NHS South of Tyne and Wear

serving Gateshead Primary Care Trust, South Tyneside Primary Care Trust and Sunderland Teaching Primary Care Trust

# SHARED CARE GUIDELINE

For

## Melatonin for the Management of Sleep – Wake Disorders in Children

**Implementation Date: April 2012**

**Review Date: March 2014**

**This guidance has been prepared and approved for use within Gateshead, South Tyneside and Sunderland in consultation with Primary and Secondary Care Trusts and Local Medical Committees.**
**The guideline sets out the details of the transfer of prescribing and respective responsibilities of GPs and specialist services within shared care prescribing arrangements. It is intended to provide sufficient information to allow GPs to prescribe these treatments within a shared care setting**

**Further copies are available from**

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**Approved by:**

| Committee | Date |
|---|---|
| **Gateshead Medicines Management Committee** | **April 2012** |
| **South Tyneside Prescribing Committee** | **March 2012** |
| **Sunderland Primary Care Prescribing Group** | **March 2012** |
| **South of Tyne and Wear Medicines Management Committee** | |
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| SHARED CARE GUIDELINE | | | |
|---|---|---|---|
| Non proprietary name | Melatonin | Brand name | Not applicable. Manufacturers include Penn Pharmaceuticals and Special Products Ltd |
| Dosage form and strength | 1mg, 2mg, 2.5mg, 3mg, 5mg, 10mg caps<br>2mg, 3mg orodispersible tabs, 1mg/ml liquid | BNF class | 4.1.1 NB: This is an unlicensed use of melatonin |
| Shared Care Status of melatonin products | NB. This shared care guideline covers the use of melatonin from UK manufacturers.<br><br>Circadin 2mg MR tablets, the licensed product which is used off label in children and young adults is classed as green plus and therefore not covered by this shared care guideline<br><br>All imported melatonin products are classed as red or hospital only and GPs should not be asked to prescribe these products | | |
| Condition(s) to be treated | For the treatment of sleep-wake cycle disorders in children and young adults. With the aims of improving the onset and duration of sleep and establishing a regular nocturnal sleep pattern. | | |
| Excluded patients | Unstable disease state, patient aged under 1 year, pregnancy or breast-feeding, Sleep disturbances due to obstructive apnoea, emotional distress or nocturnal seizures, Patients with severe allergies, auto-immune diseases or immune system cancers, patients taking immunosuppressant's. | | |
| Eligibility criteria for shared care | Following dose and drug stabilisation for at least 1 month | | |
| Initiation | Initiation of treatment will take place in secondary care | | |
| Duration of treatment | May be possible to withdraw the drug after 6months when a regular sleep pattern has been established | | |
| Usual maintenance dose | 2-6mg/day<br>The dose should be given 30 to 60 minutes before bedtime (immediate release preparations) | | |
| Maximum dose | 10mg/day | | |
| Preparations | 1mg, 2mg, 2.5mg, 3mg, 5mg, 10mg capsules, 2mg, 3mg orodispersible strawberry flavoured tablets and 1mg/ml orange-flavour SF liquid | | |
| Cost 28 days | £26.70/month (based on 5mg/day for 28days) | | |
| Adverse effects | Melatonin is generally well tolerated<br>However, the full adverse effect profile is unclear due to the small size of trials.<br>Increased seizure activity has been reported in some children with epilepsy[1,2]. It may also exacerbate asthma[3,4] in the short-term<br>Other reported side-effects include headache, depression, restlessness, confusion, nausea, tachycardia and pruritis[5,6]<br><br>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 |
|---|---|---|---|---|
| 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 |

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| Reproductive System and Breast Disorders | | | | Priapism |
| General Disorders and Administration Site Conditions | | | Asthenia | Fatigue |
| Investigations | | | Weight increased | |

Pharmacokinetic interactions[7]

• 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 melantonin 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

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| | or vice versa has not been studied.<br>Pharmacodynamic interactions<br>• Alcohol should not be taken with melatonin, because it reduces the effectiveness of melatonin on sleep.<br>• melatonin 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 melatonin and zolpidem one hour following co‑dosing. Concomitant administration resulted in increased impairment of attention, memory and co-ordination compared to zolpidem alone.<br>• melatonin 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 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[7]. |
| Contra-indications | Known hypersensitivity to the product. Pregnancy (see below) Should be used with caution in children with epilepsy, seizure frequency should be monitored. Liver disease, cerebrovascular disease |
| Renal impairment and liver disease | *Renal insufficiency*<br>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.<br>*Hepatic impairment*<br>There is no experience of the use of melatonin 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 is not recommended for use in patients with hepatic impairment. |
| Pregnancy and breast feeding | 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. In view of the lack of clinical data, use in pregnant women and by women intended to become pregnant is not recommended.<br>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[7]. |
| Monitoring | Standard monitoring of growth and sexual development is recommended, i.e. to check height, weight and pubertal development progress as expected |

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| Responsibilities | <u>Consultant</u><br>Assessing suitability of patients for treatment. Discuss the treatment options with the patient, their parent(s) and carer(s), to include explanation of the unlicensed nature of melatonin.<br>Initiation and supply of one month after dose has been stabilised, including conversion to sustained release preparation where appropriate.<br>Ensure the patient has at least 4 weeks supply remaining from the date the GP accepts the request to continue prescribing (to allow 2 weeks for the surgery to set up the prescription and provide it to the patient and then 2 weeks for the pharmacy to obtain supplies).<br>Assess and monitor patients response to treatment on a 6-12 monthly basis. | | |
| | <u>GP</u><br>Prescribe appropriate quantities of Melatonin for the patient on FP10 once dose is stabilised | | |
| Communication | <u>Consultant</u><br>Request the GP to take over prescribing in a clear letter; this letter should include full clinical details and document that the unlicensed nature of melatonin has been discussed and consent obtained.<br>Ensure the patient is fully aware of the need to obtain a prescription from their GP within 2 weeks and take it immediately to their chosen community pharmacy so that arrangements can be made to obtain stocks.<br>Report any suspected ADRs to CSM.<br>Discontinuation – advising GPs when and how a trial withdrawal of melatonin should be undertaken | | |
| | <u>GP</u><br>Relevant referrals<br>Liaison with consultant regarding any complications of treatment<br>Only ask the Consultant to take back the prescribing should unmanageable problems arise and allow an adequate notice period (4 weeks is a suggested minimum) | | |
| Re-referral criteria | Failure to attend for monitoring review<br>Intolerance of drugs<br>Monitoring parameters of acceptable range<br>Communications failure | | |
| Contact details | Patient's own consultant | | |
| Agreed date | | Expiry/Review date | |

*References*


(1)Smits MG, Nagtegaal EE, van der Heijden J *et al*. Melatonin for chronic sleep onset disorder in children: a randomised placebo controlled trial. *J Child Neurol* 2001;16:86-92

(2)Sheldon SH. Pro-convulsant effects of oral melatonin in neurologically disabled children. *Lancet* 1998;351:1254

(3)Maestroni GJM. The immunoendocrine role of melatonin. *J Pineal Res* 1993;14:1-10

(4)Sutherland ER, Ellison MC, Kraft M et al. Elevated serum melatonin is associated with nocturnal worsening of asthma. *J Allergy Clin Immun* 2003; 112:513-517

(5)Chase JE, Gidal BE. Melatonin:therapeutic uses in sleep disorders. *Ann Pharmacotherapy* 1997;31:1218-1226

(6)Jan JE, Freeman RD, Fast DK. Melatonin treatment of sleep-wake cycle disorders in children and adolescents. *Dev Med Child Neurol*;41:491-500

(7) www.medicines.org.uk SPC Circadin 2mg prolonged-release tablets (Accessed 02/01/09)

**Appendix 1 Shared Care Request Form**

- **Consultant to complete FIRST SECTION of form**
- **GP to complete SECOND section and RETURN to SECONDARY CARE TRUST CLINICIAN TEAM if transfer declined.**

**Section 1**

| | |
|---|---|
| Consultant | |
| Hospital address | |
| Contact Phone Number | |

| | |
|---|---|
| Patient's name | |
| Address | |
| This patient is stabilised on | |
| Dose | |
| Prescription for 28 days supply given on | |

| | |
|---|---|
| Compliance aid | YES/NO |
| Monitored by | |
| Designated community pharmacy | |

Their treatment has been explained to them and a review has been arranged for

…… ……..

Appointments to continue every …… months

## Section 2

| | |
|---|---|
| Patient's name | |
| Address | |
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I do **NOT ACCEPT** the proposed Shared-Care Agreement for this patient

| My reasons for not accepting:<br>Please complete this section |
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**Signed ……date……..**

**Please return to the Secondary Care Trust Clinician team at:**

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