SHARED CARE AGREEMENT: MELATONIN (ADULTS)

NHS GREATER GLASGOW AND CLYDE

NB: This document should be read in conjunction with the current Summary of Product Characteristics (SPC)

DRUG AND INDICATION:

Generic drug name:	Melatonin
Formulations:	**Modified release preparations**: 2mg modified-release tablets **Immediate release preparations**: 3mg immediate release tablets 1mg in 1ml oral solution
Intended indication:	▪ REM behaviour disorder ▪ Circadian rhythm disorders ▪ Sleep behaviour disorder ▪ Adjunct in other parasomnias or sleep medicine disorders with sleep fragmentation Benefit from melatonin therapy is not anticipated in most patients with primary insomnia but a treatment trial may be indicated to determine if there is an underlying circadian rhythm disorder component.
Status of medicine or treatment:	Melatonin 2mg modified-release tablets: licensed product in UK for those aged 55 years and over, but unlicensed for long term use for sleep disorders. Melatonin 3mg immediate-release tablets: licensed product in the UK for short term treatment of jet lag, but unlicensed for long term use for sleep disorders. Listed in the Scottish Drug Tariff (part 7). Melatonin 1mg in 1ml oral solution: licensed product in the UK for short term treatment of jet lag, but unlicensed for long term use for sleep disorders.

RESPONSIBILITIES OF ACUTE CARE/SPECIALIST SERVICE (CONSULTANT):

Acute care/specialist service role:

Where a diagnosis of a sleep disorder in adults is made by specialists in sleep medicine or neurology, psychiatry, Learning Disabilities (in liaison with sleep services where relevant) the acute care/specialist service will:

- Assess the suitability of patients for treatment
- Initiation and stabilisation of patients on appropriate dose and preparation
- Assess and monitor the patient's response to treatment and to check for possible complications with discontinuation of the treatment if ineffective and dose adjustment if necessary
- Provide initial supply of medicine to patient until stabilisation and transfer of care to GP
- Report adverse events to the CHM (yellow card reporting scheme) and inform GP
- Ensure clear arrangements for GP back-up, advice and support.
- Undertake standard sleep clinic evaluation of driving status and provide NHS GG&C agreed standard advice on sleep issues and driving safety.

Acute care/specialist service will provide the GP with:

- An initiation letter (which includes diagnosis, relevant clinical information, baseline results, treatment to date and dose of melatonin that the patient is stabilised on, treatment plan, duration of treatment before consultant review)
- Details of outpatient consultations, ideally within 14 days of seeing the patient
- Advise when treatment withdrawal should be considered

Acute care/specialist service will provide the patient with relevant drug information to enable:

- Informed consent to therapy including information that the use of the medicine is unlicensed.
- Understanding of potential side effects and appropriate action.

RESPONSIBILITIES OF PRIMARY CARE (GENERAL PRACTITIONER):

- Continue to prescribe treatment, once stabilised, in collaboration with the specialist according to this shared care agreement.

- Ensure that patients primary care medication records are kept updated to reflect advice from specialist service (e.g. dose adjustments)
- Manage any adverse effects or refer to specialist service as outlined in this shared care agreement.
- Continue to support the prescribing of the formulation selected by the specialist where clinical justification has been provided

RESPONSIBILITIES OF PATIENT:

- To attend hospital and GP clinic appointments
- Failure to attend appointments will result in medication being stopped
- To report adverse effects to their specialist or GP
- Contact the GP and community pharmacist to arrange supplies of melatonin in enough time to ensure continuity of treatment.

ADDITIONAL RESPONSIBILITIES:

Any serious reaction should be reported to the Commission of Human Medicines (CHM) by whoever they are highlighted to. Use the Yellow Card System to report adverse drug reactions. Yellow Cards and guidance on its use are available at the back of the BNF or online at http://yellowcard.mhra.gov.uk/.

CAUTIONS:

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

Cautions for melatonin 2mg modified release tablets:

- No clinical data exist concerning the use of melatonin in individuals with autoimmune diseases. Therefore melatonin is not recommended for use in patients with autoimmune diseases.
- Contains lactose: patients with rare hereditary problems of galactose intolerance, the LAPP lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Cautions for melatonin 3mg immediate release tablets:

- Caution should be exercised in patients with epilepsy, autoimmune, renal or hepatic disorders.
- Limited data suggest that melatonin taken in close proximity to ingestion of carbohydrate-rich meals may impair blood glucose control.

- For tablets that contain lactose: patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Cautions for melatonin 1mg/ml oral solution:

- Caution should be exercised in patients with epilepsy, autoimmune, renal or hepatic disorders.
- Limited data suggest that melatonin taken in close proximity to ingestion of carbohydrate-rich meals may impair blood glucose control.
- Contains sorbitol: patients with hereditary fructose intolerance should not take/be given this medicinal product.

CONTRAINDICATIONS:

- **Contraindications for melatonin 2mg modified release tablets:**
  Hypersensitivity to the active substance or to any of the excipients.

- **Contraindications for melatonin 3mg immediate release tablets:**
  Hypersensitivity to the active substance or to any of the excipients.

- **Contraindications for melatonin 1mg in 1ml oral solution:**
  Hypersensitivity to the active substance or to any of the excipients.

TYPICAL DOSAGE REGIMENS:

Dosage regimen for melatonin 2mg modified release tablets:

Route of administration:	Oral – to be taken whole.
Recommended starting dose:	2mg once daily, 1-2 hours before bedtime and after food
Titration of dose:	Increase by 2mg depending on response every 7-14 days
Maximum dose:	12mg
Adjunctive treatment regimen:	Sleep hygiene (advice). For selected patients fixed dosing time, specific advice on sleep time and rise time and/or morning light box use will be recommended.
Conditions requiring dose adjustment:	Non response (delayed time to sleep onset, disturbed sleep, continuing parasomnia, early morning awakening)
Usual response time:	Parasomnia: 7 days. Circadian rhythm disorder response usually seen over period of weeks.
Duration of treatment	REM behaviour disorder: indefinite. Other indications may require fixed duration (usually several months), periodic or indefinite treatment.

Dosage regimen for melatonin 3mg immediate release tablets:

Route of administration:	Oral – may be crushed and mixed with a small amount of water.
Recommended starting dose:	Initially 3mg daily which can be increased to 6mg - if insufficient response after 7-14 days.
Titration of dose:	Increase to 6mg depending on response after 7 – 14 days
Maximum dose:	12mg daily but additional benefits from doses above 6 - 9mg are uncertain
Adjunctive treatment regimen:	Sleep hygiene (advice)
Conditions requiring dose adjustment:	Non response (delayed time to sleep onset, disturbed sleep, early morning awakening)
Usual response time:	Parasomnia: 7 days. Circadian rhythm disorder response usually seen over period of weeks.
Duration of treatment	REM behaviour disorder: indefinite. Other indications may require fixed duration (usually several months), periodic or indefinite treatment.

Dosage regimen for melatonin 1mg in 1ml oral solution:

Route of administration:	Oral
Recommended starting dose:	Initially 2mg daily which can be increased to 6mg - if insufficient response after 7-14 days.
Titration of dose:	Increase to 6mg depending on response after 7 – 14 days
Maximum dose:	8mg
Adjunctive treatment regimen:	Sleep hygiene (advice)
Conditions requiring dose adjustment:	Non response (delayed time to sleep onset, disturbed sleep, early morning awakening)
Usual response time:	Parasomnia: 7 days. Circadian rhythm disorder response usually seen over period of weeks.
Duration of treatment	REM behaviour disorder: indefinite. Other indications may require fixed duration (usually several months), periodic or indefinite treatment.

SIGNIFICANT DRUG INTERACTIONS:

- **Nifedipine or other calcium-channel blockers**-melatonin may reduce effect of nifedipine on blood pressure. Mechanism is unknown and clinical relevance is probably minor.

- **Warfarin or other anticoagulants -** INR may be raised or lowered when melatonin is prescribed with warfarin. Mechanism is unknown.

- **CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin and other quinolones, oestrogens (e.g. oral contraceptives and hormone replacement therapy), and methoxypsoralen) –** have the potential to increase melatonin levels. BNF advises to avoid fluvoxamine.

- **CYP2D inhibitors (e.g. cimetidine) -** have the potential to increase melatonin levels.

- **CYP1A2 inducers (e.g. carbamazepine, rifampicin, smoking) –**have the potential to decrease melatonin levels.

- **Other hypnotics and CNS depressants**: melatonin may enhance the sedative properties of other drugs acting on the CNS e.g. benzodiazepines.

UNDESIRABLE EFFECTS:

Melatonin is generally well tolerated with only a few adverse side-effects having been reported. Most commonly reported side-effects include headaches, nausea and drowsiness.

ADR details	Management of ADR
Uncommon: Irritability, nervousness, restlessness, insomnia, abnormal dreams, anxiety, migraine, lethargy, psychomotor hyperactivity, dizziness, somnolence, increased seizure activity in epileptic patients.	Refer to specialist service and if ADR is clinically significant discontinue medicine prior to referral
Uncommon: Dermatitis, night sweats, pruritus, rash, pruritus generalised, dry skin.	Refer to specialist service and if ADR is clinically significant discontinue medicine prior to referral
Uncommon: Hypertension.	Refer to specialist service and discontinue medicine prior to referral
Uncommon: Abdominal pain, abdominal pain upper, dyspepsia, mouth ulceration, dry mouth, hyperbilirubinaemia.	Refer to specialist service and if ADR is clinically significant discontinue medicine prior to referral

BASELINE INVESTIGATIONS:

- None required

MONITORING (PRIMARY CARE):

- All routine monitoring relating to response is undertaken within the specialist service.

MONITORING (ACUTE SECTOR):

- The following monitoring is to be undertaken in Acute Care

Monitoring Parameters	Frequency	Laboratory results	Action to be taken
Clinical response	Annual	N/A	Consider stopping melatonin. Investigate further as required

PHARMACEUTICAL ASPECTS:

Melatonin Preparations: There are many different strengths and formulations available. Upon receipt of a GP10 prescription community pharmacists should dispense the appropriate formulation, which will normally be melatonin 2mg modified release tablets.

The simultaneous use of the standard and modified release preparations may be useful in some patients.

***Melatonin modified release*: Melatonin 2mg tablets**, 30 tablets per pack.
- The tablets must be swallowed whole
- Should be taken 1-2 hours before desired bedtime

***Melatonin immediate release*: Melatonin tablets 3mg**, 30 tablets per pack.
- The tablets may be crushed and mixed with a small amount of water to help with ingestion
- Should be taken on an empty stomach, 2 hours before or 2 hours after food
- Should be taken 30 minutes before the desired bedtime

Melatonin oral solution 1 mg in 1ml (immediate release): 150ml.
- Flavoured solution, contains sorbitol and propylene glycol as excipients
- Should be taken on an empty stomach, 2 hours before or 2 hours after food
- Should be taken 30 minutes before the desired bedtime

COST:

- Melatonin 2mg modified-release tablets 30 tablets £15.39 (BNF November 2020)
- Melatonin 3mg immediate release tablets 30 tablets £14.95 (Scottish Drug Tariff November 2020)
- Melatonin 1mg in 1mL oral solution – 150mL £130.00 (BNF November 2020)

INFORMATION FOR COMMUNITY PHARMACIST:

Melatonin 2mg modified release tablets, melatonin 3mg tablets and the 1mg in 1ml oral solution are licensed medicines in the UK and should be available from most wholesalers.

ACUTE CARE/SPECIALIST SERVICE CONTACT INFORMATION:

Name	Designation	Acute Site	Department phone number
Dr Chris Carlin	Sleep, Breathing Support & Respiratory Medicine Consultant	Queen Elizabeth University Hospital/ Gartnavel General Hospital	0141 451 6088

SUPPORTING DOCUMENTATION:

- CPD on sleep disorders is available at
  - Parasomnias: Updated review including treatment https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3480572/
  - Circadian rhythm disorders: review https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3523094/