**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

Melatonin Neurim 2 mg prolonged-release tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release tablet contains 2 mg melatonin.
Excipient with known effect: each prolonged-release tablet contains 80 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Prolonged-release tablet.

White to off-white, round, biconvex tablets

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Melatonin Neurim is indicated as monotherapy for the short-term treatment of primary insomnia characterised by poor quality of sleep in patients who are aged 55 or over.

### 4.2 Posology and method of administration

Posology

The recommended dose is 2 mg once daily, 1-2 hours before bedtime and after food. This dosage may be continued for up to thirteen weeks.

*Paediatric population*
The safety and efficacy of Melatonin Neurim in children aged 0 to 18 years has not yet been established.
Other pharmaceutical forms/strengths may be more appropriate for administration to this population.
Currently available data are described in section 5.1.

*Renal impairment*
The effect of any stage of renal impairment on melatonin pharmacokinetics has not been studied. Caution should be used when melatonin is administered to such patients.

*Hepatic impairment*
There is no experience of the use of Melatonin Neurim in patients with liver impairment. Published data demonstrates markedly elevated endogenous melatonin levels during daytime hours due to decreased clearance in patients with hepatic impairment. Therefore, Melatonin Neurim is not recommended for use in patients with hepatic impairment.

Method of Administration

Oral use. Tablets should be swallowed whole to maintain prolonged release properties. Crushing or chewing should not be used to facilitate swallowing.

## 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

## 4.4 Special warnings and precautions for use

Melatonin Neurim may cause drowsiness. Therefore the product should be used with caution if the effects of drowsiness are likely to be associated with a risk to safety.

No clinical data exist concerning the use of Melatonin Neurim in individuals with autoimmune diseases. Therefore, Melatonin Neurim is not recommended for use in patients with autoimmune diseases.

Melatonin Neurim contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

## 4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Pharmacokinetic interactions

- Melatonin has been observed to induce CYP3A *in vitro* at supra-therapeutic concentrations. The clinical relevance of the finding is unknown. If induction occurs, this can give rise to reduced plasma concentrations of concomitantly administered medicinal products.
- Melatonin does not induce CYP1A enzymes *in vitro* at supra-therapeutic concentrations. Therefore, interactions between melatonin and other active substances as a consequence of melatonin's effect on CYP1A enzymes are not likely to be significant.
- Melatonin's metabolism is mainly mediated by CYP1A enzymes. Therefore, interactions between melatonin and other active substances as a consequence of their effect on CYP1A enzymes is possible.
- Caution should be exercised in patients on fluvoxamine, which increases melatonin levels (by 17-fold higher AUC and a 12-fold higher serum $C_{max}$) by inhibiting its metabolism by hepatic cytochrome P450 (CYP) isozymes CYP1A2 and CYP2C19. The combination should be avoided.
- Caution should be exercised in patients on 5- or 8-methoxypsoralen (5 and 8-MOP), which increases melatonin levels by inhibiting its metabolism.
- Caution should be exercised in patients on cimetidine a CYP2D inhibitor, which increases plasma melatonin levels, by inhibiting its metabolism.
- Cigarette smoking may decrease melatonin levels due to induction of CYP1A2.
- Caution should be exercised in patients on oestrogens (e.g. contraceptive or hormone replacement therapy), which increase melatonin levels by inhibiting its metabolism by CYP1A1 and CYP1A2.
- CYP1A2 inhibitors such as quinolones may give rise to increased melatonin exposure.
- CYP1A2 inducers such as carbamazepine and rifampicin may give rise to reduced plasma concentrations of melatonin.
- There is a large amount of data in the literature regarding the effect of adrenergic agonists/antagonists, opiate agonists/antagonists, antidepressant medicinal products, prostaglandin inhibitors, benzodiazepines, tryptophan and alcohol, on endogenous melatonin secretion. Whether or not these active substances interfere with the dynamic or kinetic effects of Melatonin Neurim or vice versa has not been studied.

Pharmacodynamic interactions

- Alcohol should not be taken with Melatonin Neurim, because it reduces the effectiveness of Melatonin Neurim on sleep.
- Melatonin Neurim may enhance the sedative properties of benzodiazepines and non-benzodiazepine hypnotics, such as zaleplon, zolpidem and zopiclone. In a clinical trial, there was clear evidence for a transitory pharmacodynamic interaction between Melatonin Neurim and zolpidem one hour following co-dosing. Concomitant administration resulted in increased impairment of attention, memory and co-ordination compared to zolpidem alone.
- Melatonin Neurim has been co-administered in studies with thioridazine and imipramine, active substances which affect the central nervous system. No clinically significant pharmacokinetic interactions were found in each case. However, Melatonin Neurim co-administration resulted in increased feelings of tranquility and difficulty in performing tasks compared to imipramine alone, and increased feelings of "muzzy-headedness" compared to thioridazine alone.

## 4.6 Fertility, pregnancy and lactation

Pregnancy
For melatonin, no clinical data on exposed pregnancies are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). In view of the lack of clinical data, use in pregnant women and by women intending to become pregnant is not recommended.

Breast-feeding
Endogenous melatonin was measured in human breast milk thus exogenous melatonin is probably secreted into human milk. There are data in animal models including rodents, sheep, bovine and primates that indicate maternal transfer of melatonin to the foetus via the placenta or in the milk. Therefore, breast-feeding is not recommended in women under treatment with melatonin.

## 4.7 Effects on ability to drive and use machines

Melatonin Neurim has moderate influence on the ability to drive and use machines. Melatonin Neurim may cause drowsiness, therefore the product should be used with caution if the effects of drowsiness are likely to be associated with a risk to safety.

## 4.8 Undesirable effects

Summary of the safety profile
In clinical trials (in which a total of 1,931 patients were taking Melatonin Neurim and 1,642 patients were taking placebo), 48.8% of patients receiving Melatonin Neurim reported an adverse reaction compared with 37.8% taking placebo. Comparing the rate of patients with adverse reactions per 100 patient weeks, the rate was higher for placebo than Melatonin Neurim (5.743– placebo vs. 3.013– Melatonin Neurim). The most common adverse reactions were headache, nasopharyngitis, back pain, and arthralgia, which were common, by MedDRA definition, in both the Melatonin Neurim and placebo treated groups.

Tabulated list of adverse reactions
The following adverse reactions were reported in clinical trials and from post-marketing spontaneous reporting.
In clinical trials a total of 9.5% of patients receiving Melatonin Neurim reported an adverse reaction compared with 7.4% of patients taking placebo. Only those adverse reactions reported during clinical trials occurring in patients at an equivalent or greater rate than placebo have been included below.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very rare (<1/10,000); Not known (cannot be established from the available data).

| **System Organ Class** | **Very Common** | **Common** | **Uncommon** | **Rare** | **Not known:** (Cannot be established from the available data) |
|---|---|---|---|---|---|
| Infections and infestations | | | | Herpes zoster | |
| Blood and lymphatic system disorders | | | | Leukopenia, thrombocytopenia | |
| Immune system disorders | | | | | Hyper-sensitivity reaction |
| Metabolism and nutrition disorders | | | | Hypertriglyceridaemia, hypocalcaemia, hyponatraemia | |
| Psychiatric disorders | | | Irritability, nervousness, restlessness, insomnia, abnormal dreams, nightmares, anxiety | Mood altered, aggression, agitation, crying, stress symptoms, disorientation, early morning awakening, libido increased, depressed mood, depression | |
| Nervous system disorders | | | Migraine, headache, lethargy, psychomotor hyperactivity, dizziness, somnolence | Syncope, memory impairment, disturbance in attention, dreamy state, restless legs syndrome, poor quality sleep, paraesthesia | |
| Eye disorders | | | | Visual acuity reduced, vision blurred, lacrimation increased | |
| Ear and labyrinth disorders | | | | Vertigo positional, vertigo | |
| Cardiac disorders | | | | Angina pectoris, palpitations | |
| Vascular disorders | | | Hypertension | Hot flush | |

| System Organ Class | Very Common | Common | Uncommon | Rare | Not known: (Cannot be established from the available data) |
|---|---|---|---|---|---|
| Gastrointestinal disorders | | | Abdominal pain, abdominal pain upper, dyspepsia, mouth ulceration, dry mouth, nausea | Gastro-oesophageal reflux disease, gastrointestinal disorder, oral mucosal blistering, tongue ulceration, gastrointestinal upset, vomiting, bowel sounds abnormal, flatulence, salivary hypersecretion, halitosis, abdominal discomfort, gastric disorder, gastritis | |
| Hepatobiliary disorders | | | Hyperbilirubinaemia | | |
| Skin and subcutaneous tissue disorders | | | Dermatitis, night sweats, pruritus, rash, pruritus generalised, dry skin | Eczema, erythema, hand dermatitis, psoriasis, rash generalised, rash pruritic, nail disorder | Angioedema, oedema of mouth, tongue oedema |
| Musculoskeletal and connective tissue disorders | | | Pain in extremity | Arthritis, muscle spasms, neck pain, night cramps | |
| Renal and urinary disorders | | | Glycosuria, proteinuria | Polyuria, haematuria, nocturia | |
| Reproductive system and breast disorders | | | Menopausal symptoms | Priapism, prostatitis | Galactorrhoea |
| General disorders and administration site conditions | | | Asthenia, chest pain | Fatigue, pain, thirst | |
| Investigations | | | Liver function test abnormal, weight increased | Hepatic enzyme increased, blood electrolyes abnormal, laboratory test abnormal | |

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

## 4.9 Overdose

Several cases of overdose have been reported post-marketing. Somnolence was the most reported adverse event. Most were mild to moderate in severity. Melatonin Neurim has been administered at 5 mg daily doses in clinical trials over 12 months without significantly changing the nature of the adverse reactions reported.

Administration of daily doses of up to 300 mg of melatonin without causing clinically significant adverse reactions have been reported in the literature.

If overdose occurs, drowsiness is to be expected. Clearance of the active substance is expected within 12 hours after ingestion. No special treatment is required.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psycholeptics, melatonin receptor agonists, ATC code: N05CH01

Melatonin is a naturally occurring hormone produced by the pineal gland and is structurally related to serotonin. Physiologically, melatonin secretion increases soon after the onset of darkness, peaks at 2-4 am and diminishes during the second half of the night. Melatonin is associated with the control of circadian rhythms and entrainment to the light-dark cycle. It is also associated with a hypnotic effect and increased propensity for sleep.

Mechanism of action
The activity of melatonin at the MT1, MT2 and MT3 receptors is believed to contribute to its sleep-promoting properties, as these receptors (mainly MT1 and MT2) are involved in the regulation of circadian rhythms and sleep regulation.

Rationale for use
Because of the role of melatonin in sleep and circadian rhythm regulation, and the age related decrease in endogenous melatonin production, melatonin may effectively improve sleep quality particularly in patients who are over 55 with primary insomnia.

Clinical efficacy and safety
In clinical trials, where patients suffering from primary insomnia received Melatonin Neurim 2 mg every evening for 3 weeks, benefits were shown in treated patients compared to placebo in sleep latency (as measured by objective and subjective means) and in subjective quality of sleep and daytime functioning (restorative sleep) with no impairment of vigilance during the day.

In a polysomnographic (PSG) study with a run-in of 2 weeks (single-blind with placebo treatment), followed by a treatment period of 3 weeks (double-blind, placebo-controlled, parallel group design) and a 3-week withdrawal period, sleep latency (SL) was shortened by 9 minutes compared to placebo. There were no modifications of sleep architecture and no effect on REM sleep duration by Melatonin Neurim. Modifications in diurnal functioning did not occur with Melatonin Neurim 2 mg.

In an outpatient study with 2 week run-in baseline period with placebo, a randomised, double blind, placebo controlled, parallel group treatment period of 3 weeks and 2 week withdrawal period with placebo, the rate of patients who showed a clinically significant improvement in both quality of sleep and morning alertness was 47% in the Melatonin Neurim group as compared to 27% in the placebo group. In addition, quality of sleep and morning alertness significantly improved with Melatonin Neurim compared to placebo. Sleep variables gradually returned to baseline with no rebound, no increase in adverse reactions and no increase in withdrawal symptoms.

In a second outpatient study with two week run in baseline period with placebo and a randomised, double blind, placebo controlled, parallel group treatment period of 3 weeks, the rate of patients who showed a clinically significant improvement in both quality of sleep and morning alertness was 26% in the Melatonin Neurim group as compared to 15% in the placebo group. Melatonin Neurim shortened patients' reported sleep latency by 24.3 minutes vs 12.9 minutes with placebo. In addition, patients' self-reported quality of sleep, number of awakenings and morning alertness significantly improved with Melatonin Neurim compared to placebo. Quality of life was improved significantly with Melatonin Neurim 2 mg compared to placebo.

An additional randomised clinical trial (n=600) compared the effects of Melatonin Neurim and placebo for up to six months. Patients were re-randomised at 3 weeks. The study demonstrated improvements in sleep latency, quality of sleep and morning alertness, with no withdrawal symptoms and rebound insomnia. The study showed that the benefit observed after 3 weeks is maintained for up to 3 months but failed the primary analysis set at 6 months. At 3 months, about an extra 10% of responders were seen in the Melatonin Neurim treated group.

*Paediatric population*
A Paediatric study (n=125) with doses of 2, 5 or 10 mg prolonged-release melatonin in multiples of 1 mg minitablets (age-appropriate pharmaceutical form), with two week run in baseline period on placebo and a randomised, double blind, placebo controlled, parallel group treatment period of 13 weeks, demonstrated an improvement in total sleep time (TST) after 13 weeks of double-blind treatment; participants slept more with active treatment (508 minutes), compared to placebo (488 minutes).

There was also a reduction in sleep latency with active treatment (61 minutes) compared to placebo (77 minutes) after 13 weeks of double-blind treatment, without causing earlier wake-up time.

In addition, there were fewer dropouts in the active treatment group (9 patients; 15.0%) compared to the placebo group (21 patients; 32.3%). Treatment emergent adverse events were reported by 85% patients in the active group and by 77% in the placebo group. Nervous system disorders were more common in the active group with 42% patients, compared to 23% in the placebo group, mainly driven by somnolence and headache more frequent in the active group.

## 5.2 Pharmacokinetic properties

Absorption
The absorption of orally ingested melatonin is complete in adults and may be decreased by up to 50% in the elderly. The kinetics of melatonin are linear over the range of 2-8 mg.

Bioavailability is in the order of 15%. There is a significant first pass effect with an estimated first pass metabolism of 85%. $T_{max}$ occurs after 3 hours in a fed state. The rate of melatonin absorption and $C_{max}$ following Melatonin Neurim 2 mg oral administration is affected by food. The presence of food delayed the absorption of the melatonin resulting in a later ($T_{max}$=3.0 h versus $T_{max}$=0.75 h) and lower peak plasma concentration in the fed state ($C_{max}$=1020pg/ml versus $C_{max}$=1176 pg/ml).

Distribution
The *in vitro* plasma protein binding of melatonin is approximately 60%. Melatonin Neurim is mainly bound to albumin, alpha$_1$-acid glycoprotein and high density lipoprotein.

Biotransformation
Experimental data suggest that isoenzymes CYP1A1, CYP1A2 and possibly CYP2C19 of the cytochrome P450 system are involved in melatonin metabolism. The principal metabolite is 6-sulphatoxy-melatonin (6-S-MT), which is inactive. The site of biotransformation is the liver. The excretion of the metabolite is completed within 12 hours after ingestion.

Elimination
Terminal half life ($t_{½}$) is 3.5-4 hours. Elimination is by renal excretion of metabolites, 89% as sulphated and glucoronide conjugates of 6-hydroxymelatonin and 2% is excreted as melatonin (unchanged active substance).

Gender
A 3-4-fold increase in $C_{max}$ is apparent for women compared to men. A five-fold variability in $C_{max}$ between different members of the same sex has also been observed. However, no pharmacodynamic differences between males and females were found despite differences in blood levels.

Special populations

*Older People*
Melatonin metabolism is known to decline with age. Across a range of doses, higher AUC and $C_{max}$ levels have been reported in older patients compared to younger patients, reflecting the lower metabolism of melatonin in the elderly. $C_{max}$ levels around 500 pg/ml in adults (18-45) versus 1200 pg/ml in elderly (55-69); AUC levels around 3,000 pg*h/mL in adults versus 5,000 pg*h/mL in the elderly.

*Renal impairment*
Company data indicates that there is no accumulation of melatonin after repeated dosing. This finding is compatible with the short half-life of melatonin in humans.
The levels assessed in the blood of the patients at 23:00 (2 hours after administration) following 1 and 3 weeks of daily administration were 411.4 ± 56.5 and 432.00 ± 83.2 pg/ml respectively, and are similar to those found in in healthy volunteers following a single dose of Melatonin Neurim 2 mg.

*Hepatic impairment*
The liver is the primary site of melatonin metabolism and therefore, hepatic impairment results in higher endogenous melatonin levels.
Plasma melatonin levels in patients with cirrhosis were significantly increased during daylight hours. Patients had a significantly decreased total excretion of 6-sulfatoxymelatonin compared with controls.

### 5.3 Preclinical safety data

Non-clinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

The carcinogenicity study in the rat did not reveal any effect which may be relevant for humans.

In reproductive toxicology, oral administration of melatonin in pregnant female mice, rats or rabbits did not result in adverse effects on their offspring, measured in terms of foetal viability, skeletal and visceral abnormalities, sex ratio, birthweight and subsequent physical, functional and sexual development. A slight effect on post-natal growth and viability was found in rats only at very high doses, equivalent to approximately 2000 mg/day in humans.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Ammonio methacrylate copolymer type B
Calcium hydrogen phosphate dihydrate
Lactose monohydrate
Silica, colloidal anhydrous
Talc
Magnesium stearate

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years

### 6.4 Special precautions for storage

Do not store above 25°C. Store in the original package in order to protect from light.

### 6.5 Nature and contents of container

The tablets are packed in PVC/PVDC opaque blister strips with aluminium foil backing. The pack consists of one blister strip containing 7, 20 or 21 tablets, or two blister strips containing 15 tablets each (30 tablets). The blisters are then packed in cardboard boxes.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

No special requirements for disposal. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## 7. MARKETING AUTHORISATION HOLDER

RAD Neurim Pharmaceuticals EEC SARL
4 rue de Marivaux
75002 Paris
France
e-mail: regulatory@neurim.com

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1694/001
EU/1/22/1694/002
EU/1/22/1694/003
EU/1/22/1694/004

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: {DD month YYYY}

## 10. DATE OF REVISION OF THE TEXT

{DD month YYYY}

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

# ANNEX II

**A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE**

**B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

**D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

## A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Iberfar Indústria Farmacêutica S.A.
Estrada Consiglieri Pedroso 123
Queluz De Baixo
Barcarena
2734-501
Portugal

Rovi Pharma Industrial Services, S.A.
Vía Complutense, 140
Alcalá de Henares
Madrid, 28805
Spain

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

## B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

## C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

## D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency.
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

# A. LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON**

## 1. NAME OF THE MEDICINAL PRODUCT

Melatonin Neurim 2 mg prolonged-release tablets
melatonin

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 2 mg melatonin.

## 3. LIST OF EXCIPIENTS

Contains lactose monohydrate
See leaflet for further information

## 4. PHARMACEUTICAL FORM AND CONTENTS

Prolonged-release tablets
7 tablets
20 tablets
21 tablets
30 tablets

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

Do not store above 25ºC. Store in the original package in order to protect from light.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

RAD Neurim Pharmaceuticals EEC SARL
4 rue de Marivaux
75002 Paris
France
e-mail: regulatory@neurim.com

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1694/001 7 tablets
EU/1/22/1694/002 20 tablets
EU/1/22/1694/003 21 tablets
EU/1/22/1694/004 30 tablets

## 13. BATCH NUMBER

Lot:

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Melatonin Neurim 2 mg

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER STRIP**

## 1. NAME OF THE MEDICINAL PRODUCT

Melatonin Neurim 2 mg prolonged-release tablets
melatonin

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

RAD Neurim Pharmaceuticals EEC SARL

## 3. EXPIRY DATE

EXP:

## 4. BATCH NUMBER

Lot:

## 5. OTHER

# B. PACKAGE LEAFLET

**Package Leaflet: Information for the patient**

**Melatonin Neurim 2 mg prolonged-release tablets**
melatonin

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See Section 4.

**What is in this leaflet:**

1. What Melatonin Neurim is and what it is used for
2. What you need to know before you take Melatonin Neurim
3. How to take Melatonin Neurim
4. Possible side effects
5. How to store Melatonin Neurim
6. Contents of the pack and other information


## 1. What Melatonin Neurim is and what it is used for

The active substance of Melatonin Neurim, melatonin, belongs to a natural group of hormones produced by the body.

Melatonin Neurim is used on its own for the short-term treatment of primary insomnia (persistent difficulty in getting to sleep or staying asleep, or poor quality of sleep) in patients aged 55 years and older. 'Primary' means that the insomnia does not have any identified cause, including any medical, mental or environmental cause.

## 2. What you need to know before you take Melatonin Neurim

**Do not take Melatonin Neurim**
- if you are allergic to melatonin or any of the other ingredients of this medicine (listed in section 6).

**Warnings and precautions**
Talk to your doctor or pharmacist before taking Melatonin Neurim.

- If you suffer from liver or kidney problems. No studies on the use of Melatonin Neurim in people with liver or kidney diseases have been performed, you should speak to your doctor before taking Melatonin Neurim as its use is not recommended.
- If you have been told by your doctor that you have an intolerance to some sugars.
- If you have been told you suffer from an autoimmune disease (where the body is 'attacked' by its own immune system). No studies on the use of Melatonin Neurim in people with auto-immune diseases have been performed; therefore, you should speak to your doctor before taking Melatonin Neurim as its use is not recommended.
- Melatonin Neurim can make you feel drowsy, you should be careful if the drowsiness affects you as it may impair your ability on tasks such as driving.
- Smoking may make Melatonin Neurim less effective, because the components of tobacco smoke can increase the breakdown of melatonin by the liver.

**Children and adolescents**
Do not give this medicine to children between the ages of 0 to 18 years as it has not been tested and its effects are unknown. Another medicine containing melatonin may be more appropriate for administration to children between the ages of 2 to 18 - please ask your doctor or pharmacist for advice.

**Other medicines and Melatonin Neurim**
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. These medicines include:

- Fluvoxamine (used for the treatment of depression and obsessive compulsive disorder), psoralens (used in the treatment of skin disorders e.g. psoriasis), cimetidine (used in the treatment of stomach problems such as ulcers), quinolones and rifampicin (used in the treatment of bacterial infections), oestrogens (used in contraceptives or hormone replacement therapy) and carbamazepine (used in the treatment of epilepsy).
- Adrenergic agonists/antagonists (such as certain types of medicines used to control blood pressure by constricting blood vessels, nasal decongestants, blood pressure lowering medicines), opiate agonists/antagonists (such as medicinal products used in the treatment of drug addiction), prostaglandin inhibitors (such as nonsteroidal anti-inflammatory medicines), antidepressant medication, tryptophan and alcohol.
- Benzodiazepines and non-benzodiazepine hypnotics (medicines used to induce sleep such as zaleplon, zolpidem and zopiclone)
- Thioridazine (for the treatment of schizophrenia) and imipramine (for the treatment of depression).

**Melatonin Neurim with food, drink and alcohol**
Take Melatonin Neurim after you have eaten. Do not drink alcohol before, during or after taking Melatonin Neurim, because it reduces the effectiveness of Melatonin Neurim.

**Pregnancy and breast-feeding**
Do not take Melatonin Neurim if you are pregnant, think you may be pregnant, trying to become pregnant or breast-feeding. Ask your doctor or pharmacist for advice before taking this medicine.

**Driving and using machines**
Melatonin Neurim may cause drowsiness. If you are affected, you should not drive or operate machinery. If you suffer from continued drowsiness, then you should consult your doctor.

**Melatonin Neurim contains lactose monohydrate**.
Melatonin Neurim contains lactose monohydrate. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

## 3. How to take Melatonin Neurim

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is one Melatonin Neurim tablet (2 mg) taken daily by mouth, after food, 1-2 hours before bedtime. This dosage may be continued for up to thirteen weeks.

You should swallow the tablet whole. Melatonin Neurim tablets should not be crushed or cut in half.

**If you take more Melatonin Neurim than you should**
If you have accidentally taken too much of your medicine, contact your doctor or pharmacist as soon as possible.

Taking more than the recommended daily dose may make you feel drowsy.

**If you forget to take Melatonin Neurim**
If you forget to take your tablet, take another as soon as you remember, before going to sleep, or wait until it is time to take your next dose, then go on as before.

Do not take a double dose to make up for a forgotten dose.

**If you stop taking Melatonin Neurim**
There are no known harmful effects if treatment is interrupted or ended early. The use of Melatonin Neurim is not known to cause any withdrawal effects after treatment completion.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If you experience any of the following serious side effects, stop taking the medicine and contact your doctor **immediately:-**

**Uncommon**: (may affect up to 1 in 100 people)
- Chest pain

**Rare**: (may affect up to 1 in 1000 people)
- Loss of consciousness or fainting
- Severe chest pain due to angina
- Feeling your heartbeat
- Depression
- Visual impairment
- Blurred vision
- Disorientation
- Vertigo (a feeling of dizziness or "spinning")
- Presence of red blood cells in the urine
- Reduced number of white blood cells in the blood
- Reduced blood platelets, which increases risk of bleeding or bruising
- psoriasis

If you experience any of the following non-serious side effects contact your doctor and/or seek medical advice:-

**Uncommon**: (may affect up to 1 in 100 people)

Irritability, nervousness, restlessness, insomnia, abnormal dreams, nightmares, anxiety, migraine, headache, lethargy (tiredness, lack of energy), restlessness associated with increased activity, dizziness, tiredness, high blood pressure, upper abdominal pain, indigestion, mouth ulceration, dry mouth, nausea, changes in the composition of your blood which could cause yellowing of the skin or eyes, inflammation of the skin, night sweats, itching, rash, dry skin, pain in extremities, menopausal symptoms, feeling of weakness, excretion of glucose in the urine, excess proteins in the urine, abnormal liver function and weight increase.

**Rare**: (may affect up to 1 in 1000 people)

Shingles, high level of fatty molecules in the blood, low serum calcium levels in the blood, low sodium levels in the blood, altered mood, aggression, agitation, crying, stress symptoms, early

morning awakening, increased sex drive, depressed mood, memory impairment, disturbance in attention, dreamy state, restless legs syndrome, poor quality sleep, 'pins and needles' feeling, watery eyes, dizziness when standing or sitting, hot flushes, acid reflux, stomach disorder, blistering in the mouth, tongue ulceration, stomach upset, vomiting, abnormal bowel sounds, wind, excess saliva production, bad breath, abdominal discomfort, gastric disorder, inflammation of the stomach lining, eczema, skin rash, hand dermatitis, itchy rash, nail disorder, arthritis, muscle spasms, neck pain, night cramps, prolonged erection that might be painful, inflammation of the prostate gland, tiredness, pain, thirst, passing large volumes of urine, urinating during the night, increased liver enzymes, abnormal blood electrolytes and abnormal laboratory tests.

**Frequency not known:** (cannot be established from the available data)

Hypersensitivity reaction, swelling of mouth or tongue, swelling of the skin and abnormal milk secretion.

**Reporting of side effects**
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Melatonin Neurim

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton (EXP). The expiry date refers to the last day of that month.

Do not store above 25°C. Store in the original package in order to protect from light.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

## 6. Contents of the pack and other information

**What Melatonin Neurim contains**
- The active substance is melatonin. Each prolonged-release tablet contains 2 mg melatonin.
- The other ingredients are ammonio methacrylate copolymer type B, calcium hydrogen phosphate dihydrate, lactose monohydrate, silica (colloidal anhydrous), talc and magnesium stearate.

**What Melatonin Neurim looks like and contents of the pack**
Melatonin Neurim 2 mg prolonged-release tablets are available as white to off-white round bi-convex shaped tablets. Each carton of tablets contains one blister strip of 7, 20 or 21 tablets, or alternatively in a carton containing two blister strips of 15 tablets each (30 tablet pack). Not all pack sizes may be marketed.

**Marketing Authorisation Holder and Manufacturer**

Marketing Authorisation Holder:

RAD Neurim Pharmaceuticals EEC SARL
4 rue de Marivaux
75002 Paris
France
e-mail: regulatory@neurim.com

Manufacturer:

Sites responsible for Batch Release in the EEA:-

Iberfar Indústria Farmacêutica S.A.
Estrada Consiglieri Pedroso 123
Queluz De Baixo
Barcarena
2734-501
Portugal

Rovi Pharma Industrial Services, S.A.
Vía Complutense, 140
Alcalá de Henares
Madrid, 28805
Spain

**This leaflet was last revised in {month/YYYY}**.

**Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.