Reference: FOI.ICB-2627/099

Subject: Exclusion of standalone ADHD from the Melatonin Amber Pathway

I can confirm that the ICB does hold some of the information requested; please see responses below:

QUESTION	RESPONSE
This request concerns the BNSSG Adult Joint Formulary, section 4.7.1 (Insomnia), as published on the BNSSG formulary website (last edited 06-09-2024 according to the version visible to the public at the date of this letter). That section positions melatonin (both modified-release and immediate-release) at Amber (shared care, 3-month review) for an intrinsic sleep disorder accompanied by ASD, a learning disability, or a neurodevelopmental disorder/disability of which cerebral palsy is given as an example. The entry then carries an express carve-out excluding patients whose only diagnosis is Attention Deficit Hyperactivity Disorder (ADHD). I would be grateful for the following information:	
1. Decision papers and minutes a) A copy of every paper put before the BNSSG Joint Formulary Group (or any predecessor or equivalent body) at the meeting(s) at which the decision was taken to position melatonin at Amber for the conditions listed in section 4.7.1, and at the meeting(s) at which the decision was taken to exclude standalone ADHD from that pathway, including any subsequent reviews of either decision.	a) Please find enclosed b) Please find minutes enclosed c) 3rd September 2024; version history not held. Please note that FOI requests and responses are publicly available and therefore personal information has been redacted. The ICB considers the names included in the enclosed document(s) to be

b) The minutes of each such meeting, redacted only to the minimum extent necessary to comply with the Data Protection Act 2018 in respect of any individual patient identifiers. c) The date(s) on which the standalone-ADHD exclusion was added to section 4.7.1, and the version history of that section (entries added, amended or removed) from the date the section was first published to the date of this request.	personal information and therefore has applied a section 40 (Personal Information) exemption to this information.
2. Evidence base a) The clinical evidence base relied on by the Joint Formulary Group in deciding to position melatonin at Amber for ASD, learning disability and other neurodevelopmental conditions but to exclude standalone ADHD. This is to include copies of, or full references to, any published clinical guidance, peer-reviewed studies, NICE pathways, BNF entries, professional consensus statements, expert opinion or specialist advice considered. b) Any documents showing the rationale for treating ADHD differently from comparable neurodevelopmental conditions in respect of melatonin prescribing.	a) Please refer to enclosures for question 1.a) b) Please refer to enclosed minutes, provided for question 1.b, for records of decision making
3. Equality Impact Assessment (EIA) a) A copy of any Equality Impact Assessment carried out in respect of the standalone-ADHD exclusion in section 4.7.1, including any screening assessment which concluded that a full EIA was not required.	a) No EIA was carried out b) The ICB does not hold this information c) The ICB does not hold this information

b) If no EIA was conducted, please confirm that fact and identify the policy or procedure under which the decision not to carry out an EIA was made. c) Any record of consideration of the BNSSG ICB's Public Sector Equality Duty under section 149 of the Equality Act 2010 in connection with the standalone-ADHD exclusion.	
4. Exceptions / IFR a) The policy and procedure documents that govern Individual Funding Requests (IFRs) for melatonin where the patient falls within the standalone-ADHD exclusion in section 4.7.1. b) Statistics on the number of IFRs received in respect of melatonin for adult ADHD patients in the BNSSG area in each of the last three full financial years (2022/23, 2023/24, 2024/25), and the number of those IFRs that were approved, refused or withdrawn. No patient identifiers needed.	a) All EFR documents are available on our web page here: https://bnssg.icb.nhs.uk/about-us/interventions-not-normally-funded-innf/exceptional-funding/ b) No IFRs received

The information provided in this response is accurate as of 10 July 2026 and has been approved for release by Dr Aananthakrishnan Raghuram, Chief Clinical Leadership and Delivery Officer (Medical) for NHS Bristol, North Somerset and South Gloucestershire ICB.

Healthier Together
Improving health and care in Bristol, North Somerset and South Gloucestershire

BNSSG Shared Care Guidance
Please complete all sections

Section 1: Heading

Drug	Melatonin
Amber *three months*	
Indication	**Intrinsic sleep disorder in adults and children who have exhausted all behavioural sleep hygiene options and have either:** • **Autism Spectrum Disorder (ASD) diagnosis,** • **Learning Disability (LD) diagnosis,** • **a neurodevelopmental disorder / disability (e.g. cerebral palsy) (excluding those with Attention Deficit Hyperactivity Disorder as a standalone diagnosis*).** *Criteria for use:* At least one criteria from section A and B below must be satisfied to consider melatonin as a treatment option. A. Sleep disturbances can be manifested by (any of the following or in combination) • Early insomnia (getting off to sleep / delayed onset) • Problem with continuity of sleep (frequent night time waking) • Reduction in overall duration of sleep • Reversal of circadian rhythm (day night sleep pattern) B. Resulting in (any of the following or in combination to compromise quality of life) • Day time drowsiness • Unable to concentrate and engage in pleasurable activities and other activities of daily living • Increase in challenging behaviour** *For the purposes of clarity for this shared care protocol, standalone diagnosis of Attention Deficit Hyperactivity Disorder (ADHD) has not been approved by the BNSSG Joint Formulary and is not included. Patients with Attention Deficit Hyperactivity Disorder who also have an Autism Spectrum Disorder or Learning Disability or additional neurodevelopmental disorder / disability diagnosis are covered by the formulary, but those patients with only an ADHD diagnosis would not be covered and prescribing is non-formulary.

	Challenging Behaviour – 'Behaviour can be described as challenging when it is of such an intensity, frequency or duration as to threaten the quality of life and/or the physical safety of the individual or others and is likely to lead to responses that are restrictive, aversive or result in exclusion.' **REM sleep disorder in adult patients diagnosed by neurologist, or physician / psychiatrist specialising in the care of older adults. *Criteria for use:* One criteria from section A **and** all criteria in section B below must be satisfied to consider melatonin as a treatment option. A. Diagnosis of REM sleep disorder: • REM sleep behaviour disorder (diagnosed according to International classification of sleep disorders version 3 criteria) on the basis of specialist sleep clinic assessment including inpatient sleep study. **OR** • Established alphasynucleinopathy (Parkinson's Disease, Lewy Body Dementia, multi-system atrophy) or other neurodegenerative condition who presents clearly with clinical features of REM sleep behaviour disorder, with no evidence of other secondary causes). **AND** B. All of the following: • Secondary causes of REM sleep behaviour disorder have been considered and treated appropriately. • Sleep hygiene and environmental safety have been discussed with the patient. • Symptoms of REM sleep behaviour disorder are of a severity requiring medical treatment – sleep related injuries to self/partner, or disrupted nocturnal sleep resulting in impaired functioning or quality of life. **Definitions** **Learning disability** is defined as arrest or incomplete development of the mind characterized by: • lower intellectual ability (usually an IQ of less than 70) • significant impairment of social or adaptive functioning • manifested during developmental period A person's learning disability may be described as mild, moderate, severe or profound. Learning disabilities are different from specific learning difficulties such as dyslexia, which do not affect intellectual ability. It is also different from Specific Developmental Disorders and Pervasive Developmental Disorders for example Autism etc.

	Autism Spectrum Disorder/ Condition Autism is a complex neuro-developmental spectrum condition involving persistent challenges with, for example, communication and social interaction. While autism is considered a lifelong disorder, the degree of impairment in functioning because of these challenges varies between individuals with autism. **Neurodevelopmental disorders/ disability** are a heterogenous group of disorders causing behavioural and cognitive alterations in sensory and motor symptoms and language. Examples may include autism and cerebral palsy.

Section 2: Treatment Schedule

Usual dose and frequency of administration *(Please indicate if this is licensed or unlicensed and any relevant dosing information)*	**Children:** Oral: 0.5mg-6mg at night (off label for this indication) Most people will see maximum clinical benefits up to 6 mg. Very little clinical benefits are seen at doses between 6 mg - 10 mg. Up to 10 mg can be tried in cases where patients may need a referral to tertiary sleep centres. Maximum BNF (Adults and Children) dose is 10mg per day). **Adults:** Oral: 2-6mg at night (off label for this indication) REM Sleep disorder indication only - Melatonin MR 2mg-8mg at night but in special circumstances up to 12mg can be used. Higher doses most likely to be used in REM sleep disorder.
Route and formulation	Oral **Melatonin 2mg modified release tablets (generic)** are the most cost-effective formulation to BNSSG and should be used first-line for all indications. If new branded generic versions become available and are more cost-effective, GP Practices should be guided by Script Switch messages. The most cost-effective product should be used first line even if this is used on an off-label basis. Local specialists have experience of using melatonin off-label. If a faster release is thought to have an advantage for a particular individual where the modified release profile has been ineffective, the modified release tablet can be crushed to exert this immediate release effect. Alternatively, Melatonin immediate release tablets may also be considered but may be more expensive. For patients who cannot swallow tablets, the following should be considered: 1) Advise parents to start pill training prior to consideration of alternative formulations: https://www.nenc-

	healthiertogether.nhs.uk/parentscarers/medicine-children/pill-swallowing-kidzmed Helping your child to swallow tablets – Medicines For Children 2) historically, melatonin 2mg modified release tablets have been quartered, halved or crushed (changing the release profile to immediate release) and mixed in 15-30ml of water) or mixed with a small amount of soft food (unlicensed). This option remains the most cost-effective option. 3) Adaflex immediate release tablets can be crushed and mixed with water directly before administration. It is recommended that food is not consumed 2 hours before and 2 hours after intake of Adaflex tablets. (AGB-Pharma, 2022). 4) Slenyto prolonged release tablets can be put into food such as yoghurt, orange juice or ice cream to facilitate swallowing and improve compliance. If the tablets are mixed with food or drink, they should be taken immediately and the mixture not stored (Flynn Pharma, 2021). 5) **Any liquid formulation will be more expensive than a solid dosage form and should only be considered as a last resort for the shortest period of time required.** Locally, Consilient Health is the preferred brand of melatonin 1mg/1ml oral solution sugar free as this is now licensed for some paediatric cohorts aged 6 years and over. It does not contain propylene glycol or alcohol which may present concern for children, especially of younger ages. Where the Consilient Health brand is unavailable due to supply issues, reconsider whether solid oral dosages are appropriate (see steps 1-3 above). If an alternative liquid preparation is required, see appendix 1 for further information. The use of licensed liquid preparations (even off-label i.e. has a UK marketing authorisation for a different indication) should be trialled in preference to unlicensed liquids as per MHRA recommendations. **Caution** If melatonin 1mg/1ml oral solution sugar free liquid is written generically, the licensed brand Colonis may be supplied. Melatonin 1mg/1ml oral solution (Colonis Pharma Ltd) should not be used in children under 6 years old due to safety and efficacy concerns (Colonis, 2022) . The levels of propylene glycol also exceeds the recommended safety limits for some children based on their weight. To supply unlicensed formulations in line with Specials supplier policies, community pharmacies may need a letter from the prescriber confirming why the patient requires an unlicensed product where there are licensed alternatives. Furthermore, prescribers should

	make it clear to the dispensing pharmacy that an alternative liquid preparation is needed. For patients with an enteral feeding tube, the preferred first line option is melatonin 2mg modified release tablets that have been crushed (changing the release profile to immediate release) and mixed in 15-30ml of water prior to administration (unlicensed). If this is unsuitable for an individual, discuss alternative options with the specialist team.
Duration of treatment	Trial of 3 months initially prescribed and managed by specialist team. Only to be continued by primary care where an improvement in sleep disorder has been assessed by specialist team. Regular review of benefit should take place to ensure ongoing benefit. Techniques could include: weekend/school holiday melatonin breaks, considering dose reduction/weaning or trialling 1-2 weeks off melatonin periodically with the aim of eventually stopping. Specialist teams to specify which tools should/will be used to support review and to ensure patient/parents are aware of information in 'Advice to patient' section. Sleep diaries such as the SNappD app and https://thesleepcharity.org.uk/information-support/children/sleep-diary-for-kids/ are the primary tools used. For intrinsic sleep disorder a drug holiday may be considered if: - Prolonged period (6 months) with much improved (normalised) sleep pattern. - The weekend or school holiday period. - Improved Wellbeing and reduced Functional Impairment, as measured by WEMWBS and Weiss Functional Impairment rating scale https://www.intermed.com/content/uploads/Weiss-Adult-ADHD-Rating-Scale.pdf **Transition to adult services/ discharge from paediatric services** Specialist teams should consider a planned trial from melatonin prior to discharge from the paediatric services to ensure continued benefit.

Section 3: Monitoring

Please give details of any tests that are required before or during treatment, including frequency, responsibilities (please state whether they will be undertaken in primary or secondary care), cause for adjustment and when it is required to refer back to the specialist.

Baseline tests - where appropriate

Baseline clinical evidence of disrupted sleep disturbance prior to commencing melatonin (such as at least 2 weeks of sleep diaries or clinician decision based on reported symptoms and impact on life, which may include reports and interventions from school nurse/health visitor).

Subsequent tests - where appropriate *(Please indicate who takes responsibility for taking bloods and interpreting results)*

Response to treatment and whether it is appropriate to continue treatment to be reviewed by a specialist before referring patient to primary care.
Treatment response to be assessed clinically by:

a. reported improvement in subjective sleep quality, improved behaviour and quality of life using tools such as https://flynnforum.com/education_training/snappd-the-sleep-nap-diary-app/ and sleep diaries such as https://thesleepcharity.org.uk/information-support/children/sleep-diary-for-kids/
b. reported reduction in daytime sleepiness
c. REM sleep disorder - reported benefit in reduction of nocturnal awakenings, reduction of sleep related incidents, reduction in sleep related injuries. Collateral history of bed partner reporting reduction in frequency and severity of dream enactment behaviour at night.
d. Intrinsic sleep disorder - improved Wellbeing and reduced Functional Impairment, as measured by WEMWBS and Weiss Functional Impairment rating scale.
e. Re-assess suitability of most cost-effective and suitable formulation where patients have previously had difficulties swallowing tablets and are prescribed alternative formulations.

Section 4: Side Effects

Please list only the most pertinent side effects and management. Please provide guidance on when the GP should refer back to the specialist. For everything else, please see BNF or SPC.

Side effects and management

Side effect	Frequency/severity	Action/management
See BNF/ SPC for full side effects		
Nocturia	Rare	Stop if problematic and seek advice from specialist
Daytime Drowsiness/over sedation	Sometimes (anecdotal)	Stop if problematic and seek advice from specialist

Referral back to specialist

If melatonin is reported to be ineffective and/or side effects intolerable

Section 5: Other Issues

(e.g. Drug Interactions, Contra-indications, Cautions, Special Recommendations)

Please list only the most pertinent action for GP to take (For full list please see BNF or SPC)

Issues	**Caution** If melatonin 1mg/1ml oral solution sugar free liquid is written generically, the licensed brand Colonis may be

	supplied. Melatonin 1mg/1ml oral solution (Colonis Pharma Ltd) should not be used in children under 6 years old due to safety and efficacy concerns (Colonis, 2022) . The levels of propylene glycol also exceed the recommended safety limits for some children based on their weight. To supply unlicensed formulations in line with Specials supplier policies, community pharmacies may need a letter from the prescriber confirming why the patient requires an unlicensed product where there are licensed alternatives. Furthermore, prescribers should make it clear to the dispensing pharmacy that an alternative liquid preparation is needed.
Reminder to ask patient about specific problems	N/A

Section 6: Advice to the patient

Advice for prescribing clinician to inform patient

1. Melatonin prolonged release should be initiated at 2 mg taken one hour before bedtime and after food.
2. Tablets should be swallowed whole but can be halved using a tablet cutter, maintaining the prolonged release profile.
3. Tablets can be crushed and dispersed in water or mixed with a small amount of soft food for those with swallowing difficulty / too young to swallow(unlicensed).

For intrinsic sleep disorder:

A. "Treatment breaks" are an important component of prescribing this product, and best practice supports the use of treatment breaks. Stopping melatonin does not mean that it will be less effective when restarting. From local specialist experience when restarting, a slightly lower dose may be as effective as that which was last used.

B. Ensure that the following behavioural interventions/sleep hygiene measures continue to be implemented even whilst on medication:
   - Ensuring that there is an established bedtime routine and that a realistic sleep-wake schedule has been agreed.
   - Ensuring that the room conditions (temperature, light and noise) are at an optimum level to promote sleep (e.g. minimise background noise, use of a blackout blind).
   - Ensuring no late afternoon / evening caffeine consumption.
   - Removing television and electronic devices from the patient's room or advising patients to avoid using screens/phones, since it is known that the blue green light emitted by these screens can disturb sleep and could reduce melatonin efficacy. Patients should avoid looking at bright screens beginning 2-3 hours before bed.
   - Physical activity - minimum 60 minutes / day where there is a raise in heart rate / breathing rate (struggles to complete a sentence) as per UK Physical Activity Health guidelines. In addition, stretching and relaxation like yoga and mindfullness help to improve sleep.
   - Good hydration. No sugar drinks ,/caffeine / fatty foods and processed / ultra processed foods - have impact on sleep.

Patient Resources/ leaflets

- Medicines for Children: Melatonin for sleep disorders
- Medicines for Children: Helping your child to swallow tablets

- Swallowing pills (Kidsmed)
- Choice and Medication (Avon and Wiltshire Mental Health Partnership NHS Trust)
  Melatonin information
- Sleep toolkits (South Gloucestershire Council One You website)
  -Special Educational Needs and Disability
  -Early Years 0-5 years
  -Childhood 5-13 years
  -Adolescence 13-18 years
- Teen Sleep hub
- Cerebra charity sleep advice
- Sleep Charity which includes links to sleep diaries https://thesleepcharity.org.uk/information-support/children/sleep-diary-for-kids/
- SNappD: The Sleep Nap Diary App
- BNSSG Remedy Insomnia Page (adults)- includes link to two week sleep diary
- British Society of Lifestyle Medicine 'The importance of good quality sleep' page (adults)
- UK Physical Activity Guidelines includes guidance for:
  - under 5s
  -5-18 years
  -disabled children and disabled young people
  -adults and older adults
  -disabled adults
  -pregnancy and after childbirth
- https://humble.info/

Section 7: Generic principles of shared care for SECONDARY CARE

Please do not amend.

Core responsibilities

1. Initiating treatment and prescribing for the length of time specified in **section 1.**
2. Undertaking the clinical assessment and monitoring for the length of time specified in **section 1** and thereafter undertaking any ongoing monitoring as detailed in **section 3.**
3. Communicate details of the above in 1 and 2 to GP within the first month of treatment. This information should be transferred in a timely manner.
4. Refer patients to GP and provide information of further action where appropriate e.g. if blood test is due.
5. To provide advice to primary care when appropriate.
6. Review concurrent medications for potential interaction prior to initiation of drug specified in **section 1.**
7. Stopping treatment where appropriate or providing advice on when to stop.
8. Reporting adverse events to the MHRA.
9. Reminder to ask patients about particular problems see **section 5.**

Section 8: Generic principles of shared care for PRIMARY CARE

Please do not amend.

Core responsibilities

1. Responsible for taking over prescribing after the length of time specified in **section 1.**
2. Responsible for any clinical assessment and monitoring if detailed in **section 3** after the length of time specified in **section 1.**
3. Review of any new concurrent medications for potential interactions.
4. Reporting adverse events to the MHRA.
5. Refer for advice to specialist where appropriate.
6. Reminder to ask patients about particular problems see **section 5.**

Section 9: Contact Details

Name	Organisation	Telephone Number	E mail address
Care of the Elderly Consultants	North Bristol Trust	N/A	COTEConsultants@nbt.nhs.uk
Neurology team	North Bristol Trust	N/A	NMSKNeurologyConsultants@nbt.nhs.uk neurologypharmacists@nbt.nhs.uk
Dr Emma Stratton	University Hospitals Bristol and Weston	0117-3420790	N/A
Initiating clinician at AWP/Sirona teams	AWP/Sirona	As provided on patient's individual correspondence/ clinic letters	As provided on patient's individual correspondence/ clinic letters

Section 10: Document Details

Date prepared	April 2024
Prepared by	BNSSG Formulary team
Date approved by JFG	September 2024
Date of review	September 2027
Document Identification: Version	V1

Section 11: Collaboration

All shared care protocols should be BNSSG wide where possible. Specialists in any one discipline are encouraged to collaborate across the health community in preparing shared care guidance. Please give details

This shared care protocol incorporates and replaces all existing shared care protocols for both adult and paediatric patients.
Comments/input received from:

1. AWP CAMHS consultant team
   Sarah Steel, Highly Specialised Clinical Pharmacist, Lead for CAMHS.
2. Sirona Care and Health Community Paediatric team- Dr Saraswati Hosdurga, Consultant Community Paediatrician, CCHP Bristol,
   Kate Ellis, Head of Medicines Optimisation, Sirona Care and Health
   Sandra Williams, Pharmacist, Sirona Care and Health
3. NBT Neuro/neuropsych teams (Adult-REM indication)
4. UHBW Care of Elderly team (Adult-REM indication)

Shared with AWP Adult Learning Disability team and BNSSG GP ICB representatives.

Section 12: References

Please list references

1. AGB-Pharma (2022) Summary of Product Characteristics: Adaflex 1mg tablets. Available from: https://www.medicines.org.uk/emc/product/13628/smpc [accessed 1/8/24]
2. Colonis Pharmacy (2022) Summary of Product Characteristics: Melatonin 1mg/1ml oral solution. Available from: https://www.medicines.org.uk/emc/product/10419#PHARMACODYNAMIC_PROPS [accessed 1/8/24]
3. Flynn Pharma (2021) Summary of Product Characteristics: Slenyto 1mg prolonged-release tablets. Available from: https://www.medicines.org.uk/emc/product/10023/smpc [accessed 1/8/24]
4. Newcastle upon Tyne Hospitals NHS Trust, North East and North Cumbria, Child Health and Wellbeing Network- North East and North Cumbria, Royal College of Paediatrics and Child Health (2020) Swallowing pills (Kidzmed). Available at: Swallowing pills (Kidzmed) :: North East and North Cumbria Healthier Together (nenc-healthiertogether.nhs.uk) [accessed 1/8/24]

BNSSG Shared Care Guidance
Please complete all sections

Appendix 1

Product manufacturer	Indication	Propylene Glycol (E1520)	Alcohol	Sugar	Sweetener	Shelf-life	Price
Melatonin 1mg/ml (Consilient Health)	Licensed 6-17 for insomnia in ADHD	Free Unflavoured / bitter taste	Free	Free	Glycerol	6 months after first opening	Drug tariff (June 24)- fixed price for the liquids 1mg/1ml sf £124.10 150ml (0.82/ml)
Ceyesto 1mg / ml (Alturix Ltd)	Licensed 6-17 for insomnia in ADHD	52mg / ml Strawberry flavour	Benzyl alcohol 6mg/ml	Free	Sucralose	Use within 1 month of opening	Drug tariff (June 24)- fixed price for the liquids 1mg/1ml sf £124.10 150ml (0.82/ml)
Melatonin 1mg/1ml (colonis)	Licensed for 6-17 insomnia in ADHD	150.50mg/ml Strawberry flavour Melatonin 1mg/1ml oral solution (Colonis Pharma Ltd) should not be used in children under 6 years old due to safety and	140mg sorbitol/ ml	Free	Sucralose	2 months after first opening	Drug tariff (June 24)- fixed price for the liquids 1mg/1ml sf £124.10 150ml (0.82/ml)

		efficacy concerns (Colonis, 2022) . The levels of propylene glycol also exceed the recommended safety limits for some children based on their weight.					
Kidmel 1mg/ml (Veriton Pharma)	Special (unlicensed) To supply unlicensed formulations in line with Specials supplier policies, community pharmacies may need a letter from the prescriber confirming why the patient requires an unlicensed product where there are licensed alternatives. Furthermore, prescribers should make it clear to the dispensing pharmacy that an alternative liquid preparation is needed.	52mg / ml	Free	Free	Aspartame 0.5mg/ml	24 months	~£138 200ml (0.69/ml)

BNSSG Joint Formulary Group
New Pharmaceutical Drug Request

Who should complete what?

Applying clinician/CCG budget holder	**Sections A, B, C, D, E, F**
Pharmacist undertaking critical appraisal	**Section G, H and I**

- Please ensure every section of this form is filled out. Support is available from your Pharmacy team if required – either via the Trust pharmacy department, or CCG Medicines Optimisation team.
- Please ensure relevant colleagues including those at all trusts within the BNSSG system are consulted prior to submitting the application.
- Completed forms for new formulary items must be received at least 6 weeks prior to the next Joint Formulary Group.
- Send completed forms either to the formulary pharmacist / pharmacy department within the Hospital trusts or the Joint Formulary pharmacists for BNSSG - email **bnssg.formulary@nhs.net**
- Requesting clinicians will be required to attend the meeting to present their case
- Do NOT complete this document for a drug that is commissioned as part of a specialised service by NHS England* and/or approved as a NICE Technology Appraisal. *refer to the 'NHS England Manual for prescribed specialised services'.

A. Applicant details	Applying clinician to complete
Applicant name: 1. Dr Dietmar Hank 2. Dr Nathalie Leyland 3. Dr Saraswati Hosdurga	**Acute trust (Secondary care only):** 1. AWP 2. AWP 3. Sirona Care & Health
email address: 1. dietmarhank@nhs.net 2. nathalieleyland@nhs.net 3. s.hosdurga@nhs.net	**Directorate/Division (Secondary care only):** 1. Specialised Services – ADHD 2. Specialised Services – LD Adults 3. Community Children's Health Partnership
Position: 1. Consultant Psychiatrist 2. Consultant Psychiatrist 3. Consultant Community Paediatrician, Lead for Medicines Management for Community Paediatrics, Designated Doctor for Children in Care (from June 2022)	**Other (GP practice, CCG)** N/A
Second applicant (if relevant): Click here to enter text.	**Supporting applicant/s (at other trusts)** Kim Jefferson, Pharmacoeconomics Pharmacist at NBT Dr James Bowler, Consultant Psychiatrist, CAMHS LD, AWP

B. Drug details	Applying clinician to complete
Approved name: Melatonin	**Brand name:** Circadin® Slenyto® Kidmel® or Martindale.
Manufacturer: Flynn Pharma Ltd Flynn Pharma Ltd Specials Manufacturers	**Formulation(s) requested:** Modified-release tablets (2mg) Modified Release tablets (1mg and 5mg) Oral solution, 1mg/1ml, alcohol free, low in propylene glycol and sorbitol*

Is an existing formulation of this product already in the formulary? Yes ☒ / No ☐
If yes, you do not need to complete evidence for efficacy or safety and tolerability (but see guidance notes)

BNSSG formulary acceptance for melatonin TLS is amber - 3 months:
Paediatrics:

For children with neurodevelopmental disorder/disability with intrinsic sleep disorder (difficulty getting to sleep or remaining asleep) who have exhausted all behavioural sleep hygiene options

Not for use in ADHD or autism or learning disabilities (see SCP).

Adults:

For Adults with Learning Disabilities and sleep disturbance who also have a co-morbid mental illness (for example Depression, Mania, Psychosis, Dementia etc.) OR disorder (for example Autism or Autistic Spectrum, Anxiety Disorders, Adult ADHD etc.) as per shared care protocol

Licensed 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.

Slenyto® is indicated for the treatment of insomnia in children and adolescents aged 2-18 with Autism Spectrum Disorder (ASD) and / or Smith-Magenis syndrome, where sleep hygiene measures have been insufficient.

There are no licensed liquid preparations of melatonin currently available in the UK with the required composition of excipients. Therefore use of solid dose formulations (even off-label) would be trialled in preference to liquids as per MHRA recommendations.

C. Intended use	Applying clinician to complete
Define use of drug:	Define intended indication of drug: *Please also specify whether this is a licensed indication* 1) Off-label use for sleep disorder in patients with any of: a) Attention Deficit Hyperactivity Disorder (ADHD) b) Autism (Slenyto is licensed for this indication in 2-18 year olds) c) Learning Disabilities (LD) (or Intellectual Disabilities)
	Define intended cohort including starting criteria: *Adult/paed* Paediatric patients aged between 1-17 years for the conditions cited above. Adult patients aged 18 years and older for the conditions cited above. Adult patients with a learning disability occasionally require longer-term (years) treatment with melatonin. Circadian rhythm disorder: Not all patients included will have a circadian rhythm disorder. The cohort is a very diverse group, including some who do (e.g. ADHD related delayed sleep onset) and some who do not (e.g. LD syndrome specific abnormal melatonin secretion). Approximately 50% of people with a diagnosis of ADHD have a circadian rhythm disorder. Melatonin would still likely be a long-term treatment for this cohort. Specific cohort: As per our treatment plan and approach in general, non-medication measures would always be used initially. Some people respond very well to basic sleep hygiene, or more specialist environmental and behavioural strategies, some respond partially, and some not at all. Medication would usually only be offered to the group with severe sleep disorder (rather than severe ADHD, autism, LD). In adult ADHD, where treatment to manage ADHD symptoms is available, the initial approach is to treat ADHD, and only if sleep difficulties remain a problem following effective medication for ADHD core symptoms, would melatonin be considered.
	Dosage: <u>Starting dose</u>: The timing of administration should be adjusted relative to target onset of sleep time Adult: 2 mg once daily, 1-2 hours before bedtime and after food*, swallowed whole. Paediatric: 0.5-2mg dependent on age, before bedtime and after food <u>Dose titration</u>: As per clinical need. Usually an initial dose would be prescribed for 2 weeks then reviewed for effectiveness. Due to the diversity of patients within these cohorts, a constant trial period is not possible to define. Usual effective range is 0.5-6mg. In certain rare circumstances the dose can be increased up to a maximum dose of 10mg (this is the maximum dose seen in most trials for this cohort of patients and noted in the BNF).

The majority of patients are prescribed 2-6mg in LD services. Due to lack of electronic prescribing systems, and because FP10s are used to prescribe (i.e. not in-house pharmacies), an accurate average dose is difficult to ascertain. From EPACT, Adult ADHD services average a 3mg dose.

Ongoing treatment:
Melatonin usually required for longer periods in adults, i.e. more than a year. EPACT data suggests not many patients are stopped on melatonin. Organisations do not have electronic prescribing systems, so tracking is not possible.

In ADHD, for those with delayed sleep phase disorder who are unable to achieve a more permanent shift towards a normal sleep rhythm following life style changes and good sleep hygiene, it is likely to be an ongoing requirement, possibly used intermittently to counteract a tendency to returning to a delayed pattern.

In learning disabilities, many patients are likely to benefit from a long term steady approach to their sleep. However, the requirements of STOMP/STAMP are adhered to and medicines reviewed to ensure they remain in their ongoing best interest.

*This extends the duration of action of melatonin relative to an empty stomach (T_{max} 3 hours vs 45 mins), but reduces the peak plasma levels by 15%. This can be used to tailor the timing of melatonin against the patient's clinical needs.

Monitoring requirements:
Please specify relevant clinical investigations

Baseline tests - where appropriate

Baseline documentation (at least 2 weeks of sleep diaries) of disrupted sleep disturbance prior to commencing melatonin.

Subsequent tests - where appropriate

(Please indicate who it is intended will take responsibility for taking bloods and interpreting results)

Test	Frequency	Who by
No specific physiological tests		

Click here to enter text.

Define the review and stopping criteria:

- Insufficient benefit observed, despite careful dose titration, and trial at the maximum dose for 8 weeks.
- Reviewed with consideration to stop as part of annual LD/ADHD review.
- Unmitigable adverse effects - in this unlikely case, melatonin can be stopped without the need for gradual withdrawal.

Measure of effectiveness includes:

- Clinically significant improvement in sleep i.e. measured with sleep chart/record completed by patient

<table>
<tr><td></td><td>Threshold for stopping or drug holiday includes:
- Prolonged period (6 months) with much improved (normalised) sleep pattern.
- Improved Wellbeing and reduced Functional Impairment, as measured by WEMWBS and Weiss Functional Impairment rating scale
https://www.intermed.com/content/uploads/Weiss-Adult-ADHD-Rating-Scale.pdf
Post-application note
Applicant unable to advise how many patients are stopped, but it is thought most are continued longer term.</td></tr>
<tr><td>Number of people affected:</td><td>Anticipated number of patients likely to receive this treatment per year in whole of BNSSG i.e. primary and secondary care
Please liaise with your colleagues in other Trusts to obtain system wide estimates
<table>
<tr><th>Trust</th><th>Anticipated annual patient numbers</th></tr>
<tr><td>AWP</td><td>Estimated 185 patients CAMHS and 24 adult LD.</td></tr>
<tr><td>UHB</td><td>Nil</td></tr>
<tr><td>UHBW Children’s Hospital</td><td>Nil</td></tr>
<tr><td>NBT</td><td>Nil</td></tr>
<tr><td>WAHT</td><td>Nil</td></tr>
<tr><td>Primary Care</td><td>N/A</td></tr>
<tr><td>Sirona</td><td>27 in (Adult Learning Disabilities South Glos)
433 patients (Community Paediatrics based on prescription data over 12 months across all formulations of melatonin)</td></tr>
</table></td></tr>
<tr><td>Background of the application</td><td>Define the background and context of the application. Include supporting local guidelines if available.

Whilst disordered sleep is a common experience, often responding well to sleep hygiene measures, sleep disorder is diagnosed only in a minority of people. It is more common in autistic people, and those with intellectual disability, ADHD, specific syndromes and visual impairment.

The complications of sleep disorder can be significant and diverse, including challenging behaviour, drowsiness with an inability to undertake daytime activities, and in people with autism, mood disorders, gastrointestinal problems, poor social interaction, problems in communication and increased stereotypy (Rossignol and Frye, 2011). These problems can affect quality of life and risk placement breakdown. Behavioural interventions (including sleep hygiene) are the primary intervention, having a robust evidence base, and exogenous melatonin is recommended by the British Association for Psychopharmacology when medication is required.

Correctly timed, exogenous melatonin is able to act as a chronobiotic, shifting the timing of sleep onset. When non-pharmacological measures have failed initiating treatment with melatonin is a valuable tool in treating insomnia, particularly when used in conjunction with non-pharmacological methods. Behavioural therapies should be continued alongside medication as the combination has been found to be more effective than medication alone.</td></tr>
</table>

	Alternatives to using melatonin for sleep disorder include benzodiazepines, Z-drugs and sedating antihistamines. These medicines will often come with more problematic side-effects and dependence-forming potential than melatonin (which is not seen in melatonin use). Current AWP formulary accepts melatonin use for both its licensed indication, as well as in Learning Disability Services. See section G for supporting guidelines from other CCGs.
Define the current treatment pathway **State place in pathway for this intervention.**	Define the current treatment pathway for this indication and indicate where the proposed treatment would fit in: *Could it reduce/offset the use of another treatment/surgery?* 1st line: • Simple sleep hygiene measures 2nd line: • Individualised behavioural and environmental recommendations 3rd line: • **Trial of melatonin** - *Effective treatment of sleep disorder can prevent placement breakdown and family member / carer burnout* Medication review: •**Indication dependent** •Detailed in AWP guideline MG15 Melatonin prescribing for sleep disorders in adults with intellectual disability •Adult ADHD annual review •Detailed in Sirona letter to carers •Consider drug holiday if treatment efficacy is waning (in consultation with patinets and carers, 3-7 days for a drug holiday may prove sufficient to restore melatonin efficacy). Detail of reviews should be agreed when writing accompanying shared care guidance. AWP guidance MG15: MG15.docx

	Sirona have previously reviewed usage and made recommendations of how/when melatonin should be prescribed, detailed in the embedded documents below:  Letter to paed drs re melatonin Oct 19. Sirona letter to carers:  Melatonin Max 6mg Dose- October 2021 A sleep diary is used in some adult LD services, which is left intentionally basic so that care providers/family can adapt it to their needs (due to the diversity of people living with a learning disability.  Two week sleep record.xlsx ADHD services also use sleep diaries and quality of life questionnaires to measure effectiveness all attached in associated docs): • ADHD New Quality of Life Questionnaire  ADHD-new-quality-of-life-questionnair • Morning-Eveningness Questionnaire  Morning-Eveningness Questionnaire (r • Warwick Edinburgh Mental Well Being Scale  Warwick Edinburgh Mental Well Being S
Comparison with existing formulary therapies	Please detail what current formulary options are available, if any, and how this treatment differs Whilst there are alternative medications to treat sleep disorder in both adults and children, none of them are suitable for longer term prescribing. Melatonin is unique with its safety and tolerability profile. This is particularly important for autistic people, children and those with intellectual disability who may be less able than typically developed people to describe any side effects. Benzodiazepines and 'Z' drugs risk daytime sedation and the development of tolerance as well as dependence. Benzodiazepines used for sleep disorder and z-drugs are not licensed for use in children.

Anticipated health outcomes of using this drug	Please detail the anticipated health outcomes e.g. symptom control, prevention, cure and how this will be measured: • Sleep disorder in this group of patients will be effectively treated or significantly improved, resulting in fewer challenging behaviours and improved quality of life for the patient. This can be objectively measured by repeat of the 2 week sleep diary. • Improved quality of life for family members and carers, with a lower risk of burnout, and lower risk of break-down of the family home. • Improved production of appropriate amount of growth hormone secretion, leading to appropriate growth in children. • Immunoglobulins are also secreted protecting patients from infections. • Improved behaviour and concentrations during the daytime leading to better learning.
Implications of not using this treatment	Are patients at risk if this treatment is not used? If yes, how? The implications of long term poor sleep (for the person and for their carers) are well documented. Challenges to social care workers of finding placements if home or current placement break down. A consequence is that service users may require an out-of-area placement, which has significant direct financial cost implications, but most significantly an enormous impact on the emotional wellbeing of the individual, their family, their friends, their carers and their personal development, e.g. schooling, employment. With ADHD treating the primary condition can often be made significantly harder when a sleep disorder is present. Service users respond better to ADHD medicines when good sleep hygiene is established.
Patient choice	What are the views of the patients and patient groups? Feedback from individuals prescribed melatonin: "Melatonin helps me at night. It helps me to fall asleep and stay asleep and be calm, so I can be healthy for the next day. If I don't take it, I get stressed, I can't get to sleep until maybe midnight and I might cry because I don't know what to do." – child with ADHD aged 11. *"Dear Dr Hank,* *Melatonin for L allows him to feel calm and relaxed, without racing thoughts so he can fall asleep naturally and wake without feeling any side effects that occur with GP prescribed sleeping tablets. The same sleep we all require to allow us to function.* *I can't stress enough the importance within a family setting and the impact that everyone experiences. In the younger years before L had Melatonin I feared falling asleep at night as I couldn't ensure his safety and that of his younger brother. I had bolts on the kitchen door and bathroom with extra locks on exterior doors and everything locked away out of reach. Now he's an*

adult the priority has changed, his brother is working in an office which includes working from home sometimes. If L didn't have Melatonin at night he would keep everyone awake with constant banging, loud groans, wandering around the house and in and out of my bedroom talking to me with his random thoughts.

I hope my input can help in some way towards GP's prescribing Melatonin. All the best with the GP's and if I can help further then please let me know.

J"

Equity

Have other health economies (other CCGs or comparable* trusts) approved the use of this treatment for this indication?
** e.g. if a tertiary centre, have other tertiary centres approved this treatment for this indication. Please provide details.*

CCG	Indications	Status
Black Country ADHD services	Management of Poor Sleep in Children - learning and behavioural difficulties, autism, ADHD and sensory impairments (particularly visual).	With SCA
Cambridgeshire and Peterborough NHSFT	Sleep disorders in children with LD, ADHD or autism.	ADVICE Specialist Advice provided for primary care initiation.
York and Scarborough NHSFT	Sleep disorders in children - visual problems and LD, CP and autism and complex neurodisabilities.	With SCA
South East London JMF	Sleep disorders in children - visual impairment, CP, ADHD, autism and LD.	With SCA
Portsmouth and SE Hampshire PF	Sleep disorders in children	With SCA
Southampton Joint Formulary	Sleep disorders in children - neurodevelopment disability, autism, visual impairment or neuropsychiatric disorders and chronic sleep disturbance.	With SCA
Berkshire West NHSFTs	ASD, ADHD, LD	With SCA

Has this treatment been approved for use in other clinical areas?

Yes. Melatonin is on the BNSSG joint formulary for various other indications:
Adults: https://remedy.bnssgccg.nhs.uk/formulary-adult/chapters/4-central-nervous-system/47-sleep-disorders/
Children: https://remedy.bnssgccg.nhs.uk/formulary-paediatric/paediatric-chapters/4-nervous-system/46-sleep-disorders/

	This application represents an extension of some of these indications in both adults and children.
National/ International Guidance	What national or international guidance exists on the use of this drug? National guidelines: British Association of Psychopharmacology.
Local priorities	Where does this treatment rank in terms of other priorities within your specialty? High: Service: • Impact of repeat prescribing burden on team doctors for those already on treatment • The majority of paediatric patients have a sleep disorder associated with ADHD and ASD; a lot of resource is directed to assessment and repeat prescribing, when melatonin is safe for prescribing in primary care, by GPs Service users: • More timely initiation of safe prescribing for new referrals when there is a lower worry about prescribing being subsequently transferred to primary care. • ADHD patients may respond more effectively to their primary medicine(s) if sleep hygiene is addressed, meaning quicker stability, and improve patient flow of waiting list. • More timely supply of repeat prescriptions via primary care, as well as being able to receive medicines from just one prescriber (instead of two or more) • Continued secondary care prescribing means that melatonin is not always "visible" to clinicians in other sectors, e.g. during an emergency hospital admission, medicines prescribed in secondary care may not be detected as part of medicines reconciliation, leading to them being omitted and the inevitable consequences on patient care.
Who will prescribe it?	Any doctor ☐ Consultant only (secondary care only) / GPwSI ☐ Specialty Consultant teams only (Please list below) ☐ Specify team(s): Click here to enter text. Consultant initiation; GP under shared care protocol ☒ Non-Medical Prescriber under Consultant supervision ☒ Other (please state): Speciality doctors. Junior doctors under supervision

D. Evidence for efficacy	Applying clinician to complete

ESSENTIAL INFORMATION REQUIRED Provide a summary of the relevant clinical evidence and cost-effectiveness supporting this application, indicating the types of evidence available e.g. clinical trials, reviews, meta-analyses and also include any peer-support evidence e.g. Royal College guidance.

British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders: An update (2019)

- Melatonin is effective in treating delayed sleep phase syndrome (which is common in people with ADHD) and non-24-hour sleep rhythm disorder, especially in people who are blind.
- Melatonin reduces long sleep latency in children with sleep onset insomnia or delayed sleep phase syndrome and learning disability, autism and ADHD. The randomised controlled trial leading to the licensing of Slenyto demonstrated that this sustained release mini-pill was "well-tolerated, efficacious and safe". There were "clinically meaningful improvements in total sleep time, duration of uninterrupted sleep and sleep latency with corresponding behavioural improvements for the children, and improved quality of life measures in their parents".
- In terms of adults with intellectual disability, the importance of a detailed clinical assessment, considering all possible causes of sleep disturbance was emphasised, with first line environmental, behavioural and educational approaches recommended. "There is little evidence for effectiveness of sleep-promoting drugs, apart from melatonin."
- Prolonged release melatonin improves sleep onset latency and sleep quality in people over 55 years. Melatonin is recommended as the first line treatment.
- Melatonin was one of several medications recommended for pharmacological treatment of insomnia – in contrast to benzodiazepines and 'Z' drugs, "melatonin does not give rise to motor or memory effects".

International Expert Opinions and Recommendations on the Use of Melatonin in the Treatment of Insomnia and Circadian Sleep Disturbances in Adult Neuropsychiatric Disorders

In the absence of well-conducted trials, the administration of IR melatonin at sleep-promoting dose (2–6mg) before bedtime could be of interest to treat insomnia symptoms associated with ADHD.

In case of Delayed Shift Phase Sleep associated with ADHD, chronobiotic doses of IR melatonin (≤1 mg) should be proposed, e.g., 0.5 mg/d melatonin during 3 weeks starting 3 h before the individual DLMO and weekly advancing by 1 h to improve both the circadian rhythm disorder and ADHD symptoms.

Legend: IR, Immediate Release; DLMO, Dim Light Melatonin Onset

van Andel E et al 2021

Low doses of melatonin advances the circadian rhythm and reduces self-reported ADHD symptoms. Large numbers of adult ADHD patients have concurrent Delayed Sleep Phase Syndrome (DSPS). Melatonin plays an important role in the effective treatment of delayed sleep in patients with ADHD.

Please refer to section H Critical Appraisal as well, which was completed in conjunction with the applicants.

Please list the references below that support the application

Reference – List first author & title	Main points

1: Wilson, S. et al. 2019. Journal of Psychopharmacology. Vol 33(8). 923-947	See above
2: Palagini, L *et al* (2021). International Expert Opinions and Recommendations on the Use of Melatonin in the Treatment of Insomnia and Circadian Sleep Disturbances in Adult Neuropsychiatric Disorders. Frontiers in psychiatry, 12, 688890. https://doi.org/10.3389/fpsyt.2021.688890	An international consensus statement recommending the use of Melatonin for sleep onset insomnia and for delayed sleep phase disorder in ADHD in adults
3: van Andel E, Bijlenga D, Vogel SWN, Beekman ATF, Kooij JJS. Effects of chronotherapy on circadian rhythm and ADHD symptoms in adults with attention-deficit/hyperactivity disorder and delayed sleep phase syndrome: a randomized clinical trial. Chronobiol Int. 2021 Feb;38(2):260-269. doi: 10.1080/07420528.2020.1835943. Epub 2020 Oct 29. PMID: 33121289.	A placebo controlled study demonstrating the effectiveness of Melatonin in treating delayed sleep phase disorder in adults with ADHD.
4: Click here to enter text.	Click here to enter text.
5: Click here to enter text.	Click here to enter text.

E. Financial implications

Applying clinician to complete

What are the financial implications over and above existing expenditure of adopting this treatment?

Please note: the cost of the drug may differ depending on whether supplied by primary care (drug tariff price) compared to secondary care (e.g. contract price). Please consider both if the drug is intended to be prescribed in primary care. Discuss with pharmacy department if needed.

A) Cost of proposed new drug (See Appendix 1 for a more comprehensive breakdown of medication costs)
In the absence of concrete average dose data across the organisations, a dose of 4mg is used below. However, actual FP10 spend for the last 12 months (to May 2022) is used in the final column.

DT Price of Drug (original pack)	Cost per 28 days treatment (at average dose)	Cost per years treatment at average dose	Total cost per years treatment of cohort (using estimated BNSSG patient numbers provided in Part C)
£15.39/30 (Circadin mr tab 2mg)	£28.72	£374.38	£68,148 (all AWP FP10 spend for the relevant teams in last 12 months – based on actual spend not assumed dosage) £211,7520 (all Sirona FP10 spend in last 12 months)
£130/150ml (1mg/ml solution)	£97.06	£1265.25	£13,972 (all AWP FP10 spend for the relevant teams in last 12 months based on actual spend not assumed dosage)

			£5254 (Sirona Adults FP10 spend in last 12 months)
£41.20/60 Slenyto 1mg pr tab @2mg/day	£19.22	£250.63	£500 (all AWP FP10 spend for the relevant teams in last 12 months – actual spend, not assumed)
£103/30 Slenyto 5mg pr tab @5mg/day	£96.13	£1253.16	£2499 (all AWP FP10 spend for the relevant teams in last 12 months – actual spend, not assumed)
£0.69/ml (average cost) Kidmel (unlicensed) 1mg/ml solution @2mg/day No DT price available	£38.64	£503.70	AWP prescribe 1mg/ml licensed preparation. £52,1925 (Sirona Paeds FP10 spend in last 12 months)

B) Drug costs to be offset if any

C) Any other costs to be offset (e.g. staff time, surgery, care needs etc)

Senior doctor time undertaking repeat prescribing.
Care needs of service users if change of care setting can be avoided
Cost of deprescribing benzodiazepines and z-drugs if patients become dependent

Funding category (please tick as appropriate):

In PbR tariff *i.e. No additional funding from CCG therefore internal directorate financial agreement required.* ***Financial agreement required before the application can be considered***	☒
PbR excluded i.e. not NICE and/or NHSE approved *i.e. requires CCG funding*	☐
Primary Care	☐

F. Declaration of conflicts of interest - must be completed by applicant

Please list:

1. Any gifts or hospitality received from the manufacturer of the product concerned (exceeding value of £20) in the last year. Actual monetary value not required.
2. Presentations, advisory panels, consultancy work (including retainers), or written materials for which payment has been received from the product manufacturer.
3. Shares held in the company (where known).
4. Sponsorship of research, members of staff, equipment or other materials in your department, practice or clinical specialty funded by the product manufacturer.
5. Any other forms of benefit or relationships which could be classed as a potential conflict of interest

If Nil – Please state:

Dr Hank: Paid for giving a talk for Flynn Pharma (ADHD related) and has been a Flynn Pharma Advisory Board member on one occasion (ADHD related). The honoraria are channelled towards charitable causes.

Dr Leyland: Nil Dr Hosdurga: Nil
Signature of applicant: Click here to enter text. **Date:** 31.05.2022

Applications from secondary care: Please send completed application to Trust Pharmacists:
UHB – pharmacyMI@UHBristol.nhs.uk
NBT – Kimberley.jefferson@nbt.nhs.uk
WAHT – skarthauser@nhs.net
AWP- james.scott12@nhs.net
Applications from Primary Care: Please send completed applications to:
BNSSG Formulary Pharmacists bnssg.formulary@nhs.net

G. Critical Appraisal Part 1: review of clinical evidence and cost effectiveness **Trust/BNSSG Pharmacist to complete**		
Pharmacist undertaking appraisal	Acknowledgements Completion of this critical appraisal has been a collaborative piece of work, with amendments and updates made by teams listed below. Part 1 Michael Vaggas, Locum Pharmacist, AWP 'Formulary Drug Cost Comparisons', 'Other CCG Formulary sections', 'National Policy and Guidance', 'Local Guidance' sections - updated and revised by BNSSG Formulary Team Part 2 Originally completed by Michael Vaggas, Locum Pharmacist, AWP however an independent review by the BNSSG Clinical Effectiveness Team has been undertaken and incorporated into this section. 'Efficacy and Clinical effectiveness' and 'safety' sections- independent evidence review embedded into this section, information submitted by Michael Vaggas has been greyed out 'Cost effectiveness' section- revised by BNSSG Formulary Team Part 3 Reviewed in line with evidence team review and revised by BNSSG Formulary team	Date: 15/04/2022 – 30/08/2022

Licensed indications & dosage	Circadin® 2mg tablets 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. 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. Slenyto® 1mg and 5mg tablets Indicated for the treatment of insomnia in children and adolescents aged 2-18 with Autism Spectrum Disorder (ASD) and / or Smith-Magenis syndrome, where sleep hygiene measures have been insufficient. The recommended starting dose is 2 mg of Slenyto. If an inadequate response has been observed, the dose should be increased to 5 mg, with a maximal dose of 10 mg.

Formulary drug cost comparisons Include administrations costs, consumables etc.

Table 1: Cost analysis for Circadin 2mg MR tablets on an assumption that this brand is prescribed for the whole cohort. Circadin 2mg MR tablets is the most likely brand to be prescribed based on guidance from AWP (MG15), letter from Sirona (Oct 19) and based on actual spend on Melatonin from the last year.

MG15.docx

Letter to paed drs re melatonin Oct 19

Circadin 2mg MR tablets	Cost per original pack £15.39 (30 tablets)[1]			
	Cost per daily dose	**Cost per 28 days supply per patient**	**Cost per one year's supply per patient**	***Cost per one year's supply for BNSSG cohort (n = 669)***
2mg daily	£0.51	£14.28	£186.15	£124,534.35
4mg daily	£1.02	£28.56	£372.30	£249,068.70
6mg daily	£1.53	£42.84	£558.45	£373,603.50
Typical dose range 2-6mg daily				**£124,534.35 - £373,603.50**
Most common dose 4mg daily				**£249,068.70**

[1] Patent expiry of Circadin and Slenyto expected on 12.08.2022 (unless patent extension approved), which is expected to lead to a drop in acquisition price. Costs calculated based on August 2022 Drug Tariff prices.

Table 2: The applicant provided actual spend on Circadin 2mg MR tablets in the last 12 months for AWP and Sirona. This was compared to the predicted spend based on

the patient numbers and average dose provided in the application, which corroborates the figures provided.

Circadin 2mg MR tablets	AWP PREDICTED	AWP ACTUAL	SIRONA PREDICTED	SIRONA ACTUAL
	Cost per one year's supply for predicted AWP cohort (***n* = 209**)	Compared to all AWP FP10 spend for the relevant teams in last 12 months	Cost per one year's supply for predicted Sirona cohort (***n* = 460**)	Compared to all Sirona FP10 spend for the relevant teams in last 12 months
2mg daily	£38,905.35	£68,148.00	£85,629.00	£211,752.00
4mg daily	£77,810.70		£171,258.00	
6mg daily	£116,716.19		£256,887.30	

Table 3: Cost analysis for Slenyto. Slenyto is indicated for the treatment of insomnia in children and adolescents aged 2-18 with Autism Spectrum Disorder (ASD) and / or Smith-Magenis syndrome, where sleep hygiene measures have been insufficient, whereas Circadin is licensed as monotherapy for the short-term treatment of primary insomnia characterised by poor quality of sleep in patients who are aged 55 or over.

Therefore, patients with ASD may be offered Slenyto as the available licensed product for this indication. Unfortunately, the proportion of children and adolescents aged 2-18 with ASD within the cohort included in this application is unknown.

Circadin is more cost effective than Slenyto, costing £1.02 for 4mg per day vs £2.75 for 4mg per day. The table below demonstrates the significant cost impact if Slenyto was available to the wider cohort.

Slenyto 1mg MR tablets	Cost per original pack £41.20 (60 tablets)[1]			
	Cost per daily dose	Cost per 28 days supply per patient	Cost per one year's supply per patient	*Cost per one year's supply for BNSSG cohort (n = 669)*
2mg daily	£1.37	£38.45	£500.05	£334,533.45
4mg daily	£2.75	£77.00	£1,003.75	£671,508.75
6mg daily[2]	£4.11	£115.08	£1,500.15	£1,003,600.30
	Cost per original pack £103.00 (30 tablets)[1]			

Slenyto 5mg MR tablets	Cost per daily dose	Cost per 28 days supply per patient	Cost per one year's supply per patient	*Cost per one year's supply for BNSSG cohort (n = 669)*
5mg daily	£3.43	£96.13	£1,251.95	£837,554.50
6mg daily[3]	£4.12	£115.22	£1,503.80	£1,006,042.20
Typical dose range 2-6mg daily				£334,533.45 - £1,006,042.20
Most common dose 4mg daily				**£671,508.75**

[1] Patent expiry of Circadin and Slenyto expected on 12.08.2022 (unless patent extension approved), which is expected to lead to a drop in acquisition price. Costs calculated based on August 2022 Drug Tariff prices.

[2] 6mg daily dosing costed two ways - 1 of 2: Slenyto 1mg MR tablet x 6

[3] 6mg daily dosing costed two ways - 2 of 2: Slenyto 5mg MR tablet x 1 plus Slenyto 1mg MR tablet

[4] Slenyto 1mg MR tablet x 6 is marginally more cost effective than 5mg + 1mg strength to achieve 6mg daily dose, costing £2,441.90 less per year for BNSSG cohort.

Table 4: Cost analysis for melatonin liquid. According to AWP guidance, the unlicensed melatonin liquid is third line patients who can only tolerate liquid medicines. Sirona states that melatonin liquid should only be used as a last resort. Melatonin liquid is considerably more expensive than the tablet formulations. It is unknown what proportion of patients would be offered a liquid formulation. The table below demonstrates the significant cost impact of melatonin liquid for the whole cohort.

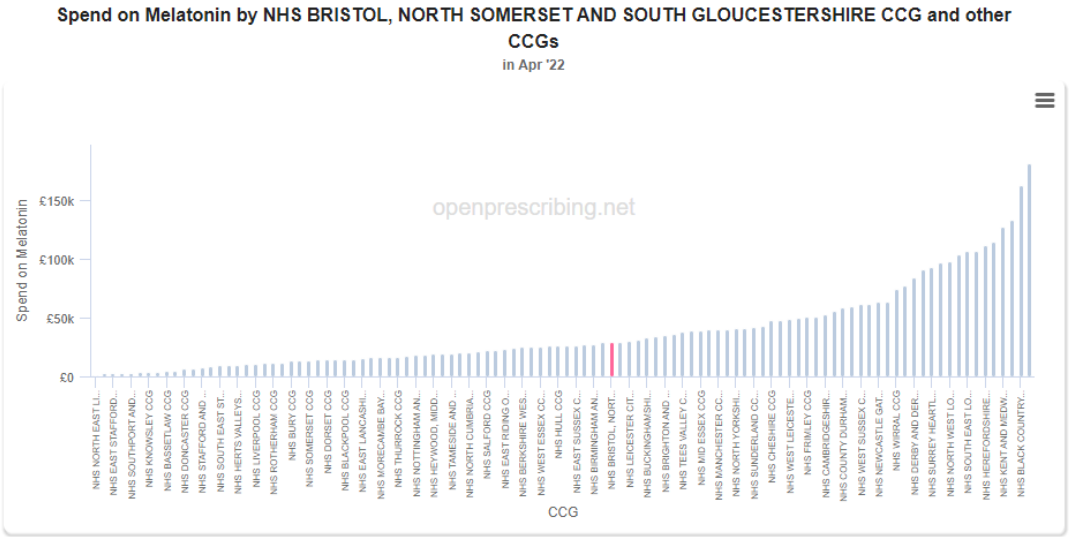
Kidmel 1mg/1ml oral solution (unlicensed)	Cost per original pack not available. No DT price. Average cost per mL = £0.69/mL			
	Cost per daily dose	Cost per 28 days supply per patient	Cost per one year's supply per patient	*Cost per one year's supply for BNSSG cohort (n = 669)*
2mg daily	£1.38	£38.64	£503.70	£336,975.30
4mg daily	£2.76	£77.28	£1,007.40	£673,950.60
6mg daily	£4.14	£115.92	£1,511.10	£1,010,925.90

Melatonin 1mg/1ml oral solution (licensed)	Cost per original pack £146.45 for 150mLs = £0.98/mL			
	Cost per daily dose	Cost per 28 days supply per patient	Cost per one year's supply per patient	*Cost per one year's supply for BNSSG cohort (n = 669)*
2mg daily	£1.96	£54.88	£715.40	£478,602.60
4mg daily	£3.92	£109.76	£1,430.80	£957,205.20
6mg daily	£5.88	£164.64	£2,146.20	£1,435,807.80

Existing melatonin prescribing in BNSSG Primary Care

According to EMIS data, there are 46,659 patients with a clinical code for ADHD, autism or learning disabilities. 739 patients are currently prescribed melatonin i.e. 1.06% of the ADHD, ASD, LD population.

In the last 12 months, BNSSG CCG spent £367,277 (9,192 items) on melatonin, which is approximately middle of the range comparing to other CCGs spend on melatonin. Note, it is not possible to extract details on formulary or non-formulary indications, dose or duration. This represents the existing overall spend on melatonin in primary care over a 12 month period.



This expenditure is in addition to the spend by AWP and Sirona which accounts for an estimated *additional* £335,191.50.

Current spend is across primary care, AWP and Sirona is approximately **£702,468.50.**

Other formulary drugs	DT Price of Drug (original pack)	Cost per 28 days treatment (at average dose)	Cost per years treatment at stated dose	Cost per years treatment at average dose	Cost per years treatment of cohort (estimated pt. numbers given in Part C)
Temazepam 10mg tablets (@5mg/day)	£1.20/28	£1.20	£15.64	£15.64	£10,463
Temazepam 10mg/5ml solution SF (@5mg/day)	£183.28/ 300ml	£42.77	£557.54	£557.54	£372,994
Promethazine HCL 10mg tab @10mg/day	£3.95/56	£1.98	£25.81	£25.81	£17,266
Promethazine HCL 25mg tab @25mg/day	£7.20/56	£3.60	£23.46	£46.92	£31,395
Zolpidem 5mg tabs (@5mg/day)	£1.71/28	£1.71	£22.29	£22.29	£14,913
Zolpidem 10mg tabs (@5mg/day)	£1.43/28	£1.43	£18.64	£18.64	£12,470
Zopiclone 3.75mg tabs (@3.75mg/day)	£0.94/28	£0.94	£12.25	£12.25	£8,198
Zopiclone 7.5mg tabs (@7.5mg/day)	£0.96/28	£0.96	£12.51	£12.51	£8,372

Due to the variable dosing for melatonin, it is not possible to perform a direct comparison of costs.
Number of patients here uses total numbers in part C.

Risk Management Issues: *e.g. training issues & storage requirements*	Patient education relating to risk of falls, cognitive impairment, dependence and withdrawal symptoms – however please refer to safety section below.
Patent expiry ***Please indicate if the new drug or any alternative(s) have a patent expiry within the next 18 months***	European Patent Office patent expiry of Circadin® and Slenyto® on 12.08.2022 (unless patent extension approved).
National policy and guidance	**National Institute for Health and Care Excellence (NICE) including NICE Evidence Summary: new medicines** Guidance: Challenging behaviour and learning disabilities: prevention and interventions for people with learning disabilities whose behaviour challenges [NG11]: Date: 29/05/2015

	"If medication is needed to aid sleep, consider melatonin. In May 2015, this was an off-label use of melatonin in people aged 55 years and under." (Section 1.1.12). NICE offers no recommendations relating to specific products.
	Scottish Medicines Consortium (SMC) Guidance: January 2021 decisions news release Date: 18/01/2021 Slenyto® was not recommended as the evidence provided by the company was not strong enough to satisfy the committee that it offers value for money to NHS Scotland. Circadin® was not recommended or use within NHS Scotland, as "The holder of the marketing authorisation [for Circadin] has not made a submission to SMC regarding this product in this indication."
	All Wales Medicines Strategy Group (AWMSG) Guidance: Final recommendation Date: 10/03/2021 Melatonin (Slenyto®) is recommended as an option for use within NHS Wales for the treatment of insomnia in children and adolescents aged 2 to 18 years with autism spectrum disorder and/or Smith-Magenis syndrome, where sleep hygiene measures have been insufficient. Use is conditional on access/contract price equivalency to the Wales Patient Access Scheme. Circadin® is recommended within Wales for use within its licensed indications. No application appears to have been made for off-label use of Circadin in children.
Other regional/national / local policy and guidance	Please list details of NHS policies and guidelines in other areas/regions Use of melatonin for sleep disorders in children is widespread amongst acute Trusts and JFCs, and many produce Patient Information Leaflets to support the same. Examples of patient information leaflets include Hull University Teaching Hospitals. Examples of guidance include North Central London JFC, Shropshire Community Health NHST, Pan Mersey APC, South East London IMOC, Derbyshire JAPC
Other CCG Formularies	29 CCG Formularies were reviewed to see whether the indications of ASD, ADHD or learning disabilities were specifically listed and what the traffic light statuses were. ASD 18 CCGs include melatonin on the formulary for ASD. Of these, 5 CCGs include melatonin for adults with a shared care status (with 1 specifying unlicensed specials are considered red). 17 CCGs include melatonin for paediatrics, 16 as shared care, 1 as red. ADHD 13 CCGs include melatonin for ADHD. 6 CCGs include melatonin for ADHD in adults and of these, 5 CCGs classify this as shared care (with 1 specifying unlicensed specials are red) and 1 CCG red. For paediatrics, 11 CCGs have a shared care status

(with 1 CCG specifying unlicensed specials are red) and 2 CCGs having a red status, noting some CCGs were also red but this is less clear within merged CCG formularies.

LD

10 CCGs include melatonin for learning disabilities on their formularies. Of these, 5 CCGs include melatonin for adults: 4 as shared care, 1 red (with 1 specify unlicensed specials are red). 11 CCGs include melatonin for children: 10 shared care and 1 red.

Neurological behaviour/development- noting the definitions of these descriptions may vary and are not clear on each formulary

10 CCGs also include melatonin for neurological behavioural problems: 2 CCGs for adults, 10 CCGs for paediatrics, all shared care.

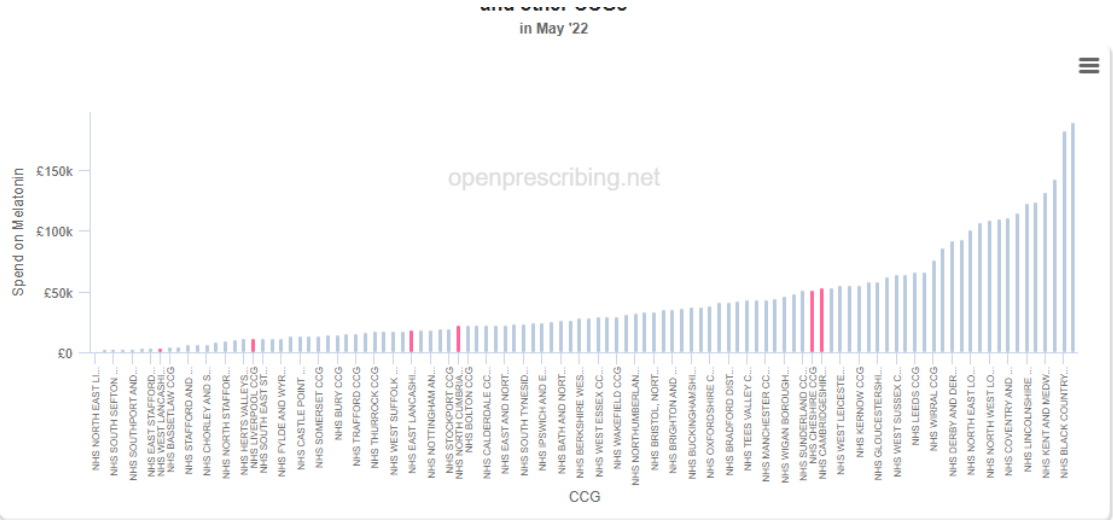
Openprescribing was used to establish whether CCGs with more indications listed on the formulary were higher prescribers. Unfortunately due to the formation of ICBs in July 2022, it is difficult to establish whether some of the CCGs had these indications included prior to this.

Pan Mersey ICB (including Cheshire and Liverpool) list ADHD, ASD, LD for adults and paeds.

Lancashire and south Cumbria (including East, West Lancashire and North Cumbria)- list ADHD, LD for adults and paeds and ASD paeds

Cambridgeshire and Peterborough -paeds for all 3 but not adults.

Spend appears to be scattered, and does not correlate with higher spending, however other indications may be responsible for higher spending (e.g general insomnia)



Reference Open Prescribing : Analyse | OpenPrescribing

	For a full breakdown of prescribing amongst the 29 CCGs, please refer to document. Formulary searchesv2.xlsx
Professional peer-support guidance e.g. Royal Colleges	**British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders: An update (2019)** British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders: An update (bap.org.uk) Melatonin improves sleep in children with ASDs (A). Melatonin administration can be used to advance sleep onset to normal values in children with ADHD who are not on stimulant medication (B). Melatonin reduces long sleep latency (following appropriate behavioural interventions) in children with sleep onset insomnia or delayed sleep phase syndrome and learning difficulties, autism and attention deficit hyperactivity disorder Several healthcare publications and groups recognise the off-label/unlicensed use of melatonin for insomnia in patients with learning disabilities and behaviour that challenges, even though it is not licensed for this indication: The BNFC, which states that “Melatonin is used for insomnia in patients with learning disabilities and behaviour that challenges, but is not licensed for this indication. Melatonin is used for sleep onset insomnia and delayed sleep phase syndrome, but is not licensed for these indications”. *Medicines for Children* produce a PIL to support the use of melatonin products in sleep disorders, and the wider NHS also recognises its use in children.
Current/future research	Please detail any known current or planned clinical trials, extension studies etc. Melatonin research has been called for, or is actively pursued in the following areas: • Bipolar Disorder (meta-analysis) • Alzheimer’s disease • Adjunctive treatment in schizophrenia • Effect of pharmacokinetics of different melatonin formulations on sleep disorders. • Pharmacokinetics of melatonin in ASD • Specific neurological disorders - head injury/retinitis pigmentosa • Sleep quality in ICU patients • Alcohol Use Disorder patients with sleeping problems • Sleep profiles in breast cancer patients

	• Haemodialysis patients - non-dipping BP and reduction in oxidative stress • Anti-inflammatory treatment of ulcerative colitis
References	**All Wales** Therapeutics and Toxicology Centre: melatonin (Slenyto®), melatonin (Circadin®) **BNFC**: Melatonin **CMS** Law-Now™: Patents Court refuses to grant interim injunction in pharmaceutical patents case. (Accessed 22.03.22) **Duan** C, Jenkins ZM, Castle D. Therapeutic use of melatonin in schizophrenia: A systematic review. World J Psychiatr 2021; 11(8): 463-476 **Electronic Medicines Compendium**: Circadin. Accessed 07.04.2022 **Gandolfi**, J.V., *et al.* The Effects of Melatonin Supplementation on Sleep Quality and Assessment of the Serum Melatonin in ICU Patients: A Randomized Controlled Trial, Critical Care Medicine: December 2020 - Volume 48 - Issue 12 - p e1286-e1293 **Gendy**, M.N.S., *et al.* Melatonin for Treatment-Seeking Alcohol Use Disorder patients with sleeping problems: A randomized clinical pilot trial. *Sci Rep***10,** 8739 (2020). **Kayumov** L, Zhdanova IV, Shapiro CM. Melatonin, sleep, and circadian rhythm disorders. Seminars in Clinical Neuropsychiatry. 2000 Jan;5(1):44-55. PMID: 10704537. **Lalanne** S*et al.* From Pharmacokinetics to Clinical Use in Autism Spectrum Disorder. *International Journal of Molecular Sciences*. 2021; 22(3):1490. **McGowan**, N.M. *et al*. Hypnotic and Melatonin/Melatonin-Receptor Agonist Treatment in Bipolar Disorder: A **Moroni**, Irene *et al.* Pharmacokinetics of exogenous melatonin in relation to formulation, and effects on sleep: A systematic review, Sleep Medicine Reviews, Volume 57, 2021, 101431, ISSN 1087-0792 **Roy**, Jaydeep, *et al.* Role of melatonin in Alzheimer's disease: From preclinical studies to novel melatonin-based therapies, Frontiers in Neuroendocrinology, Volume 65, 2022, 100986, ISSN 0091-3022. Systematic Review and Meta-Analysis. CNS Drugs (2022) **Russcher**, M., *et al*. The role of melatonin treatment in chronic kidney disease. Frontiers in Bioscience 17, 2644-2656, June 1, 2012 **NHS**: Melatonin for sleep problems **NICE** guideline [NG11]: Challenging behaviour and learning disabilities: prevention and interventions for people with learning disabilities whose behaviour challenges. Published: 29 May 2015 **Scottish Medicines Consortium** (SMC): January 2021 decisions news release **Terry**, P.D., *et al.* Melatonin and Ulcerative Colitis: Evidence, Biological Mechanisms, and Future Research, *Inflammatory Bowel Diseases*, Volume 15, Issue 1, 1 January 2009, Pages 134–140. Veriton Pharma: Data sheet Kidmel Melatonin 1mg in 1ml oral solution (requested) **Zaki**, Nevin Fw et al. "Depressive Symptoms, Sleep Profiles and Serum Melatonin Levels in a Sample of Breast Cancer Patients." Nature and science of sleep vol. 12 135-149. 13 Feb. 2020.

Part 2 to be completed in the absence of a NICE evidence summary for a new medicine.
The BNSSG Clinical Effectiveness Team have completed an independent evidence review for use of melatonin for ADHD, ASD and LD. Readers should review this document when considering 'Efficacy and clinical effectiveness' and 'Safety', sections below.
The original information submitted by AWP has been greyed out.

Melatonin Use in ADHD LD ASD FINAL

H. Critical Appraisal Part 2: clinical evidence and cost effectiveness **Trust/BNSSG Pharmacist to complete**	
Efficacy and clinical effectiveness	Summary of clinical evidence (please give an overview of the clinical evidence and detail the outcomes, strengths and limitations) Melatonin Use in ADHD LD ASD FINAL Additional information provided by AWP: McDonagh, Holmes and Hsu (2019) reviewed 19 RCTs of melatonin supplements[1] that included a total of 1,021 children of 'good' or 'fair' quality trials. The purpose was to systematically review the evidence on the efficacy and adverse effects of pharmacologic treatments for children and adolescents with sleep disorders Most of the studies were small (n=8-160), and all were relatively brief (1 to 13 weeks). The data showed that overall melatonin significantly improved outcomes: • Sleep Onset Latency (SOL: median 28 minutes; range 11-51 minutes) o Children with ASD fell asleep 37 minutes earlier. o Children with ADHD fell asleep 20 minutes earlier. o Children with chronic sleep-onset insomnia fell asleep 24 minutes earlier. • Total Sleep Time (TST: median 33 minutes; range 14-68 minutes) o Children with ASD slept 48 minutes longer. o Children with ADHD slept 33 minutes longer. o Children with chronic sleep-onset insomnia slept 25 minutes longer. • Wake Time After Sleep Onset (WASO: range 12-43 minutes) No improvement was seen in the number of awakenings per night (range 0-2.7). These findings show that melatonin was useful in improving short-term sleep outcomes in ASD, ADHD and SOL. The magnitude of effect was smaller in older children and adolescents. The authors note that the importance of the improvements to sleep in terms of functional or behavioural outcomes is not clear. It is acknowledged that it is not clear whether statistically significant improvements to sleep are clinically significant. It is noted that there is a lack of consistency in measurement of outcomes. Other limitations include the heterogeneity of studies.

	It has also been found that prolonged release melatonin is most useful in increasing TST, whereas immediate release melatonin is most beneficial in reducing SOL. PrescQIPP (Table 3): Recognises (lists) the off-label uses of melatonin, including: • Sleep disorders in ADHD without a concomitant disorder of ASD. • Circadin® use in patients <55 years or Slenyto® used in patients <2 years or >18 years and within their licensed indications. • Tablets (p/r) crushed and used for licensed indications. • Doses greater than those licensed: Circadin® >2mg, Slenyto® >10mg, melatonin 1mg/ ml oral solution >6mg. For Learning Disabilities, most of the studies were uncontrolled and the few controlled trials available were of small size. However, available data suggest similar findings to the indications mentioned above - melatonin appears effective in reducing SOL and TST, but ineffective in improving night-time awakenings. The consensus view of the British Association for Psychopharmacology in the treatment of adults with LD state that 'There is little evidence for effectiveness of sleep-promoting drugs, apart from melatonin, referring to a meta-analysis (Braam et al, 2009) (p941).' For patients with swallowing difficulties, or with PEG tubes inserted, the current NEWT guidelines state that "Circadin® is a modified-release tablet, and is not licensed to be given through enteral feeding tubes. However the manufacturers state that if necessary it can be crushed (note - this would change it from a modified-release tablet to an immediate-release one) and mixed in 15-30mL of water for administration through enteral feeding tubes. The tube should be flushed well after administration." [1] In the USA, melatonin is not licenced as a medicine by the FDA, Food and Drug Administration but is retailed as a dietary supplement. As a result, research in the USA is based on supplements. [2] The prevalence of sleep disturbance in children and adolescents with ASD ranges from 30%–53% and up to 70% in those with ADHD. If untreated, such sleep disturbances can negatively impact children, adolescents, and adults. Brand and Kirov (2011) have stated that "restoring sleep is strongly associated with a better physical, cognitive, and psychological well-being. By contrast, poor or disordered sleep is related to impairment of cognitive and psychological functioning and worsened physical health."
Safety	Please see Evidence Team's evidence review: Melatonin Use in ADHD LD ASD FINAL **General Safety** Melatonin is generally well tolerated, with no reports of any very common or common adverse drug reaction (ADRs), or reports of patients experiencing tolerance, dependence or withdrawal symptoms within Circadin's SmPC. A substantial body of evidence all

corroborate melatonin's safety profile across multiple products (Gringas, Braam, Coppola, Appleton and Malow.)

Circadin's SmPC (UK) states that in combined clinical trial and post-marketing data, ADRs rates were 9.5% (and 7.4% for placebo, producing a relative risk ratio of 1.3). It also states that melatonin:

- Should be avoided in hepatic impairment, autoimmune disease (no safety data), pregnancy, breastfeeding and in women planning a pregnancy, children under 1 year of age and co-administration of fluvoxamine (levels markedly increased).
- Used with caution in renal impairment (no safety data), and the elderly (higher AUC and C_{max} levels), driving and using machines (residual drowsiness).
- In overdose will cause drowsiness. Clearance of the active substance is expected within 12 hours after ingestion. No special treatment is required.
- Is metabolised by CYP1A enzymes – caution in coadministration of quinolones, oestrogens, carbamazepine, rifampicin, fluvoxamine and alcohol – (reduced effectiveness of Circadin on sleep).
- The m/r tablets contain lactose - patients with rare hereditary problems of galactose intolerance, the LAPP lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Falls, cognitive impairment, dependence and withdrawal

The previous body of evidence seems to conflict with NICE melatonin CKS which states that the risks associated with hypnotics, such as "falls, cognitive impairment, dependence and withdrawal symptoms, are well recognised. Be aware that recent data also suggest that risks such as falls are associated with melatonin" [NICE 2021]. This evidence was based on NICE KTT6 (2019), but the source of this data was not transparent, and in any case has since been withdrawn.

However, the EMA did NOT mention falls, dependence or withdrawal symptoms in relation to melatonin. It did mention cognitive impairment (single dose toxicity) at 'even higher doses' (see 2.7.3), but did NOT expect this to occur at '5mg melatonin (maximum 0.42mg/kg)'. Again, it is not clear whether these observations were derived from humans, or what the evidence base for this evidence was as it was not referenced.

The EMA also reports that comparing the rate of patients with ADRs per 100 patient weeks, the rate was higher for placebo than Circadin, and that the most common ADRs were headache, nasopharyngitis, back pain, and arthralgia, which matched placebo treated groups. Appleton and Malow found the same.

Arthralgia, headaches, infection and pain.

The BNF lists 'Arthralgia; headaches; increased risk of infection; pain' and either very common or common ADRs for melatonin. These ADRs are NOT found in the list of ADRs stated in the SmPC for Circadin, but rather taken from a quotation from the same which states that these ADRs were from a "MedDRA definition, in both the Circadin and placebo treated groups." In short, these ADRS were no more frequent for the placebo treated groups, as they were for melatonin. The source for the MedDRA data could not be traced.

Alternative sedatives

In comparison to alternatives to melatonin in the treatment of this indication, melatonin has a highly favourable reward:risk benefit, as alternative medications are indeed known to have high levels of confusion, sedation, falls and withdrawal risks. Such alternatives include benzodiazepines (BDZ) and BDZ receptor agonists (such as zopiclone). These alternatives are well known to be potentially inappropriate medication (PIMs), and are included in the STOPP/START criteria for medicines prescribed in many elderly patients (65+ years). These criteria are outlined in NHSE's *Toolkit for general practice in supporting older people living with frailty* documentation, which highlights the ADRs involved in using the following medication in elderly patients:

Medication class	Common indication	Adverse Drug Reactions
Benzodiazepines	Panic attack sedation and insomnia	Prolonged sedation, confusion, impaired balance, falls. Sedative, may cause reduced sensorium, impair balance
Neuroleptics >1 month (haloperidol, risperidone etc)	hypnotics	Confusion, hypotension, extrapyramidal side effects, falls. Gait dyspraxia, parkinsonism.
Anticholinergics (Procyclidine, orphenadrine, trihexyphenidyl)	To treat extra-pyramidal side- effects of neuroleptics	Anticholinergic toxicity
Old antihistamines (cyclizine, chlorpheniramine, alimemazine etc)	Sedation	Sedation & anti-cholinergic side effects

While not directly relevant to this application, this does highlight the risks associated with alternative options in those patients of advancing years with the included diagnoses, and a sleep disorder.

Growth and Puberty

A clinical trial using PedPRM (marketed as Slenyto®) recruited 80 children and adolescents with ASD for up to 2 years , and were given doses of 2,5 and 10mg melatonin nightly. They found melatonin to be safe with 'no observed detrimental effects on children's growth and pubertal development and no withdrawal or safety issues related to the use or discontinuation of the drug' (Malow, 2019). Van Geijlswijk found the same (n=51, up to 4.6 years, 0.3-10mg).

Cost-effectiveness

Melatonin has cost implications for the NHS health economy in terms of medicine spend. Some costs might be offset if alternative sedative medicines were to be prescribed instead which may be associated with adverse effects.
Circadin is the most cost effective formulation for melatonin.
The evidence review refers to a study in progress aiming to evaluate the cost-effectiveness of melatonin for stimulant treated children with ADHD and insomnia in Australia.

References	Summary
Appleton RE *et al*. The use of Melatonin in children with neurodevelopmental disorders and impaired sleep: a randomised, double-blind, placebo-controlled, parallel study (MENDS). Health Technol Assess. 2012;16(40):i-239. PMID: 23098680.	A paper supporting the use of melatonin in this indication, and suggesting more detailed research in specific formulations of melatonin.
Braam W, *et* al. Melatonin treatment in individuals with intellectual disability and chronic insomnia: a randomized placebo-controlled study. J Intellect Disabil Res. 2008 Mar;52(Pt 3):256-64. PMID: 18261024.	Research showing that melatonin treatment improves some aspects of chronic sleep disturbance in individuals with LD.
Chua, H.M. *et al* (2016). Dissolution of intact, divided and crushed Circadin tablets: Prolonged vs. Immediate release of melatonin. PMID: 34513608.	Research looking at some of the remarkable release profiles of whole, cut and crushed Circadin tablets.
Coppola G, *et al.* Melatonin in wake-sleep disorders in children, adolescents and young adults with mental retardation with or without epilepsy: a double-blind, cross-over, placebo-controlled trial. Brain Dev. 2004 Sep;26(6):373-6. PMID: 15275698.	Research supporting the use of melatonin in LD patients – data from a small trial.
Gringras,P. et al. Efficacy and Safety of Paediatric Prolonged – Release Melatonin for Insomnia in Children with Autism Spectrum Disorder. J Am Acad Child Adolesc Psychiatry. 2017;56(11):948- 95	Clinical trial data demonstrating the safety of melatonin over a 13 week period.
Gringras P *et al.* Melatonin for sleep problems in children with neurodevelopmental disorders: randomised double masked placebo controlled trial *BMJ* 2012; 345 :e6664	An open clinical trial showing efficacy of IR melatonin in reducing SOL in this population, with a modest effect in TST.
Gringras P. When to use drugs to help sleep. Arch Dis Child. 2008 Nov;93(11):976-81. Epub 2008 Aug 1. PMID: 18676436.	A paper looking at the role of behavioural therapies and medicines in treating insomnia in children.
Jan JE, et at. Clinical trials of controlled-release melatonin in children with sleep-wake cycle disorders. J Pineal Res. 2000 Aug;29(1):34-9. PMID: 10949538.	A small clinical trial looking at both the average effective dose of CR melatonin (5.7mg), and highlighting the benefit of CR tablets for TST, and IR forms being more helpful in treating SOL.
Malow BA, *et al.* Sleep, Growth, and Puberty After 2 Years of Prolonged-Release Melatonin in Children With Autism Spectrum Disorder. J Am Acad Child Adolesc Psychiatry. 2021 Feb;60(2):252-261.e3. Epub 2020 Jan 23. PMID: 31982581.	Clinical trial data demonstrating the safety of melatonin, including pubertal development, over a 2 year period.
Medicines for Children: Melatonin for Sleep Disorders (leaflet 2020).	Highly readable information leaflet for carers.
Medicines for Children: Melatonin for sleep disorders (Accessed 22.03.22)	Comprehensive yet plain English information from the NHS on melatonin and sleep disorders.
McDonagh MS, Holmes R, Hsu F. Pharmacologic Treatments for Sleep Disorders in Children: A Systematic Review. J Child Neurol. 2019 Apr;34(5):237-247. Epub 2019 Jan 23. PMID: 30674203.	An important meta-analysis of 22 trials data (2018) , summarising the generally supportive findings of melatonin use f melatonin in children.
MHRA: The supply of unlicensed medicinal products ("specials") (2014)	A useful guide from the MHRA in managing off-label and off-licence medicines.
NICE CKS: Melatonin. What issues should I be aware of when prescribing modified released melatonin? Last revised in March 2021	NICE guidance for using melatonin (includes a reference to falls, cognitive impairment, dependence and withdrawal symptoms in relation to melatonin).

Sack RL et al. Sleep-promoting effects of melatonin: at what dose, in whom, under what conditions, and by what mechanisms? Sleep 1997; 20:908–915.	A paper looking at the scientific mechanisms of action of melatonin (adjustment of correcting circadian phase abnormalities and/or by a modest direct soporific effect).
Sivertsen, B, *et al.* Sleep problems in children with autism spectrum problems: a longitudinal population-based study. Autism. 2012 Mar;16(2):139-50. Epub 2011 Apr 8. PMID: 21478225.	A large trial (n=3,700) looking at sleep problems in patients with ASD, highlighting the magnitude of this issue.
Riemann D, *et al* (2017). European guideline for the diagnosis and treatment of insomnia. *J Sleep Res* **26**(6), 675-700.	A pan-European guide to treating insomnia, with apparently contradictory recommendations relating to melatonin (2.9.2)
The Maudsley: Prescribing Guidelines in Psychiatry, 13th Ed.	A pivotal guide to psychiatry in general.
van Geijlswijk et al. Evaluation of sleep, puberty and mental health in children with long-term melatonin treatment for chronic idiopathic childhood sleep onset insomnia. Psychopharmacology (Berl). 2011 Jul;216(1):111-20. Epub 2011 Feb 22. PMID: 21340475.	A paper looking at any postulated interference of melatonin with puberty – it finds in favour of melatonin not causing any pubertal developmental problems.

I. Critical Appraisal Part 3: conclusion & recommendations	
Conclusion	Please summarise the critical appraisal using the JFG decision making criteria as below. **1.Patient safety** Studies found melatonin to be safe and well tolerated, with less risk associated with melatonin than other sedative medicine options. **2.Clinical effectiveness** When clinical trial data was pooled together in meta-analysis, statistically significant results were found showing an improvement of sleep latency and total sleep time. A pertinent meta-analysis by McDonagh et al (2019), concluded that for children and adolescents, Melatonin significantly improved sleep latency and duration, although the range of improvement in sleep latency varied between studies (11-51 minutes, median 28 minutes) and sleep duration improved by 14-68 minutes (median 33 minutes). It was reported within this meta-analysis that children with ASD improved the most compared to other neurodevelopmental disorders (sleep latency by 37 minutes and sleep duration by 48 minutes). Evidence for improvement was stronger for younger children than adolescents. However the Evidence team noted limitations with the study as measurements of awakenings or time spent awake after sleep onset were inconsistent with each other and varied from getting worse to improving significantly leaving little confidence in the trial's findings. A systematic review conducted by Salanitro (2022) concluded that melatonin improved sleep onset latency and total sleep time in adults across sleep disorders and across all disorders including ADHD/LD/ASD. There was no evidence that melatonin improved night awakenings. It is not clear whether the reported statistically significant improvements to sleep

	latency and total sleep time translate to clinically significant outcomes. Further studies are recommended to explore the effects of longer term use of melatonin and the impact of improvements to sleep on function, behaviour and improvement of condition. Further studies are also needed with a larger population size and use of a controlled environment to exclude bias. **3.Strength of evidence** Low quality- despite the volume of evidence and use of melatonin for nearly 30 years, the quality of studies were variable with studies often of low quality with limitations such as absence of large scale RCTs, smaller sample size; short duration (the majority are 13 weeks duration or less); subjective outcome measures and risk of bias (e.g. sleep diaries); lack of methodology detail; lack of reproducibility. The majority of evidence reviewed focussed on children, and studies did not routinely focus on ADHD, LD or ASD in isolation. The evidence review completed by the BNSSG evidence team focussed on available data from the 2020-2022 period only, however this included meta-analyses which included trials prior to this date range. **4.Cost effectiveness or resource impact** Current prescribing of melatonin already presents a substantial cost to the system of £702,468.50 per annum (£335,191.50 for AWP and Sirona combined and £367,277 by GP Practices). If the application for these additional indications were approved as shared care on the BNSSG Formulary, the costs of prescribing currently held with AWP and Sirona would shift to primary care. Prescription administration workload currently managed by AWP and Sirona would transfer to GP Practices, which may relieve pressure in those settings, but increase pressure in GP Practices. It is expected the majority of prescribing would be longer-term. **5.Place in therapy relative to available treatments** 3rd line, following non-pharmacological treatments. **6.National guidance and priorities** NICE guideline Challenging behaviour and learning disabilities NG11 includes melatonin to 'consider' if medication is needed, noting it's off-label use in patients aged under 55 years. Melatonin is recognised as an option by the British Association of Psychopharmacology for patients with LD, ASD and children with ADHD who are not on stimulant medication after behavioural strategies. **7.Local health priorities** Considered a high priority for local specialists who wish to make melatonin shared care for the indications ADHD, ASD and LD for both adult and paediatric patients. It is currently non-formulary for the majority of these patient cohorts, meaning potentially some prescribing occurs in primary care 'non formulary' and prescribing occurs within AWP and Sirona outside of formulary recommendations. **8.Equity of access**

	At a national level, the inclusion of melatonin on formularies varies greatly in terms of indications covered, traffic light status and whether it is included for adults or paediatrics or both. **Other considerations:** For cost effective prescribing: 1) First line use for all stated off-label conditions: Circadin m/r 2mg tablets. These may be titrated by halving the tablets if needed, and still maintain their prolonged release properties. 2) Second line: Circadin m/r 2mg tablets use in swallowing difficulties – halved or crushed with a spoon. 3) Third line: Slenyto tablets, where the small diameter (3mm) of the tablet is a significant aid for people with swallowing difficulties, who cannot manage crushing tablets effectively. 4) Fourth line: melatonin 1mg/1ml soluble solution that is alcohol free, low in propylene glycol and low in sorbitol (E.g. Martindale® or Kidmel® brands). For use in rare hereditary conditions of galactose intolerance, the LAPP lactase deficiency or glucose-galactose malabsorption. Also for use in people who cannot manage any solid dose form of medication, e.g. with a percutaneous endoscopic gastrostomy (PEG) tube.
Recommendation	Please state your recommendation for use of this drug in the BNSSG Joint Formulary. JFG to consider whether melatonin should be included on the formulary for use in ADHD, ASD and LD for both adult and paediatric populations and if so, where the prescribing is most appropriate.

Appendix 1

Comparator costs for melatonin sought in this application against alternative melatonin products

Product	Indication	Strength	Width	Excipients	Pack size	Pack DT price[1]	Cost/ 1mg dose	Cost ratio %	Single patient costs 28 days/Daily dose (usual range)										80 patient cost 28 days/Daily dose				AWP Rx[2]	AWP Rx[2]
	(abridged)	mg or mg/ml	mm		Tab, cap, or ml		(theor-etical)	Relative to Circadin	0.5 mg	1mg	2mg	3mg	4mg	5mg	6mg	7mg	8mg	9mg	10 mg	2mg	5mg	10mg		
Circadin m/r tablets	insomnia: 55Y+	2	8.1	80 mg lactose monohydrate	30	£15.39	£0.26	100%	£4	£7	£14	£22	£29	£36	£43	£50	£57	£65	£72	£1,149	£2,873	£5,746	468	70%
Slenyto p/r tablets (film-coated)	insomnia: 2-18Y with ASD/SM syndrome	1	3.0	8.32mg lactose	60	£41.20	£0.69	268%	£10	£19	£38	£58	£77	£96	£115	£135	£154	£173	£192	£3,076	£7,691	£15,381	0	0%
Slenyto p/r tablets (film-coated)	insomnia: 2-18Y with ASD/SM syndrome	5	3.0	8.86mg lactose	30	£103.00	£0.69	268%	£10	£19	£38	£58	£77	£96	£115	£135	£154	£173	£192	£3,076	£7,691	£15,381	0	0%
(Colonis) i/r Caps	Jet lag	3	13.6	Gelatin shell	30	£62.50	£0.69	271%	£10	£19	£39	£58	£78	£97	£117	£136	£156	£175	£194	£3,111	£7,778	£15,556	32	5%
Ceyesto i/r Tab (film-coated)	Jet lag	3	7.0	Lactose-free	30	£19.81	£0.22	86%	£3	£6	£12	£18	£25	£31	£37	£43	£49	£55	£62	£986	£2,465	£4,930	20	3%[4]
Syncrodin i/r Tab (film-coated)	Jet lag	3	7.5	Lactose-free	30	£19.81	£0.22	86%	£3	£6	£12	£18	£25	£31	£37	£43	£49	£55	£62	£986	£2,465	£4,930	0	0%
(Colonis) Solution	Jet lag	1	N/A	-PG[3] 151 mg/ml -Sorbitol 140mg/ml	150	£130.00[5]	£0.87	338%	£12	£24	£49	£73	£97	£121	£146	£170	£194	£218	£243	£3,883	£9,707	£19,413	0	0%
Kidmel Solution 200ml	N/A	1	N/A	-PG 52mg/ml -Sorbitol 0mg Alcohol free	150	£130.00 – price varies because it is an unlicensed special.	£0.87	338%	£12	£24	£49	£73	£97	£121	£146	£170	£194	£218	£243	£3,883	£9,707	£19,413	104	16%[4]
Martindale Solution 200ml	N/A	1	N/A	-PG49mg/ml -Sorbitol 0mg	150	£130.00	£0.87	338%	£12	£24	£49	£73	£97	£121	£146	£170	£194	£218	£243					

[1]Drug Tariff April 2022
[2]Annualised data -extrapolated from 6/12
[3]Propylene Glycol
[4]Brand unknown
AWP: 333 Rx in 6/12-some NF, total cost of £40k/6 months. Ave 56 Rx/month
[5]DT Category A - Drugs which are readily available.

National average Rx cost	Melatonin cost vs National Ave	Colour Coding
£44.11*	0-1X	
	1-1.9X	
	2-2.9X	
	>3x	
	Unviable dose	

Others (solid):	18	3%
Others (liquid):	24	4%
Totals:	666	100%

*Data kept on file.

Form Approved by the BNSSG JFG January 2020
Review: January 2022

Appendix 2

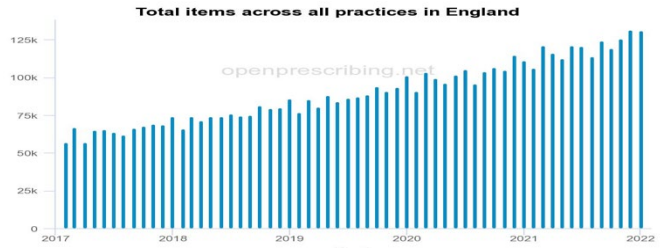
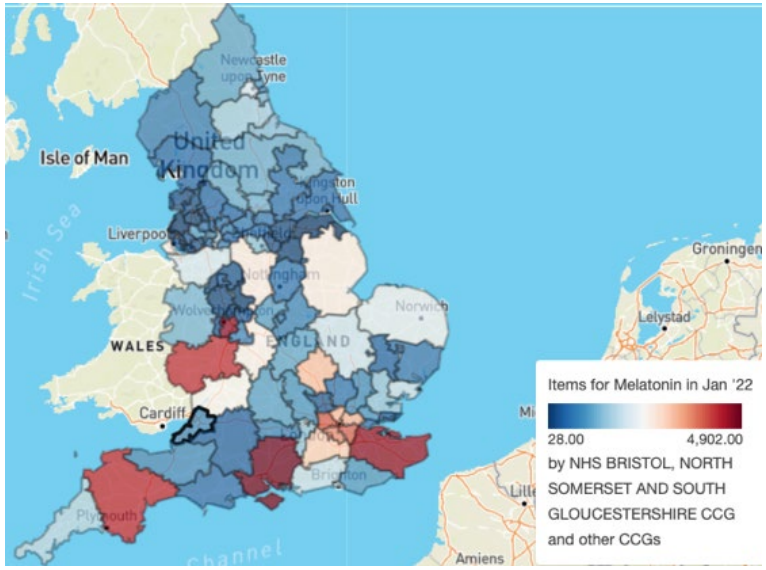


Table 1

Table 1* shows the total items prescribed for melatonin in the UK has risen from 57K in Feb 2017 to 131k in Jan 2022 (approximately a 50% increase pa.) During this period, 5.3M prescriptions were dispensed, costing £183M. This represents an average prescribing cost of a little under £35/item.

Table 2* shows melatonin prescribing spends for all CCGs in England for the 12 months up to January 2022. It shows that during this time BNSSG spent just under £24k, which is well below the mean average spend for CCGs of £49k pa. Put another way, the mean daily spend on melatonin for BNSSG is currently just under £66/day, in comparison with almost £79/day across all English CCGs.

This accompanying map* shows the number of items prescribed by region, illustrating a relatively modest spend by BNSSG on melatonin.



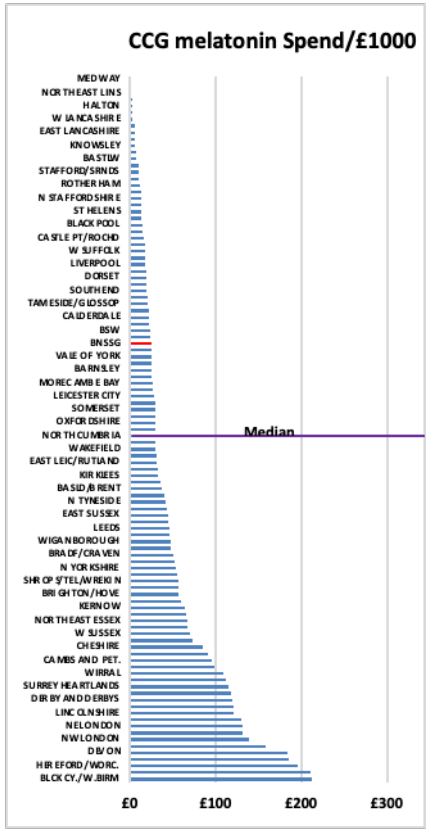


Table 2

*From OpenPrescribing.net, EBM DataLab, University of Oxford, 2020).

Form Approved by the BNSSG JFG January 2020
Review: January 2022

BNSSG Joint Formulary Group
New Pharmaceutical Drug Request

Who should complete what?

Applying clinician/CCG budget holder	**Sections A, B, C, D, E, F**
Pharmacist undertaking critical appraisal	**Section G, H and I**

- Please ensure every section of this form is filled out. Support is available from your Pharmacy team if required – either via the Trust pharmacy department, or CCG Medicines Optimisation team.
- Please ensure relevant colleagues including those at all trusts within the BNSSG system are consulted prior to submitting the application.
- Completed forms for new formulary items must be received at least 6 weeks prior to the next Joint Formulary Group.
- Send completed forms either to the formulary pharmacist / pharmacy department within the Hospital trusts or the Joint Formulary pharmacists for BNSSG - email **bnssg.formulary@nhs.net**
- Requesting clinicians will be required to attend the meeting to present their case
- Do NOT complete this document for a drug that is commissioned as part of a specialised service by NHS England* and/or approved as a NICE Technology Appraisal. *refer to the 'NHS England Manual for prescribed specialised services'.

A. Applicant details	Applying clinician to complete
Applicant name: 1. Dr Dietmar Hank 2. Dr Nathalie Leyland 3. Dr Saraswati Hosdurga	**Acute trust (Secondary care only):** 1. AWP 2. AWP 3. Sirona Care & Health
email address: 1. dietmarhank@nhs.net 2. nathalieleyland@nhs.net 3. s.hosdurga@nhs.net	**Directorate/Division (Secondary care only):** 1. Specialised Services – ADHD 2. Specialised Services – LD Adults 3. Community Children's Health Partnership
Position: 1. Consultant Psychiatrist 2. Consultant Psychiatrist 3. Consultant Community Paediatrician, Lead for Medicines Management for Community Paediatrics, Designated Doctor for Children in Care (from June 2022)	**Other (GP practice, CCG)** N/A
Second applicant (if relevant): Click here to enter text.	**Supporting applicant/s (at other trusts)** Kim Jefferson, Pharmacoeconomics Pharmacist at NBT Dr James Bowler, Consultant Psychiatrist, CAMHS LD, AWP

B. Drug details	Applying clinician to complete
Approved name: Melatonin	**Brand name:** Circadin® Slenyto® Kidmel® or Martindale.
Manufacturer: Flynn Pharma Ltd Flynn Pharma Ltd Specials Manufacturers	**Formulation(s) requested:** Modified-release tablets (2mg) Modified Release tablets (1mg and 5mg) Oral solution, 1mg/1ml, alcohol free, low in propylene glycol and sorbitol*

Is an existing formulation of this product already in the formulary? Yes ☒ / No ☐
If yes, you do not need to complete evidence for efficacy or safety and tolerability (but see guidance notes)

BNSSG formulary acceptance for melatonin TLS is amber - 3 months:
Paediatrics:

For children with neurodevelopmental disorder/disability with intrinsic sleep disorder (difficulty getting to sleep or remaining asleep) who have exhausted all behavioural sleep hygiene options

Not for use in ADHD or autism or learning disabilities (see SCP).

Adults:

For Adults with Learning Disabilities and sleep disturbance who also have a co-morbid mental illness (for example Depression, Mania, Psychosis, Dementia etc.) OR disorder (for example Autism or Autistic Spectrum, Anxiety Disorders, Adult ADHD etc.) as per shared care protocol

Licensed 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.

Slenyto® is indicated for the treatment of insomnia in children and adolescents aged 2-18 with Autism Spectrum Disorder (ASD) and / or Smith-Magenis syndrome, where sleep hygiene measures have been insufficient.

There are no licensed liquid preparations of melatonin currently available in the UK with the required composition of excipients. Therefore use of solid dose formulations (even off-label) would be trialled in preference to liquids as per MHRA recommendations.

C. Intended use	Applying clinician to complete
Define use of drug:	Define intended indication of drug: *Please also specify whether this is a licensed indication* 1) Off-label use for sleep disorder in patients with any of: a) Attention Deficit Hyperactivity Disorder (ADHD) b) Autism (Slenyto is licensed for this indication in 2-18 year olds) c) Learning Disabilities (LD) (or Intellectual Disabilities)
	Define intended cohort including starting criteria: *Adult/paed* Paediatric patients aged between 1-17 years for the conditions cited above. Adult patients aged 18 years and older for the conditions cited above. Adult patients with a learning disability occasionally require longer-term (years) treatment with melatonin. Circadian rhythm disorder: Not all patients included will have a circadian rhythm disorder. The cohort is a very diverse group, including some who do (e.g. ADHD related delayed sleep onset) and some who do not (e.g. LD syndrome specific abnormal melatonin secretion). Approximately 50% of people with a diagnosis of ADHD have a circadian rhythm disorder. Melatonin would still likely be a long-term treatment for this cohort. Specific cohort: As per our treatment plan and approach in general, non-medication measures would always be used initially. Some people respond very well to basic sleep hygiene, or more specialist environmental and behavioural strategies, some respond partially, and some not at all. Medication would usually only be offered to the group with severe sleep disorder (rather than severe ADHD, autism, LD). In adult ADHD, where treatment to manage ADHD symptoms is available, the initial approach is to treat ADHD, and only if sleep difficulties remain a problem following effective medication for ADHD core symptoms, would melatonin be considered.
	Dosage: <u>Starting dose</u>: The timing of administration should be adjusted relative to target onset of sleep time Adult: 2 mg once daily, 1-2 hours before bedtime and after food*, swallowed whole. Paediatric: 0.5-2mg dependent on age, before bedtime and after food <u>Dose titration</u>: As per clinical need. Usually an initial dose would be prescribed for 2 weeks then reviewed for effectiveness. Due to the diversity of patients within these cohorts, a constant trial period is not possible to define. Usual effective range is 0.5-6mg. In certain rare circumstances the dose can be increased up to a maximum dose of 10mg (this is the maximum dose seen in most trials for this cohort of patients and noted in the BNF).

The majority of patients are prescribed 2-6mg in LD services. Due to lack of electronic prescribing systems, and because FP10s are used to prescribe (i.e. not in-house pharmacies), an accurate average dose is difficult to ascertain. From EPACT, Adult ADHD services average a 3mg dose.

Ongoing treatment:
Melatonin usually required for longer periods in adults, i.e. more than a year. EPACT data suggests not many patients are stopped on melatonin. Organisations do not have electronic prescribing systems, so tracking is not possible.

In ADHD, for those with delayed sleep phase disorder who are unable to achieve a more permanent shift towards a normal sleep rhythm following life style changes and good sleep hygiene, it is likely to be an ongoing requirement, possibly used intermittently to counteract a tendency to returning to a delayed pattern.

In learning disabilities, many patients are likely to benefit from a long term steady approach to their sleep. However, the requirements of STOMP/STAMP are adhered to and medicines reviewed to ensure they remain in their ongoing best interest.

*This extends the duration of action of melatonin relative to an empty stomach (T_{max} 3 hours vs 45 mins), but reduces the peak plasma levels by 15%. This can be used to tailor the timing of melatonin against the patient's clinical needs.

Monitoring requirements:
Please specify relevant clinical investigations

Baseline tests - where appropriate

Baseline documentation (at least 2 weeks of sleep diaries) of disrupted sleep disturbance prior to commencing melatonin.

Subsequent tests - where appropriate

(Please indicate who it is intended will take responsibility for taking bloods and interpreting results)

Test	Frequency	Who by
No specific physiological tests		

Click here to enter text.

Define the review and stopping criteria:

- Insufficient benefit observed, despite careful dose titration, and trial at the maximum dose for 8 weeks.
- Reviewed with consideration to stop as part of annual LD/ADHD review.
- Unmitigable adverse effects - in this unlikely case, melatonin can be stopped without the need for gradual withdrawal.

Measure of effectiveness includes:

- Clinically significant improvement in sleep i.e. measured with sleep chart/record completed by patient

<table>
<tr><td></td><td>Threshold for stopping or drug holiday includes:
- Prolonged period (6 months) with much improved (normalised) sleep pattern.
- Improved Wellbeing and reduced Functional Impairment, as measured by WEMWBS and Weiss Functional Impairment rating scale
https://www.intermed.com/content/uploads/Weiss-Adult-ADHD-Rating-Scale.pdf
Post-application note
Applicant unable to advise how many patients are stopped, but it is thought most are continued longer term.</td></tr>
<tr><td>Number of people affected:</td><td>Anticipated number of patients likely to receive this treatment per year in whole of BNSSG i.e. primary and secondary care
Please liaise with your colleagues in other Trusts to obtain system wide estimates
<table>
<tr><th>Trust</th><th>Anticipated annual patient numbers</th></tr>
<tr><td>AWP</td><td>Estimated 185 patients CAMHS and 24 adult LD.</td></tr>
<tr><td>UHB</td><td>Nil</td></tr>
<tr><td>UHBW Children’s Hospital</td><td>Nil</td></tr>
<tr><td>NBT</td><td>Nil</td></tr>
<tr><td>WAHT</td><td>Nil</td></tr>
<tr><td>Primary Care</td><td>N/A</td></tr>
<tr><td>Sirona</td><td>27 in (Adult Learning Disabilities South Glos)
433 patients (Community Paediatrics based on prescription data over 12 months across all formulations of melatonin)</td></tr>
</table></td></tr>
<tr><td>Background of the application</td><td>Define the background and context of the application. Include supporting local guidelines if available.

Whilst disordered sleep is a common experience, often responding well to sleep hygiene measures, sleep disorder is diagnosed only in a minority of people. It is more common in autistic people, and those with intellectual disability, ADHD, specific syndromes and visual impairment.

The complications of sleep disorder can be significant and diverse, including challenging behaviour, drowsiness with an inability to undertake daytime activities, and in people with autism, mood disorders, gastrointestinal problems, poor social interaction, problems in communication and increased stereotypy (Rossignol and Frye, 2011). These problems can affect quality of life and risk placement breakdown. Behavioural interventions (including sleep hygiene) are the primary intervention, having a robust evidence base, and exogenous melatonin is recommended by the British Association for Psychopharmacology when medication is required.

Correctly timed, exogenous melatonin is able to act as a chronobiotic, shifting the timing of sleep onset. When non-pharmacological measures have failed initiating treatment with melatonin is a valuable tool in treating insomnia, particularly when used in conjunction with non-pharmacological methods. Behavioural therapies should be continued alongside medication as the combination has been found to be more effective than medication alone.</td></tr>
</table>

	Alternatives to using melatonin for sleep disorder include benzodiazepines, Z-drugs and sedating antihistamines. These medicines will often come with more problematic side-effects and dependence-forming potential than melatonin (which is not seen in melatonin use). Current AWP formulary accepts melatonin use for both its licensed indication, as well as in Learning Disability Services. See section G for supporting guidelines from other CCGs.
Define the current treatment pathway **State place in pathway for this intervention.**	Define the current treatment pathway for this indication and indicate where the proposed treatment would fit in: *Could it reduce/offset the use of another treatment/surgery?* 1st line: • Simple sleep hygiene measures 2nd line: • Individualised behavioural and environmental recommendations 3rd line: • **Trial of melatonin** - *Effective treatment of sleep disorder can prevent placement breakdown and family member / carer burnout* Medication review: •**Indication dependent** •Detailed in AWP guideline MG15 Melatonin prescribing for sleep disorders in adults with intellectual disability •Adult ADHD annual review •Detailed in Sirona letter to carers •Consider drug holiday if treatment efficacy is waning (in consultation with patinets and carers, 3-7 days for a drug holiday may prove sufficient to restore melatonin efficacy). Detail of reviews should be agreed when writing accompanying shared care guidance. AWP guidance MG15: MG15.docx

	Sirona have previously reviewed usage and made recommendations of how/when melatonin should be prescribed, detailed in the embedded documents below:  Letter to paed drs re melatonin Oct 19. Sirona letter to carers:  Melatonin Max 6mg Dose- October 2021 A sleep diary is used in some adult LD services, which is left intentionally basic so that care providers/family can adapt it to their needs (due to the diversity of people living with a learning disability.  Two week sleep record.xlsx ADHD services also use sleep diaries and quality of life questionnaires to measure effectiveness all attached in associated docs): • ADHD New Quality of Life Questionnaire  ADHD-new-quality-of-life-questionnair • Morning-Eveningness Questionnaire  Morning-Eveningness Questionnaire (r • Warwick Edinburgh Mental Well Being Scale  Warwick Edinburgh Mental Well Being S
Comparison with existing formulary therapies	Please detail what current formulary options are available, if any, and how this treatment differs Whilst there are alternative medications to treat sleep disorder in both adults and children, none of them are suitable for longer term prescribing. Melatonin is unique with its safety and tolerability profile. This is particularly important for autistic people, children and those with intellectual disability who may be less able than typically developed people to describe any side effects. Benzodiazepines and 'Z' drugs risk daytime sedation and the development of tolerance as well as dependence. Benzodiazepines used for sleep disorder and z-drugs are not licensed for use in children.

Anticipated health outcomes of using this drug	Please detail the anticipated health outcomes e.g. symptom control, prevention, cure and how this will be measured: • Sleep disorder in this group of patients will be effectively treated or significantly improved, resulting in fewer challenging behaviours and improved quality of life for the patient. This can be objectively measured by repeat of the 2 week sleep diary. • Improved quality of life for family members and carers, with a lower risk of burnout, and lower risk of break-down of the family home. • Improved production of appropriate amount of growth hormone secretion, leading to appropriate growth in children. • Immunoglobulins are also secreted protecting patients from infections. • Improved behaviour and concentrations during the daytime leading to better learning.
Implications of not using this treatment	Are patients at risk if this treatment is not used? If yes, how? The implications of long term poor sleep (for the person and for their carers) are well documented. Challenges to social care workers of finding placements if home or current placement break down. A consequence is that service users may require an out-of-area placement, which has significant direct financial cost implications, but most significantly an enormous impact on the emotional wellbeing of the individual, their family, their friends, their carers and their personal development, e.g. schooling, employment. With ADHD treating the primary condition can often be made significantly harder when a sleep disorder is present. Service users respond better to ADHD medicines when good sleep hygiene is established.
Patient choice	What are the views of the patients and patient groups? Feedback from individuals prescribed melatonin: "Melatonin helps me at night. It helps me to fall asleep and stay asleep and be calm, so I can be healthy for the next day. If I don't take it, I get stressed, I can't get to sleep until maybe midnight and I might cry because I don't know what to do." – child with ADHD aged 11. *"Dear Dr Hank,* *Melatonin for L allows him to feel calm and relaxed, without racing thoughts so he can fall asleep naturally and wake without feeling any side effects that occur with GP prescribed sleeping tablets. The same sleep we all require to allow us to function.* *I can't stress enough the importance within a family setting and the impact that everyone experiences. In the younger years before L had Melatonin I feared falling asleep at night as I couldn't ensure his safety and that of his younger brother. I had bolts on the kitchen door and bathroom with extra locks on exterior doors and everything locked away out of reach. Now he's an*

adult the priority has changed, his brother is working in an office which includes working from home sometimes. If L didn't have Melatonin at night he would keep everyone awake with constant banging, loud groans, wandering around the house and in and out of my bedroom talking to me with his random thoughts.

I hope my input can help in some way towards GP's prescribing Melatonin. All the best with the GP's and if I can help further then please let me know.

J"

Equity

Have other health economies (other CCGs or comparable* trusts) approved the use of this treatment for this indication?
** e.g. if a tertiary centre, have other tertiary centres approved this treatment for this indication. Please provide details.*

CCG	Indications	Status
Black Country ADHD services	Management of Poor Sleep in Children - learning and behavioural difficulties, autism, ADHD and sensory impairments (particularly visual).	With SCA
Cambridgeshire and Peterborough NHSFT	Sleep disorders in children with LD, ADHD or autism.	ADVICE Specialist Advice provided for primary care initiation.
York and Scarborough NHSFT	Sleep disorders in children - visual problems and LD, CP and autism and complex neurodisabilities.	With SCA
South East London JMF	Sleep disorders in children - visual impairment, CP, ADHD, autism and LD.	With SCA
Portsmouth and SE Hampshire PF	Sleep disorders in children	With SCA
Southampton Joint Formulary	Sleep disorders in children - neurodevelopment disability, autism, visual impairment or neuropsychiatric disorders and chronic sleep disturbance.	With SCA
Berkshire West NHSFTs	ASD, ADHD, LD	With SCA

Has this treatment been approved for use in other clinical areas?

Yes. Melatonin is on the BNSSG joint formulary for various other indications:
Adults: https://remedy.bnssgccg.nhs.uk/formulary-adult/chapters/4-central-nervous-system/47-sleep-disorders/
Children: https://remedy.bnssgccg.nhs.uk/formulary-paediatric/paediatric-chapters/4-nervous-system/46-sleep-disorders/

	This application represents an extension of some of these indications in both adults and children.
National/ International Guidance	What national or international guidance exists on the use of this drug? National guidelines: British Association of Psychopharmacology.
Local priorities	Where does this treatment rank in terms of other priorities within your specialty? High: Service: • Impact of repeat prescribing burden on team doctors for those already on treatment • The majority of paediatric patients have a sleep disorder associated with ADHD and ASD; a lot of resource is directed to assessment and repeat prescribing, when melatonin is safe for prescribing in primary care, by GPs Service users: • More timely initiation of safe prescribing for new referrals when there is a lower worry about prescribing being subsequently transferred to primary care. • ADHD patients may respond more effectively to their primary medicine(s) if sleep hygiene is addressed, meaning quicker stability, and improve patient flow of waiting list. • More timely supply of repeat prescriptions via primary care, as well as being able to receive medicines from just one prescriber (instead of two or more) • Continued secondary care prescribing means that melatonin is not always "visible" to clinicians in other sectors, e.g. during an emergency hospital admission, medicines prescribed in secondary care may not be detected as part of medicines reconciliation, leading to them being omitted and the inevitable consequences on patient care.
Who will prescribe it?	Any doctor ☐ Consultant only (secondary care only) / GPwSI ☐ Specialty Consultant teams only (Please list below) ☐ Specify team(s): Click here to enter text. Consultant initiation; GP under shared care protocol ☒ Non-Medical Prescriber under Consultant supervision ☒ Other (please state): Speciality doctors. Junior doctors under supervision

D. Evidence for efficacy	Applying clinician to complete

ESSENTIAL INFORMATION REQUIRED Provide a summary of the relevant clinical evidence and cost-effectiveness supporting this application, indicating the types of evidence available e.g. clinical trials, reviews, meta-analyses and also include any peer-support evidence e.g. Royal College guidance.

British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders: An update (2019)

- Melatonin is effective in treating delayed sleep phase syndrome (which is common in people with ADHD) and non-24-hour sleep rhythm disorder, especially in people who are blind.
- Melatonin reduces long sleep latency in children with sleep onset insomnia or delayed sleep phase syndrome and learning disability, autism and ADHD. The randomised controlled trial leading to the licensing of Slenyto demonstrated that this sustained release mini-pill was "well-tolerated, efficacious and safe". There were "clinically meaningful improvements in total sleep time, duration of uninterrupted sleep and sleep latency with corresponding behavioural improvements for the children, and improved quality of life measures in their parents".
- In terms of adults with intellectual disability, the importance of a detailed clinical assessment, considering all possible causes of sleep disturbance was emphasised, with first line environmental, behavioural and educational approaches recommended. "There is little evidence for effectiveness of sleep-promoting drugs, apart from melatonin."
- Prolonged release melatonin improves sleep onset latency and sleep quality in people over 55 years. Melatonin is recommended as the first line treatment.
- Melatonin was one of several medications recommended for pharmacological treatment of insomnia – in contrast to benzodiazepines and 'Z' drugs, "melatonin does not give rise to motor or memory effects".

International Expert Opinions and Recommendations on the Use of Melatonin in the Treatment of Insomnia and Circadian Sleep Disturbances in Adult Neuropsychiatric Disorders

In the absence of well-conducted trials, the administration of IR melatonin at sleep-promoting dose (2–6mg) before bedtime could be of interest to treat insomnia symptoms associated with ADHD.

In case of Delayed Shift Phase Sleep associated with ADHD, chronobiotic doses of IR melatonin (≤1 mg) should be proposed, e.g., 0.5 mg/d melatonin during 3 weeks starting 3 h before the individual DLMO and weekly advancing by 1 h to improve both the circadian rhythm disorder and ADHD symptoms.

Legend: IR, Immediate Release; DLMO, Dim Light Melatonin Onset

van Andel E et al 2021

Low doses of melatonin advances the circadian rhythm and reduces self-reported ADHD symptoms. Large numbers of adult ADHD patients have concurrent Delayed Sleep Phase Syndrome (DSPS). Melatonin plays an important role in the effective treatment of delayed sleep in patients with ADHD.

Please refer to section H Critical Appraisal as well, which was completed in conjunction with the applicants.

Please list the references below that support the application

Reference – List first author & title	Main points

1: Wilson, S. et al. 2019. Journal of Psychopharmacology. Vol 33(8). 923-947	See above
2: Palagini, L *et al* (2021). International Expert Opinions and Recommendations on the Use of Melatonin in the Treatment of Insomnia and Circadian Sleep Disturbances in Adult Neuropsychiatric Disorders. Frontiers in psychiatry, 12, 688890. https://doi.org/10.3389/fpsyt.2021.688890	An international consensus statement recommending the use of Melatonin for sleep onset insomnia and for delayed sleep phase disorder in ADHD in adults
3: van Andel E, Bijlenga D, Vogel SWN, Beekman ATF, Kooij JJS. Effects of chronotherapy on circadian rhythm and ADHD symptoms in adults with attention-deficit/hyperactivity disorder and delayed sleep phase syndrome: a randomized clinical trial. Chronobiol Int. 2021 Feb;38(2):260-269. doi: 10.1080/07420528.2020.1835943. Epub 2020 Oct 29. PMID: 33121289.	A placebo controlled study demonstrating the effectiveness of Melatonin in treating delayed sleep phase disorder in adults with ADHD.
4: Click here to enter text.	Click here to enter text.
5: Click here to enter text.	Click here to enter text.

E. Financial implications

Applying clinician to complete

What are the financial implications over and above existing expenditure of adopting this treatment?

Please note: the cost of the drug may differ depending on whether supplied by primary care (drug tariff price) compared to secondary care (e.g. contract price). Please consider both if the drug is intended to be prescribed in primary care. Discuss with pharmacy department if needed.

A) Cost of proposed new drug (See Appendix 1 for a more comprehensive breakdown of medication costs)
In the absence of concrete average dose data across the organisations, a dose of 4mg is used below. However, actual FP10 spend for the last 12 months (to May 2022) is used in the final column.

DT Price of Drug (original pack)	Cost per 28 days treatment (at average dose)	Cost per years treatment at average dose	Total cost per years treatment of cohort (using estimated BNSSG patient numbers provided in Part C)
£15.39/30 (Circadin mr tab 2mg)	£28.72	£374.38	£68,148 (all AWP FP10 spend for the relevant teams in last 12 months – based on actual spend not assumed dosage) £211,7520 (all Sirona FP10 spend in last 12 months)
£130/150ml (1mg/ml solution)	£97.06	£1265.25	£13,972 (all AWP FP10 spend for the relevant teams in last 12 months based on actual spend not assumed dosage)

			£5254 (Sirona Adults FP10 spend in last 12 months)
£41.20/60 Slenyto 1mg pr tab @2mg/day	£19.22	£250.63	£500 (all AWP FP10 spend for the relevant teams in last 12 months – actual spend, not assumed)
£103/30 Slenyto 5mg pr tab @5mg/day	£96.13	£1253.16	£2499 (all AWP FP10 spend for the relevant teams in last 12 months – actual spend, not assumed)
£0.69/ml (average cost) Kidmel (unlicensed) 1mg/ml solution @2mg/day No DT price available	£38.64	£503.70	AWP prescribe 1mg/ml licensed preparation. £52,1925 (Sirona Paeds FP10 spend in last 12 months)

B) Drug costs to be offset if any

C) Any other costs to be offset (e.g. staff time, surgery, care needs etc)

Senior doctor time undertaking repeat prescribing.
Care needs of service users if change of care setting can be avoided
Cost of deprescribing benzodiazepines and z-drugs if patients become dependent

Funding category (please tick as appropriate):

In PbR tariff *i.e. No additional funding from CCG therefore internal directorate financial agreement required.* ***Financial agreement required before the application can be considered***	☒
PbR excluded i.e. not NICE and/or NHSE approved *i.e. requires CCG funding*	☐
Primary Care	☐

F. Declaration of conflicts of interest - must be completed by applicant

Please list:

1. Any gifts or hospitality received from the manufacturer of the product concerned (exceeding value of £20) in the last year. Actual monetary value not required.
2. Presentations, advisory panels, consultancy work (including retainers), or written materials for which payment has been received from the product manufacturer.
3. Shares held in the company (where known).
4. Sponsorship of research, members of staff, equipment or other materials in your department, practice or clinical specialty funded by the product manufacturer.
5. Any other forms of benefit or relationships which could be classed as a potential conflict of interest

If Nil – Please state:

Dr Hank: Paid for giving a talk for Flynn Pharma (ADHD related) and has been a Flynn Pharma Advisory Board member on one occasion (ADHD related). The honoraria are channelled towards charitable causes.

Dr Leyland: Nil Dr Hosdurga: Nil
Signature of applicant: Click here to enter text. **Date:** 31.05.2022

Applications from secondary care: Please send completed application to Trust Pharmacists:
UHB – pharmacyMI@UHBristol.nhs.uk
NBT – Kimberley.jefferson@nbt.nhs.uk
WAHT – skarthauser@nhs.net
AWP- james.scott12@nhs.net
Applications from Primary Care: Please send completed applications to:
BNSSG Formulary Pharmacists bnssg.formulary@nhs.net

G. Critical Appraisal Part 1: review of clinical evidence and cost effectiveness **Trust/BNSSG Pharmacist to complete**		
Pharmacist undertaking appraisal	Acknowledgements Completion of this critical appraisal has been a collaborative piece of work, with amendments and updates made by teams listed below. Part 1 Michael Vaggas, Locum Pharmacist, AWP 'Formulary Drug Cost Comparisons', 'Other CCG Formulary sections', 'National Policy and Guidance', 'Local Guidance' sections - updated and revised by BNSSG Formulary Team Part 2 Originally completed by Michael Vaggas, Locum Pharmacist, AWP however an independent review by the BNSSG Clinical Effectiveness Team has been undertaken and incorporated into this section. 'Efficacy and Clinical effectiveness' and 'safety' sections- independent evidence review embedded into this section, information submitted by Michael Vaggas has been greyed out 'Cost effectiveness' section- revised by BNSSG Formulary Team Part 3 Reviewed in line with evidence team review and revised by BNSSG Formulary team	Date: 15/04/2022 – 30/08/2022

Licensed indications & dosage	Circadin® 2mg tablets 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. 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. Slenyto® 1mg and 5mg tablets Indicated for the treatment of insomnia in children and adolescents aged 2-18 with Autism Spectrum Disorder (ASD) and / or Smith-Magenis syndrome, where sleep hygiene measures have been insufficient. The recommended starting dose is 2 mg of Slenyto. If an inadequate response has been observed, the dose should be increased to 5 mg, with a maximal dose of 10 mg.

Formulary drug cost comparisons Include administrations costs, consumables etc.

Table 1: Cost analysis for Circadin 2mg MR tablets on an assumption that this brand is prescribed for the whole cohort. Circadin 2mg MR tablets is the most likely brand to be prescribed based on guidance from AWP (MG15), letter from Sirona (Oct 19) and based on actual spend on Melatonin from the last year.

MG15.docx

Letter to paed drs re melatonin Oct 19

Circadin 2mg MR tablets	Cost per original pack £15.39 (30 tablets)[1]			
	Cost per daily dose	**Cost per 28 days supply per patient**	**Cost per one year's supply per patient**	***Cost per one year's supply for BNSSG cohort (n = 669)***
2mg daily	£0.51	£14.28	£186.15	£124,534.35
4mg daily	£1.02	£28.56	£372.30	£249,068.70
6mg daily	£1.53	£42.84	£558.45	£373,603.50
Typical dose range 2-6mg daily				**£124,534.35 - £373,603.50**
Most common dose 4mg daily				**£249,068.70**

[1] Patent expiry of Circadin and Slenyto expected on 12.08.2022 (unless patent extension approved), which is expected to lead to a drop in acquisition price. Costs calculated based on August 2022 Drug Tariff prices.

Table 2: The applicant provided actual spend on Circadin 2mg MR tablets in the last 12 months for AWP and Sirona. This was compared to the predicted spend based on

the patient numbers and average dose provided in the application, which corroborates the figures provided.

Circadin 2mg MR tablets	AWP PREDICTED	AWP ACTUAL	SIRONA PREDICTED	SIRONA ACTUAL
	Cost per one year's supply for predicted AWP cohort (***n* = 209**)	Compared to all AWP FP10 spend for the relevant teams in last 12 months	Cost per one year's supply for predicted Sirona cohort (***n* = 460**)	Compared to all Sirona FP10 spend for the relevant teams in last 12 months
2mg daily	£38,905.35	£68,148.00	£85,629.00	£211,752.00
4mg daily	£77,810.70		£171,258.00	
6mg daily	£116,716.19		£256,887.30	

Table 3: Cost analysis for Slenyto. Slenyto is indicated for the treatment of insomnia in children and adolescents aged 2-18 with Autism Spectrum Disorder (ASD) and / or Smith-Magenis syndrome, where sleep hygiene measures have been insufficient, whereas Circadin is licensed as monotherapy for the short-term treatment of primary insomnia characterised by poor quality of sleep in patients who are aged 55 or over.

Therefore, patients with ASD may be offered Slenyto as the available licensed product for this indication. Unfortunately, the proportion of children and adolescents aged 2-18 with ASD within the cohort included in this application is unknown.

Circadin is more cost effective than Slenyto, costing £1.02 for 4mg per day vs £2.75 for 4mg per day. The table below demonstrates the significant cost impact if Slenyto was available to the wider cohort.

Slenyto 1mg MR tablets	Cost per original pack £41.20 (60 tablets)[1]			
	Cost per daily dose	Cost per 28 days supply per patient	Cost per one year's supply per patient	*Cost per one year's supply for BNSSG cohort (n = 669)*
2mg daily	£1.37	£38.45	£500.05	£334,533.45
4mg daily	£2.75	£77.00	£1,003.75	£671,508.75
6mg daily[2]	£4.11	£115.08	£1,500.15	£1,003,600.30
	Cost per original pack £103.00 (30 tablets)[1]			

Slenyto 5mg MR tablets	Cost per daily dose	Cost per 28 days supply per patient	Cost per one year's supply per patient	*Cost per one year's supply for BNSSG cohort (n = 669)*
5mg daily	£3.43	£96.13	£1,251.95	£837,554.50
6mg daily[3]	£4.12	£115.22	£1,503.80	£1,006,042.20
Typical dose range 2-6mg daily				£334,533.45 - £1,006,042.20
Most common dose 4mg daily				**£671,508.75**

[1] Patent expiry of Circadin and Slenyto expected on 12.08.2022 (unless patent extension approved), which is expected to lead to a drop in acquisition price. Costs calculated based on August 2022 Drug Tariff prices.

[2] 6mg daily dosing costed two ways - 1 of 2: Slenyto 1mg MR tablet x 6

[3] 6mg daily dosing costed two ways - 2 of 2: Slenyto 5mg MR tablet x 1 plus Slenyto 1mg MR tablet

[4] Slenyto 1mg MR tablet x 6 is marginally more cost effective than 5mg + 1mg strength to achieve 6mg daily dose, costing £2,441.90 less per year for BNSSG cohort.

Table 4: Cost analysis for melatonin liquid. According to AWP guidance, the unlicensed melatonin liquid is third line patients who can only tolerate liquid medicines. Sirona states that melatonin liquid should only be used as a last resort. Melatonin liquid is considerably more expensive than the tablet formulations. It is unknown what proportion of patients would be offered a liquid formulation. The table below demonstrates the significant cost impact of melatonin liquid for the whole cohort.

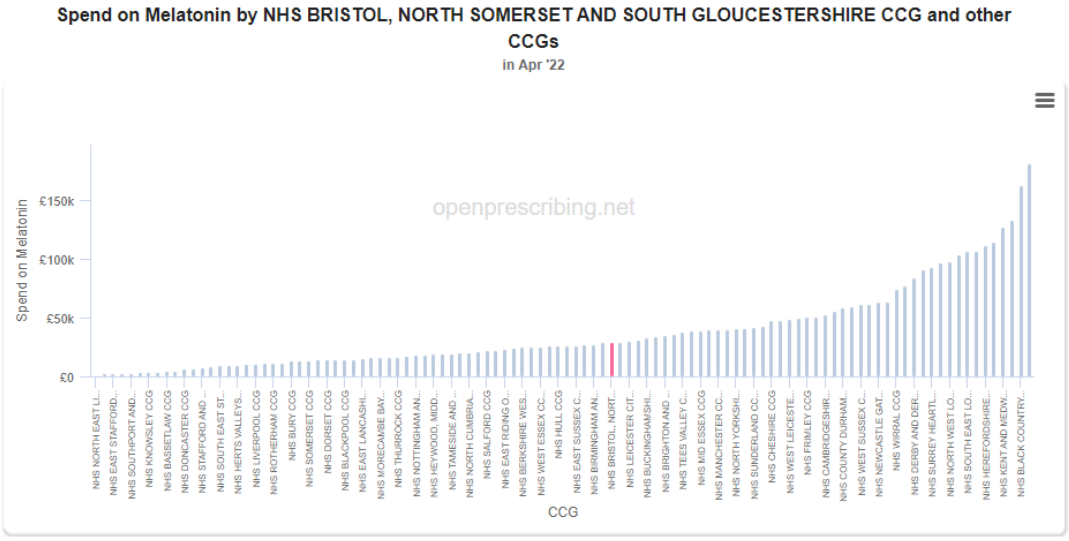
Kidmel 1mg/1ml oral solution (unlicensed)	Cost per original pack not available. No DT price. Average cost per mL = £0.69/mL			
	Cost per daily dose	Cost per 28 days supply per patient	Cost per one year's supply per patient	*Cost per one year's supply for BNSSG cohort (n = 669)*
2mg daily	£1.38	£38.64	£503.70	£336,975.30
4mg daily	£2.76	£77.28	£1,007.40	£673,950.60
6mg daily	£4.14	£115.92	£1,511.10	£1,010,925.90

Melatonin 1mg/1ml oral solution (licensed)	Cost per original pack £146.45 for 150mLs = £0.98/mL			
	Cost per daily dose	Cost per 28 days supply per patient	Cost per one year's supply per patient	*Cost per one year's supply for BNSSG cohort (n = 669)*
2mg daily	£1.96	£54.88	£715.40	£478,602.60
4mg daily	£3.92	£109.76	£1,430.80	£957,205.20
6mg daily	£5.88	£164.64	£2,146.20	£1,435,807.80

Existing melatonin prescribing in BNSSG Primary Care

According to EMIS data, there are 46,659 patients with a clinical code for ADHD, autism or learning disabilities. 739 patients are currently prescribed melatonin i.e. 1.06% of the ADHD, ASD, LD population.

In the last 12 months, BNSSG CCG spent £367,277 (9,192 items) on melatonin, which is approximately middle of the range comparing to other CCGs spend on melatonin. Note, it is not possible to extract details on formulary or non-formulary indications, dose or duration. This represents the existing overall spend on melatonin in primary care over a 12 month period.



This expenditure is in addition to the spend by AWP and Sirona which accounts for an estimated *additional* £335,191.50.

Current spend is across primary care, AWP and Sirona is approximately **£702,468.50.**

Other formulary drugs	DT Price of Drug (original pack)	Cost per 28 days treatment (at average dose)	Cost per years treatment at stated dose	Cost per years treatment at average dose	Cost per years treatment of cohort (estimated pt. numbers given in Part C)
Temazepam 10mg tablets (@5mg/day)	£1.20/28	£1.20	£15.64	£15.64	£10,463
Temazepam 10mg/5ml solution SF (@5mg/day)	£183.28/ 300ml	£42.77	£557.54	£557.54	£372,994
Promethazine HCL 10mg tab @10mg/day	£3.95/56	£1.98	£25.81	£25.81	£17,266
Promethazine HCL 25mg tab @25mg/day	£7.20/56	£3.60	£23.46	£46.92	£31,395
Zolpidem 5mg tabs (@5mg/day)	£1.71/28	£1.71	£22.29	£22.29	£14,913
Zolpidem 10mg tabs (@5mg/day)	£1.43/28	£1.43	£18.64	£18.64	£12,470
Zopiclone 3.75mg tabs (@3.75mg/day)	£0.94/28	£0.94	£12.25	£12.25	£8,198
Zopiclone 7.5mg tabs (@7.5mg/day)	£0.96/28	£0.96	£12.51	£12.51	£8,372

Due to the variable dosing for melatonin, it is not possible to perform a direct comparison of costs.
Number of patients here uses total numbers in part C.

Risk Management Issues: *e.g. training issues & storage requirements*	Patient education relating to risk of falls, cognitive impairment, dependence and withdrawal symptoms – however please refer to safety section below.
Patent expiry ***Please indicate if the new drug or any alternative(s) have a patent expiry within the next 18 months***	European Patent Office patent expiry of Circadin® and Slenyto® on 12.08.2022 (unless patent extension approved).
National policy and guidance	**National Institute for Health and Care Excellence (NICE) including NICE Evidence Summary: new medicines** Guidance: Challenging behaviour and learning disabilities: prevention and interventions for people with learning disabilities whose behaviour challenges [NG11]: Date: 29/05/2015

	"If medication is needed to aid sleep, consider melatonin. In May 2015, this was an off-label use of melatonin in people aged 55 years and under." (Section 1.1.12). NICE offers no recommendations relating to specific products.
	Scottish Medicines Consortium (SMC) Guidance: January 2021 decisions news release Date: 18/01/2021 Slenyto® was not recommended as the evidence provided by the company was not strong enough to satisfy the committee that it offers value for money to NHS Scotland. Circadin® was not recommended or use within NHS Scotland, as "The holder of the marketing authorisation [for Circadin] has not made a submission to SMC regarding this product in this indication."
	All Wales Medicines Strategy Group (AWMSG) Guidance: Final recommendation Date: 10/03/2021 Melatonin (Slenyto®) is recommended as an option for use within NHS Wales for the treatment of insomnia in children and adolescents aged 2 to 18 years with autism spectrum disorder and/or Smith-Magenis syndrome, where sleep hygiene measures have been insufficient. Use is conditional on access/contract price equivalency to the Wales Patient Access Scheme. Circadin® is recommended within Wales for use within its licensed indications. No application appears to have been made for off-label use of Circadin in children.
Other regional/national / local policy and guidance	Please list details of NHS policies and guidelines in other areas/regions Use of melatonin for sleep disorders in children is widespread amongst acute Trusts and JFCs, and many produce Patient Information Leaflets to support the same. Examples of patient information leaflets include Hull University Teaching Hospitals. Examples of guidance include North Central London JFC, Shropshire Community Health NHST, Pan Mersey APC, South East London IMOC, Derbyshire JAPC
Other CCG Formularies	29 CCG Formularies were reviewed to see whether the indications of ASD, ADHD or learning disabilities were specifically listed and what the traffic light statuses were. ASD 18 CCGs include melatonin on the formulary for ASD. Of these, 5 CCGs include melatonin for adults with a shared care status (with 1 specifying unlicensed specials are considered red). 17 CCGs include melatonin for paediatrics, 16 as shared care, 1 as red. ADHD 13 CCGs include melatonin for ADHD. 6 CCGs include melatonin for ADHD in adults and of these, 5 CCGs classify this as shared care (with 1 specifying unlicensed specials are red) and 1 CCG red. For paediatrics, 11 CCGs have a shared care status

(with 1 CCG specifying unlicensed specials are red) and 2 CCGs having a red status, noting some CCGs were also red but this is less clear within merged CCG formularies.

LD

10 CCGs include melatonin for learning disabilities on their formularies. Of these, 5 CCGs include melatonin for adults: 4 as shared care, 1 red (with 1 specify unlicensed specials are red). 11 CCGs include melatonin for children: 10 shared care and 1 red.

Neurological behaviour/development- noting the definitions of these descriptions may vary and are not clear on each formulary

10 CCGs also include melatonin for neurological behavioural problems: 2 CCGs for adults, 10 CCGs for paediatrics, all shared care.

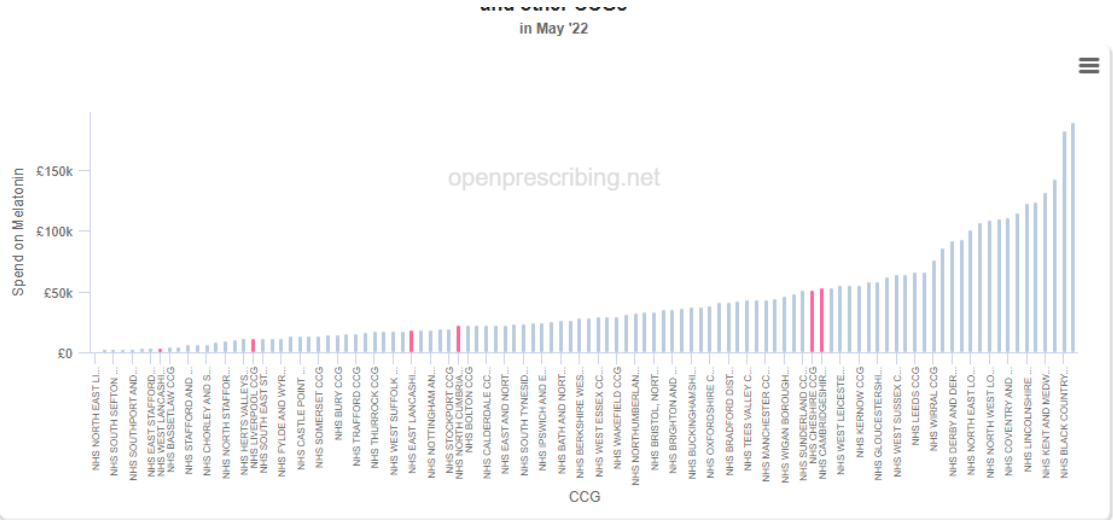
Openprescribing was used to establish whether CCGs with more indications listed on the formulary were higher prescribers. Unfortunately due to the formation of ICBs in July 2022, it is difficult to establish whether some of the CCGs had these indications included prior to this.

Pan Mersey ICB (including Cheshire and Liverpool) list ADHD, ASD, LD for adults and paeds.

Lancashire and south Cumbria (including East, West Lancashire and North Cumbria)- list ADHD, LD for adults and paeds and ASD paeds

Cambridgeshire and Peterborough -paeds for all 3 but not adults.

Spend appears to be scattered, and does not correlate with higher spending, however other indications may be responsible for higher spending (e.g general insomnia)



Reference Open Prescribing : Analyse | OpenPrescribing

	For a full breakdown of prescribing amongst the 29 CCGs, please refer to document. Formulary searchesv2.xlsx
Professional peer-support guidance e.g. Royal Colleges	**British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders: An update (2019)** British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders: An update (bap.org.uk) Melatonin improves sleep in children with ASDs (A). Melatonin administration can be used to advance sleep onset to normal values in children with ADHD who are not on stimulant medication (B). Melatonin reduces long sleep latency (following appropriate behavioural interventions) in children with sleep onset insomnia or delayed sleep phase syndrome and learning difficulties, autism and attention deficit hyperactivity disorder Several healthcare publications and groups recognise the off-label/unlicensed use of melatonin for insomnia in patients with learning disabilities and behaviour that challenges, even though it is not licensed for this indication: The BNFC, which states that “Melatonin is used for insomnia in patients with learning disabilities and behaviour that challenges, but is not licensed for this indication. Melatonin is used for sleep onset insomnia and delayed sleep phase syndrome, but is not licensed for these indications”. *Medicines for Children* produce a PIL to support the use of melatonin products in sleep disorders, and the wider NHS also recognises its use in children.
Current/future research	Please detail any known current or planned clinical trials, extension studies etc. Melatonin research has been called for, or is actively pursued in the following areas: • Bipolar Disorder (meta-analysis) • Alzheimer’s disease • Adjunctive treatment in schizophrenia • Effect of pharmacokinetics of different melatonin formulations on sleep disorders. • Pharmacokinetics of melatonin in ASD • Specific neurological disorders - head injury/retinitis pigmentosa • Sleep quality in ICU patients • Alcohol Use Disorder patients with sleeping problems • Sleep profiles in breast cancer patients

	• Haemodialysis patients - non-dipping BP and reduction in oxidative stress • Anti-inflammatory treatment of ulcerative colitis
References	**All Wales** Therapeutics and Toxicology Centre: melatonin (Slenyto®), melatonin (Circadin®) **BNFC**: Melatonin **CMS** Law-Now™: Patents Court refuses to grant interim injunction in pharmaceutical patents case. (Accessed 22.03.22) **Duan** C, Jenkins ZM, Castle D. Therapeutic use of melatonin in schizophrenia: A systematic review. World J Psychiatr 2021; 11(8): 463-476 **Electronic Medicines Compendium**: Circadin. Accessed 07.04.2022 **Gandolfi**, J.V., *et al.* The Effects of Melatonin Supplementation on Sleep Quality and Assessment of the Serum Melatonin in ICU Patients: A Randomized Controlled Trial, Critical Care Medicine: December 2020 - Volume 48 - Issue 12 - p e1286-e1293 **Gendy**, M.N.S., *et al.* Melatonin for Treatment-Seeking Alcohol Use Disorder patients with sleeping problems: A randomized clinical pilot trial. *Sci Rep***10,** 8739 (2020). **Kayumov** L, Zhdanova IV, Shapiro CM. Melatonin, sleep, and circadian rhythm disorders. Seminars in Clinical Neuropsychiatry. 2000 Jan;5(1):44-55. PMID: 10704537. **Lalanne** S*et al.* From Pharmacokinetics to Clinical Use in Autism Spectrum Disorder. *International Journal of Molecular Sciences*. 2021; 22(3):1490. **McGowan**, N.M. *et al*. Hypnotic and Melatonin/Melatonin-Receptor Agonist Treatment in Bipolar Disorder: A **Moroni**, Irene *et al.* Pharmacokinetics of exogenous melatonin in relation to formulation, and effects on sleep: A systematic review, Sleep Medicine Reviews, Volume 57, 2021, 101431, ISSN 1087-0792 **Roy**, Jaydeep, *et al.* Role of melatonin in Alzheimer's disease: From preclinical studies to novel melatonin-based therapies, Frontiers in Neuroendocrinology, Volume 65, 2022, 100986, ISSN 0091-3022. Systematic Review and Meta-Analysis. CNS Drugs (2022) **Russcher**, M., *et al*. The role of melatonin treatment in chronic kidney disease. Frontiers in Bioscience 17, 2644-2656, June 1, 2012 **NHS**: Melatonin for sleep problems **NICE** guideline [NG11]: Challenging behaviour and learning disabilities: prevention and interventions for people with learning disabilities whose behaviour challenges. Published: 29 May 2015 **Scottish Medicines Consortium** (SMC): January 2021 decisions news release **Terry**, P.D., *et al.* Melatonin and Ulcerative Colitis: Evidence, Biological Mechanisms, and Future Research, *Inflammatory Bowel Diseases*, Volume 15, Issue 1, 1 January 2009, Pages 134–140. Veriton Pharma: Data sheet Kidmel Melatonin 1mg in 1ml oral solution (requested) **Zaki**, Nevin Fw et al. "Depressive Symptoms, Sleep Profiles and Serum Melatonin Levels in a Sample of Breast Cancer Patients." Nature and science of sleep vol. 12 135-149. 13 Feb. 2020.

Part 2 to be completed in the absence of a NICE evidence summary for a new medicine.
The BNSSG Clinical Effectiveness Team have completed an independent evidence review for use of melatonin for ADHD, ASD and LD. Readers should review this document when considering 'Efficacy and clinical effectiveness' and 'Safety', sections below.
The original information submitted by AWP has been greyed out.

Melatonin Use in ADHD LD ASD FINAL

H. Critical Appraisal Part 2: clinical evidence and cost effectiveness **Trust/BNSSG Pharmacist to complete**	
Efficacy and clinical effectiveness	Summary of clinical evidence (please give an overview of the clinical evidence and detail the outcomes, strengths and limitations) Melatonin Use in ADHD LD ASD FINAL Additional information provided by AWP: McDonagh, Holmes and Hsu (2019) reviewed 19 RCTs of melatonin supplements[1] that included a total of 1,021 children of 'good' or 'fair' quality trials. The purpose was to systematically review the evidence on the efficacy and adverse effects of pharmacologic treatments for children and adolescents with sleep disorders Most of the studies were small (n=8-160), and all were relatively brief (1 to 13 weeks). The data showed that overall melatonin significantly improved outcomes: • Sleep Onset Latency (SOL: median 28 minutes; range 11-51 minutes) o Children with ASD fell asleep 37 minutes earlier. o Children with ADHD fell asleep 20 minutes earlier. o Children with chronic sleep-onset insomnia fell asleep 24 minutes earlier. • Total Sleep Time (TST: median 33 minutes; range 14-68 minutes) o Children with ASD slept 48 minutes longer. o Children with ADHD slept 33 minutes longer. o Children with chronic sleep-onset insomnia slept 25 minutes longer. • Wake Time After Sleep Onset (WASO: range 12-43 minutes) No improvement was seen in the number of awakenings per night (range 0-2.7). These findings show that melatonin was useful in improving short-term sleep outcomes in ASD, ADHD and SOL. The magnitude of effect was smaller in older children and adolescents. The authors note that the importance of the improvements to sleep in terms of functional or behavioural outcomes is not clear. It is acknowledged that it is not clear whether statistically significant improvements to sleep are clinically significant. It is noted that there is a lack of consistency in measurement of outcomes. Other limitations include the heterogeneity of studies.

	It has also been found that prolonged release melatonin is most useful in increasing TST, whereas immediate release melatonin is most beneficial in reducing SOL. PrescQIPP (Table 3): Recognises (lists) the off-label uses of melatonin, including: • Sleep disorders in ADHD without a concomitant disorder of ASD. • Circadin® use in patients <55 years or Slenyto® used in patients <2 years or >18 years and within their licensed indications. • Tablets (p/r) crushed and used for licensed indications. • Doses greater than those licensed: Circadin® >2mg, Slenyto® >10mg, melatonin 1mg/ ml oral solution >6mg. For Learning Disabilities, most of the studies were uncontrolled and the few controlled trials available were of small size. However, available data suggest similar findings to the indications mentioned above - melatonin appears effective in reducing SOL and TST, but ineffective in improving night-time awakenings. The consensus view of the British Association for Psychopharmacology in the treatment of adults with LD state that 'There is little evidence for effectiveness of sleep-promoting drugs, apart from melatonin, referring to a meta-analysis (Braam et al, 2009) (p941).' For patients with swallowing difficulties, or with PEG tubes inserted, the current NEWT guidelines state that "Circadin® is a modified-release tablet, and is not licensed to be given through enteral feeding tubes. However the manufacturers state that if necessary it can be crushed (note - this would change it from a modified-release tablet to an immediate-release one) and mixed in 15-30mL of water for administration through enteral feeding tubes. The tube should be flushed well after administration." [1] In the USA, melatonin is not licenced as a medicine by the FDA, Food and Drug Administration but is retailed as a dietary supplement. As a result, research in the USA is based on supplements. [2] The prevalence of sleep disturbance in children and adolescents with ASD ranges from 30%–53% and up to 70% in those with ADHD. If untreated, such sleep disturbances can negatively impact children, adolescents, and adults. Brand and Kirov (2011) have stated that "restoring sleep is strongly associated with a better physical, cognitive, and psychological well-being. By contrast, poor or disordered sleep is related to impairment of cognitive and psychological functioning and worsened physical health."
Safety	Please see Evidence Team's evidence review: Melatonin Use in ADHD LD ASD FINAL **General Safety** Melatonin is generally well tolerated, with no reports of any very common or common adverse drug reaction (ADRs), or reports of patients experiencing tolerance, dependence or withdrawal symptoms within Circadin's SmPC. A substantial body of evidence all

corroborate melatonin's safety profile across multiple products (Gringas, Braam, Coppola, Appleton and Malow.)

Circadin's SmPC (UK) states that in combined clinical trial and post-marketing data, ADRs rates were 9.5% (and 7.4% for placebo, producing a relative risk ratio of 1.3). It also states that melatonin:

- Should be avoided in hepatic impairment, autoimmune disease (no safety data), pregnancy, breastfeeding and in women planning a pregnancy, children under 1 year of age and co-administration of fluvoxamine (levels markedly increased).
- Used with caution in renal impairment (no safety data), and the elderly (higher AUC and C_{max} levels), driving and using machines (residual drowsiness).
- In overdose will cause drowsiness. Clearance of the active substance is expected within 12 hours after ingestion. No special treatment is required.
- Is metabolised by CYP1A enzymes – caution in coadministration of quinolones, oestrogens, carbamazepine, rifampicin, fluvoxamine and alcohol – (reduced effectiveness of Circadin on sleep).
- The m/r tablets contain lactose - patients with rare hereditary problems of galactose intolerance, the LAPP lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Falls, cognitive impairment, dependence and withdrawal

The previous body of evidence seems to conflict with NICE melatonin CKS which states that the risks associated with hypnotics, such as "falls, cognitive impairment, dependence and withdrawal symptoms, are well recognised. Be aware that recent data also suggest that risks such as falls are associated with melatonin" [NICE 2021]. This evidence was based on NICE KTT6 (2019), but the source of this data was not transparent, and in any case has since been withdrawn.

However, the EMA did NOT mention falls, dependence or withdrawal symptoms in relation to melatonin. It did mention cognitive impairment (single dose toxicity) at 'even higher doses' (see 2.7.3), but did NOT expect this to occur at '5mg melatonin (maximum 0.42mg/kg)'. Again, it is not clear whether these observations were derived from humans, or what the evidence base for this evidence was as it was not referenced.

The EMA also reports that comparing the rate of patients with ADRs per 100 patient weeks, the rate was higher for placebo than Circadin, and that the most common ADRs were headache, nasopharyngitis, back pain, and arthralgia, which matched placebo treated groups. Appleton and Malow found the same.

Arthralgia, headaches, infection and pain.

The BNF lists 'Arthralgia; headaches; increased risk of infection; pain' and either very common or common ADRs for melatonin. These ADRs are NOT found in the list of ADRs stated in the SmPC for Circadin, but rather taken from a quotation from the same which states that these ADRs were from a "MedDRA definition, in both the Circadin and placebo treated groups." In short, these ADRS were no more frequent for the placebo treated groups, as they were for melatonin. The source for the MedDRA data could not be traced.

Alternative sedatives

In comparison to alternatives to melatonin in the treatment of this indication, melatonin has a highly favourable reward:risk benefit, as alternative medications are indeed known to have high levels of confusion, sedation, falls and withdrawal risks. Such alternatives include benzodiazepines (BDZ) and BDZ receptor agonists (such as zopiclone). These alternatives are well known to be potentially inappropriate medication (PIMs), and are included in the STOPP/START criteria for medicines prescribed in many elderly patients (65+ years). These criteria are outlined in NHSE's *Toolkit for general practice in supporting older people living with frailty* documentation, which highlights the ADRs involved in using the following medication in elderly patients:

Medication class	Common indication	Adverse Drug Reactions
Benzodiazepines	Panic attack sedation and insomnia	Prolonged sedation, confusion, impaired balance, falls. Sedative, may cause reduced sensorium, impair balance
Neuroleptics >1 month (haloperidol, risperidone etc)	hypnotics	Confusion, hypotension, extrapyramidal side effects, falls. Gait dyspraxia, parkinsonism.
Anticholinergics (Procyclidine, orphenadrine, trihexyphenidyl)	To treat extra-pyramidal side- effects of neuroleptics	Anticholinergic toxicity
Old antihistamines (cyclizine, chlorpheniramine, alimemazine etc)	Sedation	Sedation & anti-cholinergic side effects

While not directly relevant to this application, this does highlight the risks associated with alternative options in those patients of advancing years with the included diagnoses, and a sleep disorder.

Growth and Puberty

A clinical trial using PedPRM (marketed as Slenyto®) recruited 80 children and adolescents with ASD for up to 2 years , and were given doses of 2,5 and 10mg melatonin nightly. They found melatonin to be safe with 'no observed detrimental effects on children's growth and pubertal development and no withdrawal or safety issues related to the use or discontinuation of the drug' (Malow, 2019). Van Geijlswijk found the same (n=51, up to 4.6 years, 0.3-10mg).

Cost-effectiveness

Melatonin has cost implications for the NHS health economy in terms of medicine spend. Some costs might be offset if alternative sedative medicines were to be prescribed instead which may be associated with adverse effects.
Circadin is the most cost effective formulation for melatonin.
The evidence review refers to a study in progress aiming to evaluate the cost-effectiveness of melatonin for stimulant treated children with ADHD and insomnia in Australia.

References	Summary
Appleton RE *et al*. The use of Melatonin in children with neurodevelopmental disorders and impaired sleep: a randomised, double-blind, placebo-controlled, parallel study (MENDS). Health Technol Assess. 2012;16(40):i-239. PMID: 23098680.	A paper supporting the use of melatonin in this indication, and suggesting more detailed research in specific formulations of melatonin.
Braam W, *et* al. Melatonin treatment in individuals with intellectual disability and chronic insomnia: a randomized placebo-controlled study. J Intellect Disabil Res. 2008 Mar;52(Pt 3):256-64. PMID: 18261024.	Research showing that melatonin treatment improves some aspects of chronic sleep disturbance in individuals with LD.
Chua, H.M. *et al* (2016). Dissolution of intact, divided and crushed Circadin tablets: Prolonged vs. Immediate release of melatonin. PMID: 34513608.	Research looking at some of the remarkable release profiles of whole, cut and crushed Circadin tablets.
Coppola G, *et al.* Melatonin in wake-sleep disorders in children, adolescents and young adults with mental retardation with or without epilepsy: a double-blind, cross-over, placebo-controlled trial. Brain Dev. 2004 Sep;26(6):373-6. PMID: 15275698.	Research supporting the use of melatonin in LD patients – data from a small trial.
Gringras,P. et al. Efficacy and Safety of Paediatric Prolonged – Release Melatonin for Insomnia in Children with Autism Spectrum Disorder. J Am Acad Child Adolesc Psychiatry. 2017;56(11):948- 95	Clinical trial data demonstrating the safety of melatonin over a 13 week period.
Gringras P *et al.* Melatonin for sleep problems in children with neurodevelopmental disorders: randomised double masked placebo controlled trial *BMJ* 2012; 345 :e6664	An open clinical trial showing efficacy of IR melatonin in reducing SOL in this population, with a modest effect in TST.
Gringras P. When to use drugs to help sleep. Arch Dis Child. 2008 Nov;93(11):976-81. Epub 2008 Aug 1. PMID: 18676436.	A paper looking at the role of behavioural therapies and medicines in treating insomnia in children.
Jan JE, et at. Clinical trials of controlled-release melatonin in children with sleep-wake cycle disorders. J Pineal Res. 2000 Aug;29(1):34-9. PMID: 10949538.	A small clinical trial looking at both the average effective dose of CR melatonin (5.7mg), and highlighting the benefit of CR tablets for TST, and IR forms being more helpful in treating SOL.
Malow BA, *et al.* Sleep, Growth, and Puberty After 2 Years of Prolonged-Release Melatonin in Children With Autism Spectrum Disorder. J Am Acad Child Adolesc Psychiatry. 2021 Feb;60(2):252-261.e3. Epub 2020 Jan 23. PMID: 31982581.	Clinical trial data demonstrating the safety of melatonin, including pubertal development, over a 2 year period.
Medicines for Children: Melatonin for Sleep Disorders (leaflet 2020).	Highly readable information leaflet for carers.
Medicines for Children: Melatonin for sleep disorders (Accessed 22.03.22)	Comprehensive yet plain English information from the NHS on melatonin and sleep disorders.
McDonagh MS, Holmes R, Hsu F. Pharmacologic Treatments for Sleep Disorders in Children: A Systematic Review. J Child Neurol. 2019 Apr;34(5):237-247. Epub 2019 Jan 23. PMID: 30674203.	An important meta-analysis of 22 trials data (2018) , summarising the generally supportive findings of melatonin use f melatonin in children.
MHRA: The supply of unlicensed medicinal products ("specials") (2014)	A useful guide from the MHRA in managing off-label and off-licence medicines.
NICE CKS: Melatonin. What issues should I be aware of when prescribing modified released melatonin? Last revised in March 2021	NICE guidance for using melatonin (includes a reference to falls, cognitive impairment, dependence and withdrawal symptoms in relation to melatonin).

Sack RL et al. Sleep-promoting effects of melatonin: at what dose, in whom, under what conditions, and by what mechanisms? Sleep 1997; 20:908–915.	A paper looking at the scientific mechanisms of action of melatonin (adjustment of correcting circadian phase abnormalities and/or by a modest direct soporific effect).
Sivertsen, B, *et al.* Sleep problems in children with autism spectrum problems: a longitudinal population-based study. Autism. 2012 Mar;16(2):139-50. Epub 2011 Apr 8. PMID: 21478225.	A large trial (n=3,700) looking at sleep problems in patients with ASD, highlighting the magnitude of this issue.
Riemann D, *et al* (2017). European guideline for the diagnosis and treatment of insomnia. *J Sleep Res* **26**(6), 675-700.	A pan-European guide to treating insomnia, with apparently contradictory recommendations relating to melatonin (2.9.2)
The Maudsley: Prescribing Guidelines in Psychiatry, 13th Ed.	A pivotal guide to psychiatry in general.
van Geijlswijk et al. Evaluation of sleep, puberty and mental health in children with long-term melatonin treatment for chronic idiopathic childhood sleep onset insomnia. Psychopharmacology (Berl). 2011 Jul;216(1):111-20. Epub 2011 Feb 22. PMID: 21340475.	A paper looking at any postulated interference of melatonin with puberty – it finds in favour of melatonin not causing any pubertal developmental problems.

I. Critical Appraisal Part 3: conclusion & recommendations	
Conclusion	Please summarise the critical appraisal using the JFG decision making criteria as below. **1.Patient safety** Studies found melatonin to be safe and well tolerated, with less risk associated with melatonin than other sedative medicine options. **2.Clinical effectiveness** When clinical trial data was pooled together in meta-analysis, statistically significant results were found showing an improvement of sleep latency and total sleep time. A pertinent meta-analysis by McDonagh et al (2019), concluded that for children and adolescents, Melatonin significantly improved sleep latency and duration, although the range of improvement in sleep latency varied between studies (11-51 minutes, median 28 minutes) and sleep duration improved by 14-68 minutes (median 33 minutes). It was reported within this meta-analysis that children with ASD improved the most compared to other neurodevelopmental disorders (sleep latency by 37 minutes and sleep duration by 48 minutes). Evidence for improvement was stronger for younger children than adolescents. However the Evidence team noted limitations with the study as measurements of awakenings or time spent awake after sleep onset were inconsistent with each other and varied from getting worse to improving significantly leaving little confidence in the trial's findings. A systematic review conducted by Salanitro (2022) concluded that melatonin improved sleep onset latency and total sleep time in adults across sleep disorders and across all disorders including ADHD/LD/ASD. There was no evidence that melatonin improved night awakenings. It is not clear whether the reported statistically significant improvements to sleep

	latency and total sleep time translate to clinically significant outcomes. Further studies are recommended to explore the effects of longer term use of melatonin and the impact of improvements to sleep on function, behaviour and improvement of condition. Further studies are also needed with a larger population size and use of a controlled environment to exclude bias. **3.Strength of evidence** Low quality- despite the volume of evidence and use of melatonin for nearly 30 years, the quality of studies were variable with studies often of low quality with limitations such as absence of large scale RCTs, smaller sample size; short duration (the majority are 13 weeks duration or less); subjective outcome measures and risk of bias (e.g. sleep diaries); lack of methodology detail; lack of reproducibility. The majority of evidence reviewed focussed on children, and studies did not routinely focus on ADHD, LD or ASD in isolation. The evidence review completed by the BNSSG evidence team focussed on available data from the 2020-2022 period only, however this included meta-analyses which included trials prior to this date range. **4.Cost effectiveness or resource impact** Current prescribing of melatonin already presents a substantial cost to the system of £702,468.50 per annum (£335,191.50 for AWP and Sirona combined and £367,277 by GP Practices). If the application for these additional indications were approved as shared care on the BNSSG Formulary, the costs of prescribing currently held with AWP and Sirona would shift to primary care. Prescription administration workload currently managed by AWP and Sirona would transfer to GP Practices, which may relieve pressure in those settings, but increase pressure in GP Practices. It is expected the majority of prescribing would be longer-term. **5.Place in therapy relative to available treatments** 3rd line, following non-pharmacological treatments. **6.National guidance and priorities** NICE guideline Challenging behaviour and learning disabilities NG11 includes melatonin to 'consider' if medication is needed, noting it's off-label use in patients aged under 55 years. Melatonin is recognised as an option by the British Association of Psychopharmacology for patients with LD, ASD and children with ADHD who are not on stimulant medication after behavioural strategies. **7.Local health priorities** Considered a high priority for local specialists who wish to make melatonin shared care for the indications ADHD, ASD and LD for both adult and paediatric patients. It is currently non-formulary for the majority of these patient cohorts, meaning potentially some prescribing occurs in primary care 'non formulary' and prescribing occurs within AWP and Sirona outside of formulary recommendations. **8.Equity of access**

	At a national level, the inclusion of melatonin on formularies varies greatly in terms of indications covered, traffic light status and whether it is included for adults or paediatrics or both. **Other considerations:** For cost effective prescribing: 1) First line use for all stated off-label conditions: Circadin m/r 2mg tablets. These may be titrated by halving the tablets if needed, and still maintain their prolonged release properties. 2) Second line: Circadin m/r 2mg tablets use in swallowing difficulties – halved or crushed with a spoon. 3) Third line: Slenyto tablets, where the small diameter (3mm) of the tablet is a significant aid for people with swallowing difficulties, who cannot manage crushing tablets effectively. 4) Fourth line: melatonin 1mg/1ml soluble solution that is alcohol free, low in propylene glycol and low in sorbitol (E.g. Martindale® or Kidmel® brands). For use in rare hereditary conditions of galactose intolerance, the LAPP lactase deficiency or glucose-galactose malabsorption. Also for use in people who cannot manage any solid dose form of medication, e.g. with a percutaneous endoscopic gastrostomy (PEG) tube.
Recommendation	Please state your recommendation for use of this drug in the BNSSG Joint Formulary. JFG to consider whether melatonin should be included on the formulary for use in ADHD, ASD and LD for both adult and paediatric populations and if so, where the prescribing is most appropriate.

Appendix 1

Comparator costs for melatonin sought in this application against alternative melatonin products

Product	Indication	Strength	Width	Excipients	Pack size	Pack DT price[1]	Cost/ 1mg dose	Cost ratio %	Single patient costs 28 days/Daily dose (usual range)										80 patient cost 28 days/Daily dose				AWP Rx[2]	AWP Rx[2]
	(abridged)	mg or mg/ml	mm		Tab, cap, or ml		(theor-etical)	Relative to Circadin	0.5 mg	1mg	2mg	3mg	4mg	5mg	6mg	7mg	8mg	9mg	10 mg	2mg	5mg	10mg		
Circadin m/r tablets	insomnia: 55Y+	2	8.1	80 mg lactose monohydrate	30	£15.39	£0.26	100%	£4	£7	£14	£22	£29	£36	£43	£50	£57	£65	£72	£1,149	£2,873	£5,746	468	70%
Slenyto p/r tablets (film-coated)	insomnia: 2-18Y with ASD/SM syndrome	1	3.0	8.32mg lactose	60	£41.20	£0.69	268%	£10	£19	£38	£58	£77	£96	£115	£135	£154	£173	£192	£3,076	£7,691	£15,381	0	0%
Slenyto p/r tablets (film-coated)	insomnia: 2-18Y with ASD/SM syndrome	5	3.0	8.86mg lactose	30	£103.00	£0.69	268%	£10	£19	£38	£58	£77	£96	£115	£135	£154	£173	£192	£3,076	£7,691	£15,381	0	0%
(Colonis) i/r Caps	Jet lag	3	13.6	Gelatin shell	30	£62.50	£0.69	271%	£10	£19	£39	£58	£78	£97	£117	£136	£156	£175	£194	£3,111	£7,778	£15,556	32	5%
Ceyesto i/r Tab (film-coated)	Jet lag	3	7.0	Lactose-free	30	£19.81	£0.22	86%	£3	£6	£12	£18	£25	£31	£37	£43	£49	£55	£62	£986	£2,465	£4,930	20	3%[4]
Syncrodin i/r Tab (film-coated)	Jet lag	3	7.5	Lactose-free	30	£19.81	£0.22	86%	£3	£6	£12	£18	£25	£31	£37	£43	£49	£55	£62	£986	£2,465	£4,930	0	0%
(Colonis) Solution	Jet lag	1	N/A	-PG[3] 151 mg/ml -Sorbitol 140mg/ml	150	£130.00[5]	£0.87	338%	£12	£24	£49	£73	£97	£121	£146	£170	£194	£218	£243	£3,883	£9,707	£19,413	0	0%
Kidmel Solution 200ml	N/A	1	N/A	-PG 52mg/ml -Sorbitol 0mg Alcohol free	150	£130.00 – price varies because it is an unlicensed special.	£0.87	338%	£12	£24	£49	£73	£97	£121	£146	£170	£194	£218	£243	£3,883	£9,707	£19,413	104	16%[4]
Martindale Solution 200ml	N/A	1	N/A	-PG49mg/ml -Sorbitol 0mg	150	£130.00	£0.87	338%	£12	£24	£49	£73	£97	£121	£146	£170	£194	£218	£243					

[1]Drug Tariff April 2022
[2]Annualised data -extrapolated from 6/12
[3]Propylene Glycol
[4]Brand unknown
AWP: 333 Rx in 6/12-some NF, total cost of £40k/6 months. Ave 56 Rx/month
[5]DT Category A - Drugs which are readily available.

National average Rx cost	Melatonin cost vs National Ave	Colour Coding
£44.11*	0-1X	
	1-1.9X	
	2-2.9X	
	>3x	
	Unviable dose	

Others (solid):	18	3%
Others (liquid):	24	4%
Totals:	666	100%

*Data kept on file.

Form Approved by the BNSSG JFG January 2020
Review: January 2022

Appendix 2

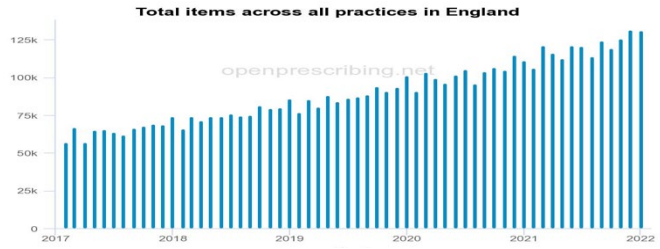
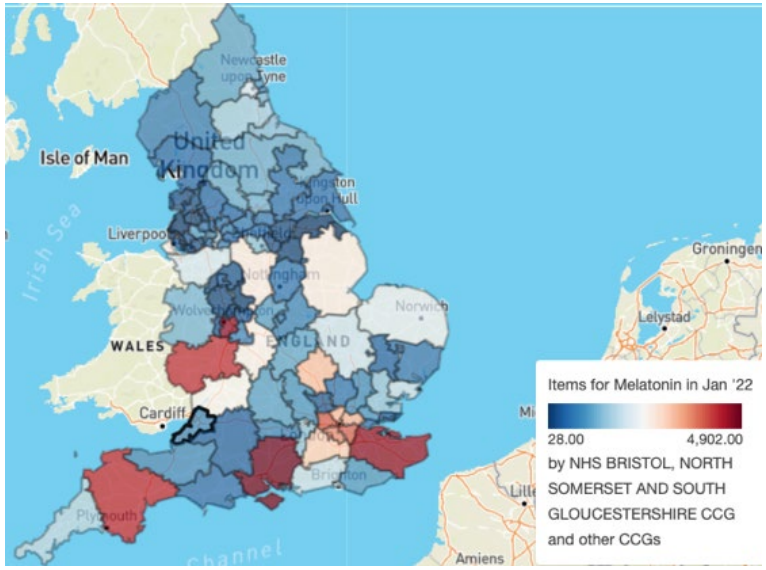


Table 1

Table 1* shows the total items prescribed for melatonin in the UK has risen from 57K in Feb 2017 to 131k in Jan 2022 (approximately a 50% increase pa.) During this period, 5.3M prescriptions were dispensed, costing £183M. This represents an average prescribing cost of a little under £35/item.

Table 2* shows melatonin prescribing spends for all CCGs in England for the 12 months up to January 2022. It shows that during this time BNSSG spent just under £24k, which is well below the mean average spend for CCGs of £49k pa. Put another way, the mean daily spend on melatonin for BNSSG is currently just under £66/day, in comparison with almost £79/day across all English CCGs.

This accompanying map* shows the number of items prescribed by region, illustrating a relatively modest spend by BNSSG on melatonin.



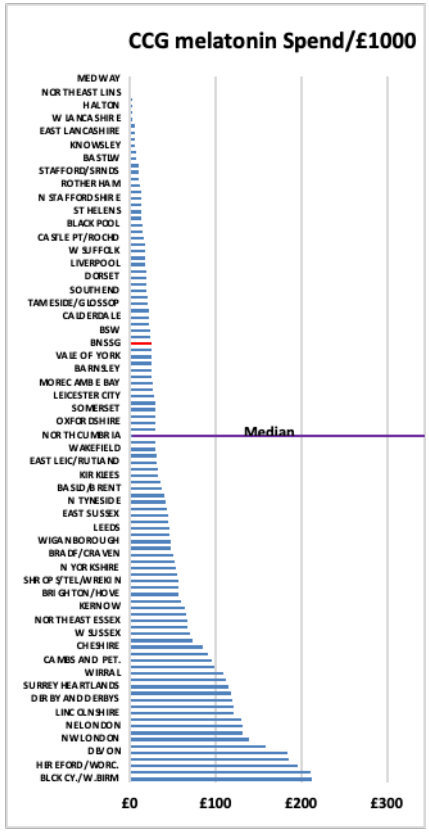


Table 2

*From OpenPrescribing.net, EBM DataLab, University of Oxford, 2020).

Form Approved by the BNSSG JFG January 2020
Review: January 2022

Bristol, North Somerset and South Gloucestershire Integrated Care Board

Use of Melatonin on sleep outcomes in ADHD / LD / ASD

Date: 10th August 2022

Author: Cathy Holloway

Introduction

The Medicines Optimisation team in Bristol, North Somerset, and South Gloucestershire Integrated Care Board (BNSSG ICB) are reviewing formulary indications for the use of melatonin, including its use for treating sleep disorders in patients with Attention-Deficit Hyperactivity Disorder (ADHD) / Learning Disability (LD) and Autism Spectrum Disorder (ASD).

The purpose of this report is to highlight findings and recent evidence to support formulary decision-making.

Points to note

This briefing presents the findings of a rapid, yet systematic, evidence search of several sources and provides some quality appraisal.

Key Points

- There has been extensive study into melatonin on sleep outcomes and focus on ADHD / LD / ASD since 1993 ***Tordjman et al***

- Despite the volume of clinical evidence there is a varying degree of evidence quality due to lack of methodology detail, limited study design and risk of bias with subjective measurement techniques e.g. relance on sleep diaries. There are limitations associated with these studies such as smaller sample size, few adverse effects, and shorter durations of study. Future studies can be warranted in the direction of a sizeable population, including the subjects of a wide variety of demographic, ethnic, and social backgrounds. ***Ashtar (2021)***

- Melatonin improved sleep onset latency and total sleep time in children/adolescents with neurodevelopmental disorders. Melatonin also improved and sleep onset latency and total

sleep time in adults with delayed sleep phase disorder. Future studies should explore effects in the longer-term use and the benefit of how useful the gains in sleep latency and duration are on function and behaviour ***Salanitro (systematic review 2022) / McDonagh et al (2019)***

- Some conflicting evidence as ***Salanitro (systematic review 2022)*** stated no evidence that melatonin improved night awakenings or shifted the DLMO in any of the analyses performed. ***Surman et al 2021*** stated Melatonin advanced DLMO by 1 hour and 28 minutes Placebo had no effect on DLMO within n= 51 ADHD cohort.

- Melatonin reduced in ADHD symptoms by 14% which returned to baseline post 2 weeks post-treatment. Further study needed on long term use. ***Surman et al 2021***

- Melatonin represents a well-validated treatment for sleep disorders in children with ASD but future clinical trials are necessary to examine therapeutic benefits of melatonin administration for autistic behavioural impairments based on dose-effect relationship studies. ***Lalanne et al (2021)***

- Melatonin was significantly better in improving sleep onset latency in adults across sleep disorders and across all disorders including ADHD / LD and ASD. ***Salanitro (systematic review 2022)***

Findings

There is an extensive volume of evidence relating to melatonin use in relation to sleep outcomes. The search was limited to papers with a focus on ASD, LD or ADHD from 2022-2020 to include the most recent and robust evidence given the short time frame of this review, however these systematic reviews do include studies throughout the 2000s.

Findings included, Systematic Reviews: 2 (including 34 RCTs), Registry Cohort Study: 2, Literature scoping: 3, Randomised Control Trial:1.

These have been summarised in Evidence Summaries, and the relevant findings have been highlighted under the following sub-headings: Patient Safety, Efficacy and Clinical Effectiveness, Strength of Evidence, Cost Effectiveness and National Guidance.

➢ Patient safety

No serious adverse effects were reported in any of the studies reviewed.

Ashtar (2021) reported that in clinical trials with melatonin revealed the attainable efficacy and acceptable safety.

McDonagh et al (2019) reported the authors report that there were no serious adverse events reported in the survey responses.

➢ Efficacy and clinical effectiveness

Salanitro (systematic review 2022) concluded that Melatonin significantly improved sleep onset latency and total sleep time, but not sleep awaking in children and adolescents with a variety of neurodevelopmental disorders.

- When considering significant meta-analytic results with no evidence of significant across-studies they found that compared to placebo in children and adolescents melatonin was significantly better in improving: sleep onset latency, measured with sleep diary, in ASD neurodevelopmental disorders with comorbid insomnia, intellectual disability (with insomnia), and all neurodevelopmental disorders or all sleep disorders pooled together; sleep onset latency measured with actigraphy in ADHD, ASD, and neurodevelopmental disorders with comorbid insomnia; total sleep time measured with diary in ASD, ASD with comorbid insomnia, insomnia, and in all sleep disorders; and total sleep time measured with actigraphy in ASD with comorbid insomnia.

- In adults, melatonin was significantly better in improving sleep onset latency, measured with diary, when pooling RCTs across sleep disorders and across all disorders. It was also significantly better in improving total sleep time, measured with polysomnography, in adults with delayed sleep phase disorder.

- There was no evidence that melatonin improved night awakenings or shifted the DLMO in any of the analyses that we performed.

- They stated that no evidence of significant differences between melatonin and placebo was found in terms of tolerability.

Table 1 below highlights the studies and main findings from the systematic review.

Author (s), Year	Age Group	Disorder	Main Findings
Abdelgadir et al. (2018)	Children and adolescents	Neurodevelopmental disorders	Melatonin significantly improved total sleep time and reduced sleep onset latency. No significant difference in the frequency of nocturnal awakenings for children with neurodevelopmental disorders
Braam et al. (2009)	Children and adolescents	Intellectual disabilities	Melatonin significantly improved total sleep time, reduced sleep onset latency, and reduced the frequency of nocturnal awakenings for both children and adults with intellectual disabilities.
Parker et al. (2019)	Children and adolescents	Neurodevelopmental disorders	Melatonin significantly improved total sleep time and reduced sleep onset latency for children with neurodevelopmental disorders
Rossignol and Frye (2011)	Children and adolescents	Autism spectrum disorder	Melatonin significantly improved total sleep time and reduced sleep onset latency. No significant difference was found in the frequency of nocturnal awakenings for children with autism spectrum disorder

Table 1: Summary of evidence from *Salanitro systematic review (2022) highlighting key findings to sleep outcomes by disorder and cohort age group.*

Surman et al (2021) reviewed a three-arm randomised placebo-controlled study on 51 adults with ADHD and reported findings of

- Melatonin advanced Dim Light Melatonin Onset (DLMO) by 1 hour and 28 minutes and placebo had no effect on DLMO.

- Melatonin reduced in ADHD symptoms by 14% which returned to baseline post 2 weeks post-treatment.

Ashtar (2021) reported that the effectiveness of the melatonin treatment was least in curing the core symptoms of ADHD and that the quality of life and cognitive performance were improved only very slightly.

The study reported significant differences were depicted in melatonin-treated groups as compared to placebo groups. Additional outcomes were reported in terms of reduced wakefulness, movement, and variability during and between the nights.

There were more improvements realized when treatment duration increased and gave significantly improved benefits as compared to the baseline readings.

The quality of life and cognitive performance were improved only very slightly.

They also highlighted that despite extensive clinical studies done on this topic, there are limitations associated with these studies such as smaller sample size, few adverse effects, and shorter durations. Future studies can be warranted in the direction of a sizeable population, including the subjects of a wide variety of demographic, ethnic, and social backgrounds. Likewise, advanced techniques and a controlled environment to record the outcomes will provide more defined accuracy. This approach can potentially exclude bias.

Lalanne et al (2021) study concluded that Melatonin represents a well-validated treatment for sleep disorders in children with ASD. However, there are to date insufficient data to determine the extent to which response variability has been dependent on interindividual exposure variability (PK and bioavailability effects) new therapeutic perspectives on melatonin are opening promising avenues for improving autistic behavioural impairments. However, it was also noted that future clinical trials are necessary to examine therapeutic benefits of melatonin administration for autistic behavioural impairments based on dose-effect relationship studies.

McDonagh et al (2019) found that Melatonin significantly improved sleep latency and sleep duration. Although the range of improvement in sleep latency ranged from 11 to 51 minutes (medium 28 minutes) and sleep duration improved by 14 to 68 minutes (median 33 minutes). It was stated that children with ASD improved the most compared to other neurodevelopmental disorders (sleep latency by 37 minutes vs 6.8-24 minutes, and sleep duration by nearly 48 minutes vs 32-35 minutes in other conditions). Although the measurements of awakenings or time spent awake after sleep onset were inconsistent with each other and varied from getting worse to improving significantly leaving little confidence in the trial's findings. They concluded that melatonin improved some sleep outcomes in the short term (1-13 weeks) and there is a lack of information on the potential harms of longer-term use. However, it is not clear how useful the gains in sleep latency and duration are and the impact on functional and behavioural improvement varied and is unclear.

Strength of Evidence

Melatonin supplementation has been studied in ASD patients since 1993 – several studies reported therapeutic benefits following night-time administration of melatonin for decreasing sleep latency as well as improving sleep duration and night awakenings in individuals with autism despite the small number of subjects ***Tordjman et al.***

Many studies have investigated the role of melatonin on sleep in ASD. There is now a growing literature suggesting that melatonin could also have a positive effect on other mental and physical health problems often associated with ASD, such as anxiety, pain/sensory processing, and gastrointestinal dysfunction.

Briefly, animal, and human studies have shown that melatonin improves anxiety and gastrointestinal dysfunction, whereas studies in animals have demonstrated positive results on sensory processing but results in humans are heterogeneous. Anxiety, sensory processing dysfunction/pain, and gastrointestinal problems are known to have a negative effect on sleep. It is thus reasonable to think that melatonin could at least partially draw some of its positive effects on sleep in ASD by acting on these alternative routes.

Many studies also highlighted that despite extensive clinical studies done on this topic, there are limitations associated with these studies such as smaller sample size, few adverse effects, and shorter durations.

Future studies are needed with a sizeable population, including the subjects of a wide variety of demographic, ethnic, and social backgrounds. Likewise, advanced techniques and a controlled environment to record the outcomes will provide more defined accuracy. This approach can potentially exclude bias. ***Ashtar (2021)***

It was also noted that future clinical trials are necessary to examine therapeutic benefits of melatonin administration for autistic behavioural impairments based on dose-effect relationship studies. ***Lalanne et al (2021)***

➢ Cost-effectiveness

No conclusive evidence found.

Planned study and potential source of future evidence: ***Edelson et al 2020***

➢ National guidance and priorities

NICE Guidelines regarding Melatonin use states: **Melatonin | Drugs | BNFC | NICE**

The use of melatonin in children and adults with sleep and mental health conditions is supported by several guidelines. Based on a narrative overview of the literature, an international consensus established a series of recommendations on the use of melatonin in children/ adolescents (Bruni et al., 2015). This consensus conference suggested that, when considered as a sleep inductor, 1–3 mg of melatonin should be administered 30 min before bedtime, and slowly increased up to 5 mg/nocte if there is no effect. As a chrono biotic, 0.2–0.5 mg should be administered 2–3 h before the dim light melatonin onset (DLMO) – a marker of circadian phase - and slowly increased if there is no effect. More recently, Geoffroy et al. (2019) provided recommendations on the use of melatonin for adults. They highlighted the need of specific recommendations for each disorder. For instance, they suggested that both immediate- and prolonged-release melatonin improve insomnia symptoms in adults with depression, whilst they suggest phase shifting benefits using a low dose 0.1 mg melatonin for individuals with seasonal affective disorders.

Evidence Summaries

Salanitro et al (2022)

Title: Efficacy on sleep parameters and tolerability of melatonin in individuals with sleep or mental disorders: A systematic review and meta-analysis.

Source: Google Scholar

Study: Systematic review and series of meta-analyses to assess the efficacy and tolerability of melatonin in children/adolescents or adults with sleep or mental health disorders, using the same set of criteria across disorders and ages.

Based on a pre-registered protocol and searched a broad range of electronic databases up to February 2021 for randomized control trials (RCTs) of melatonin. The study quality was assessed by using the Risk of Bias tool, v2.

Included a total of 34 RCTs (21 in children/adolescents: N = 984; 13 in adults: N = 1014).

Reported key findings:

- The review found evidence that melatonin significantly improved sleep onset latency and total sleep time, but not sleep awaking, in children and adolescents with a variety of neurodevelopmental disorders, and sleep onset latency (measured by diary) as well as total sleep time (measured with polysomnography) in adults with delayed sleep phase disorder.

- No evidence of significant differences between melatonin and placebo was found in terms of tolerability.

- When considering significant meta-analytic results with no evidence of significant across-studies they found that, in children and adolescents, compared to placebo, melatonin was significantly better in improving: sleep onset latency, measured with sleep diary, in autism spectrum disorder, autism spectrum disorder and comorbid insomnia, delayed sleep phase disorder, insomnia, neurodevelopmental disorders with comorbid insomnia, intellectual disability (with insomnia), and all neurodevelopmental disorders or all sleep disorders pooled together; sleep onset latency measured with actigraphy in ADHD, ASD, and neurodevelopmental disorders with comorbid insomnia; total sleep time measured with diary in ASD, ASD with comorbid insomnia, insomnia, and in all sleep disorders; and total sleep time measured with actigraphy in ASD with comorbid insomnia.

- In adults, melatonin was significantly better in improving sleep onset latency, measured with diary, when pooling RCTs across sleep disorders and across all disorders. It was also significantly better in improving total sleep time, measured with polysomnography, in adults with delayed sleep phase disorder.

- There was no evidence that melatonin improved night awakenings or shifted the DLMO in any of the analyses that we performed.

Surman et al (2021)

Title: Managing Sleep in Adults with ADHD: From Science to Pragmatic Approaches

Source: Google Scholar

Study: A literature review was conducted to present the clinical science informing treatment of sleep-in adults with ADHD. Six systematic prospective studies of sleep intervention in adults with ADHD were identified. Three of these, all including well-characterized ADHD patients, offered evidence for a significant effect of morning light therapy. Across the studies, preliminary evidence for melatonin, behavioural therapy, and weighted blankets were also found.

Reported key findings:

Study	Population	Intervention	Design	Baseline	Findings
Van Andel et al 2021	N=51 (ADHD)	Melatonin 0.5mg/d timed to dim light	Three-arm randomised	DLMO sleep diagnosis list (SDL) and	Melatonin advanced DLMO by 1 hour and 28 minutes

		melatonin onset (DLMO) with and without bright light therapy – 3 weeks	placebo controlled	sleep hygiene questionnaire (VSH)	Placebo had no effect on DLMO Melatonin reduced in ADHD symptoms by 14% which returned to baseline post 2 weeks post-treatment.

Table 2: 1 study included a three-armed randomised control study with their results summarised below.

Kimland et al (2021)

Title: Paediatric use of prescribed melatonin in Sweden 2006–2017: a register-based study

Source: Google Scholar

Study: Data was retrieved by linking the national population-based registers, the Swedish Prescribed Drug register, and the National Patient register.

Objective: To characterise the prevalence and incidence of dispensed melatonin prescriptions, long-term treatment, concomitant dispensation of psychotropic medication, and psychiatric comorbidity, in children and adolescents aged 0–17 years living in Sweden during 2006–2017.

Participants: The study population was comprised of children between 0–17 years living in Sweden, between the years 2006 (number of children 1,934,080) and 2017 (number of children 2,099,005).

Reported key findings:

- The study found that in 2017, nearly 2% of the paediatric population 0–17 years was dispensed at least one prescription of melatonin, which was more than a 15-fold increase for girls and a 20-fold increase for boys, when compared to 2006.

- Among the children in the age group 5–9 who initiated a melatonin treatment in 2009, 15% of girls and 17% of boys were found to be continuously prescribed melatonin 8 years later.

- Nearly 80% of all children with dispensed melatonin had concomitant dispensations of psychotropic medications. The most common combination was melatonin together with centrally acting sympathomimetic medicines (23% of girls and 43% of boys).

- About half of the children (47% of girls and 50% of boys) had at least one registered diagnosis of mental or behavioural disorders - the most common diagnosis was attention deficit hyperactive disorder, across all age groups and genders.

The study concluded that the continuous increase of use of melatonin in children is often concomitant with other psychotropic medications, together with a high proportion of younger children with prescriptions of melatonin on a long-term basis and that this suggests the need for further structured follow up studies of long-term use.

The study showed an exponentially increased dispensation of melatonin in children 0–17 years of age from 2006 to 2017 in Sweden. The increase in both prevalence and incidence of melatonin users was most noticeable in teenage girls and boys. Prescribed doses reported in this study correspond to recommended daily doses among adults. Nearly one-fifth of children aged 5–9 years being treated with melatonin, were continuously dispensed melatonin up to 8 years after their first prescription. More than three out of four of those with a melatonin treatment had a concomitant psychotropic medication, most related to a hyperkinetic disorder. Similarly, around half of the children had a recent recording of psychiatric disorders, foremost related to hyperkinetic disorders.

If the increased prevalence and incidence of melatonin dispensation reflects an unmet need for medical treatment of increased sleeping disorders among children and adolescents, or perhaps an overtreatment, is not possible to answer based on the outcome of this study.

Ashtar *(2021)*

Title: Role of Melatonin in children with insomnia and ADHD: Mini review

Source: Google Scholar

Study: An open-label study in a small sample size and randomized placebo-controlled double-blind trials. Studies were conducted in hospitals, research institutes, or pharmacies and the doses of melatonin was around 3-6 mg according to the body weight of individuals. Administration of melatonin to the patients was directed almost one hour before going to bed. Sleep hygiene was maintained by fixed bedtime, minimum light, dark, and sound of the room and the surroundings. The studies lasted several weeks to months and only a small number of patients dropped out during the study period. Results were compared with the baseline and placebo-controlled groups using different statistical methods like t-test or ANOVA with the help of the software.

Items	Descriptions
Individuals	Children, Parents, Physicians, Pharmacists
Treatments	Methylphenidate, Melatonin, Placebo
Strategies	Sleep hygiene with balance dark/light, Sound, Fixed bedtime, and Properly made bed, Consent of participants
Parameters	Sleep latency, Sleep onset time, Total sleep time, and Cognitive functions
Instruments	Somnolog, Actigraphy, Electronic sleep diary, Questionnaire, ABC-J, SPSS software
Statistical tests	t-test, ANOVA, Linear regression analysis, Pearson test, Wilcoxon signed-rank test
Outcomes/measurements	Safety, Efficacy, Sleep quality, Wakefulness, Movements
Adverse effects	Irritation, Lethargy, Migraine, Diarrhoea, Headache, and Dizziness

Objective: To measure and record the sleeping pattern, sleep onset, sleep latency, sleep disturbances, and wakefulness by using actigraphy, somnolog, or questionnaires.

Participants: Children in the age range of 5-15 years. Almost 50-100 subjects were screened based on exclusion and inclusion criteria like ADHD diagnosis, comorbidity, premedication, aggressive attitude, and willingness to participate. Grouping of the selected subjects was done in a randomized way as treatment and placebo-controlled groups.

Reported key findings:

The results revealed that melatonin treatment reduced the sleep-onset time, sleep latency, and enhanced total sleep duration in ADHD children.

- The study reported significant differences were depicted in melatonin-treated groups as compared to placebo groups. Additional outcomes were reported in terms of reduced wakefulness, movement, and variability during and between the nights.
- There were more improvements realized when treatment duration increased and gave significantly improved benefits as compared to the baseline readings.
- The onset of sleep time in the range of 20-40 min was perceived as normal. However, exceeding 60 min was in the category of faulty sleep patterns.
- In clinical trials with melatonin revealed the attainable efficacy and acceptable safety. Interestingly, the effectiveness of the melatonin treatment was least in curing the core symptoms of ADHD.
- The quality of life and cognitive performance were improved only very slightly.

- No serious adverse effects were noted down.

In addition to basic findings, advanced studies were necessitated to corroborate and validate earlier reports. Almost all the studies conducted on children suffering from ADHD and sleep-onset insomnia revealed that melatonin had the potential to relieve sleep disorders. Series of reports justified the use of melatonin in a fixed dosage regimen.

However, attention deficiency, hyperactive behaviour, tiredness, speaking difficulty, concentration ability was not much changed. The reason could be the different molecular or neurochemical mechanisms of ADHD and insomnia. It has also given an inference of the essentiality of separate therapy for ADHD-related pathological hallmarks. The studies gave a fair indication that these approaches like melatonin in combination with sleep hygiene, subject variability, and dosage regimen fluctuations were significantly effective and safer to larger parameters. Still, cautions have to be built to produce a declined level of toxicity.

Most of the results of the latest study pertaining to melatonin efficacy were in line with previously reported studies with smaller samples or limited study design. Despite extensive clinical studies done on this topic, there are limitations associated with these studies such as smaller sample size, few adverse effects, and shorter durations. Future studies can be warranted in the direction of a sizeable population, including the subjects of a wide variety of demographic, ethnic, and social backgrounds. Likewise, advanced techniques and a controlled environment to record the outcomes will provide more defined accuracy. This approach can potentially exclude bias. The exploitation of the field can further be done by determining the mechanistic aspects of melatonin.

Lalanne *et al. (2021)*

Title: Melatonin: From Pharmacokinetics to Clinical Use in Autism Spectrum Disorder (ASD)

Source: PubMed

Objective: Review factors influencing treatment response and possible side effects following melatonin administration.

Study: Reviews of Clinical Studies of Melatonin Supplementation in ASD

Therapeutic Benefits Based on Melatonin Dose and Formulation Melatonin supplementation in children with ASD was studied in 26 clinical trials from 1996 to 2017 (0.75 to 12 mg of oral melatonin), (*Tordjman et al.)* Only eight randomized placebo-controlled trials (which represents a total of 621 subjects)

Some of these trials were escalation studies or titration studies, none of them was a dose-effect relationship study comparing separated groups of ASD individuals for each different dose of melatonin.

Reported key findings:

- The study concluded that Melatonin represents a well-validated treatment for sleep disorders in children with ASD. However, there are to date insufficient data to determine the extent to which response variability has been dependent on interindividual exposure variability (PK and bioavailability effects).
- That new therapeutic perspectives on melatonin are opening promising avenues for improving autistic behavioural impairments.
- Future clinical trials are necessary to examine therapeutic benefits of melatonin administration for autistic behavioural impairments based on dose-effect relationship studies.

Dose effect relationship studies should take into consideration inter- and intra-individual variability factors of melatonin exposure to improve therapeutic effects of melatonin administration

Rzepka-Migut *et al. (2020)*

Title: Efficacy and Safety of Melatonin Treatment in Children with Autism Spectrum Disorder and Attention-Deficit/Hyperactivity Disorder - A Review of the Literature

Source: PubMed

Study: Literature Review

Reported key results: This review indicates the significance of sleep disorders in the paediatric group, especially in children with neurodevelopmental disorders. They state it remains unclear whether sleep problems are part of the clinical picture of ASD and ADHD or are provoked by anxiety or behavioural disorders. The authors point out circadian arrhythmias in this group of patients.

The authors seemed to agree that exogenous melatonin improves sleep delay as well as extends overall sleep duration in the group of patients with ASD and ADHD.

- In the group of ASD patients, researchers agree that melatonin has a positive effect on behaviour.
- **(*Van der Heijden et al. and Mohammadi et al.*)** Did not find a beneficial effect of melatonin supplementation on the behaviour of patients with ADHD.

In the above studies, adverse reactions were absent or rare. MLT is considered safe and well-tolerated. High availability and a low price of MLT are its advantages.

The review presented extensively presents the protocols used for melatonin supplementation, which may facilitate the work of clinicians because there has not been a uniform dosage standard to date.

The review has several limitations:

- This is not a systematic review
- Research groups are not limited to patients with ASD and ADHD
- No homogeneous test reports
- The use of various melatonin preparations in studies
- Various methods used (objective - actigraphy, polysomnography and subjective - sleep diaries, questionnaires); and - lack of careful monitoring also of light side effects.

Despite the limitations, the review confirms the efficacy and safety of melatonin in the treatment of sleep disorders in the group of paediatric patients.

Overall, they noticed a small amount of work on the effect of melatonin on behaviour and the need to design a large long-term study using both subjective and objective methods to assess the effectiveness of melatonin.

Table 1. Melatonin level assessment in the group of patients with autism spectrum disorder (ASD).

References	Number of Patients	Material	Results
Nir I et al., 1995 [49]	10 patients with ASD 5 controls	serum	1. Similar results of mean daily melatonin levels were measured in serum in the group of patients with ASD and the control group. 2. Patients with ASD showed lower melatonin levels at night and higher during the day relative to the control group.
Tordjman S et al., 2005 [47]	49 patients with ASD 88 controls	urine	1. Low melatonin levels were observed in 63% (31/49) of patients with ASD. 2. In pre-pubertal period, a reduction in 6-SM was apparently observed in patients with ASD relative to the control group.
Melke J et al., 2008 [37]	43 patients with ASD 34 parents 48 controls	plasma	1. Low melatonin levels were observed in 65% of patients with ASD. 2. There is a genetic potential for reduced melatonin levels in ASD, as asymptomatic parents also have abnormally low melatonin levels. 3. The results suggest that in patients with ASD and low melatonin levels we can get sleep improvement through supplementation.
Tordjman S et al., 2012 [43]	43 patients with ASD 26 controls	urine	Patients with ASD showed lower levels of nocturnal 6-SM excretion in urine than those in the control group.
Pagan C et al., 2014 [41]	278 patients with ASD 129 unaffected siblings 377 parents 416 controls	plasma	Melatonin levels in patients with ASD and their relatives were significantly lower than in the control group.
Abdulamir HA et al., 2016 [50]	60 patients with ASD 26 controls	serum	1. Patients with ASD presented lower levels of melatonin than the control group. 2. A relationship has been demonstrated between the severity of autism and lower melatonin levels.
Benabou M et al., 2017 [51]	157 patients with ASD 100 unaffected siblings 264 parents	plasma	Phenotypic variation and changes in melatonin levels in patients with ASD and their families are the result of environmental and genetic factors.
Braam W et al., 2018 [11]	60 mothers of a child with ASD 15 controls	urine	1. Mothers of children with ASD had significantly lower levels of 6-SM in urine compared to the control group. 2. Mothers of children with ASD were older at the time of child birth compared to mothers of children without ASD.
Maruani A et al., 2019 [52]	78 patients with ASD 90 unaffected relatives 47 controls	plasma	1. Patients with ASD presented lower levels of melatonin than their relatives and people from the control group. 2. Lower levels of melatonin were observed in relatives of patients with ASD, however, the result was not statistically significant.

Table 3: There are a number of studies indicating a relationship between lowered melatonin levels and the incidence of ASD.

Table 2. Melatonin level assessment in the group of patients with attention-deficit/hyperactivity disorder (ADHD).

References	Number of Patients	Material	Results
Van der Heijden KB et al., 2005 [53]	87 patients with ADHD-SOI 33 patients with ADHD-noSOI	saliva	ADHD patients with concomitant chronic idiopathic insomnia at the onset of sleep presented significantly delayed DLMO and sleep phase relative to the ADHD-noSOI group.
Van Veen MM et al., 2010 [54]	34 patients with ADHD 38 controls	saliva	1. Melatonin production in the ADHD group began 83 min later than the control group. 2. Patients with ADHD showed less effective sleep and longer sleep delay.
Baird AL et al., 2012 [56]	13 patients with ADHD 19 controls	saliva	1. In the group of patients with ADHD disturbed rhythm of melatonin relative to the control group was observed.
Bijlenga D et al., 2013 [55]	12 patients with ADHD 12 controls	saliva	1. In the group of people with ADHD, DLMO was delayed by about 1.5 h relative to the control group. 2. An average one hour longer interval between the onset of DLMO and onset of sleep was observed in subjects with ADHD relative to the control group.
Büber A et al., 2016 [57]	27 patients with ADHD 28 controls	urine	Patients with ADHD had significantly higher levels of total 24-h urinary excretion of 6-OH MS than controls.

(ADHD-SOI)—ADHD-related sleep-onset insomnia, (ADHD-noSOI)—ADHD without sleep-onset insomnia.

Table 4: There are a number of studies indicating a relationship between lowered melatonin levels and the incidence of ADHD.

Parvantaneni *et al. (2020)*

Title: Perspective on Melatonin Use for Sleep Problems in Autism and Attention-Deficit Hyperactivity Disorder: A Systematic Review of Randomized Clinical Trials

Source: Medline

Study: Systematic review of randomized clinical trials (RCTs) on Medline and included six studies that met inclusion criteria.

RCTs were conducted in patients from two to 18 years of age with a diagnostic and statistical manual of mental disorders (DSM)-IV diagnosis of autism spectrum disease (ASD) and/or attention-deficit hyperactivity disorder (ADHD) in both short-term and long-term RCTs ranging from eight-week to 52-week studies.

Reported key results:

- The mean difference in the children's sleep disorder showed statistically significant improvement in sleep duration and sleep latency onset compared to the placebo. Overall, a high response rate was observed in the melatonin group compared to the placebo in treating sleep problems in children. Melatonin is a well-tolerated and safe medication in the dose range of 2-10 mg/day in the child and adolescent population.

- Patients with ASD and/or ADHD showed improvement in total sleep time, sleep latency and improved uninterrupted sleep with melatonin, and augmented by combination management with melatonin and CBT.

- There was an improvement in externalizing behaviour and subsequent improvement in the caregiver's quality of life.

- Melatonin is a well-tolerated and safe medication in the dose range of 2-10 mg/day in the child and adolescent population.

The efficacy and safety were proved by both short-term and long-term Double Blind (DB) RCTs. Five studies conducted in an outpatient setting evaluated the efficacy of melatonin on sleep ***2020 Parvataneni et al.***

Double-blinded-RCT (DB-RCT) conducted by ***Maras et al.*** included 95 paediatric patients with ASD and 51 patients received prolonged-release melatonin (2-10 mg/day) for 52 weeks and compared with placebo (N = 44). They found:

- There was a statistically significant mean difference in the reduction of sleep latency ($P<0.001$).

RCT by ***Maras et al***. was open-label and a follow-up study of ***Gringras et al.*** study, and so it is possible that the improvement in the intervention group could be due to the efficacy of melatonin versus spontaneous remission in this long-term study

Similar results were also seen in a short-term study conducted by ***Gringras et al.*** In the DB-RCT by ***Gringras et al***. sleep monitoring was measured by actigraphy due to refusal to wear the device by the patient

Study	Study details			Melatonin		Control	
	Demographic	Diagnosis	Trial	N	Dosage	N	Dosage
Malow et al.	Total N: 23 Age: 3-12 years	ASD	Length: 14 weeks, OP setting	23	1-6 mg	None	
Cortesi et al.	Total N:66 Age: 4-10 years	ASD	Length: 12 weeks, OP setting	34	3 mg*	32	Similar dosage of melatonin
Gringras et al.	Total N: 119 Age: 2-17 years	ASD	Length: 13 weeks, OP setting	58	2-5 mg	61	Similar dosage of placebo
Maras et al.	Total N: 95 Age: 2-17 years	ASD	Length: 52 weeks, OP setting	51	2-10 mg	44	Similar dosage of placebo
Schroder et al.	Total N: 119 Age: 2-17 years	ASD	Length: 13 weeks, OP setting	58	2-5mg	61	Similar dosage of placebo
Mohammadi et al.	Total N: 50 Age: 7-12 years	ASD and ADHD	Length: 8 weeks, OP setting	26	3-6 mg*	24	MTP only

TABLE 1: Study design

N, number of patients; ASD, autism spectrum disorder; ADHD, attention-deficit/hyperactivity disorder; OP, outpatient; CBT, Cognitiv behavioral therapy; MTP, methylphenidate

*Intervention group with CBT in Cortesi et al. and methylphenidate in Mohammadi et al. study.

Table 5: An overview of the study design of included RCTs in shown

Edelson *et al. (2020)*

Title: Protocol for a longitudinal study of melatonin therapy and cost effectiveness analysis in stimulant-treated children with ADHD and insomnia: An N-of-1 trial.

Source: PubMed

Study: The Melatonin in Youth: N-of-1 trial in a stimulant-treated ADHD Population study (MYNAP) - a series of individual double-blind N-of-1 randomized controlled trials. Timeline 6 weeks, recruited caregivers of Australian children aged 6–17 who have been diagnosed with ADHD. The dosage will need to remain constant during the study (6 weeks) for the data to be included in analysis.

The relevant stakeholders for this research are caregivers of children with ADHD, who have trouble sleeping, doctors of children with ADHD, and the patients themselves.

We hope that this research will generate new knowledge about the societal effects of ADHD and sleep troubles. ADHD is a very prevalent disease that not only effects the person with symptoms, but those caring for them and society at large. Moreover, the associated effects of poor sleep for children with ADHD, and the further effects on caregivers, seems to not be adequately addressed at this time.

We hypothesize that caregivers' and patients' quality life will improve when their child's sleep onset latency is decreased using melatonin.

This study is replicable in other countries with easy access to home internet and a reliable pharmacy to administer the melatonin and placebo medications. This outcome will be significant because this information can be used as part of development of management plans for poor sleep, if present, when a patient is first diagnosed with ADHD. This is especially important in Australia (where this study took place), because melatonin requires a prescription from one's doctor in that country. Caregivers should be made aware of the common association between ADHD and insomnia and what options they have to manage their children's sleep problems, including ones that will improve their own perceived quality of life. We hope that those doctors with an interest in ADHD treatment will use this knowledge in creating a treatment plan for their patients.

Economic analysis The within trial economic analysis will be conducted on an intention-to-treat basis. This means that all patients will be analyzed within the group to which they were allocated for that period of the study, regardless of, for example, whether or not they had taken the melatonin or placebo as expected.

With regards to handling missing data, we will conduct a sensitivity analysis using various missing data methods. These methods will include complete-case analysis for cost outcome measures, and last observation carried forward for clinical measures.

A within-trial, cost–utility analysis will be conducted. It will estimate any potential incremental gain in utility, measured in quality-adjusted life years (QALYs), as well as the incremental change in costs between those who continue melatonin and those who do not. Responses to the SF-12v2

will be converted into SF-6D utility values using the Australian utility algorithm in order to calculate QALYs. PedsQL responses will be converted into utility values using a mapping algorithm.

The primary outcome will be the incremental cost–utility ratio (ICUR) with incremental costs, benefits and net monetary benefits also reported, where the ICUR is estimated as per the following equation: *ICUR*¼ *C*1 □ *C*0 *QALY*1 □ *QALY*0 Where C1 and C0 are the costs for the intervention and control groups respectively and QALY1 and QALY0 are the quality adjusted life years for the intervention and control groups respectively.

To estimate the mean incremental cost and incremental effect (QALY gain) associated with melatonin, regression analysis will be undertaken. The system of a seemingly unrelated regression method will be used, which is generally robust to skewed data and to allow for any correlation between costs and effects [16]. The cost and QALY regressions will be run simultaneously, with allocation to intervention included as an explanatory variable along with baseline demographic and sleep descriptive variables being included (as covariates) only where an a priori expectation exists that the covariate might be associated with cost and/or QALY scores. Assuming that neither melatonin nor placebo is both more costly and less effective, the ICUR will be reported. However, if either the incremental cost and/or incremental effect is negative, owing to the potential for misinterpretation, the incremental net benefit will be calculated at the cost-effectiveness threshold (λ) value of $50,000 per quality adjusted life year (QALY) [15]. Additionally, to estimate the level of uncertainty associated with the decision as to whether or not melatonin is cost-effective, the non-parametric bootstrap technique with 5,000 replications sampled (with replacement) will be used to estimate the probability that the intervention is cost-effective at a λ of $50,000 per QALY. In addition, the probability of the intervention being cost-effective at alternative threshold values will be presented.

McDonagh et al (2019)

Title: Pharmacologic Treatments for Sleep Disorders in Children: Systematic Review

Source: PubMed

Study: Systematic Review (also comparing trialling of zolpidem and eszopiclone)

Reported key results:

- In 19 randomized controlled trials, it was concluded in these studies that melatonin significantly improved sleep latency and sleep duration. Although the range of improvement in sleep latency ranged from 11 to 51 minutes (medium 28 minutes) and sleep duration improved by 14 to 68 minutes (median 33 minutes). It was stated that children with ASD

improved the most compared to other neurodevelopmental disorders (sleep latency by 37 minutes vs 6.8-24 minutes, and sleep duration by nearly 48 minutes vs 32-35 minutes in other conditions). Although the measurements of awakenings or time spent awake after sleep onset were inconsistent with each other and varied from getting worse to improving significantly leaving little confidence in the trial's findings.

- Reported limitations in these findings are there were few trials in adolescents, and the findings favoured melatonin, the magnitude of effect was smaller than in younger children.

- It is unclear if the findings favoured melatonin because the review was also comparing to sleep treatments zolpidem and eszopiclone which may be more intense medications e.g. they also stated that adverse events were infrequent with melatonin, but more frequent than placebo in children taking eszopiclone or zolpidem.

- They concluded that melatonin improved some sleep outcomes in the short term (1-13 weeks) and there is a lack of information on the potential harms of longer-term use.

- Impact on functional and behavioural improvement varied and is unclear. It is not clear how useful the gains in sleep latency and duration are.

- Improvement in sleep was compared to ''other neurodevelopmental disorders'' which is very broad.

Method

The following PICO search strategy was used:

Population: Individuals with ADHD or LD or ASD

Intervention: Melatonin

Comparison: Other treatments

Outcomes: Patient safety, clinical effectiveness in sleep management, strength of the evidence, cost-effectiveness, national guidance.

Searches took place on 03/08/2022.

Search strategy (including truncation (*) and index terms):

Melatonin AND ADHD OR LD OR ASD

Included article types:

2022 – 2020. clinical trials, meta-analysis, systematic review, randomised controlled trials

Exclusion criteria:

Outside of time limit 2022-2020, lack of relevance to PICO, not included article types (see above), duplicates, protocols and ongoing trials, out of date version abstract not included, not available in English, not peer-reviewed, already included in an included systematic review, studies which exclude sleep outcomes

Databases and sources searched included:

Cochrane Library: 0 results.

PubMed/Google Scholar: 33 results. Abstracts screened against exclusion criteria. 17 articles subjected to full-text screen. 10 articles included.

Recommended article sent with application[1]: 18 articles recommended. Abstracts screened against exclusion criteria. 18 articles subjected to full-text screen. 3 articles included.

References

Salanitro (systematic review 2022)

Matthew Salanitro, Torsten Wrigley, Hisham Ghabra, Edward de Haan, Catherine M. Hill, Marco Solmi, Samuele Cortese, Efficacy on sleep parameters and tolerability of melatonin in individuals with sleep or mental disorders: A systematic review and meta-analysis,

Neuroscience & Biobehavioral Reviews, Volume 139, 2022, 104723, ISSN 0149-7634,

Surman et al 2021

Surman, C.B.H.; Walsh, D.M. Managing Sleep in Adults with ADHD: From Science to Pragmatic Approaches. *Brain Sci.* **2021**, *11*, 1361. https://doi.org/10.3390/brainsci11101361

Ashtar (2021)

Role of melatonin in children with insomnia and ADHD: Mini-review
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International Journal of Science and Technology Research Archive, 2021, 01(02), 010–012

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Lalanne et al (2021)

Lalanne S, Fougerou-Leurent C, Anderson GM, Schroder CM, Nir T, Chokron S, Delorme R, Claustrat B, Bellissant E, Kermarrec S, Franco P, Denis L, Tordjman S. Melatonin: From Pharmacokinetics to Clinical Use in Autism Spectrum Disorder. Int J Mol Sci. 2021 Feb 2;22(3):1490. doi: 10.3390/ijms22031490. PMID: 33540815; PMCID: PMC7867370.

Tordjman et al

Tordjman S, Najjar I, Bellissant E, Anderson GM, Barburoth M, Cohen D, Jaafari N, Schischmanoff O, Fagard R, Lagdas E, Kermarrec S, Ribardiere S, Botbol M, Fougerou C,

Bronsard G, Vernay-Leconte J. Advances in the research of melatonin in autism spectrum disorders: literature review and new perspectives. Int J Mol Sci. 2013 Oct 14;14(10):20508-42. doi: 10.3390/ijms141020508. PMID: 24129182; PMCID: PMC3821628.

Kimland et al 2021

Kimland, E.E., Bardage, C., Collin, J. *et al.* Pediatric use of prescribed melatonin in Sweden 2006–2017: a register based study. *Eur Child Adolesc Psychiatry* **30**, 1339–1350 (2021).

Rzepka-Migut et al 2020

Rzepka-Migut, B.; Paprocka, J. Efficacy and Safety of Melatonin Treatment in Children with Autism Spectrum Disorder and Attention-Deficit/Hyperactivity Disorder—A Review of the Literature. *Brain Sci.* **2020**, *10*, 219. https://doi.org/10.3390/brainsci10040219

Parvantaneni et al 2020

Parvataneni T, Srinivas S, Shah K, Patel RS. Perspective on Melatonin Use for Sleep Problems in Autism and Attention-Deficit Hyperactivity Disorder: A Systematic Review of Randomized Clinical Trials. Cureus. 2020 May 28;12(5):e8335. doi: 10.7759/cureus.8335. PMID: 32617211; PMCID: PMC7325410.

Edelson et al 2020

Edelson J, Byrnes J, Mitchell G, Heussler H, Melaku M, Nikles J. Protocol for a longitudinal study of melatonin therapy and cost effectiveness analysis in stimulant-treated children with ADHD and insomnia: An N-of-1 trial. Contemp Clin Trials Commun. 2020 Jan 22;17:100530. doi: 10.1016/j.conctc.2020.100530. PMID: 32025588; PMCID: PMC6997492

McDongh et al 2019

McDonagh MS, Holmes R, Hsu F. Pharmacologic Treatments for Sleep Disorders in Children: A Systematic Review. J Child Neurol. 2019 Apr;34(5):237-247. doi: 10.1177/0883073818821030. Epub 2019 Jan 23. PMID: 30674203.

Healthier Together

Improving health and care in Bristol, North Somerset and South Gloucestershire

BNSSG Joint Formulary Group Meeting – Adults and Paediatrics

Meeting Held on: Tuesday 13th September 2022
Time: 09:30 – 13:30
Venue: Virtual – Microsoft Teams

Minutes

Present:

[redacted] (Chair)	Principal Medicines Optimisation Pharmacist, BNSSG ICB
[redacted] (Minutes)	Team Administrator & Minute Taker, BNSSG ICB
[redacted]	GP Clinical Lead in Prescribing for BNSSG ICB
[redacted]	Interface Pharmacist, BNSSG ICB
[redacted]	Interface Pharmacist, BNSSG, ICB
[redacted]	Interface Pharmacist, BNSSG, ICB
[redacted]	Formulary Pharmacist, NBT
[redacted]	Medicines Information Pharmacist, UHBW
[redacted]	Medicine Safety Officer, Sirona Care and Health
[redacted]	Chief Pharmacist, Bristol Children's Hospital, UHBW
[redacted]	Clinical Effectiveness Programme Officer, BNSSG, ICB
[redacted]	Clinical Effectiveness Programme Officer, BNSSG, ICB
[redacted]	Clinical Effectiveness Programme Officer, BNSSG, ICB
[redacted]	Associate Medical Director, Research and Evidence, BNSSG, ICB
[redacted]	GP and Clinical Lead in Exceptional Funding and Policy Development

Apologies:

[redacted]	Deputy Director (Medicines Optimisation), BNSSG, ICB
[redacted]	Clinical Pharmacy Manager, UHBW
[redacted]	Lead for Pharmacoeconomics & High Cost Drugs, NBT

Applicants:

[redacted]	Senior Pharmacist, Medicines Optimisation, BNSSG, ICB
[redacted]	Lead Echocardiographer, UHBW
[redacted]	Consultant Dermatologist, UHBW
[redacted]	Consultant Old Age Psychiatrist/Clinical Lead, Bristol Dementia Wellbeing Service
[redacted]	Consultant Psychiatrist for Older Adults, Medical Lead North Somerset
[redacted]	Consultant in Mental Health (Adults of all ages), Devon Partnership NHS Trust
[redacted]	Deputy Chief Pharmacist, AWP
[redacted]	Consultant Psychiatrist of Intellectual Disability for Salisbury and South Wiltshire, AWP
[redacted]	Consultant Psychiatrist Adult ADHD, AWP
[redacted]	Consultant Community Pediatrician, CCHP
[redacted]	Consultant Community Pediatrician and Clinical Director for Community Paediatrics, Sirona Care and Health
[redacted]	PICU Pharmacist and Lead Pharmacist for Paediatric Surgery

1 Welcome and Apologies

[redacted] opened the meeting as chair. Introductions were made and apologies were noted as above. The meeting was not quorate due to no secondary care representation at the meeting, therefore any decisions made will need to be ratified via email. There were no declarations of interest recorded.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Conclusion

[redacted]

[redacted]

[redacted]

11 Melatonin - Joint Adults and Paediatrics

Melatonin Circadin® (MR tablets) ***(Adults)*****:** off-label use in patients with dementia experiencing circadian sleep disorders, in whom conventional sedation is considered too risky. [redacted], Consultant Psychiatrist, Devon Partnership NHS Trust. [redacted], Consultant Psychiatrist, North Somerset Complex Intervention Team, AWP.

Discussion

[redacted] presented the new drug request application for melatonin Circadin (Adults) for off-label use in patients with dementia experiencing circadian sleep disorders, in whom conventional sedation is considered too risky. [redacted] advised the application is for patients with dementia experiencing sleep disturbance for more than 2 weeks. The anticipated number of patients likely to receive treatment within BNSSG is 146, with the possibility of additional patients from UHBW (estimated 8). Treatment is likely to be long-term but with programmed trial reductions to see whether patients can manage without melatonin. The aim is generally not to reset the circadian rhythm.

In terms of cost, [redacted] advised if Circadin (preferred brand) were to be used the cost will be between £55K - £57K per year. Although it has been noted the quoted patient cohort may be an underestimate.

The ICB Research and Evidence team completed an evidence review. This identified 6 systematic reviews. based on 11 trials. The systematic reviews contained overlapping evidence from these 11 trials. There is some evidence for use of melatonin for dementia. However, this is not supported by all of the systematic reviews identified, including a recent Cochrane Review from 2020. Sleep latency was shown to be reduced slightly and sleep efficacy and total sleep time increased. The evidence is mostly for use in Alzheimer's disease and there is little evidence for other forms of dementia. The trials varied in size, length, doses and time of administration. The applicants acknowledge there is a poor evidence base, however for this cohort of patients there are no other suitable treatment options. Traditional hypnotics are not suitable due to the side effects of increased confusion, increased falls risk and behavioural disturbance. The applicants have requested that melatonin is a first-line treatment before moving to hypnotics.

The average dose in practice is 4mg at night, doses above this are uncommon. Melatonin Circadin's European patent is due to expire in August (unless extended) and a new immediate release brand has is now available. The formulary team have asked the applicant whether the new immediate release brand is appropriate and is awaiting a response.

In regard to NICE guidance, NICE guideline (2018) provides a do not use recommendation for melatonin which was based on a 2016 Cochrane review containing very low-to moderate evidence from RCTs. NICE agreed that the evidence did not show significant benefit from using melatonin to treat insomnia in people with Alzheimer's disease. NICE agreed this evidence could not be extrapolated to other subtypes of dementia e.g. REM sleep disorder in Parkinson's disease. The Cochrane review has been updated since (2020) and the updated Cochrane review continues to not recommend melatonin due to the low-quality evidence.

[redacted], [redacted], [redacted] and [redacted] joined the meeting to discuss the application. [redacted] advised whilst there is low-moderate evidence for the use of melatonin for patients with dementia, patients with Alzheimer's will experience elements of vascular and Lewy body dementia in their life. Within the studies some patients have responded to treatment and some have not. [redacted] advised the proposal would be to trial melatonin and if there is clear benefit treatment will continue. If the patient does not show any benefit treatment will be stopped.

In terms of alternative hypnotics available (benzodiazepine and z-drugs). Hypnotics work primarily through sedation leading to increased confusion, increased falls risk and behavioural disturbance. This can cause difficulty for elderly patients who are a risk to fractures/falls. Melatonin is used in preference to alternative hypnotics to avoid harm to these patients. Similarly sedating hypnotics do not induce natural sleep and are known to interfere with the normal neurochemistry of sleep, reducing its restorative value. Melatonin avoids these risks being comparatively far safer and using an entirely different mechanism of action as an endogenous compound. [redacted] advised there is also a benefit to family and carers, where a partner, family member or carer is needing to stay awake all night due to a person with dementia being awake and trying to leave their home in a vulnerable state. Simply resolving the issue of not sleeping at night can mean the difference between remaining at home, or admission to institutional care. Similarly, wakefulness at night for some with dementia is associated with increased confusion and agitation, even aggression, and restoring sleep at night can again enable a carer to support them in the community and remove the burden of managing challenging behaviours during the night in care facilities. [redacted] advised from clinical experience in a significant proportion of cases, using melatonin can resolve insomnia or sleep-wake reversal and avoid harmful alternatives such as benzodiazepines and z-drugs, indirectly improving patient safety through decreased falls risk and worsening cognition.

The group discussed whether it would be possible to identify which patient groups will respond and will not respond. [redacted] advised it is difficult to determine which patients would benefit the most from melatonin. The proposal is to conduct a rigorous trial of treatment and if the patient does not benefit treatment will be

stopped. The group discussed whether it would be possible to collate local evaluation data to support evidence and clinical effectiveness. It was recommended for this data to include the number of falls experienced and the cost impact caring for patients who are experiencing lack of sleep. [redacted] advised it would be difficult to collate data for patient falls and acute admissions as well as providing finance data. [redacted] advised patients will be initiated on melatonin for 7-10 days and if no benefit is seen during this period, treatment will be stopped. The group discussed whether patients responding to melatonin can stop treatment and remain off treatment for a period of time or whether this is a long-term treatment. JM advised there are patients who benefit from melatonin and after 3-6 months of treatment have a successful trial of a reduced dose.

In terms of the initiation protocol which states patients should not intake caffeine after 12pm.The group recommended that patients prescribed medication for sleep should not take any caffeine though out the day. [redacted] advised that carers and care homes are told patients should not have tea, coffee or coca cola and to consume naturally caffeine free alternatives. In terms of the trial duration for melatonin, [redacted] advised the data suggests the treatment duration should be 4/5 weeks to see full benefit. The ideal time to titrate the dose would be 7-10 days, however due to the lack of capacity this is not possible.

Decision Criteria used by JFG for NDR

- **Patient safety –** Melatonin has not been associated with serious adverse effects and is well tolerated. Use may be preferable as associated with less risk than other sedatives.
- **Clinical effectiveness –** Statistically significant improvements in sleep efficiency, total sleep time at night and sleep latency were found but this was not reproduced in all systematic reviews including the Cochrane Review by McCleary and Sharpley (2020). See table 2 (page 7) of the evidence review for a summary of findings from the systematic reviews that included an assessment of strength / certainty of findings. Most studies were based on short-term outcome measures and long-term outcome data is limited. **Sleep efficiency:** Xu et al., 2015, found statistically significant improvement in sleep efficiency by 2.23%, measured using mean difference in wrist actigraphy, after administration of melatonin for more than 4 weeks in all dementia types. **Total Sleep Time:** Xu et al., 2015, also found a statistically significant prolongation in total sleep time due to melatonin treatment using all data of 24.36 minutes. Total sleep time was lengthened by 28.78 minutes over a 4 week follow-up. **Sleep latency:** Blackman et al., 2021, found that melatonin was associated with a statistically significant reduction in sleep latency, using actigraphy, of 14.7 and 15.25 minutes for melatonin compared to 26.08 and 34.75 for placebo.
- **Strength of evidence –** The evidence base is limited by a shortage of studies. 6 systematic reviews were included in the evidence review, relying on 11 RCTs. Most findings were of low to moderate strength / certainty. The evidence base is predominantly for patients with Alzheimer's Disease rather than other types of dementia. Longer duration studies are needed to enable analysis of long-term outcomes. There is limited evidence on the place of melatonin relative to available treatments.
- **Cost effectiveness or resource impact –** No studies of cost-effectiveness were identified. Significantly more expensive than alternative sedatives. The cost pressure for the anticipated cohort is £54,356. Some additional non-formulary prescribing may already be occurring in primary care. Most prescribing is expected to be long-term. Circadin's European patent expiry (unless extended) may precipitate a reduction in acquisition price.
- **Place in therapy relative to available treatments –** To be used if non-pharmacological treatments e.g. sleep hygiene have not been effective, instead of alternative sedatives which may be less suitable due to potential adverse effects.
- **National guidance and priorities –** NICE guidance includes a "do not offer" recommendation for melatonin for insomnia in Alzheimer's disease. This recommendation does not extend to use in other subtypes of dementia. The guideline is relatively old (published in 2018). The British Association for Psychopharmacology recommends that prolonged release melatonin should be tried first when a hypnotic is indicated in patients over 55 years.
- **Local health priorities –** High priority for local specialists to include melatonin for adults with dementia on the formulary, as shared care. It is currently non-formulary for this indication outside of REM sleep disorder. Some non-formulary prescribing for this indication is already happening in secondary care and may be occurring in primary care.
- **Equity of access –** Inclusion of melatonin, indications and TLS status on other formularies varies greatly. It is TLS Red for inpatient use for dementia / care of the elderly in two local areas and Amber in a couple of other formulary areas.

- **Other considerations –** Recommended formulations:
  1. First line: Circadin m/r 2mg tablets. These may be titrated by halving the tablets, and still maintain their prolonged release properties.

2. Second line: Circadin m/r 2mg tablets use in swallowing difficulties – halved or crushed with a spoon.
3. Third line: melatonin 1mg/1ml soluble solution, preferably alcohol free, where a lactose-free product is required, and no solid-dose preparation is suitable for the patient.

Conclusion

The group considered the application, the evidence and the information submitted. The group agreed there is low quality evidence for the use of melatonin in patients with dementia, as well as a high-cost pressure to the system. The group noted anecdotal evidence of benefit to individual patients but that benefit at a population health level is not supported by the published evidence. The applicant has advised there is no resource within the clinical team to collect local evaluation data to determine efficacy and cost. The group noted that melatonin is already being used in for this indication in BNSSG on a non-formulary basis.

Based on the decision-making criteria above, the group agreed that melatonin should not be included onto the BNSSG Adult Formulary for off-label use in patients with dementia experiencing circadian sleep disorders, in whom conventional sedation is considered too risky, due to lack of clinical and cost effectiveness evidence and the cost pressure to the system. However, the Joint Formulary Group recommended that if further evidence/local data can be collected to better inform the application and model use, the group could re-review and reconsider a new drug request application if this was presented by the applicant in the future. The group advised that the resource of the BNSSG ICB Research and Evidence Team could be drawn on to support with collection of additional local evidence.

Post Meeting Note – Update from ICB Research and Evidence Team – There is a researcher within the ICB who can work with the clinical team to build up a cost-effectiveness analysis, which may include an audit/data collection to develop a simple model to project costs and savings under a range of assumptions.

The Formulary team to include the melatonin decision onto decision making page on the BNSSG formulary website.

Action:

1. The Formulary team to inform the applicant that due to the lack of clinical and cost-effectiveness evidence and the cost pressure to the system it was agreed to not include Melatonin onto the BNSSG Adult Formulary for off-label use in patients with dementia experiencing circadian sleep disorders, in whom conventional sedation is considered too risky. The Formulary team to also advise that the Joint Formulary Group recommend that if further evidence/local data can be collected to better inform the application and model use, the group could re-review and reconsider a new drug request application, if this is presented by the applicant in the future. This data collection will be supported by a researcher within the ICB.
2. The Formulary team to include the melatonin decision onto decision making page on the BNSSG formulary website.

Melatonin *(Adults and Paediatrics)*: off-label use for sleep disorder in adult and paediatric patients with any of:

- Attention Deficit Hyperactivity Disorder (ADHD)
- Autism Spectrum Disorder (ASD)
- Learning Disabilities (LD)

Discussion

[redacted] presented the new drug request application for melatonin (Adults and Paediatrics) for use for sleep disorder in adult and paediatric patients with attention deficit hyperactivity disorder (ADHD), autism or patients with learning disabilities (LD).

[redacted] advised melatonin is currently on the BNSSG Adult Formulary for adults with learning disabilities and sleep disturbance who also have either depression, mania, psychosis, dementia or disorder (e.g. autism, autistic spectrum, anxiety disorders, adult ADHD etc) as per shared care protocol. In terms of paediatric patients, melatonin is currently on the BNSSG Paediatric Formulary for children with neurodevelopmental disorder/disability with intrinsic sleep disorder (difficulty getting to sleep or remaining asleep) who have exhausted all behavioural sleep hygiene options. This excludes children with ADHD or autism or learning disabilities. [redacted] advised the new drug request application is to widen the patient cohort group and to include all patients with a sleep disorder who have ADHD or autism or learning disabilities. The typical treatment dose is 2mg-6mg per day.

In terms of patient numbers, there is a high volume of prescribing taking place already despite being non formulary. AWP estimate around 185 patients prescribed by CAMHS and 24 patients for learning disabilities. In terms of Sirona there are 433 patients prescribed within Community Paediatrics and 27 in the Adult Learning Disabilities.

In regards to melatonin's place within the pathway, the first-line option is simple sleep hygiene measures, second-line option is individualised behavioural and environmental recommendations, finally the third-line option would be a trial of melatonin.

A sleep diary is used in some adult LD services, which is left intentionally basic so that care providers/family can adapt it to their needs. The ADHD services also use sleep diaries and quality of life questionnaires to measure effectiveness.

In terms of cost, the Circadin brand is more cost effective than Slenyto, costing £1.02 for 4mg per day vs £2.75 for 4mg per day. Slenyto is licensed for autism spectrum disorder for 2-18 year olds. If everyone within a community provider setting was prescribed Circadin this would cost between £124K - £373K per year. According to EMIS data, there are 46,659 patients with a clinical code for ADHD, autism or learning disabilities. 739 patients are already being prescribed melatonin by primary care. In the last 12 months, BNSSG CCG spent £367,277 (9,192 items) on melatonin within primary care, which is approximately middle of the range comparing to other CCGs spend on melatonin. This represents the existing overall spend on melatonin in primary care over a 12-month period. It is not possible to extract details on formulary or non-formulary indications, dose or duration.

In regards to other ICB formularies. The most common indication approved is for autism. Within the 29 ICB formularies reviewed, 18 include melatonin for ASD. Of these, 5 ICBs include melatonin for adults with a shared care status (with 1 specifying unlicensed specials are considered red). 17 ICBs include melatonin for paediatrics, 16 as shared care, 1 as red. 13 ICBs include melatonin for ADHD. 6 ICBs include melatonin for ADHD in adults and of these, 5 ICBs classify this as shared care (with 1 specifying unlicensed specials are red) and 1 ICB red. For paediatrics, 11 ICBs have a shared care status (with 1 ICB specifying unlicensed specials are red) and 2 ICBs having a red status, noting some ICBs were also red but this is less clear within merged ICB formularies. In regards to learning disabilities, 10 ICBs include melatonin for learning disabilities on their formularies. Of these, 5 ICBs include melatonin for adults: 4 as shared care, 1 red (with 1 specify unlicensed specials are red). 11 ICBs include melatonin for children: 10 shared care and 1 red.

The British Association for Psychopharmacology acknowledge melatonin is used for insomnia in patients with learning disabilities and behaviour that challenges after non-pharmacological options, but melatonin is not licensed for this indication. The guidelines also acknowledge melatonin administration can be used to advance sleep onset to normal values in children with ADHD who are not on stimulant medication. NICE guideline on Challenging behaviour and learning disabilities NG11 includes melatonin to 'consider' if medication is needed, noting it's off-label use in patients aged under 55 years. Furthermore, NICE CG170 include melatonin to 'consider' if a pharmacological intervention is needed to aid sleep, following consultation with a specialist paediatrician.

The evidence review completed by the BNSSG evidence team focussed on available data from the 2020-2022 period only, however this included meta-analyses which included trials prior to this date range.

In terms of safety, melatonin is generally well tolerated, with no reports of any common or common adverse drug reactions, or reports of patients experiencing tolerance, dependence or withdrawal symptoms with Circadin.

[redacted], [redacted], [redacted] and [redacted] joined the meeting to discuss the application.

Paediatric cohort

[redacted] advised melatonin is widely used within Community Paediatrics. Melatonin is useful in improving the sleep initiation phase and quality of life. The family/carers of these patients also experience distress and this affects their quality of life due to sleep disturbances. This patient cohort can be vulnerable and often already have complex needs with neurodevelopmental disorders/disability. Treatment can improve quality of life for family members and carers, with a lower risk of burnout, and lower risk of break-down of the family home. Treatment can also improve production of appropriate amount of growth hormone secretion, leading to appropriate growth in children as well as improved behaviour and concentration during the daytime leading to better learning. [redacted] advised there is evidence for children taking melatonin which improves sleep for

children with ASD. [redacted] advised it is difficult to conduct research and evidence trials for paediatric patients. Some patients would benefit from melatonin on a short term basis to help re-set body clocks and cycle and once stable treatment can stop, however the majority with neurodevelopmental difficulties will need treatment longer term. [redacted] noted that individuals with neurodevelopmental disorders have been shown to have intrinsically lower melatonin levels, which is why melatonin can be helpful. Patients will have regular breaks off melatonin to determine whether treatment is still required. If symptoms do not improve treatment will be stopped.

[redacted] noted the overlap between ADHD and ASD and other neurodevelopmental issues and concurred with the feedback from patients and families regarding the benefits of melatonin. The improvement of sleep by thirty minutes every day of a patient's life can be significant for children.

Adult service - ADHD

[redacted] advised patients will be referred to the adult service and they will already be taking melatonin, which has helped historically. ADHD is associated with increased rates of sleep apnoea, insomnia and restless legs syndrome but most commonly sleep disorder. Most patients present with a delayed sleep phase pattern. [redacted] advised the patient's ADHD will be optimised with medication and behavioural interventions which may improve day time functioning/sleep onset problems however, there is a cohort of patients where medication does not treat these symptoms and melatonin will be indicated. Melatonin will help re-set the patient's sleep pattern and this can improve cognition to support further education, work and quality of life. The treatment duration will be dependent on patient basis, some patients may require ongoing prescriptions subject to review.

Inclusion of melatonin to the formulary would permit clinicians to use all of the tools available to attempt to get a patient's ADHD under control.

Adult service – LD

[redacted] advised patients with learning disabilities are a highly heterogeneous cohort in the context of the cause and severity of their disability along with individual co-morbidities. There is a lack of research into prescribing and management of these patients due to ethical concerns and many patients are unable to describe the side effects of medication due to being non-verbal. This cohort of patients are at risk of polypharmacy. The STOMP initiative is very prominent in prescribing practice and there is an emphasis on deprescribing where clinically appropriate.

[redacted] advised the anticipated numbers prescribed melatonin for this indication are smaller than the other indications being presented but that treatment with melatonin would be long term/ lifelong. The evidence shows there is no tolerance or withdrawal concerns with melatonin compared to benzodiazepines and Z-drugs. There is a lower risk for falls. There is a minimal hangover from melatonin. In regard to evidence, the British Association for Psychopharmacology consensus states melatonin is effective in treating delayed sleep phase syndrome, treating sleep disorder in patients who are blind and treating adults with an intellectual disability. In terms of the treatment pathway melatonin will be a third-line option. First-line will be sleep hygiene methods, second-line treatment would be behavioural interventions/reviewing a wide range of health complaints which might be affecting the patient's sleep pattern or a physio sleep system. [redacted] noted the wider implications of poor sleep such as placement breakdown, loss of carers, impact on families/carers.

Further discussion with the applicants

The group asked whether melatonin would replace benzodiazepine and Z-drugs and the risks of dual therapy. [redacted] advised they would not prescribe melatonin and Benzodiazepines/Z-drugs. [redacted] confirmed that Z drugs or benzodiazepine drugs would not be an appropriate alternative for this patient cohort and are not routinely prescribed. If these drugs were to be prescribed it would be strictly short term and for a co-morbid illness not for the sleep disorder itself.
The group discussed whether it would be possible to determine which patients melatonin would be most beneficial for treatment. The applicants advised this would not be possible.

The group recognised the applicants were able to provide compelling social anecdotal evidence of benefit of melatonin for individuals and asked about whether there would be the potential for further audit work to capture this benefit locally on a population basis. Applicants noted difficulty with undertaking such work such as the learning disability patient cohort being very heterogenous, issues with consent, ethical considerations and lack of capacity within the teams.

Decision Criteria used by JFG for NDR

- **Patient safety –** Studies found melatonin to be safe and well tolerated, with less risk associated with melatonin than other sedative medicine options. However for these indications, the alternatives would not be routinely used for these patient cohorts.
- **Clinical effectiveness –** When clinical trial data was pooled together in meta-analysis, statistically significant results were found showing an improvement of sleep latency and total sleep time. A pertinent meta-analysis by McDonagh et al (2019), concluded that for children and adolescents, Melatonin significantly improved sleep latency and duration, although the range of improvement in sleep latency varied between studies (11-51 minutes, median 28 minutes) and sleep duration improved by 14-68 minutes (median 33 minutes). It was reported within this meta-analysis that children with ASD improved the most compared to other neurodevelopmental disorders (sleep latency by 37 minutes and sleep duration by 48 minutes). Evidence for improvement was stronger for younger children than adolescents. However the Evidence team noted limitations with the study as measurements of awakenings or time spent awake after sleep onset were inconsistent with each other and varied from getting worse to improving significantly leaving little confidence in the trial's findings. A systematic review conducted by Salanitro (2022) concluded that melatonin improved sleep onset latency and total sleep time in adults across sleep disorders and across all disorders including ADHD/LD/ASD. There was no evidence that melatonin improved night awakenings. It is not clear whether the reported statistically significant improvements to sleep latency and total sleep time translate to clinically significant outcomes. Further studies are recommended to explore the effects of longer term use of melatonin and the impact of improvements to sleep on function, behaviour and improvement of condition. Further studies are also needed with a larger population size and use of a controlled environment to exclude bias.
  Applicants acknowledged that whilst the evidence may only report small improvements to sleep that for these patient cohorts there is significant benefit by this improvement of sleep and that the results are perhaps skewed by being averaged out with other patient cohorts who are included in the trials. The applicants were able to share anecdotal reports of how melatonin has improved their patient's quality of life and carer/ family quality of life, noting improvements on performance at school and at home.
- **Strength of evidence –** Low quality- despite the volume of evidence and use of melatonin for nearly 30 years, the quality of studies were variable with studies often of low quality with limitations such as absence of large scale RCTs, smaller sample size; short duration (the majority are 13 weeks duration or less); subjective outcome measures and risk of bias (e.g. sleep diaries); lack of methodology detail; lack of reproducibility. The majority of evidence reviewed focussed on children, and studies did not routinely focus on ADHD, LD or ASD in isolation. The evidence review completed by the BNSSG evidence team focussed on available data from the 2020-2022 period only, however this included meta-analyses which included trials prior to this date range.
  Anecdotal evidence was provided by applicants for melatonin use for this cohort, which can be considered 'weaker' strength of evidence.
- **Cost effectiveness or resource impact –** Current prescribing of melatonin already presents a substantial cost to the system of £702,468.50 per annum (£335,191.50 for AWP and Sirona combined and £367,277 by GP Practices). If the application for these additional indications were approved as shared care on the BNSSG Formulary, the costs of prescribing currently held with AWP and Sirona would shift to primary care. Prescription administration workload currently managed by AWP and Sirona would transfer to GP Practices, which may relieve pressure in those settings, but increase pressure in GP Practices. It is expected the majority of prescribing would be longer-term.
  The applicants reported wider potential cost benefits in terms of improving sleep such as ability to work, perform better at school, retention of placements for LD, improve quality of life for patient and other family members, however these potential cost benefits are anecdotal reports and costs are not confirmed by evidence.
- **Place in therapy relative to available treatments –** 3rd line, following non-pharmacological treatments.
- **National guidance and priorities –** NICE guideline Challenging behaviour and learning disabilities NG11 includes melatonin to 'consider' if medication is needed, noting it's off-label use in patients aged under 55 years. NICE CG170 advises to 'consider' melatonin for patients with autism only if a pharmacological intervention is needed to aid sleep, following consultation with a specialist paediatrician or psychiatrist with expertise in management of autism or sleep medicine in conjunction with non-pharmacological interventions. Melatonin is recognised as an option by the British Association of Psychopharmacology for patients with LD, ASD and children with ADHD who are not on stimulant medication after behavioural strategies.
- **Local health priorities –** Considered a high priority for local specialists who wish to make melatonin shared care for the indications ADHD, ASD and LD for both adult and paediatric patients. It is currently non-formulary for the majority of these patient cohorts, meaning potentially some prescribing occurs in

primary care 'non formulary' and prescribing occurs within AWP and Sirona outside of formulary recommendations.

- **Equity of access –** At a national level, the inclusion of melatonin on formularies varies greatly in terms of indications covered, traffic light status and whether it is included for adults or paediatrics or both. Of those reviewed, ASD was the most frequent indication included on formularies, followed by LD then ADHD. In comparison to neighbouring CCGs, in BSW melatonin is TLS Red for paediatric patients, restricted to patients with ASD or ASD with ADHD. It is not recommended for routine use for ADHD alone. For young people approaching 18 who will be discharged from paediatric services, melatonin is TLS Amber shared care, noting this should be for a small patient cohort.
- **Other considerations –** For cost effective prescribing:
    1) First line use for all stated off-label conditions: Circadin m/r 2mg tablets. These may be titrated by halving the tablets if needed, and still maintain their prolonged release properties. In 2022, a new immediate release formulation called Adaflex was launched and is licensed for insomnia in children and adolescents aged 6-17 years with ADHD, where sleep hygiene measures have been insufficient. It was noted that there would be considerable cost savings for patients on doses of 4mg or more a day and that this should be explored further to see where this may be appropriate, noting that this is an immediate release formulation compared to Circadin which is modified release.
    2) Second line: Circadin m/r 2mg tablets use in swallowing difficulties – halved or crushed with a spoon.
    3) Third line: Slenyto tablets, where the small diameter (3mm) of the tablet is a significant aid for people with swallowing difficulties, who cannot manage crushing tablets effectively.
    4) Fourth line: melatonin 1mg/1ml soluble solution that is alcohol free, low in propylene glycol and low in sorbitol (E.g. Martindale® or Kidmel® brands). For use in rare hereditary conditions of galactose intolerance, the LAPP lactase deficiency or glucose-galactose malabsorption. Also for use in people who cannot manage any solid dose form of medication, e.g. with a percutaneous endoscopic gastrostomy (PEG) tube.

Conclusion

The group considered the application, the evidence and the information submitted.

The group acknowledged the challenges and issues that sleep disorders can present and recognised the compelling social anecdotal evidence provided by clinicians at the meeting to support melatonin use for these patients. It was noted that despite being prescribed 'non-formulary' in many cases, significant prescribing across the system for melatonin already takes place and due to this, the implications for existing patients will also need considering when decision making.

The application requested the addition of melatonin on the formulary for use in ADHD, autism and LD as independent indications. The evidence focuses on a wider patient cohort rather than focussing on individual indications, although some evidence suggests greater improvement to sleep in autism patients overall. It was noted that there is a placebo-controlled trial for use of Slenyto for ASD. Discussions took place around the value of melatonin on a population health basis. Recognising the anecdotal evidence, the group discussed the possibility of potential support from teams within the ICB to collate the evaluation data on melatonin use locally.

The group recognised that the impact of any formulary change could present a significant cost to the system and that this decision would need agreement from the appropriate senior team within the ICS.

The group recognised that the BNSSG Adult Formulary includes melatonin use for adults with Learning Disabilities and sleep disturbance who also have a co-morbid mental illness (for example Depression, Mania, Psychosis, Dementia etc.) OR disorder (for example Autism or Autistic Spectrum, Anxiety Disorders, Adult ADHD etc, however the BNSSG Paediatric formulary explicitly excludes ADHD. The paediatric formulary includes melatonin use for children with neurodevelopmental disorder/disability with intrinsic sleep disorder (difficulty getting to sleep or remaining asleep) who have exhausted all behavioural sleep hygiene options, but *not* for use in ADHD or autism or learning disabilities. The group agreed the formulary should be consistent and equitable across adults and paediatrics and a review of this should be prioritised. The group noted the importance of ensuring there are clear guidelines in terms of starting treatment, stopping treatment, duration of treatment and drug holidays/management of melatonin.

The group considered the guidelines and evidence around melatonin, acknowledging the NICE recommendations for ASD and LD patient cohorts in particular and were minded to explore including on the

formulary. It was agreed that further discussion is needed for all indications and if included onto the Formulary, the traffic light status would also need to be discussed and agreed.

The group were not quorate during the meeting but also felt that due to the complexity of the application and financial impact across the system, that further reflection and wider discussion was needed at the December Joint Formulary Group meeting.

Action:

1. The Formulary team to summarise discussions from October meeting and bring back to December meeting for further discussion
2. Formulary team to find out what representation is needed at December JFG and if anyone else needs inviting

Melatonin *(Paediatrics)*: Off-label for use on PICU and HDU (during hospital stay only) to aid onset of sleep in patients with neurodevelopmental disorders/ASD and other conditions e.g. bone marrow transplant and renal patients who are suffering from sleep cycle disorder following prolonged stays and who have not responded to standard sleep hygiene measures.

Discussion

[redacted] presented the new drug request application for melatonin for off-label for use on PICU and paediatric HDU during hospital stay only to aid onset of sleep in patients with neurodevelopmental disorders/ASD and other conditions e.g. bone marrow transplant and renal patients who are suffering from sleep cycle disorder following prolonged stays and who have not responded to standard sleep hygiene measures. The anticipated number of patients likely to receive treatment within BNSSG are 50 patients per year for short term use (1-4 weeks). [redacted] advised approximately half of the patients who are issued melatonin on PICU/HDU are already on melatonin at home, therefore the number of new initiations would be much smaller than the estimated 50 patients per year which is based on annual dispensing data. [redacted] advised patients who have prolonged stays at PICU and HCU can often suffer from disordered sleep once they are weaned from sedation. Careful weaning of sedative medications is undertaken to reduce the risk of any withdrawal effects that could be contributing to impaired sleep pattern. Any possible improvements in relation to sleep hygiene are the first line option for treating disordered sleeping in PICU and HDU (although not always as easy to comply with in a hospital setting where noise and light cannot be fully removed from the setting). If nursing staff and parents report significant impairment to sleep cycle such as frequent waking, prolonged time taken to get to sleep and/or daytime somnolence then this will be reported to the doctors who will decide if a short term course of melatonin may be suitable. The medication is only used short term and, in most patients, will be at a dose of 2 or 4mg every night. If there is no improvement after a few nights then a higher dose may be considered or switching to another sedating agent such as chloral hydrate may be considered. Medication will be reviewed regularly (at least weekly) with the medication stopped if sleep significantly improves and will always be stopped prior to step down to a general ward.

Decision Criteria used by JFG for NDR

- **Patient safety –** None of articles reviewed provided evidence for patient safety in the use of melatonin in a PICU/HDU setting. However, there is evidence that demonstrates a good safety profile more broadly in paediatric populations for sleep indications. The evidence on adverse events (AEs) lacks support from systematic and rigorous safety studies and meta-analyses (Kennaway, 2015). The studies identified in this review found little evidence of serious AEs. Where AEs were reported, they were minor and infrequent and included headaches, migraine, feeling cold, mood dip, decreased appetite, dizziness, bed-wetting, hyperactivity, drowsiness, agitation, and fatigue (van Geijlswijk, 2010 and McDonagh, 2019). Bruni et al (2015b) identified that there is a need for long-term safety studies as well as for studies on fertility, for which animal data are variable and human data are lacking.
- **Clinical effectiveness –** None of the articles reviewed provided evidence for clinical effectiveness in the use of melatonin in a PICU/HDU setting. Procaccini and Kudchadkar (2021) found that prescriptions of melatonin for sleep indications in paediatric inpatients of a tertiary hospital, including those on PICU, has increased substantially over a 4-year period, despite a lack of evidence. This study relied on dispensing data and did not reveal anything about the efficacy of treatment with melatonin. There is evidence to suggest that the use of melatonin in paediatric populations for sleep indications have statistically significant beneficial effects. Systematic reviews by McDonagh et al (2019), Ferracioli-Oda et al. (2013) and van Geijlswijk, (2010) all assessed the efficacy of melatonin in terms of sleep latency and sleep duration. Results were variable and the range of improvement was variable across the

studies, however overall study findings showed an improvement in sleep onset latency and sleep duration. Although, effect sizes might be too modest to be clinically significant.

	McDonagh et al (2019)	***Ferracioli-Oda et al. (2013)***	***van Geijlswijk, (2010)***
Sleep latency	28 minutes (11 - 51)	7.06 minutes (4.37 - 9.75)	16.04 minutes
Sleep duration	33 minutes (14 - 68)	8.25 minutes (1.74 - 14.75)	28.39 minutes

- **Strength of evidence –** There is a lack of evidence on the use of melatonin in PICU and HDU environments, and only one retrospective study analysed the use of melatonin in paediatric patients in these settings. This study relied on dispensing data and did not reveal anything about the safety and efficacy of treatment with melatonin. However, there is evidence that may support the use of melatonin for sleep indications in paediatric patients including systematic reviews, two randomised controlled trials and other quantitative evidence such as a retrospective analysis, consensus findings from a conference and a letter to the editor. Of the higher quality evidence available, overall, the evidence is limited to mostly small samples and heterogeneity between studies. Research questions focused on sleep latency, sleep duration and sleep quality, the effect sizes of which may be too small to be clinically significant.
- **Cost effectiveness or resource impact –** No studies of cost-effectiveness were identified. Circadin® MR tablets costs £0.30 - £1.50 per day (based on current UHBW contract price) for a dose range of 2-10mg. The most common dose is 3mg daily which costs £0.45 per patient day. It has been estimated that approximately 50 patients per year will be prescribed melatonin in PICU/HDU for up to 4 weeks. For this cohort and for the maximum treatment duration, this would have a relatively small cost implication of approximately £735 per year. Costs estimated based on common doses used in practice. Melatonin liquid, which is more expensive, has not been dispensed to any patients on PICU for this indication in the last year and would only be used in exceptional circumstances.
- **Place in therapy relative to available treatments –** Melatonin use for this indication would be offered second line following a review of any medication causing insomnia and sleep hygiene improvement. The third line option for this cohort is chloral hydrate. Use of melatonin would replace or at the very least reduce the use of other sedatives which may have a more harmful side effect profile. Melatonin for this indication would be TLS Red on the BNSSG Paediatric Formulary, restricted to use on PICU/HDU only and not to be continued on discharge.
- **National guidance and priorities –** There is no national guidance relative to the use of melatonin in paediatric patients on an ICU or HDU setting. Various NICE guidelines include melatonin as an option for sleep indications in children.
- **Local health priorities –** Formulary review of melatonin indications is a high priority locally.
- **Equity of access –** A total of 29 CCG Formularies were reviewed to determine whether other areas include melatonin for use in PICU/HDU on their formulary. No other formularies specified use for this indication/cohort, however many formularies included the use of melatonin in paediatrics for other sleep indications. In BNSSG, melatonin is already on the paediatric formulary as TLS amber 3 months for children with neurodevelopmental disorder/disability with intrinsic sleep disorder (difficulty getting to sleep or remaining asleep) who have exhausted all behavioural sleep hygiene options. In BNSSG, for adult patients, melatonin is included on the formulary for ICU to prevent delirium.

Conclusion

The group considered the application, the evidence and the information submitted. The evidence supports the use of Melatonin for short term use for the specified patient cohort. Melatonin is included onto the BNSSG Adult Formulary for ICU patients (to prevent delirium). Melatonin has a good safety profile, and there is sufficient evidence to suggest melatonin is effective in improving onset and duration of sleep, despite variation in improvement found in the evidence. The group agreed to include Melatonin onto the BNSSG Paediatric Formulary as TLS red as the perceived benefits on sleep may support healing and recovery in this cohort of patients with a small financial impact.

Action:

1. The Formulary team to include Melatonin for off-label for use on PICU and HDU (during hospital stay only) to aid onset of sleep in patients with neurodevelopmental disorders/ASD and other conditions e.g. bone marrow transplant and renal patients who are suffering from sleep cycle disorder following prolonged stays and who have not responded to standard sleep hygiene measures onto the BNSSG Paediatric Formulary as TLS red.

Date of Meeting	Time	Venue	Meeting Type
~~25-Jan-2022~~	~~13:00 – 16:00~~	~~Virtual, Microsoft Teams~~	~~Adults Only~~
~~15 March 2022~~	~~09:30 – 13:30~~	~~Virtual, Microsoft Teams~~	~~Adults & Paediatrics~~
~~26 April 2022~~	~~13:00 – 16:00~~	~~Virtual, Microsoft Teams~~	~~Adults Only~~
~~14 June 2022~~	~~09:30 – 13:30~~	~~Virtual, Microsoft Teams~~	~~Adults & Paediatrics~~
~~26 July 2022~~	~~13:00 – 16:00~~	~~Virtual, Microsoft Teams~~	~~Adults Only~~
~~13 Sept 2022~~	~~09:30 – 13:30~~	~~Virtual, Microsoft Teams~~	~~Adults & Paediatrics~~
01-Nov-2022	13:00 – 16:00	Virtual, Microsoft Teams	Adults Only
13-Dec-2022	09:30 – 13:30	Virtual, Microsoft Teams	Adults & Paediatrics

Healthier Together

Improving health and care in Bristol, North Somerset and South Gloucestershire

BNSSG Joint Formulary Group Meeting – Adults and Paediatrics

Meeting Held on: Tuesday 13th December 2022
Time: 09:30 – 13:30
Venue: Virtual – Microsoft Teams

Minutes

Present:

[redacted] (Chair)	Deputy Director (Medicines Optimisation), BNSSG, ICB
[redacted] (Minutes)	Team Administrator & Minute Taker, BNSSG ICB
[redacted]	Principal Medicines Optimisation Pharmacist, BNSSG ICB
[redacted]	GP Clinical Lead in Prescribing for BNSSG ICB
[redacted]	Interface Pharmacist, BNSSG ICB
[redacted]	Interface Pharmacist, BNSSG, ICB
[redacted]	Interface Pharmacist, BNSSG, ICB
[redacted]	Medicines Information Pharmacist, UHBW
[redacted]	Chief Pharmacist, Bristol Children's Hospital, UHBW
[redacted]	Lead for Pharmacoeconomics & High Cost Drugs, NBT
[redacted]	Principal Clinical Scientist, UHBW
[redacted]	Medicines Safety Officer, Sirona Care and Health
[redacted]	High Cost Drugs Pharmacist Technician, BNSSG, ICB
[redacted]	UHBW Pharmacist, UHBW
[redacted]	Consultant Pharmacist, Rheumatology, NBT
[redacted]	Director of Pharmacy, NBT
[redacted]	Neonatal Consultant, NBT
[redacted]	Head of Clinical Engineering, UHBW
[redacted]	Senior Medicines Optimisation Pharmacist, BNSSG, ICB
[redacted]	Senior Medicines Optimisation Pharmacist, Diabetes Lead, BNSSG, ICB
[redacted]	GP and Clinical Lead in Exceptional Funding and Policy Development

Apologies:

[redacted]	Clinical Pharmacy Manager, UHBW
[redacted]	Formulary Pharmacist, NBT

Applicants:

[redacted]	Stroke Consultant, NBT
[redacted]	Consultant Ophthalmologist, UHBW
[redacted]	Consultant Gastroenterologist, NBT
[redacted]	Hypertension, Clinical Nurse Specialist, UHBW
[redacted]	Clinical Nurse Specialist, UHBW

1 Welcome and Apologies

[redacted] opened the meeting as chair. Introductions were made and apologies were noted as above. The meeting was quorate. There were no declarations of interest recorded.

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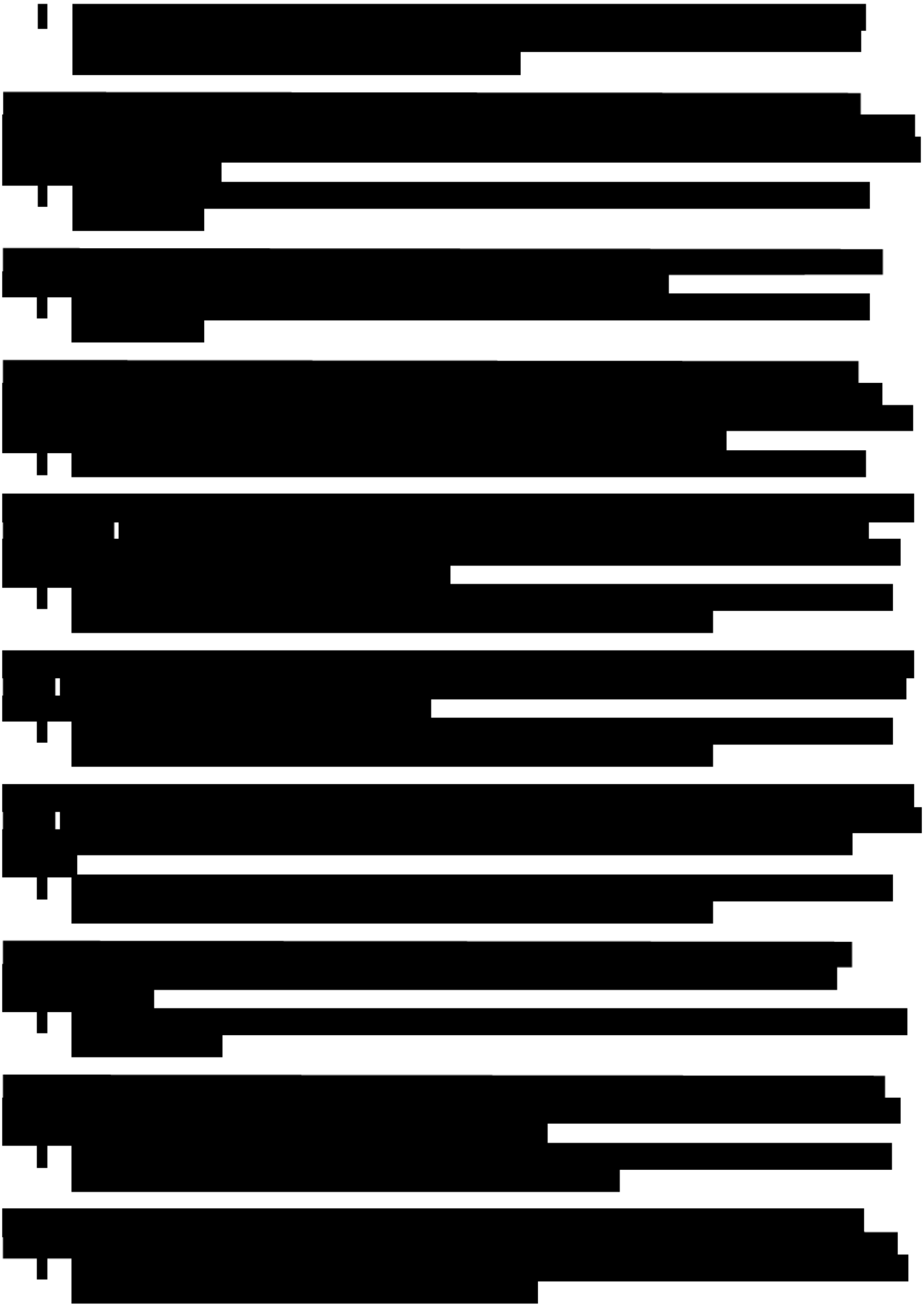

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Ref 27.5 – Melatonin (Adults and Paediatrics): off-label use for sleep disorder in adult and paediatric patients with any of: ADHD, ASD or LD - *The Formulary team to summarise discussions from October meeting and bring back to December meeting for further discussion*

- The formulary team advised Melatonin is due to be discussed at today's meeting. This action is can be closed

Ref 27.6 – Melatonin (Adults and Paediatrics): off-label use for sleep disorder in adult and paediatric patients with any of: ADHD, ASD or LD - *The Formulary team to find out what representation is needed at December JFG and if anyone else needs inviting.*

- The formulary team advised Melatonin is due to be discussed at today's meeting. This action is can be closed

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doses. Tenecteplase is given as a bolus injection over 2 minutes whereas alteplase is given as an infusion

[redacted]

Insulin eye drops for patients with corneal persistent epithelial defects that are refractory to usual

[redacted]

[redacted]

Discussion

[redacted]

topically acting oral corticosteroids such as budesonide MMX can be used as an alternative treatment

invited to provide comments on the chapter, along with the proposed changes from Secondary care. There

[redacted]

Melatonin for off-label use for sleep disorder in adult and paediatric patients with any of: ADHD/ASD/LD. *Summary of September JFG discussions to be circulated, for further discussion at JFG to agree a formulary position.*

Discussion

[redacted] introduced the new drug request application for Melatonin for off-label use for sleep disorder in adult and paediatric patients with any of: Attention Deficit Hyperactivity Disorder (ADHD), Autism Spectrum Disorder (ASD) or Learning Disabilities (LD) which was discussed at the September Joint Formulary Group meeting (2022). The group felt that due to the complexity of the application and financial impact across the system, further reflection and a wider quorate discussion was needed at the December Joint Formulary Group meeting to further consider the evidence including the local clinical experience.

The following options were suggested for consideration by the Joint Formulary Group and used as a guide to aid discussion:

Option 1 – To approve Melatonin in line with the new drug request application.

- **Formulary position** – This would include all adult and paediatric patients with sleep disorder and either ADHD, ASD or LD.
- **Evidence** –In a Meta-analysis of 19 RCTs, statistically significant results were found showing an improvement of sleep latency and total sleep time. Local clinical evidence, as verbal anecdotal case reports, supports benefit of effect and wider implications on individual, family and social factors.
- **Financial Impact** – £702,469 per annum currently spent across the system. Assumed that this cost is formulary and non-formulary indications the exact split is not known from prescribing spend data. The annual cost will range from £212,956 - £638, 867. The most common dose of 4mg daily would be £425,911 per year. Incremental increase costs for 2023/24 are estimated at:
    - 10% increase would range from £234,252 - £702,754 with the most common dose (4g) at £468,502.
    - 25% increase would range from £266,195 - £789,584 with the most common dose (4g) at £532,389.
    - 50% increase would range from £319,434 - £958,301 with the most common dose (4g) at £638,867.
- **Risks** – CAHMS already prescribing in these cohorts, expect that the financial impact would increase overall with more freedom to prescribe for these cohorts.
- **Benefits** – This would allow equitable access to all.
- **Mitigation** – Agreed initiation, assessment of benefit of effect and discontinuation criteria required. Use of most cost-effective preparation; this may involve off-label use and identification of other prescribing cost-saving initiatives within this patient cohort or wider.

Option 2 – To align adult and paediatric formularies.

- **Formulary position** – Wording to incorporate both current formulary indications:
  Patients with LD and sleep disturbance who also have either: depression, mania, psychosis, dementia or disorder (e.g. ASD, anxiety disorders, ADHD) + Patients with neurodevelopmental disorder/ disability with intrinsic sleep disorder who have exhausted all behavioural sleep hygiene options. Those outside of this indication to remain 'non-formulary.'

- **Evidence –** As per option 1.
- **Financial Impact –** The annual cost will range from £29,598 - £88,794. The most common dose of 4mg daily would be £59,196 per year. Incremental increase costs for 2023/24 are estimated at:
    - 10% increase would range from £32,558 - £97,673 with the most common dose (4g) at £65,116
    - 25% increase would range from £36,998 - £110,993 with the most common dose (4g) at £73,995
    - 50% increase would range from £44,397 - £133,191 with the most common dose (4g) at £88,794.
- **Risks –** Management of non-formulary use. Patient pressure from those without an LD diagnosis i.e. those with ASD, ADHD alone.
- **Benefits –** Equitable access for adult and paediatric patients and facilitates transition prescribing.
- **Mitigation –** Agreed initiation, assessment of benefit of effect and discontinuation criteria required. Use of most cost-effective preparation; this may involve off-label use. Identification of other prescribing cost-saving initiatives within this patient cohort or wider. Develop searches to determine formulary and non-formulary prescribed indications for audit. Review of non-formulary indications.

Option 3 – To approve in line with NICE 'Consider' recommendations and ensure the existing neurodevelopmental disorders indication is incorporated

- **Formulary position –** Wording to incorporate current formulary indication of: Patients with neurodevelopmental disorder/ disability with intrinsic sleep disorder who have exhausted all behavioural sleep hygiene options or patients with LD or patients with ASD. Not for patients with ADHD alone.
  Consider wording such as: Patients with intrinsic sleep disorder who have exhausted all behavioral sleep hygiene options and have either: ASD diagnosis, LD diagnosis, a neurodevelopmental disorder/disability (excluding those with ADHD). Patients with ADHD who also have an ASD or LD or neurodevelopmental disorder/ disability diagnosis are covered by the formulary, but those patients with only an ADHD diagnosis are non-formulary.
- **Evidence –** As per option 1. Also supported by NICE guidance.
- **Financial Impact –** The annual cost will range from £109,084 - £327,252 The most common dose of 4mg daily would be £218,168 per year. Incremental increase costs for 2023/24 are estimated at:
    - 10% increase would range from £119,992 - £359,997 with the most common dose (4g) at £239,985
    - 25% increase would range from £136,355 - £409,065 with the most common dose (4g) at £272,710.
    - 50% increase would range from £163,626 - £490,878 with the most common dose (4g) at £327,252.
- **Risks –** Management of non-formulary use. Patient pressure from those with an ADHD diagnosis. However, 227 (40%) of patients with an ADHD diagnosis who are prescribed Melatonin would be covered by option 3 due to having a co-existing diagnosis of LD or ASD.
- **Benefits –** Equitable access for adult and paediatric patients; facilitates transition prescribing and in line with bordering BSW ICB principles. Supported by national recommendations from NICE where there is an evidence base albeit weak but also supported by local clinical experience. In the 2021 NICE Exceptional Surveillance of ADHD NICE guideline, NICE did not update guideline to include melatonin, advising evidence for its effect on QoL and ADHD symptoms is lacking or equivocal.
- **Mitigation –** Agreed initiation, assessment of benefit of effect and discontinuation criteria required. Use of most cost-effective preparation; this may involve off-label use. Identification of other prescribing cost-saving initiatives within this patient cohort or wider. Develop searches to determine formulary and non-formulary prescribed indications for audit. Review of non-formulary indications.

Option 4 – To not approve Melatonin for any new patient cohorts.

- **Formulary position –** Formulary to remain the same, with the majority of patients remaining 'non-formulary' and this clearly stated.
- **Evidence –** As per option 1.
- **Financial Impact –** The annual cost will range from £17,498 - £52,494 The most common dose of 4mg daily would be £34,996 per year. Incremental increase costs for 2023/24 are estimated at:
    - 10% increase would range from £19,248 - £57,743 with the most common dose (4g) at £38,496.

    - 25% increase would range from £21,873 - £65,618 with the most common dose (4g) at £43,745.
    - 50% increase would range from £26,247 - £78,741 with the most common dose (4g) at £52,494.
- **Risks –** CAHMS already prescribing in these cohorts (n=1144 patients). Not equitable patient cohorts across adult and paediatric patients resulting in variation in prescribing. Prescribing problems through transition. Does not follow NICE guidance, patients with LD or ASD diagnosis only would not be covered by formulary.
- **Benefits –** Clear formulary position for patients and prescribers.
- **Mitigation –** Agreed initiation, assessment of benefit of effect and discontinuation criteria required. Use of most cost-effective preparation; this may involve off-label use. Identification of other prescribing cost-saving initiatives within this patient cohort or wider. Develop searches to determine formulary and non-formulary prescribed indications for audit. Review of non-formulary indications and agreement of how this is managed.

Conclusion

The group considered the application, the further information submitted and the options provided. The group recognised the complexity of the application request and the role melatonin plays in the management of sleep disorder across the system.

The group reached a consensus in support of option 3. Option 3 would include patients with intrinsic sleep disorder who have exhausted all behavioral sleep hygiene options and have either: ASD diagnosis, LD diagnosis, a neurodevelopmental disorder/disability (excluding those with ADHD). Patients with ADHD who also have an ASD or LD or neurodevelopmental disorder/ disability diagnosis would be covered by this clinical recommendation, but those patients with only an ADHD diagnosis would not and would remain non-formulary. Based on current prescribing data and coding available, it was estimated that 227 (40%) of patients with an ADHD diagnosis who are prescribed Melatonin would be covered by option 3 due to having a co-existing diagnosis of LD or ASD.

The group agreed that option 3 reflected NICE recommendations which advise melatonin can be 'considered' for LD or ASD patients. In the 2021 NICE Exceptional Surveillance of ADHD NICE guideline, NICE did not update their guideline to include melatonin. Furthermore, within some meta-analysis, it was reported that children with ASD improved the most compared to other neurodevelopmental disorders. The group acknowledged some of the difficulties presented with obtaining further evidence for these cohorts. The group felt that option 3 also provided equity between adult and paediatric patients across BNSSG.

The group agreed that if melatonin was approved financially for option 3 to be included onto the formulary, a TLS Amber 3 month status would be most appropriate, pending incorporation into a shared care protocol. This indication would need incorporating into the existing shared care protocol on the paediatric BNSSG formulary, which is due for review. The most cost-effective modified release preparation would still need to be prescribed, recognising this may include continuing to prescribe an off-label product. Clear review criteria would need to be agreed. Further resources may need developing such as patient communication/ letters. The formulary and shared care protocol would need to clearly define the approved indication and clarify the definition for learning disability/ neurodevelopmental disorder, with input from applicants to avoid mixed messaging. The formulary page will need to mirror what is added within the SCP for consistency and clarity.

As with all non-formulary prescribing, if clinicians choose to deviate from the formulary it would be expected that the specialist would retain this prescribing and therefore AWP/ Sirona would remain responsible for managing clinician's non-formulary prescribing. Existing patients prescribed non formulary across the system would require ongoing review and further work could take place to support this. Practice searches could be run to monitor formulary and non-formulary prescribing.

Summary

The group made the clinical recommendation that option 3, for patients with intrinsic sleep disorder who have exhausted all behavioral sleep hygiene options and have either: ASD diagnosis, LD diagnosis, a neurodevelopmental disorder/disability (excluding those with ADHD) should be considered for addition to the BNSSG Joint Formulary. Financial approval of the recommendation will need to be sought. The group were asked to reach a clinical recommendation today. The group acknowledged that before any formulary changes could be made, further work would be required to allow review of the financial implications of this

clinical recommendation alongside competing investment priorities across the system. This work would take place outside of the Joint Formulary Group meeting.

Actions:

1. The Formulary team to proceed with work required to seek financial approval for option 3 to be added to the adult and paediatric formulary. Option 3 to remain non-formulary until financial approval gained.

2. Formulary team to add to formulary as TLS Amber 3 months once financial approval and SCP protocol including review criteria is agreed.

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Ref 13.9 – Melatonin (Adults and Paediatrics): off-label use for sleep disorder in adult and paediatric patients with any of: ADHD, ASD or LD – *The Formulary team to summarise discussions from October meeting and bring back to December meeting for further discussion*

- The formulary team advised Melatonin for adults and paediatrics: off-label use for sleep disorder in adult and paediatric patients with any of: ADHD, ASD or LD has been discussed during today's meeting. The group agreed this action can be closed.

Ref 14 – Melatonin (Adults and Paediatrics): off-label use for sleep disorder in adult and paediatric patients with any of: ADHD, ASD or LD – *The Formulary team to find out what representation is needed at December JFG and if anyone else needs inviting*

- The formulary team advised Melatonin for adults and paediatrics: off-label use for sleep disorder in adult and paediatric patients with any of: ADHD, ASD or LD has been discussed during today's meeting. The group agreed this action can be closed.

Ref 14.1 – Melatonin (Paediatrics): Off-label for use on PICU and HDU (during hospital stay only) to aid onset of sleep in patients with neurodevelopmental disorders/ASD and other conditions e.g. bone marrow transplant and renal patients who are suffering from sleep cycle disorder following prolonged stays and who have not responded to standard sleep hygiene measures – *The Formulary team to include Melatonin for off-label for use on PICU and HDU (during hospital stay only) to aid onset of sleep in patients with neurodevelopmental disorders/ASD and other conditions e.g. bone marrow transplant and renal patients who are suffering from sleep cycle disorder following prolonged stays and who have not responded to standard sleep hygiene measures onto the BNSSG Paediatric Formulary as TLS red.*

- The formulary team have included Melatonin for off-label for use on PICU and HDU (during hospital stay only) to aid onset of sleep in patients with neurodevelopmental disorders/ASD and other conditions e.g. bone marrow transplant and renal patients who are suffering from sleep cycle disorder following prolonged stays and who have not responded to standard sleep hygiene measures onto the BNSSG Paediatric Formulary as TLS red. The group agreed this action can be closed.

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December 2022

Date of Meeting 2023	Time	Venue
Tuesday 31st January Adults only	13:00-16:00	Microsoft Teams
Tuesday 21st March Adult and Paediatrics	09:30 – 13:30	Microsoft Teams
Tuesday 9th May Adults only	13:00-16:00	Microsoft Teams
Tuesday 27th June Adults & Paediatrics	09:30 – 13:30	Microsoft Teams
Tuesday 29th August Adults only	13:00-16:00	Microsoft Teams
Tuesday 17th October Adult & Paediatrics	09:30 – 13:30	Microsoft Teams
Tuesday 12th December Adults only	13:00-16:00	Microsoft Teams

BNSSG Joint Formulary Group Meeting – Adults & Paediatrics

Meeting Held on: Tuesday 3rd September 2024
Time: 09:30 – 13:30
Venue: Virtual – Microsoft Teams

Minutes

Present:

[redacted] (Minutes)	Chief Pharmacist, BNSSG, ICB
[redacted]	Team Administrator & Minute Taker, BNSSG, ICB
[redacted]	Principal Medicines Optimisation Pharmacist, BNSSG, ICB
[redacted]	Interface Pharmacist, BNSSG, ICB
[redacted]	Interface Pharmacist, BNSSG, ICB
[redacted]	Formulary Pharmacist, NBT
[redacted]	GPCB Clinical Lead, BNSSG ICB & One Care
[redacted]	High Cost Drugs Technician, BNSSG, ICB
[redacted]	Neonatal Consultant, NBT
[redacted]	Consultant in Acute Medicine & General Internal Medicine, NBT
[redacted]	Principal Pharmacoeconomics Pharmacist, NBT
[redacted]	Associate Director of Pharmacy, Lead Pharmacist for Women's and Children's services, UHBW
[redacted]	Clinical Pharmacy Manager, UHBW

Apologies

[redacted]	Deputy Chief Medical Officer, Primary and Community Care, BNSSG, ICB
[redacted]	Consultant Medical Oncologist, UHBW
[redacted]	Head of Medicines Optimisation, Sirona
[redacted]	Interface Pharmacist, BNSSG, ICB

Applicants

[redacted]	Consultant Gynaecologist, UHBW
[redacted]	GPWER Dermatology, UHBW
[redacted]	Consultant Rheumatologist, NBT
[redacted]	Consultant Anaesthetist, UHBW
[redacted]	Plastic Surgery Registrar, UHBW
[redacted]	Highly Specialised Clinical Pharmacist, AWP
[redacted]	Principal Pharmacist, BNSSG ICB

1 Welcome, Apologies and Declaration of Interests

[redacted] opened the meeting as chair. Introductions were made and apologies were noted as above. The meeting today was quorate. There were no declarations of interest recorded.

2 [redacted]

3 Joint Formulary Group Adults Action Log

Ref 31.6 - Melatonin – NDR - *Formulary team to add to formulary as TLS Amber 3 months once financial approval and SCP protocol including review criteria is agreed.*

- To be discussed at September JFG agenda. Action agreed to close.

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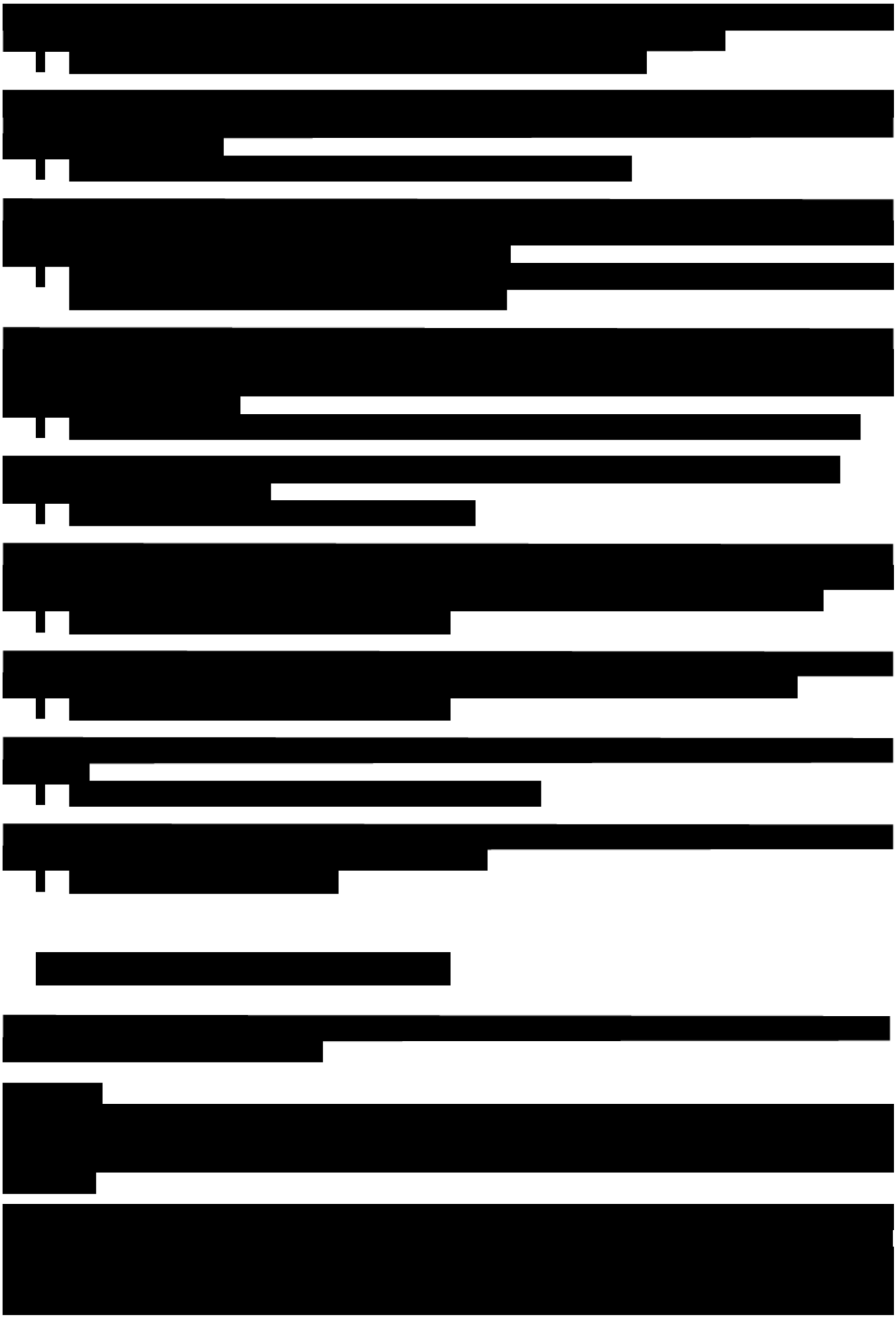

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been produced to date and this would involve a lot more work due to the amount of medicines which do not [redacted]

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Updated SCPs

Melatonin- to include recently approved indications and incorporation of existing REM SCP.

[redacted] presented the Melatonin Shared Care Protocol for adults and paediatrics to the group. Two years ago further indications were approved and work has been underway in incorporating these indications into the Shared Care Protocol along with incorporating the REM Shared Care Protocol. [redacted] highlighted the key points of the Shared Care Protocol with the group. [redacted], Consultant Community Paediatrician, Sirona Care and Health Community Paediatric team and CCHP Bristol, [redacted], Senior Clinical Pharmacist, and [redacted], Highly Specialised Clinical Pharmacist, Lead for CAMHS, Avon and Wiltshire Partnership attended today's meeting to provide comment and answers questions from the group. Following the group's discussion the consensus from the group approved the SCP and the increased dose for REM sleep disorder.

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9 Paediatric Action Log

Ref 14.3 - Melatonin – NDR - *The Formulary team to proceed with work required to seek financial approval for option 3 to be added to the adult and paediatric formulary. Option 3 to remain non-formulary until financial approval gained.*

- Added to September's meeting Agenda for discussion. Action agreed to close.

Ref 14.4 - Melatonin – NDR - *Formulary team to add to formulary as TLS Amber 3 months once financial approval and SCP protocol including review criteria is agreed.*

- Finance paper discussed at APMOC. APMOC were supportive of proposed work. The Formulary Team will liaise with applicants to take this forward. Action agreed to close.

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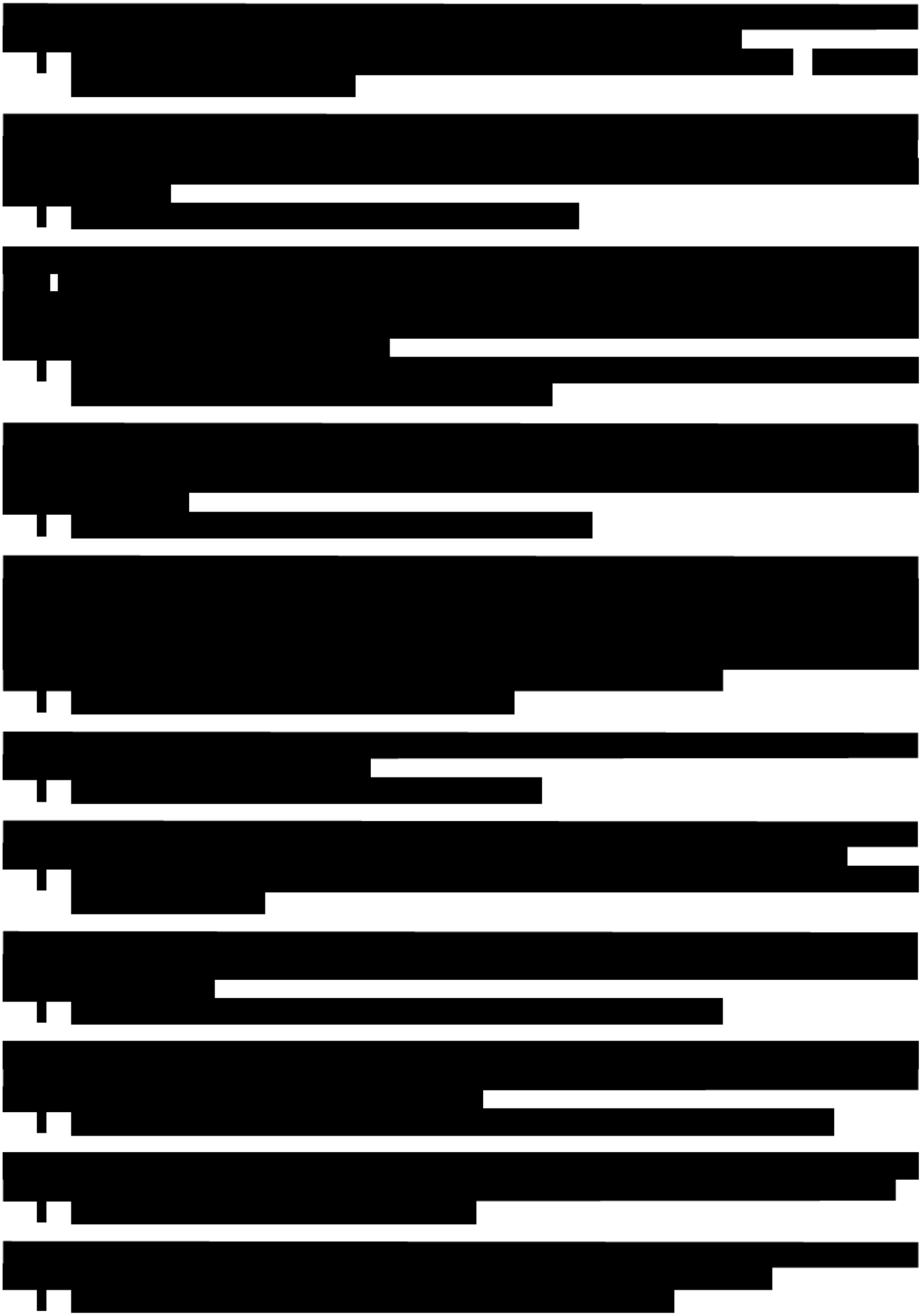

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September 2024

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BNSSG Joint Formulary briefing: Melatonin New Drug Request Application- Further Discussion

Executive Summary

At the September Joint Formulary Group meeting (2022), a joint application for Melatonin was discussed for off-label use for sleep disorder in adult and paediatric patients with any of the following indications:

- Attention Deficit Hyperactivity Disorder (ADHD)
- Autism Spectrum Disorder (ASD)
- Learning Disabilities (LD)

The group felt that due to the complexity of the application and financial impact across the system, further reflection and a wider quorate discussion was needed at the December Joint Formulary Group meeting to further consider the evidence including the local clinical experience.

This report has been produced to summarise the discussions held at the September JFG meeting and to provide the JFG with a list of suggested options to consider to support reaching a decision; whether melatonin should be approved for the requested indications on the Formulary. Further information on patient numbers and impact of prescribing has been sought and is presented within this paper. The September JFG minutes (p16-21) and NDR application are attached for further information.

The Group is asked to consider all the information and make a formulary decision for the melatonin application.

Options for JFG consideration

The following options are to be considered by the Joint Formulary Group and used as a guide to aid discussion with respect to the new drug request application for melatonin for off-label use for sleep disorder in adult and paediatric patients with any of:

- Attention Deficit Hyperactivity Disorder (ADHD)
- Autism Spectrum Disorder (ASD)
- Learning Disabilities (LD)

<table>
<tr><th>Options</th><th>Formulary Position</th><th>Evidence</th><th>Financial Impact</th><th>Risks/Benefit</th><th>Mitigation</th></tr>
<tr>
<td>Option 1: Approve melatonin in line with the application</td>
<td>All adult and paediatric patients with sleep disorder and any of: ADHD, ASD or LD.</td>
<td>Heterogenous evidence base.

Meta-analysis of 19 RCTs statistically significant results were found showing an improvement of sleep latency and total sleep time.

Local clinical evidence, as verbal anecdotal case reports, supports benefit of effect and wider implications on individual, family and social factors.</td>
<td><u>Total System Cost</u>

£702,469 per annum currently spent across the system. Assumed that this cost is formulary and non-formulary indications the exact split is not known due to coding.

<u>Current Costs of Option 1</u>

(n=1144, adults= 241, paediatrics= 843)

Range: £212,956- £638,867

(Most common dose 4mg daily: £425,911)

Costing based on emis data, see appendix 2

<u>Future Costs of Option 1</u>
<table>
<tr><th>Incremental increase for 2023/2024</th><th>Typical dose range</th><th>Most common dose</th></tr>
<tr><td>10%</td><td>£234,252 - £702,754</td><td>£468,502</td></tr>
<tr><td>25%</td><td>£266,195 - £789,584</td><td>£532,389</td></tr>
<tr><td>50%</td><td>£319,434 - £958,301</td><td>£638,867</td></tr>
</table>
</td>
<td>Risks
• CAHMS already prescribing in these cohorts; expect that the financial impact would increase overall.
Benefit
• Equitable access to all.</td>
<td>Agreed initiation, assessment of benefit of effect and discontinuation criteria required.

Use of most cost-effective preparation; this may involve off-label use.

Identification of other prescribing cost-saving initiatives within this patient cohort or wider.</td>
</tr>
</table>

<table>
<tr>
<td>Option 2:
Align adult and paediatric formularies</td>
<td>Wording to incorporate both current formulary indications:
Patients with LD and sleep disturbance who also have either: depression, mania, psychosis, dementia or disorder (e.g. ASD, anxiety disorders, ADHD).
+
Patients with neurodevelopmental disorder/ disability with intrinsic sleep disorder who have exhausted all behavioural sleep hygiene options.

Those outside of this indication to remain ‘non-formulary’.</td>
<td>As per option 1.</td>
<td><u>Current Costs of Option 2</u>

(n=159, adults=78, paediatrics= 81)

Range: £29,598- £88,794

(Most common dose 4mg daily: £59,196)

Costing based on emis data, see appendix 2. Financial impact would be less than option 1 due to restricted cohort.

<u>Future Costs of Option 2</u>
<table>
<tr><th>Incremental increase for 2023/2024</th><th>Typical dose range</th><th>Most common dose</th></tr>
<tr><td>10%</td><td>£32,558 - £97,673</td><td>£65,116</td></tr>
<tr><td>25%</td><td>£36,998 - £110,993</td><td>£73,995</td></tr>
<tr><td>50%</td><td>£44,397 - £133,191</td><td>£88,794</td></tr>
</table>
</td>
<td>Risks
• Management of non-formulary use
• Patient pressure from those without an LD diagnosis i.e. those with ASD, ADHD alone.
Benefit
• Equitable access for adult and paediatric patients; facilitates transition prescribing</td>
<td>Agreed initiation, assessment of benefit of effect and discontinuation criteria required.

Use of most cost-effective preparation; this may involve off-label use.

Identification of other prescribing cost-saving initiatives within this patient cohort or wider.

Develop searches to determine formulary and non-formulary prescribed indications for audit.

Review of non-formulary indications.</td>
</tr>
</table>

<table>
<tr>
<td>Option 3:
Approve in line with NICE ‘Consider’ recommendations and ensure the existing neurodevelopmental disorders indication is incorporated</td>
<td>Wording to incorporate current formulary indication of

Patients with neurodevelopmental disorder/ disability with intrinsic sleep disorder who have exhausted all behavioural sleep hygiene options.
or
Patients with LD
or
Patients with ASD

Not for ADHD alone.

Consider wording such as:

Patients with intrinsic sleep disorder who have exhausted all behavioural sleep hygiene options and have either:

-ASD diagnosis
-LD diagnosis
-a neurodevelopmental disorder/disability (excluding those with ADHD).

Patients with ADHD who also have an ASD or LD or neurodevelopmental disorder/ disability diagnosis are covered by the</td>
<td>As per Option 1

Also supported by NICE guidance.</td>
<td><u>Current Costs of Option 3</u>

(n=586, adults= 130, paediatrics= 456)

Range: £109,084- £327,252

(Most common dose 4mg daily: £218,168)

Costing based on emis data, see appendix 2. Financial impact would be less than option 1 due to restricted cohort but greater than option 2.

<u>Future Costs of Option 3</u>
<table>
<tr><th>Incremental increase for 2023/2024</th><th>Typical dose range</th><th>Most common dose</th></tr>
<tr><td>10%</td><td>£119,992 - £359,977</td><td>£239,985</td></tr>
<tr><td>25%</td><td>£136,355 - £409,065</td><td>£272,710</td></tr>
<tr><td>50%</td><td>£163,626 - £490,878</td><td>£327,252</td></tr>
</table>
</td>
<td>Risks
• Management of non-formulary use
• Patient pressure from those with an ADHD diagnosis. However, 227 (40%) of patients with an ADHD diagnosis who are prescribed melatonin would be covered by Option 3 due to having a co-existing diagnosis of LD or ASD.
Benefit
• Equitable access for adult and paediatric patients; facilitates transition prescribing and in line with bordering BSW ICB
• Supported by national recommendations from NICE where there is an evidence base albeit weak but also supported by local clinical experience.</td>
<td>Agreed initiation, assessment of benefit of effect and discontinuation criteria required.

Use of most cost-effective preparation; this may involve off-label use.

Identification of other prescribing cost-saving initiatives within this patient cohort or wider.

Develop searches to determine formulary and non-formulary prescribed indications for audit.

Review of non-formulary indications.</td>
</tr>
</table>

<table>
<tr>
<td></td>
<td>formulary, but those patients with only an ADHD diagnosis are non-formulary.</td>
<td></td>
<td></td>
<td>In the 2021 NICE Exceptional Surveillance of ADHD NICE guideline, NICE did not update guideline to include melatonin, advising evidence for its effect on QoL and ADHD symptoms is lacking or equivocal.</td>
<td></td>
</tr>
<tr>
<td>Option 4:
Do not approve melatonin for any new patient cohorts.

Keep the formulary as status quo</td>
<td>Formulary to remain the same, with the majority of patients remaining ‘non-formulary’ and this clearly stated.</td>
<td>As per option 1.</td>
<td>Total System Cost

£702,469 per annum currently spent across the system. Assumed that this cost is formulary and non-formulary indications the exact split is not known due to coding.

Current Costs of Option 4

(n=94, adults= 73, paediatrics= 21)

Range: £17,498- £52,494

(Most common dose 4mg daily: £34,996)

Future Costs of Option 4

<table>
<tr><th>Incremental increase for 2023/2024</th><th>Typical dose range</th><th>Most common dose</th></tr>
</table>
</td>
<td>Risks
• CAHMS already prescribing in these cohorts (n=1144 patients)
• Not equitable patient cohorts across adult and paediatric patients resulting in variation in prescribing
• Prescribing problems through transition
• Does not follow NICE guidance, patients with LD or ASD diagnosis only would not be</td>
<td>Agreed initiation, assessment of benefit of effect and discontinuation criteria required.

Use of most cost-effective preparation; this may involve off-label use.

Identification of other prescribing cost-saving initiatives within this patient cohort or wider.</td>
</tr>
</table>

			10%	£19,248 - £57,743	**£38,496**	covered by formulary **Benefit** • Clear formulary position for patients and prescribers	Develop searches to determine formulary and non-formulary prescribed indications for audit. Review of non-formulary indications and agreement of how this is managed.
			25%	£21,873 - £65,618	**£43,745**		
			50%	£26,247 - £78,741	**£52,494**		

Background

Current formulary positions for adult and children

Adult	Paediatric
Adults with learning disabilities and sleep disturbance who **also have either**: Depression, mania, psychosis, dementia or disorder (e.g. ASD, anxiety disorders, adult ADHD etc)	Children with neurodevelopmental disorder/ disability with intrinsic sleep disorder who have exhausted all behavioural sleep hygiene options. This excludes ADHD or ASD or learning disabilities.

Review of 29 CCGs: Inclusion of melatonin on formulary (any traffic light status)	**Adults**	**Paediatrics**
ASD	18	17
LD	10	11
ADHD	6	13
Neurological behaviour/ development	2	10

Applicant's Summary/ Further information:

All applicants reported a melatonin deficit in the indications for which melatonin treatment was requested. Improvements to sleep and the beneficial impact on quality of life by the patient and also the family/carer were reported by all.

For children, melatonin was noted to improve behaviour and concentration in school and reduce the risk of placement breakdowns with families. It was acknowledged that the majority of these patients will require long term treatment with melatonin, although regular review breaks are used in addition to maintaining sleep diaries. It was noted that hypnotics (benzodiazepines and Z-drugs) are not appropriate to use in children.

For adult patients with ADHD, re-setting the delayed sleep phase pattern could improve cognition to support further work, education and quality of life. Treatment is often started as a child and the applicant reported that adults notice a difference if this is stopped when patients are in transition between paediatric and adult services. Prescribing may also be long-term.

For adult LD patients (a smaller patient cohort), treatment would be life-long. These patients are at risk of polypharmacy and hypnotics would not be a suitable option.

Questions posed to the applicants during the meeting:

1. The JFG asked applicants whether it would be possible to determine a more restricted cohort who would most benefit from treatment but applicants advised this is not possible. Melatonin levels are known to be low in all the requested indications.

Applicants were also unable to provide any further breakdown of their patient numbers between ASD and ADHD due to their prescribing systems and records. Emis searches have been used to estimate a breakdown of patient numbers for each indication and have been included in Appendix 2.

2. The JFG asked applicants whether there would be the potential for further audit work to capture melatonin's benefit locally on a population basis. Applicants noted difficulty with undertaking such work because the patient cohort are heterogenous (especially those with LD), issues with consent, ethical considerations and lack of capacity within the teams.

Summary of JFG Discussion

The JFG acknowledged the challenges and issues that sleep disorders can present and recognised the compelling social anecdotal evidence provided by clinicians at the meeting. The group discussed the possibility of potential support from teams within the ICB to collate evaluation data on melatonin use locally but it was not clear how this would significantly contribute to the decision making much further, noting there is already evidence (albeit low quality trials) and there are now licensed formulations for some indications (e.g. Slenyto brand is licensed for 2-18 year olds with ASD).

The group agreed addressing the inequity between the adult and paediatric formulary should be the first priority.

The group noted the importance of ensuring there are clear guidelines in terms of starting treatment, stopping treatment, duration of treatment and drug holidays/management of melatonin.

Sept 2022 Discussion of Decision-Making Criteria- Summary

- **Patient safety – Met -**Studies found melatonin to be safe and well tolerated with less risk associated with melatonin than Z drugs or BDZs that may be given in adults, but would not be used for children.
- **Clinical effectiveness – Met (individual basis met, population level undetermined).**
  In meta-analysis of 19 RCTs (McDonagh et al 2019), statistically significant results were found showing an improvement of sleep latency (11-51 minutes, median 28 minutes) and total sleep time (14-68 minutes, median 33 minutes).
  The applicants were able to share anecdotal reports of how melatonin has improved their patient's quality of life and carer/ family quality of life, noting improvements on performance at school and at home.
- **Strength of evidence – Met (but poor quality).** Generally low quality trials and anecdotal evidence from applicants (weak). Limitations include: research groups are not limited to patients with ASD, ADHD or LD; heterogeneity of populations; risk of

bias (use of sleep diaries); short term duration; various melatonin preparations used; various methods used to assess efficacy. NICE recommend clinicians to 'consider' melatonin in LD and autism. NICE use 'consider' to reflect a recommendation for which the evidence of benefit is less certain.

- **Cost effectiveness or resource impact – For further discussion?**
  The group were not able to conclude whether melatonin provided good value to the system on a population basis.
  Current prescribing of melatonin already presents a substantial cost to the system of £702,468.50 per annum (£335,191.50 for AWP and Sirona combined and £367,277 by GP Practices). The applicants reported wider potential cost benefits in terms of improving sleep such as ability to work, performance at school, retention of placements for LD, improved quality of life for patient and other family members, however these potential cost benefits are anecdotal reports and costs are not confirmed by evidence.
- **Place in therapy relative to available treatments – Agreed.** 3rd line, following non-pharmacological treatments.
- **National guidance and priorities –NICE NG11 and NICE CG170: 'consider' melatonin for LD and autism.**
- **Local health priorities – Unclear for the system but considered a high priority by specialists to make shared care and reduce prescription workload.**
- **Equity of access – Formulary positions vary widely for inclusion and traffic light status.** In comparison to neighbouring BSW, melatonin is TLS Red for paediatric patients, restricted to patients with ASD alone or ASD with ADHD. It is not recommended for routine use for ADHD alone. For young people approaching 18 who will be discharged from paediatric services, melatonin is TLS Amber shared care, noting this should be for a small adult patient cohort.

Key issues for further discussion:

1. Based on the evidence available, the Group needs to determine whether melatonin provides good value to the system on a population health basis. The Group must consider the opinion of the local specialist's clinical experience, patient reported outcomes and trial data that supports individual patient and the wider benefits melatonin is reported to give.
2. Although there is a Formulary position supported by determined patient groups within the current shared care protocols, significant prescribing across the system for melatonin is already taking place and the implications for existing patients will need considering when decision making.
3. Noting the NICE recommendations for ASD and LD, along with the evidence from meta-analysis showing children with ASD having most improvement, the group were minded to explore and discuss including melatonin on the formulary for ASD and LD in particular.

Post JFG decision, the commissioning implications of any formulary change which may impact on system budgets would need agreement within the ICS. This includes any impact on TLS status.

Recommendation

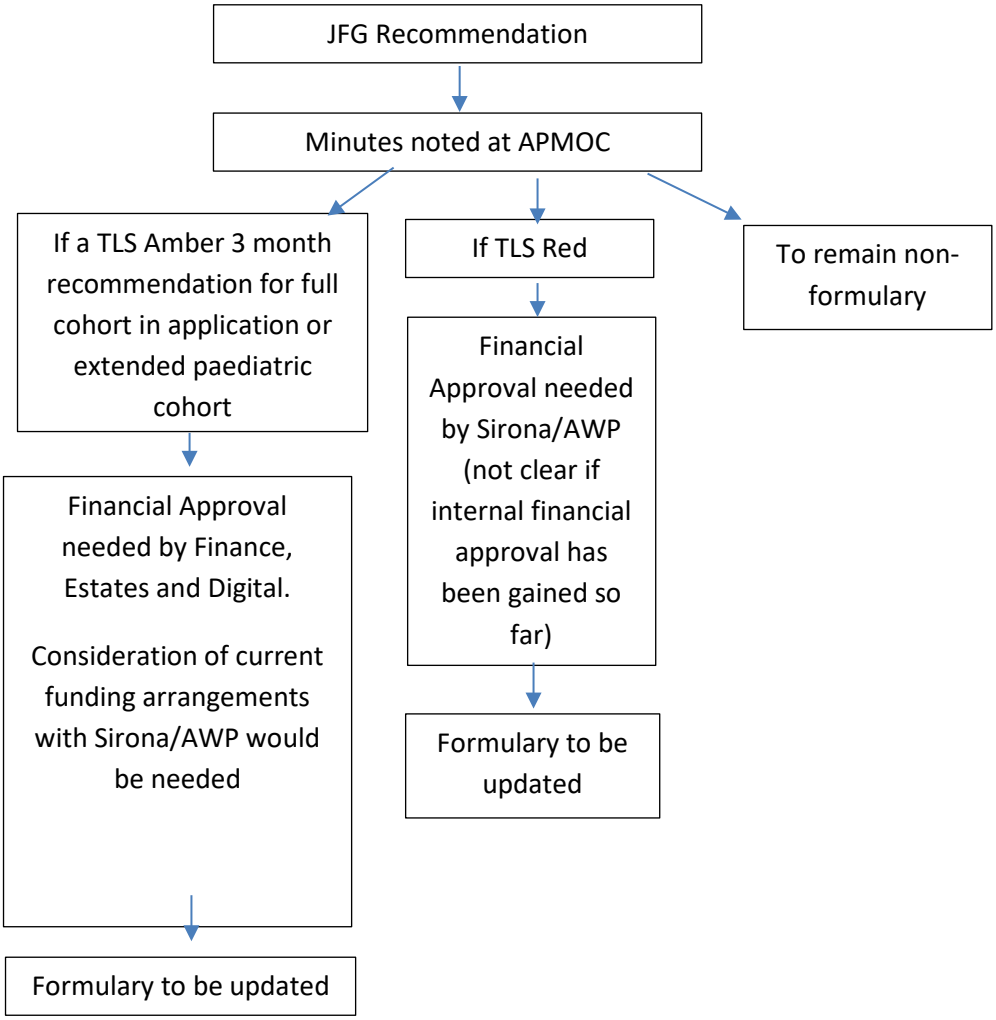
1. JFG are asked to make a clinical recommendation on the formulary application for melatonin in line with the decision-making criteria.

2. JFG are asked to make a recommendation on the TLS of the decision made.
3. JFG to agree the next steps for the application to be ratified. See *Appendix 1 for Next steps following JFG Decision Flow Chart.*

Appendices

Appendix 1

Next steps following JFG decision



Appendix 2

Separate Excel attachment: *Patient Numbers and Cost Analysis*