integrated working

West Suffolk
Clinical Commissioning Group

Melatonin

ESCA: For Treatment of Sleep Disorders in Children and Adolescents with Neurological/Neurodevelopmental Disorders including Attention Deficit Hyperactivity Disorder (ADHD), Autism and Visual Impairment (Unlicensed Use)

AREAS OF RESPONSIBILITY FOR THE SHARING OF CARE

This shared care agreement outlines suggested ways in which the responsibilities for managing the prescribing of Melatonin for sleep disorders in children and adolescents can be shared between the specialist and general practitioner (GP). GPs are **invited** to participate. If GPs are not confident to undertake these roles, then they are under no obligation to do so. In such an event, the total clinical responsibility for the patient for the diagnosed condition remains with the specialist. **If a specialist asks the GP to prescribe this drug, the GP should reply to this request as soon as practicable.**

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. Children and adolescents with neurological disorders, ADHD, autism and visual impairment are under regular specialist 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 consequences of its use.

RESPONSIBILITIES and ROLES

	Specialist responsibilities
1	Assess suitability of patient for treatment
2	Discuss benefits and side effects of treatment with the patient/parent/carer to include explanation of the unlicensed nature of melatonin for use in children and adolescents.
3	Provide Patient Information Leaflet (Appendix 1)
4	Initiate treatment with melatonin if agreed. Select appropriate product and formulation (see Appendix 2)
5	Titrate the dose to a satisfactory effect over a minimum of 8 weeks
6	Send a letter to the GP suggesting that shared care is agreed for the patient
7	Ensure patient has at least a 4 week 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 arrange supplies.
8	Ensure the family 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
9	Continue regular review of patient every 6-12 months to ensure continuing benefit of melatonin and ensure that appropriate monitoring is undertaken (see below). Communicate any changes or recommendations to the GP.
10	Advise GP when a trial withdrawal of melatonin should be undertaken
11	Report adverse events to the MHRA www.mhra.gov.uk/Safetyinformation/Reportingsafetyproblems/index.htm
12	Take back care of the patient should the GP feel unable to continue to manage the prescribing of melatonin.

General Practitioner responsibilities

1 Reply to the request for shared care as soon as practicable.
2 Prescribe the brand and formulation of melatonin specified by the specialist.
3 Follow specialist advice on any changes in treatment.
4 Monitor parameters below
5 Communicate any problems to the specialist looking after the patient
6 Report adverse events to specialist and MHRA
www.mhra.gov.uk/Safetyinformation/Reportingsafetyproblems/index.htm
7 Stop treatment on advice of specialist
8 Only ask the specialist to take back the prescribing should unmanageable problems arise and allow an adequate notice period (e.g. 4 weeks)

EFFECTIVE SHARED CARE AGREEMENT (Melatonin for the Treatment of Sleep Disorders in Children and Adolescents)

Patient's role

1 Agree to request prescriptions from the GP in good time, obtain the first GP prescription within 2 weeks of being informed that shared care is in operation.

2 Stick with one chosen community pharmacy unless there is good reason to change
3 Take the prescriptions to the pharmacy as soon as possible so that they have enough time to order it (may take up to 2 weeks to come in)
4 Report any concerns to the GP or specialist.

BACK-UP ADVICE AND SUPPORT

Ipswich Hospital

Contact details	Telephone No.	Bleep:	Fax:	Email address:
Specialist doctor **Dr J. Gould** **Dr M. James** **Dr C. Yale** **Dr K O'Neill** **Dr J. Buck** **Dr P Desai**	01473 712233	 551 553 552 548 550 559	01473 702180	 james.gould@ipswichhospital.nhs.uk matthew.james@ipswichhospital.nhs.uk
Specialist nurse				
Hospital Pharmacy dept **Sara Bolton** **Alison Robinette**	01472 712233	 287 287	01473 703607	 sara.bolton@ipswichhospital.nhs.uk Alison.robinette@ipswichhospital.nhs.uk
Medicines Information	01473 704431		01473 703607	Eastanglia.mis@ipswichhospital.nhs.uk

Suffolk Mental Health Partnership Trust – Child and Adolescent Mental Health Service (CAMHS)

Contact details	Telephone No.	Bleep:	Fax:	Email address:
Specialist doctor **Dr R Davey**	01284 775000			Robert.davey@smhp.nhs.uk
Specialist nurse **Kelley Osman**	01473 220300			Kelley.osman@smhp.nhs.uk
Hospital Pharmacy dept **Karen Barker**	01473 329798			karen.barker@smhp.nhs.uk
Medicines Information	01473 329747			

SUPPORTING INFORMATION

Background to sleep disorders

Sleep disorders are common in children with neurological/neurodevelopmental disorders including ADHD, autism and visual impairment. These children often have disturbed sleep patterns, with delayed onset, fragmentation and frequent nocturnal wakening. Sleep disorders can be a major source of stress for the whole family and limited solutions are available. Behavioural modification and appropriate sleep hygiene measures are usually tried, but may be ineffective. Hypnotics and sedatives are generally effective initially but tolerance quickly develops and many cause unacceptable adverse effects. There is significant clinical experience with the use of melatonin for the treatment of paediatric sleep-wake cycle disorders. Results in terms of improved sleep patterns have been generally favourable and adverse effects minimal.

Indications

For use in children over 3 years of age with neurodevelopment disability, autism, visual impairment or neuropsychiatric disorders and chronic sleep disturbance where: -

- Symptoms of sleep disturbance have been present for at least six months or sleep disturbance is so severe that the family are heading for crisis.
- After failure of sleep hygiene improving measures e.g. a fixed bedtime routine.

Dosage and Administration
The recommended starting dose is 2 or 3mg given 30-60 minutes before desired sleep time.

If there has been insufficient response after 7-14 days, the dose can be increased in 2or 3mg steps every 7-14 days, up to a maximum of 10mg

If there is no improvement in the child's sleep pattern after 7-14 days on the maximum dose, there is no indication to try higher doses and melatonin should be discontinued. This can be done immediately and without the need for gradual withdrawal.

Formulation
Melatonin (Circadin®) is only licensed for use in adults aged over 55 years for primary insomnia and so use in children and adolescents is an unlicensed use.

- Problems with sleep initiation;
  Standard release melatonin at the dose described above will be used

- Problems with sleep maintenance/fragmental sleep and/or early morning awakening;
  Controlled release melatonin at the dose described above will be used in the first instance. The licensed preparation (Circadin® - melatonin modified release tablet 2mg) is used first line

- Problems with both sleep initiation and sleep maintenance/fragmental sleep and/or early morning awakening;
  The licensed modified release melatonin (Circadin®) is used first line.

See Appendix 2 for further information

Contraindication

- Contra-indicated in pregnancy due to unknown effects.
- Should be used in caution in children with epilepsy, seizure frequency should be monitored.
- The manufacturers of Circadin® state that it should not be taken in patients with rare hereditary problems of galactose intolerance, the LAPP lactase deficiency or glucose-galactose malabsorption.
- It is also not recommended for use in patients with autoimmune diseases.

Side Effects
Melatonin is generally well tolerated and no significant adverse effects have been reported with pharmacologically regulated melatonin. Both increased and reduced seizure frequency has been reported in children with epilepsy.

Tachycardia, confusion, dysphoria, increased seizure activity, psychosis, gynaecomastia, decreased luteinizing hormone levels, decreased temperature autoimmune hepatitis, elevated liver enzymes, flushing, rashes and withdrawal effects have been reported rarely.

***All** suspected reactions (including those considered not to be serious and even where the causal link is uncertain) should be reported to the CSM.*

Monitoring

Parameter	Frequency of monitoring	Action
Height	Annual	By Specialist or GP by agreement
Weight	Annual	By Specialist or GP by agreement
Pubertal development	Annual	By Specialist or GP by agreement

Drug Interactions
Levels of melatonin are increased by fluvoxamine.
Increased blood pressure with nifedipine.
Reduced prothrombin with warfarin.

Preparations and Availability
In the UK melatonin is classified as a medicine and is only available on a doctor's prescription.
Melatonin (Circadin®) is only licensed for use in adults aged over 55 years for primary insomnia and so use in children and adolescents is an unlicensed use.

The melatonin used is synthetic.

See Appendix 2 for further information

Cost

Formulation	Name	Licensing	Manufacturer	Cost per dose unit
2mg modified release tablet	Circadin®	UK licensed for 55 years + over	Lundbeck 01908649966	£0.51
3mg tablet	Bio-melatonin®	EU licensed	PharmaNord (UK) 01670519989 Special Products (UK) 01483 736950	£0.38
1mg,2mg,3mg,5mg capsules 1mg/ml liquid	Generic name	No UK or EU license, UK manufacturer licensed	Penn Pharmaceuticals 01495711222	£0.85 to £2.25
1mg,3mg tablets 2.5mg caps 3mg modified release capsule	Generic name	No UK or EU license, imported.	Import specialist supplier e.g. Idis World Medicines 01932 824000	Unpredictable (£0.19 to £0.85)

Prices as of Nov 2009

See Appendix 2 for further details

References

Shared Care Guidelines Melatonin from:-
Northampton General Hospital NHS Trust
NHS Lothian
Bolton Hospital NHS Trust/Bolton NHS Primary Care Trust
Leeds NHS Trust
Luton and Dunstable NHS Trust

Produced by –

Dr J. Gould, Consultant Paediatrician, Ipswich Hospital NHS Trust
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Sara Bolton, Paediatric Pharmacist, Ipswich Hospital NHS Trust
Karen Barker, Clinical Pharmacist, Suffolk Mental Health Partnership Trust

November 2009

Appendix 1
Information for patients, parents and carers.

What is melatonin?

Melatonin is a natural hormone produced by the pineal gland in the brain. It is produced at night and helps us to fall asleep.

Melatonin has been used to treat jet lag and some sleep problems in adults. The results from a small number of studies in children show that melatonin can help children fall asleep.

When is melatonin used?

Many Specialist doctors (Paediatricians and Child Psychiatrists) are using melatonin to treat severe sleep problems seen in some children and teenagers.

Many children with behavioural problems learning disabilities, autism and certain forms of blindness have significant sleep problems. The most common problems are: difficulties settling, waking up repeatedly and waking too early. Sleep problems can cause daytime sleepiness and behavioural problems during the day.
First, we try to change behaviour without any medicines and this can be very successful. However, this does not work for some children. For these patients, we may try a sedative medicine such as alimemazine (the brand name is Vallergan®) or promethazine (the brand name is Phenergan®). These medicines may not work or may have side effects (especially feeling very sleepy the following morning) and can sometimes make sleep problems worse.

Melatonin can help children to fall asleep without feeling very sleepy the next morning.

How is melatonin supplied?

Melatonin is currently an unlicensed medicine in children and adolescents in the UK but can be prescribed by doctors on a prescription.

Melatonin is usually started by a community or hospital Specialist doctor and prescribing can be taken over by your General Practitioner (GP) using our 'shared care guideline'. This is so you can get supplies from your local pharmacy (chemist) near your home or work. Melatonin has to be specially ordered and it can take 10 to 14 days for your pharmacist (chemist) to get a supply for you - so hand in your prescription before you run out and give them plenty of time.

It is supplied as capsules that can be opened if needed and the contents of the capsule can be mixed in water, milk or orange juice. It is also available as tablets or liquid.

What is the usual dosage?

We usually start on a low dose of between 2mg or 3mg and this should be given about 30 to 60 minutes before your child's regular bedtime. If this does not work or seems to help a little, the dose can be increased slowly up to 10mg a night.

Can I boost melatonin naturally for my child?

Exposure to daylight or bright artificial light first thing in the morning and low lighting in the evening can help to boost melatonin production naturally in the brain. Certain foods also provide a naturally rich source of melatonin: oats, sweet corn, rice, ginger, tomatoes and barley. A banana "smoothie" (banana and milk liquidised together), a cup of tomato soup or a bowl of corn flakes, made with warm full-cream milk, taken an hour before bedtime may have a similar effect. Another naturally occurring chemical, tryptophan, is one of the building blocks of melatonin and foods containing this can also boost melatonin production in the evening. Foods that are rich in tryptophan include: cottage cheese, instant breakfast cereals (made with full cream milk), chicken and turkey, nuts

(almonds and peanuts), milk, ice-cream and yoghurt. Foods rich in calcium, magnesium, vitamin B6 and nicotinamide (B3) can also boost melatonin production.
These can be tried instead of taking melatonin capsules.

What should my child avoid?
Avoid anti-inflammatory drugs (such as aspirin or steroids), caffeine (tea, coffee, cola drinks and chocolate) and exposure to bright lights before bedtime.
Strong electromagnetic fields from computers, radios, TVs, clocks, baby monitors, electric blankets, etc. can also reduce melatonin and are best removed from the bedroom or switched off at the wall socket.

How long should treatment last?
This is a difficult question to answer because there is not much information.
A simple answer is “as long as we believe it is helping and is safe”.
After trying melatonin for one month, your Specialist's team will review whether the melatonin is helping and whether there have been any problems, like side effects.
If it has not helped then they will discuss increasing the dose or stopping melatonin with you. If it has helped then they may ask your General Practitioner (GP) to prescribe it so you can get the melatonin from a pharmacist (chemist) near your home or work.

The Specialist's team will review your child about every 12 months, or earlier if there are any concerns.

Some children can eventually stop taking melatonin and will be able to sleep normally. But some children will need to take melatonin long term. To see if the medicine needs to be continued the drug will be stopped once a year, usually a month before the annual review. You will be asked to keep a sleep diary to see how the treatment is working. Treatment will be stopped if there is evidence of lack of effect from the sleep diary or your report a lack of effect.

Sometimes parents forget to give a bedtime dose. If your child sleeps well without the melatonin then it is a good idea to stop the melatonin and see if this pattern continues for the next few nights. Tell your doctor of any forgotten doses and how your child slept without melatonin.

Sleep problems in children tend to change so it is very helpful to keep a sleep diary before and during any treatment to show whether the treatment is working.

Side effects
Melatonin is generally well tolerated. Some patients report they get headaches.
A small number of children may become excitable and agitated and some may have vivid dreams or nightmares and the melatonin may need to be stopped.
There has been concern about using melatonin in children with epilepsy but for most it is safe to use.
Children suffering from illnesses that affect the immune system (severe allergies, autoimmune conditions and some forms of immune system cancer) should avoid melatonin because it may make these illnesses worse.

Appendix 2
Information on Melatonin Preparations and Product Selection

Background

The MHRA want to ensure that the choice of melatonin products is made rationally and takes product quality and safety into consideration. They recognise that it may be necessary to use the non-pharmaceutical products on occasion, especially in patients that may not be able to take solid dosage forms and require liquids or where, for example, they cannot swallow tablets, but can use capsules. There is also the possibility that certain high or low doses may be required, or that capsule contents may be needed for alternative modes of administration. They will consider such cases sympathetically, but will need to know the clinical reason for requiring the product.

MHRA Product Selection Principles

The MHRA specific advice is as follows:

1. Although the MHRA does not recommend "off-label" use of products, if the UK licensed product (Circadian®) can meet the patient's clinical need, even "off-label", it should be used. UK licensed products have been assessed for quality, safety and efficacy. If used "off-label" some of this assessment may not apply, but much will still be valid. This is a better risk position than in the use of an un-assessed, unlicensed product.

2. If the UK product cannot meet the patient's clinical need, then another (imported) pharmaceutical should be considered, which is licensed in the country of origin. For example, there is an immediate release 3mg capsule licensed in Hungary (Bio-Melatonin®, Pharma-Nord), that is manufactured in GMP inspected facilities in Denmark. This is also packed into English language packs in Denmark and may be available in this form from Pharma-Nord, rather than in the Hungarian licensed pack.

3. If option 1 or 2 does not meet the patient's clinical need, then a completely unlicensed product may have to be used. There are UK manufactured "specials" such as those manufactured by Penn Pharmaceutical Services, which are made in GMP inspected facilities, but which are otherwise un-assessed (GMP inspection is not product specific). There are also many US products sold over the counter, but these are not pharmaceuticals and are made to unknown quality standards. They would therefore be classified as a last resort to meet patient's clinical need.

What is a "special clinical need" letter?

Imported melatonin orders need a letter from the prescriber stating the special clinical need. In other words, why the patient can not take the licensed 2mg modified release tablets, Circadin®.

There are no notification requirements for UK manufactured "specials". The MHRA are therefore not in a position to routinely review compliance for these products in the manner they can for imports. However, "special clinical need" is still a requirement. Importers and "specials" manufacturers must therefore be able to provide evidence of "special clinical need" for the products they supply. There should be a documented audit trail leading to the prescriber and evidence of the "special clinical need". The MHRA recommends that the best evidence of "special clinical need" is a letter from the prescriber.

What melatonin preparations are available?

1. UK Licensed preparation (which would be used "off-label")

Circadin® - Melatonin 2mg prolonged-release tablets is the only melatonin product licensed in the UK. It is licensed for short-term use for insomnia in the over 55s only. However, the MHRA have stipulated that licensed products should be used wherever possible, even if it means using a product "off-label" and outside its licensed indications. Hence, Circadin® 2mg prolonged release is the preferred option for children. The tablets can be crushed after which they could be expected to be immediate release.

Circadin® 2mg prolonged-release tablets £10.77 for 21 x 2mg tablets (Nov 2009 prices). Tablets should be swallowed whole.

If this formulation, controlled release mechanism or dosage is not suitable then option 2 should be considered.

2. European Licensed preparation

The European licensed immediate release melatonin preparation is called Bio-Melatonin® 3mg Filmtabletta and is made by Pharma Nord.

These 3mg tablets can be crushed and mixed with water if there are swallowing difficulties (information from Bio-Melatonin® patient information leaflet).

In accordance with MHRA guidance, a letter confirming "special clinical need" will be required with orders.

Availability
Imported from Denmark (English packaging) may be available from:

- local wholesaler, or
- PharmaNord (UK), Telford Court
  Morpeth
  Northumberland
  NE61 2DB
  Tel: 01670 519989
  Fax: 01670 534903 or
- specials manufacturers such as the specials laboratory www.specialslab.co.uk/ Bio-Melatonin® 3mg tablets
  60 x 3mg tablets approximate cost= £22.50 (The prices that are included on the list are as of Nov 09 and may change. The prices are direct and could therefore change if pharmacies were to order via groups (Mawdsleys/Craig and Hayward etc.).

If preparations in option 1 or 2 are not appropriate for the patient's clinical need then option 3 should be considered.

3. "Specials" Preparations of Melatonin

Various unlicensed UK Specials and imports, especially from the USA where melatonin is classed as a food supplement and where they may not be made according to good pharmaceutical manufacturing standards, are not recommended.

The following strengths of immediate release capsules, orodispersible tablets and liquid preparations of melatonin are available from Penn Pharmaceutical Services manufactured under its UK "specials" license 4351:

PRODUCT	LIST PRICE	PACK SIZE
Melatonin 1mg capsules	£85	100
Melatonin 2mg capsules	£90	100
Melatonin 2mg orodispersible strawberry tablets	£90	100
Melatonin 2.5mg capsules	£95	100
Melatonin 3mg capsules	£100	100
Melatonin 3mg orodispersible strawberry tablets	£100	100
Melatonin 5mg capsules	£110	100
Melatonin 10mg capsules	£115	100
Melatonin oral solution 1mg/ml orange flavour (sugar, colour & alcohol free)	£90	200ml

Penn Pharmaceutical Services Specials Price List Correct as of Nov 2009 For a current price list contact Penn Pharmaceutical Services.

The liquid preparation may be preferable in children with a gastrostomy tube.

Contact Information:
Penn Pharmaceutical Services, 23/24 Tafarnaubach Industrial Estate, Tredegar, Gwent, NP22 3AA, UK
Tel: 01495 713600, Fax: 01495 713613, e-mail: sales@pennpharm.co.uk

Other Specials are available from Specials Products (UK) 01483 736950 or as a last resort can be imported by companies such as Idis World Medicines 01932 824000; e.g. Kid-naps 1mg/1ml oral solution =£15.48/200ml, Modified release 3mg melatonin capsules (contents can be sprinkled) cost £22.10 for 60