

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Circadin 2 mg prolonged-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release tablet contains 2 mg melatonin.

Excipient: each prolonged-release tablet contains 80 mg lactose monohydrate.

For a 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

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

4.2 Posology and method of administration

Oral use. Tablets should be swallowed whole.

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

Paediatric use

Circadin is not recommended for use in children and adolescents below age 18 due to insufficient data on safety and efficacy.

Renal insufficiency

The effect of any stage of renal insufficiency 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 Circadin 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, Circadin is not recommended for use in patients with hepatic impairment.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

Circadin 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 Circadin in individuals with autoimmune diseases. Therefore Circadin is not recommended for use in patients with autoimmune diseases.

Patients with rare hereditary problems of galactose intolerance, the LAPP lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

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 drugs.
- 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 (eg. 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 Circadin or vice versa has not been studied.

Pharmacodynamic interactions

- Alcohol should not be taken with Circadin, because it reduces the effectiveness of Circadin on sleep.
- Circadin may enhance the sedative properties of benzodiazepines and non-benzodiazepine hypnotics, such as zalepon, zolpidem and zopiclone. In a clinical trial, there was clear evidence for a transitory pharmacodynamic interaction between Circadin and zolpidem one hour following co-dosing. Concomitant administration

resulted in increased impairment of attention, memory and co-ordination compared to zolpidem alone.

- Circadin 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, Circadin 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 Pregnancy and lactation

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 intended to become pregnant is not recommended.

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

Circadin has moderate influence on the ability to drive and use machines. Circadin 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

In clinical trials (in which a total of 1361 patients were taking Circadin and 1247 patients were taking placebo), 37.0% of patients receiving Circadin reported an adverse reaction compared with 31.8% taking placebo. Comparing the rate of patients with adverse reactions per 100 patient weeks, the rate was higher for placebo than Circadin (8.21 – placebo vs. 3.17 – Circadin). The most common adverse reactions were headache, pharyngitis, back pain, and asthenia, which were common, by MedDRA definition, in both the Circadin and placebo treated groups.

The following adverse reactions were reported in clinical trials and were defined as possibly, probably or definitely related to treatment. A total of 6.9% of subjects receiving Circadin reported an adverse reaction compared with 5.9% of subjects taking placebo. Only those adverse events occurring in subjects 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 ($\geq 1/10$); Common ($\geq 1/100$ to $<1/10$); Uncommon ($\geq 1/1,000$ to $<1/100$); Rare ($\geq 1/10,000$ 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
Infections and Infestations				Herpes zoster
Blood and Lymphatic System Disorders				Leukopenia, Thrombocytopenia
Metabolism and Nutrition Disorders				Hypertriglyceridaemia
Psychiatric Disorders			Irritability, Nervousness, Restlessness, Insomnia, Abnormal dreams	Mood altered, Aggression, Agitation, Crying, Early morning awakening, Libido increased
Nervous System Disorders			Migraine, Psychomotor hyperactivity, Dizziness, Somnolence	Memory impairment, Disturbance in attention, Poor quality sleep
Eye Disorders				Visual acuity reduced, Vision blurred, Lacrimation increased
Ear and Labyrinth Disorders				Vertigo positional
Vascular Disorders				Hot flush
Gastrointestinal Disorders			Abdominal pain, Constipation, Dry mouth	Gastrointestinal disorder, Gastrointestinal upset, Vomiting, Bowel sounds abnormal, Flatulence, Salivary hypersecretion, Halitosis
Hepatobiliary Disorders			Hyperbilirubinaemia	Hepatic enzyme increased, Liver function test abnormal, laboratory test abnormal
Skin and Subcutaneous Tissue Disorders			Hyperhidrosis	Eczema, Erythema, Rash pruritic, Pruritus, Dry skin, Nail disorder, Night sweats,
Musculoskeletal and Connective Tissue Disorders				Muscle cramp, Neck pain
Reproductive System and Breast Disorders				Priapism
General Disorders and Administration Site Conditions			Asthenia	Fatigue
Investigations			Weight increased	

4.9 Overdose

No case of overdose has been reported. Circadin 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: Other Hypnotics and Sedatives, ATC code: N05CM17

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

In clinical trials where patients suffering from primary insomnia, received Circadin 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 Circadin. Modifications in diurnal functioning did not occur with Circadin 2 mg.

In an outpatient study with two week run in baseline period with placebo, a randomised, double blind, placebo controlled, parallel group treatment period of 3 weeks and two 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 Circadin group as compared to 27% in the placebo group. In addition, quality of sleep and morning alertness significantly improved with Circadin compared to placebo. Sleep variables gradually returned to baseline with no rebound, no increase in adverse events 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 Circadin group as compared to 15% in the placebo group. Circadin 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 Circadin compared to placebo. Quality of life was improved significantly with Circadin 2 mg compared to placebo.

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 Circadin 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 ($C_{max}=1020$ versus $C_{max}=1176$ pg/ml).

Distribution

The in vitro plasma protein binding of melatonin is approximately 60%. Circadin is mainly bound to albumin, alpha₁-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 ($t_{1/2}$) is 3.5-4 hours. Elimination is by renal excretion of metabolites, 89% as sulphated and glucuronide conjugates of 6-hydroxymelatonin and 2% is excreted as melatonin (unchanged drug).

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

Elderly

Melatonin metabolism is known to decline with age. Across a range of doses, higher AUC and C_{max} levels have been reported in older subjects compared to younger subjects, 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 healthy volunteers following a single dose of Circadin 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 and genotoxicity.

The No Observed Adverse Effect Level (NOAEL) at 15 mg/kg/day in rats, is equivalent to an AUC which is considerably higher (x 15000) than the human exposure after ingestion of Circadin 2 mg.

In the carcinogenicity study, an increased incidence of benign tumors of the thyroid was observed at the high dose level (150 mg/kg; equivalent to an AUC x 1,500,000 than the human exposure after ingestion of Circadin 2 mg) in male rats. The probable mechanism of a liver induction of thyroid hormones metabolism, which is well known with other xenobiotics especially in rodents, is under investigation.

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

5 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 21 tablets. The blisters are then packed in cardboard boxes.

6.6 Special precautions for disposal

Medicines no longer required should not be disposed of via wastewater or the municipal sewage system. Return them to a pharmacy or ask your pharmacist how to dispose of them in accordance with the national regulations. These measures will help to protect the environment.

7. MARKETING AUTHORISATION HOLDER

Neurim Pharmaceuticals EEC Limited
6 Fortuna Court
Calleva Park
Aldermaston
Berkshire RG7 8UB
United Kingdom
e-mail: neurim@neurim.com

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency (EMA) <http://www.emea.europa.eu>

ANNEX II

- A. MANUFACTURING AUTHORISATION HOLDERS
RESPONSIBLE FOR BATCH RELEASE**

- B. CONDITIONS OF THE MARKETING AUTHORISATION**

A. MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Penn Pharmaceutical Services Ltd
Units 23-24 Tafarnaubach Industrial Estate
Tredegar
Gwent
NP22 3AA
UK

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 OF THE MARKETING AUTHORISATION

• CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER

Medicinal product subject to medical prescription.

• CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

Not applicable.

• OTHER CONDITIONS

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance is in place and functioning prior to placing the product on the market .

Risk Management System

The MAH commits to performing the study detailed in the Pharmacovigilance Plan.

An updated Risk Management Plan should be provided as per the CHMP Guideline on Risk Management System for medicinal products for human use.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Circadin 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
21 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 REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C. 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

Neurim Pharmaceuticals EEC Limited
6 Fortuna Court
Calleva Park
Aldermaston
Berkshire RG7 8UB
United Kingdom
e-mail: neurim@neurim.com

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Circadin 2 mg prolonged-release tablets

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER STRIP

1. NAME OF THE MEDICINAL PRODUCT

Circadin 2 mg prolonged-release tablets
melatonin

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Neurim Pharmaceuticals EEC Limited

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Circadin 2 mg prolonged-release tablets Melatonin

Read all of this leaflet carefully before you start taking this medicine.

- 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. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Circadin is and what it is used for
2. Before you take Circadin
3. How to take Circadin
4. Possible side effects
5. How to store Circadin
6. Further information

1. WHAT CIRCADIN IS AND WHAT IT IS USED FOR

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

Circadin is used as monotherapy for the short-term treatment of primary insomnia (difficulty in getting to sleep or staying asleep, or poor quality of sleep for at least one month), characterised by poor quality of sleep in patients aged 55 years and older.

2. BEFORE YOU TAKE CIRCADIN

Do not take Circadin

- if you are allergic (hypersensitive) to melatonin or any of the other ingredients of Circadin.

Take special care with Circadin

- if drowsiness is likely to cause a risk to your safety;
- if you suffer from any liver problems;
- if you suffer from kidney problems;
- if you suffer from any autoimmune disease (where the body is 'attacked' by its own immune system).

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription BEFORE you start the treatment as they may affect the action of Circadin. These medicines include hypnotics and tranquilisers (e.g. benzodiazepines), fluvoxamine, thioridazine and imipramine (used to treat depression or psychiatric problems), oestrogen (contraceptives or hormone replacement therapy), cimetidine and psoralens (used to treat skin problems e.g. psoriasis).

Taking Circadin with food and drink

Take Circadin after you have eaten. Do not drink alcohol before, during or after taking Circadin.

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

It is not recommended to take Circadin if you are pregnant or suspect that you may be pregnant. It is not recommended to take Circadin if you are breast feeding.

Driving and using machines

Circadin 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.

Important information about some of the ingredients of Circadin

Each prolonged-release tablet contains 80 mg of 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 CIRCADIN

Always take Circadin exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. The dose is one Circadin tablet taken daily by mouth, after food, 1-2 hours before bedtime, for 3 weeks. You should swallow the tablet whole. Circadin tablets should not be crushed or cut in half.

If you take more Circadin 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 Circadin

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 Circadin

There are no known harmful effects if treatment is interrupted or ended early. The use of Circadin is not known to cause any withdrawal effects after treatment completion.

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

4. POSSIBLE SIDE EFFECTS

Like all medicines, Circadin can cause side effects, although not everybody gets them. The following events are considered to be uncommon (i.e., likely to occur in fewer than 1 in 100 patients):

Irritability, nervousness, restlessness insomnia, abnormal dreams, migraine, psychomotor hyperactivity (restlessness associated with increased activity), dizziness, somnolence (tiredness), abdominal pain, constipation, dry mouth, hyperbilirubinaemia (changes in the composition of your blood which could cause yellowing of the skin or eyes (jaundice), hyperhidrosis (excessive sweating), asthenia (feeling of weakness) and weight increase.

The following events are considered to be rare (i.e., likely to occur in fewer than 1 in 1,000 patients):

Herpes Zoster (shingles), leukopenia, thrombocytopenia, hypertriglyceridaemia, altered mood, aggression, agitation, crying, early morning awakening, increased libido (increased sex drive), memory impairment, disturbance in attention, poor quality sleep, reduced visual acuity (visual impairment), blurred vision, increased lacrimation (watery eyes), positional vertigo (dizziness when standing), hot flushes, gastrointestinal upset, vomiting, abnormal bowel sounds, flatulence (wind), salivary hypersecretion (excess saliva production), halitosis (bad breath), abnormal liver function test (increased liver enzymes), eczema, erythema (skin rash), pruritic rash (itchy rash), pruritus (itching), dry skin, nail disorder, night sweats, muscle cramp, neck pain, priapism (increased duration of erection) and fatigue (tiredness).

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE CIRCADIN

Keep out of the reach and sight of children.

Do not use Circadin after the expiry date which is stated on the carton. 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.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Circadin 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 Circadin looks like and contents of the pack

Circadin 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 21 tablets.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:

Neurim Pharmaceuticals EEC Limited
6 Fortuna Court
Calleva Park
Aldermaston
Berkshire RG7 8UB
United Kingdom
e-mail: neurim@neurim.com

Manufacturer:

Site responsible for Batch Release in the EEA:-

Penn Pharmaceutical Services Ltd
Units 23-24 Tafarnaubach Industrial Estate
Tredegar
Gwent
NP22 3AA
UK

This leaflet was last approved in {MM/YYYY}.

Detailed information on this medicine is available on the European Medicines Agency (EMA) web site: <http://www.emea.europa.eu>