



Cambridgeshire and Peterborough  
Clinical Commissioning Group

**CAMBRIDGESHIRE AND PETERBOROUGH JOINT PRESCRIBING GROUP**

**Model shared care guidelines for melatonin treatment in children and adolescents.**

**The following guidelines are designed to provide information relating to melatonin and to outline the responsibilities of the primary and secondary care teams in the prescribing of this drug for paediatric patients.**

**Local specialists are asked to supply a copy of this guideline to GPs at the time that they request a sharing of care.** At that time current contact details of local specialists need to be checked/completed by secondary care teams (page 6).

**Areas of responsibility for the sharing of care**

“Shared care” occurs when a secondary care specialist retains a responsibility for the on going monitoring or review of a patient after the point in time when they consider it clinically appropriate for the patient’s General Practitioner (GP) to take over the responsibility of routine prescribing. This usually only applies to long-term treatment with drugs that are not part of most GPs’ routine practice.

GPs are **invited** to participate. If the GP is not confident and competent to undertake these roles, then they are under no obligation to do so. Local specialists may have individual arrangements as to how this works practically with their GP’s.

**The overall clinical responsibility for the patient for the diagnosed condition remains with the specialist.**

**If a specialist asks a GP to prescribe these drugs, the GP should reply to this request as soon as practicable.**

Sharing of care assumes communication between the specialist, GP and patient and/or carers. The intention to share care should be explained to the patient and/or carers by the doctor initiating treatment. It is important that patients and/or carers are consulted about treatment and are in agreement with it.

This model guideline contains:

An introduction to the use of melatonin; Indications and dose in children; Cautions, Contraindications, Side-effects; Drug interactions; Costs, Funding, Responsibilities and roles of GP, Consultant, patient/guardian, contact details for advice and support, references and supporting information.

Appendix 1 – London New Drugs Group summary of evidence on melatonin

Appendix 2 – Summary of Product Characteristics for Circadin

Appendix 3 – Principles of shared care

## **Introduction**

- Melatonin is a pineal hormone which may affect sleep pattern<sup>1</sup>.
- Melatonin is generally prescribed locally<sup>2</sup> for children with sleep disturbances associated with learning difficulties, Attention Deficit Hyperactivity Disorder (ADHD) or autism. Occasional reports of its use for children with chronic fatigue syndrome or Asperger's syndrome have also been noted.
- A comprehensive review of the available evidence has been conducted by the London New Drugs Group<sup>3</sup>, a summary of which appears at Appendix 1. This confirms that trial data (including at least one systematic review, two meta-analyses and several randomised controlled trials) is limited, but typically supports the use of melatonin in sleep disorders, and is more substantial than that available to support the use of any alternative hypnotic in children. This review notes that, whilst behavioural therapies can be effective in children, those with neuropsychiatric disorders have lower response rates to non-drug treatments. Such patients might therefore be expected to be the target population for melatonin treatment.
- An infoPOEM<sup>4</sup> confirms that children have a better response to melatonin than do adults, and that it is particularly effective in patients with delayed sleep phase syndrome, in which a person's circadian rhythm is misaligned **without** an external cause (such as jet lag or shift work).
- The BNF for children<sup>1</sup> also confirms that melatonin treatment may be beneficial for children with sleep onset insomnia and delayed sleep phase syndrome **in children with conditions such as visual impairment, cerebral palsy, ADHD, autism and learning difficulties**. Treatment should be initiated and supervised by a specialist, but may be continued by a GP under a shared-care arrangement, with review every 6 months<sup>1</sup>.
- NICE<sup>5</sup> supports the use of melatonin in children with chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) who have sleep difficulties. Again, specialist supervision is recommended. However, NICE acknowledges that results from trials were mixed, and the London New Drugs Group<sup>3</sup> suggests that the recommendation appears to be based on expert consensus opinion rather than evidence.
- One licensed preparation of melatonin is available in the UK (Circadin), but this is a modified-release (MR) formulation, and the licence does not cover use in patients under 55 years of age<sup>6</sup> (Appendix 2). Nevertheless, the MHRA has advised<sup>7</sup> that the licensed product (Circadin) should be used wherever possible (even if off-licence), since the licence will at least carry reassurance concerning quality of manufacture, which is lacking for unlicensed products.
- Much of the evidence from the London New Drugs Group<sup>3</sup> (see above) is derived from studies using immediate release products, although two trials are included, which used controlled release (CR) formulations. One further small study has compared CR with FR (fast-release) melatonin, and concluded that FR formulations are most effective when there is delayed sleep onset, and that the CR form is more useful for sleep maintenance. CR formulations generally produce a slightly later sleep onset, but can improve sleep fragmentation and early morning awakening in children with sleep-wake disorders.<sup>8</sup>
- It is possible, therefore, that a CR or MR formulation may not be appropriate in all cases, and an immediate release formulation may be preferred.
- Information available from the manufacturer of Circadin suggests that the MR tablets can be crushed and dispersed in water or milk or added to soft food like yoghurt, without losing its efficacy<sup>9</sup>. However, this will result in a loss of the MR property of the tablets. In view of the MHRA advice<sup>7</sup>, this should still be the first option to be considered in patients who might not benefit from the MR formulation or who can not swallow tablets whole.
- Unlicensed liquid formulations are expensive (see "costs" below), and are available from various specials manufacturers with possible variations in melatonin content. Unlicensed capsule formulations are also available in varying strengths, either as imported food supplements with no guarantee of quality of manufacture or as manufactured specials (more expensive). The capsule contents can usually be emptied onto food but confirmation from the manufacturer is required to guarantee efficacy.
- Melatonin from animal sources should be avoided due to the possibility of contamination<sup>3</sup>.

<sup>1</sup> BNF for Children 2012-2013

<sup>2</sup> Local information from GP practices, Community Paediatricians, April 2009.

<sup>3</sup> London New Drugs Group APC/DTC briefing – Melatonin in paediatric sleep disorders, September 2008

<sup>4</sup> BMJ 2005; 330 (25 June) – POEM Melatonin is effective for some sleep disorders

<sup>5</sup> NICE Clinical Guideline 53 – Chronic fatigue syndrome/myalgic encephalomyelitis, August 2007

<sup>6</sup> Summary of Product Characteristics Circadin, Flynn Pharma Ltd. [www.medicines.org.uk/emc](http://www.medicines.org.uk/emc). Date of revision of the text 12/08/2011, last updated on the eMC 14/08/2012, date accessed 06/09/2012.

<sup>7</sup> Medicines and Healthcare Products Regulatory Agency Drug Procurement Advice MDR 13-08/08. 15/08/2008. Restrictions on the import of unlicensed Melatonin products following the grant of a marketing authorisation for Circadin 2mg tablets.

<sup>8</sup> Jan et al. J Pineal Res 2000; 29:34-39. Clinical trials of CR melatonin in children with sleep-wake disorders

<sup>9</sup> Personal communication from Flynn Pharma Ltd. 07/09/2012

- Little is known about long-term effects of melatonin in children, and there is uncertainty as to its effect on endocrine or reproductive hormone secretion<sup>1</sup>. There have also been conflicting reports on the effect of melatonin on seizure activity, and caution may therefore be advisable in epileptic patients<sup>3</sup>.
- Melatonin concentration is elevated in nocturnal asthmatic patients, and caution is also advised in this group, although clinical trial data has not yet indicated any increase in asthma symptoms with treatment<sup>3</sup>.
- This shared-care guideline details the expectations and responsibilities of specialists and primary care prescribers in the care of patients requiring this treatment.

### **Indications**

In the absence of licensed indications for melatonin in children, melatonin should be used only for the indications listed in the BNFc<sup>1</sup> – i.e. **in children with conditions such as visual impairment, cerebral palsy, attention deficit hyperactivity disorder, autism and learning difficulties when good sleep hygiene measures have failed and there remains:**

- **Sleep onset insomnia or**
- **Delayed sleep phase syndrome**

### **Dosage**

In the absence of licensed doses for children, melatonin should be prescribed according to doses in the BNFc<sup>1</sup>:

- By mouth: Child 1 month – 18 years, initially 2-3mg before bedtime, increased if necessary after 1-2 weeks to 4-6 mg before bedtime.  
Maximum 10mg daily.

### **Cautions**

Caution is advised in renal impairment<sup>1</sup>, asthma<sup>3</sup>, and epilepsy<sup>3</sup>.

### **Contra-indications**

Melatonin treatment should be avoided in<sup>1</sup>:

- Autoimmune disease
- Hepatic impairment
- Pregnancy
- Breast-feeding

### **Side-effects**

Possible side-effects include<sup>1, 6</sup>:

- Uncommon: Abdominal pain, dyspepsia, dry mouth, mouth ulceration, weight gain, hypertension, chest pain, malaise, dizziness, anxiety, migraine, asthenia, insomnia, abnormal dreams, somnolence, restlessness, nervousness, irritability, night sweats, proteinuria, glycosuria, pruritus, rash, dry skin.
- Rare: Thirst, flatulence, halitosis, hypersalivation, vomiting, gastritis, hypertriglyceridaemia, aggression, agitation, fatigue, impaired memory, mood changes, hot flushes, priapism, increased libido, leucopenia, thrombocytopenia, muscle cramp, lacrimation, visual disturbances, skin reactions.

### **Drug Interactions**

Melatonin interacts specifically with the following drugs<sup>1, 6</sup>:

- Cimetidine, fluvoxamine, 5- or 8- methoxypsoralen, quinolones, carbamazepine, rifampicin, oestrogens.

Melatonin also belongs to the class of anxiolytics/hypnotics, which may interact with:

- ACE inhibitors, adrenergic neurone blockers, alcohol, alpha-blockers, anaesthetics, Angiotensin-II receptor antagonists, tricyclics or tricyclic-related antidepressants, antihistamines, antipsychotics, baclofen, beta-blockers, calcium-channel blockers, clonidine, diazoxide, diuretics, hydralazine, lofexidine, methyl dopa, minoxidil, mirtazapine, moxonidine, nitrates, opioid analgesics, ritonavir, tizanidine.

Further information on the above interactions can be found in the BNFc<sup>1</sup>.

For more detailed advice on drug interactions, contact the Pharmacy Department at Peterborough, Hinchingbrooke, Addenbrooke's or Fulbourn Hospitals, or the UK Medicines Information Service.

**Costs**

Costs will vary, depending on the formulation and dose prescribed, and the source of any specially manufactured item.

The following are therefore for illustrative purposes only:

	<b>Cost per year (Net ingredient cost)</b>
Circadin 2mg MR tablet daily <sup>10</sup>	£187
Unlicensed melatonin 2.5mg capsule daily <sup>11</sup>	£384
Unlicensed melatonin 2mg capsule daily <sup>11</sup>	£379
Unlicensed melatonin 3mg capsule daily <sup>11</sup>	£328
Unlicensed melatonin 5mg capsule daily <sup>11</sup>	£379
Unlicensed melatonin liquid 2mg daily <sup>11</sup>	£1,673
Unlicensed melatonin liquid 5mg daily <sup>11</sup>	£1,058
Unlicensed melatonin 5mg/5ml oral solution 2mg daily <sup>12</sup>	£517
Unlicensed melatonin 5mg/5ml oral suspension 2mg daily <sup>12</sup>	£1347

**It is expected that Consultants prescribe Circadin MR 2mg tablets or multiples of 2mg tablet unless very specific reasons prevent it. Any request other than for Circadin should be checked to ensure that circadin cannot be used.**

**Funding**

- PRIMARY CARE

GP prescribing will be funded from baseline budgets. Further information on this and any concerns regarding funding may be discussed with local Pharmaceutical Advisers

- SECONDARY CARE

Secondary care trust clinicians should identify cost pressures to their managers for anticipated changes, not on an ad hoc basis.

**Responsibilities and Roles**

<b>Specialist responsibilities</b>
To identify those patients who will benefit from treatment with medication.
<b>Undertake pre-treatment assessment and advise the GP of any concerns.</b>
Check drug-drug and drug-disease interactions
<b>Consider which formulation of melatonin is most appropriate (noting the MHRA guidance to use Circadin where possible, and the high cost of liquid preparations).</b>
<b>Initially prescribe and stabilise the patient on the chosen medication. Review every 6 months or until it is taken over by primary care (according to local arrangements).</b>
Issue the patient with a patient held record, if implemented locally, when treatment is initiated.
When appropriate, ask GP if they are willing to participate in shared care.
Advise GP of information provided to the patient/guardian about the treatment and/or about the proposed shared care arrangement e.g. what patient/guardian should report, potential side effects, and to whom.
Continue to prescribe for the patient after initiation of treatment until such time as the patient's GP agrees to accept prescribing responsibility and provide prescriptions for the patient under an agreed shared care arrangement.
<b>Communicate promptly with the GP about any changes in treatment.</b>
<b>Monitor the efficacy of the treatment at least annually, considering whether continued treatment is necessary.</b>

<b>Advise the GP on frequency of monitoring to be undertaken by GP and/or hospital.</b>
<b>Advise the GP what to do when each of the defined parameters alters and when (if at all) to make an emergency referral back to the specialist team.</b>
Agree how the outcome of monitoring will be communicated between specialist, GP and patient.
Ensure clear arrangements are in place for back up, advice and support e.g. out of hours and/or when the consultant initiating therapy is not available.
Educate the family about the drug therapy to maximise compliance and be aware of when to seek medical advice.
Liaise with the school, providing education about drug therapy if required.
Evaluate any adverse effects reported by the GP (Any adverse effects which are suspected to relate to the drug should be reported to the CSM).
<b>Refer for additional behavioural therapy (social skills, anger management or parents group/parenting skills) if appropriate.</b>

<b>General Practitioner</b>
Ensure that shared care arrangements are in place before taking over prescribing/monitoring and: <ul style="list-style-type: none"> <li>• That the patient/guardian is clear what is being monitored and by whom.</li> <li>• That the patient/guardian knows what significant adverse effects/events to report urgently and to whom they should report (specialist or GP).</li> </ul>
Confirm that proposed therapy is not contra-indicated because of concurrent therapy for other conditions the patient may be suffering from e.g. check drug-drug and drug-disease interactions.
<b>Prescribe melatonin at the dose and in the formulation recommended by the specialist once the patient is stabilised on treatment and side effects have been excluded as far as possible by the specialist team.</b>
Confirm with the patient/guardian that they have a clear picture of the treatment from the specialist and answer any outstanding queries.
<b>Monitor response to treatment as agreed with specialist. (Review at least every 6 months).</b> <b>Confirm with specialist the circumstances that should trigger urgent referral back to the specialist.</b>
Update the patient held record if implemented locally.
Ensure clear arrangements are in place for back up, advice and support e.g. out of hours and/or when the consultant initiating therapy is not available
<b>Check for possible drug interactions when newly prescribing or stopping concurrent medication.</b>
<b>Report any suspected adverse drug reactions to the consultant who initiated therapy under the shared care agreement.</b> <b>Report adverse events to the Medicines and Healthcare Regulatory Agency (MHRA).</b> Whilst these drugs remain unlicensed (or have black triangle status), all adverse events should be reported even if causal relationship is not known or if the adverse event is already known about.
<b>Monitor compliance through rates of prescription.</b>

<b>Patient's and/or guardian's role</b>
Discuss potential benefits and side effects of treatment with the specialist, to ensure they have a clear picture of these from the specialist and to raise any outstanding queries.
Check that, where possible, the specialists have provided a patient-held record or information sheet for monitoring and/or to alert other clinical staff to the treatment they are receiving
Share any concerns they have in relation to treatment with their medicine(s)
Report any adverse effects to their specialist or GP whilst taking the medicine(s)
Report to the specialist or GP if they do not have a clear understanding of their treatment

Participate in the monitoring of therapy and the assessment of outcomes, to assist health professionals to provide safe, appropriate treatment

### **Advice and Support**

- Cambridgeshire and Peterborough NHS Foundation Trust Pharmacy Team  
Cavell Centre, Peterborough 01733 776006 or Fulbourn Hospital, Cambridge 01223 218518
  
- Hinchingsbrooke Health Care NHS Trust / Cambridgeshire Community Services NHS Trust  
Pharmacy department – 01480 416141
  
- Cambridge University Hospitals NHS Foundation Trust

### **Supporting Information**

This Shared Care Guideline should be read in conjunction with:

The Summary of Product Characteristics for Circadin ([www.medicines.org.uk/emc](http://www.medicines.org.uk/emc))

Current edition of British National Formulary for Children.

### **References**

As footnote on pages 2 and 4.

This guideline was originally written in consultation with:

Clare Mundell Chief Pharmacist, Cambridgeshire and Peterborough Mental Health Trust

Sue Ashwell, Previous Chief Pharmacist, NHS Cambridgeshire

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It has been reviewed and updated in 2012 by:

Bunmi Olokode, Paediatric Pharmacist, Hinchingsbrooke Health Care NHS Trust,

**APPENDIX1****London New Drugs Group “Melatonin in Paediatric Sleep Disorders”, September 2008**


**London New Drugs Group**  
**APC/DTC Briefing**  
**Melatonin in paediatric sleep disorders**

**September 2008**

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**Summary**

Insomnia and other non-respiratory sleep disorders in children and adolescents are a widespread problem, with a higher prevalence in children with neurodevelopmental or psychiatric co-morbidities. Although non-drug treatments, such as behavioural therapy can be extremely effective in some forms of paediatric insomnia, clinical experience and studies with children with neuropsychiatric disorders indicate that these patients have lower response rates to behavioural therapy. There are no drugs licensed for the treatment of sleep disorders in children in the UK.

Melatonin (N-acetyl-5-methoxytryptamine) is a neurohormone produced by the pineal gland during the dark hours of the day-night cycle. Its use is supported by NICE in their Clinical Guideline on the diagnosis and management of chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) in adults and children. Within that Guideline it is stated that melatonin may be considered for children and young people with CFS/ME who have sleep difficulties, but only under specialist supervision.

There is at least one systematic review, two meta-analyses and several subsequently published randomised controlled trial which assesses the safety and efficacy of melatonin in children and adolescents. Although somewhat limited by trial size, heterogeneity and specificity, typically these pieces of research support the use of melatonin in that they show it has some beneficial effect in measures of sleep efficiency. Although the evidence base for melatonin is limited, it is actually more substantial than that available to support the use of any alternative hypnotic in this population.

A prolonged release formulation of melatonin (Circadin®) was licensed in the UK in April 2008 as a short term treatment of primary insomnia characterised by poor quality sleep, but only in patients aged 55 years or over. This preparation has not been evaluated in children and its use in this age group will be off-label. Unlicensed preparations of melatonin are available from several pharmaceutical companies on a named patient basis – it is believed that there are at least 50 melatonin preparations that are either being imported into, or manufactured in, the UK. In the US it is freely available to purchase as a food supplement.

Following the UK launch of Circadin®, the MHRA has issued drug procurement advice stating that unlicensed imports of melatonin products will now only be authorised in the case of a special clinical need. The licensed product should be used wherever possible, including off-label use if deemed suitable by the clinician. Importation of unlicensed melatonin products remains possible where there is clinical need (e.g. requirement for alternative dosage forms, or strengths, or for an immediate release product); however prescribers will need to provide details of the special clinical need to the importer for submission to the MHRA. The MHRA requirements only apply to imported melatonin products, they will not apply to those manufactured under 'specials' license in the UK.

The most commonly reported side-effects with melatonin are headaches, dizziness, nausea, and drowsiness (although several studies report similar incidence of side-effects in placebo groups). There are also concerns that melatonin may adversely affect seizure control, gonadal development and asthma control and at present there are no robust data available to support or refute any of these concerns.

The costs of treating a patient with melatonin can vary substantially, for example the costs of product available from two of the major specials suppliers in the UK vary between £4.20 and £30 a month to treat a patient with 3mg daily. The cost of using Circadin® (as recommended by the MHRA where clinically appropriate) at a dose of 2mg daily would be £14.40 for 28 days, but any paediatric use would be off-label.

Produced for the  
**London New Drugs Group**

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September 2008

London New Drugs Group—APC/DTC Briefing

**APPENDIX 2****Flynn Pharma Ltd**

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**Before you contact this company:** often several companies will market medicines with the same active ingredient. Please check that this is the correct company before contacting them. [Why?](#)

Summary of Product Characteristics last updated on the eMC: 14/08/2012

**Circadin****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 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 Circadin in children aged 0 to 18 years has not yet been established.

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.

### Method of Administration

Oral use. Tablets should be swallowed whole.

### **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**

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 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 (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 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 zaleplon, 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 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.

### Breastfeeding

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 1931 patients were taking Circadin and 1642 patients were taking placebo), 48.8% of patients receiving Circadin 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 Circadin (5.743– placebo vs. 3.013– Circadin). The most common adverse reactions were headache, nasopharyngitis, back pain, and arthralgia, 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 9.5% of subjects receiving Circadin reported an adverse reaction compared with 7.4% 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
Cardiac disorders				Angina pectoris,

				palpitations
Metabolism and nutrition disorders				Hypertriglyceridaemia, hypocalcaemia, hyponatraemia
Psychiatric disorders			Irritability, nervousness, restlessness, insomnia, abnormal dreams, anxiety	Mood altered, aggression, agitation, crying, stress symptoms, disorientation, early morning awakening, libido increased, depressed mood, depression
Nervous system disorders			Migraine, 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
Vascular disorders			Hypertension	Hot flush
Gastrointestinal disorders			Abdominal pain, abdominal pain upper, dyspepsia, mouth ulceration, dry mouth	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
Musculoskeletal and connective tissue disorders			Pain in extremity	Arthritis, muscle spasms, neck pain, night cramps
Reproductive system			Menopausal	Priapism, prostatitis

and breast disorders			symptoms	
General disorders and administration site conditions			Asthenia, chest pain	Fatigue, pain, thirst
Renal and urinary disorders			Glycosuria, proteinuria	Polyuria, haematuria, nocturia
Investigations			Liver function test abnormal, weight increased	Hepatic enzyme increased, blood electrolytes abnormal, laboratory test abnormal

#### 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: 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 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 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 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.

An additional randomised clinical trial (n=600) compared the effects of Circadin 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 Circadin treated 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 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 ( $C_{max}=1020$  pg/ml versus  $C_{max}=1176$  pg/ml).

### Distribution

The *in vitro* plasma protein binding of melatonin is approximately 60%. Circadin 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 ( $t_{1/2}$ ) 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  $411.4 \pm 56.5$  and  $432.00 \pm 83.2$  pg/ml respectively, and are similar to those found in 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, 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 pack age 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 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 and other handling**

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**

RAD Neurim Pharmaceuticals EEC Limited

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**8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/07/392/001

EU/1/07/392/002

EU/1/07/392/003

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

29/06/2007

**10. DATE OF REVISION OF THE TEXT**

12/08/2011

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

## **APPENDIX 3**

### **Principles of shared care**

#### **Advice from CJPG on the implementation of effective shared care arrangements locally**

Sharing of care assumes communication between the specialist, GP and patient. The intention to share care should be explained to the patient by the doctor initiating treatment. It is important that patients are consulted about treatment and are in agreement with it. Patients requiring shared care will need regular follow up, which provides an opportunity to discuss drug therapy.

The doctor who prescribes the medication legally assumes clinical responsibility for the drug and the consequence of its use. A balance is needed between meeting patient need for appropriate treatment delivered in a timely and accessible manner, and the need under clinical governance for GPs to undertake shared care in a manner that ensures their competence and the patient's safety.

"Shared care" occurs when a hospital specialist retains a responsibility for the on-going monitoring or review of a patient after the point in time when they consider it clinically appropriate for the patient's GP to take over the responsibility of routine prescribing. Shared care usually only applies to long-term treatment with drugs that are not part of most GPs' routine practice or where some part of a patient's care e.g. monitoring and/or stopping therapy, could not be taken over safely by anyone other than specialist practitioners.

The NHS Management Executive issued its guidance on prescribing at the hospital/GP interface through EL(91)127 – "Responsibility for prescribing between hospitals and GPs". Although issued in November 1991 this guidance is still applicable. It reinforces the basic premise that it is for the doctor who has clinical responsibility for a patient to undertake prescribing, and focuses on the concept of shared care, emphasising the need for proper handover procedures from hospitals. Where there is doubt or dispute about where clinical and prescribing responsibility rests, it will be generally be considered to lie in secondary care if the patient is still under the care of the consultant. See also section on funding.

**The consultant should initiate and maintain treatment until the situation is resolved. Patients should not be left without necessary treatment as a result of a dispute over who prescribes.**

The financial implications of prescribing usually rest with the clinician that prescribes (and their organisation). Exceptions to this are rare, but include arrangements under the NHS guidance on "Hi-Tech at Home" EL(95)5.

Guidance on shared care is also available from the GMC

[http://www.gmc-uk.org/guidance/current/library/prescriptions\\_faqs.asp#5f](http://www.gmc-uk.org/guidance/current/library/prescriptions_faqs.asp#5f)

and from the GPC [http://www.bma.org.uk/images/Infoprescribingp0904\\_tcm41-20363.pdf](http://www.bma.org.uk/images/Infoprescribingp0904_tcm41-20363.pdf)

**Shared care guidelines are intended to provide clear guidance to General Practitioners and hospital prescribers regarding the procedures to be adopted when clinical (and therefore prescribing and financial) responsibility for a patient's treatment with a shared-care drug is transferred from secondary to primary care.**

An important aspect of shared care, that is often overlooked, is that before clinical care is transferred from secondary care there needs to be agreement from the patient's GP that they are prepared to, and are competent to, accept clinical responsibility (and the associated financial and prescribing responsibility) given a defined level of support from secondary care. Just because a Shared Care Guideline exists this does not mean that clinical responsibility can automatically transfer to GPs.

Shared care arrangements for individual patients do **not** always require that a comprehensive written guideline of this type is produced. A verbal agreement between the Consultant and GP may suffice, provided that written confirmation is supplied to the GP of what they are required to monitor and what the key indicators are for referral of the patient back to secondary/tertiary care services for review or to manage suspected adverse effects.

New financial arrangements for enhanced services from April 2004, under the GPs' new GMS contract may have an effect on shared care arrangements in the future. Advice on this is available from your local PCT.

Note: shared care arrangements must always be specific to the indication(s) for which the information has been provided by the specialist to the patient's GP. It is essential that any shared care arrangement makes explicit the arrangements for monitoring therapy and triggers for intervention by specialists.

The existence of a shared care guideline for a drug used for one indication does **not** mean that specialists may assume that shared care arrangements are appropriate for the same drug in other indications.

These variations exist for a single drug because the evidence base and /or level of expertise needed to manage/monitor therapy and patient outcomes may be very different between indications e.g. epoetin/darbepoetin is now routinely prescribed by GPs for sub-cutaneous administration, under shared care arrangements for chronic renal failure however use of the same drugs by the IV route in chronic renal failure or use to manage anaemia arising from cancer and its treatment is not generally considered suitable at this stage for GP prescribing.

Unlicensed drugs and unlicensed indications for drugs may be included in shared care arrangements provided the specialist provides sufficient information to the GP to support the effectiveness and appropriateness of the recommended treatment.

The Department of Health has made NHS Chief Pharmacists directly accountable (with NHS Chief Executives) for safe medication practices within and on behalf of their organisations. Chief Pharmacists in hospitals and PCTs must therefore be involved in drawing up and ratifying any written shared care guidelines.

It is recommended that Chief Pharmacists, or their senior staff, are made aware of informal shared care arrangements that are established.

The role of pharmacists in the clinical team can be pivotal in ensuring that all parties to the supply of medicines under shared care arrangements are known to all those who are affected, including community pharmacists who will be supplying the medicines once they are prescribed by GPs.

From an original template developed by MTRAC in August 2002

Adapted in 2004 for CJPG use, including information and comments received through stakeholder meetings held to inform the development of the NatPaCT PCT competencies framework for Medicines Management, Pharmacy and Prescribing toolkit

Comments on this guideline and submissions of drafts of new shared care guidelines to CJPG should be sent to [c-pct.prescribingpartnership@nhs.net](mailto:c-pct.prescribingpartnership@nhs.net)