatonin Neurim may be a symptom of hypersensitivity. Therefore, previous hypersensitivity reactions to medications could be a possible predictive factor. There is no clear dose relationship. The dose was reported in 7 of the 20 cases (35%) and was 2 mg daily in 6 of them which is the approved dose for melatonin. In the 6th case (NEU-001062-2015)

	the dose was 3 mg but the brand of melatonin was unspecified making it unlikely to be Circadin/Melatonin Neurim. Cases NEU-001036-2016 and NEU-001890-2017 originated from clinical trials and the treatments were blinded.
Risk minimisation measures	Routine risk minimisation measures: Pack size of 7, 20, 21 or 30 tablets Prescription-only medicine

Important potential risk: Hallucinations	
Evidence for linking the risk to the medicine	Clinical trial and post-marketing case reports; published studies in the scientific and medical literature.
Risk factors and risk groups	Strong predictive factors for developing hallucinations include an underlying medical history of hallucination or taking concomitant medications which are known to cause hallucinations. For the 32 cases of hallucinations, 16 (50%) contained either confounding medical history (Alzheimer's disease, previous hallucinations and psychosis) or medications which are known to cause hallucinations (duloxetine, fluoxetine guanfacine, methylphenidate, metoprolol, midazolam, oxycodone, promethazine, sertraline, zolpidem and zopiclone). There was no clear association with dose. In 17 cases (53.1%) either no dose was specified or a dose size was specified but not a dosing schedule. Only 5 cases (19.2%) clearly stated that the dose was 2 mg daily. In case NEU-001028-2017, the patient developed hallucinations after receiving Circadin/Melatonin Neurim at 8 mg per dose (but with an unspecified dose schedule), but the hallucinations resolved when the dose was reduced to 4 mg per dose. In 6 cases that involved multi-drug overdoses, the size of the melatonin overdose was not specified.
Risk minimisation measures	Routine risk minimisation measures: Pack size of 7, 20, 21 or 30 tablets Prescription-only medicine

Missing information: Use in pregnancy / lactation	
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.6 and PL section 2 where advice is given in relation to pregnancy and breastfeeding Pack size of 7, 20, 21 or 30 tablets Prescription-only medicine

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 Circadin/Melatonin Neurim.

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

There are no studies required for Circadin/Melatonin Neurim.