Medicines Optimisation 20222/23 QIPP Implementation

Clinical Area
Branded generic prescribing for melatonin preparations

Background – Local and national drivers

Melatonin is a hormone produced by the pineal gland in the brain and helps to regulate the sleep-wake cycles.

Melatonin is mainly used to treat short-term sleep problems in people aged 55 years and over. It can also be prescribed by specialists to help people with longer-term sleep disorders and this may include children and adults including those with ADHD or other neurodevelopmental disorders.

In recent years there has been a significant increase in the prescribing of both different formulations and strengths that are available from a number of manufacturers. Melatonin comes as both immediate release (IR), modified release (MR) tablets and capsules. Both formulations come in preparations that are licensed and unlicensed.
The various different strengths and formulations available amongst the different preparations may have varying licensing statuses for specific populations. Capsules are significantly costlier than tablets.

There are various liquid solutions and suspensions available, many of these products are “specials” and may also have an unlicensed status/” off-label” use. The liquid formulations have varying quantities of required excipients needed for the proper functioning of the product. The sugar, alcohol and propylene glycol (PEG) content varies between the products. An upper threshold for PEG excipient has been set for children under 5 years of age, the EU considers that PEG content should not be exceed and anything above this would be deemed unsafe: 50mg/kg/day in children between 1month-4 years of age.

It is good practice to prescribe by brand from a clinical safety perspective to ensure that the patient receives a consistent product and licensing considerations have been made at point of prescribing. Brand also reduces the risk of confusion in dispensing and administration. From a clinical safety perspective this is especially important when a liquid brand is specified due to the varying amounts of excipients between different liquids
Furthermore, this will provide best value to the NHS when a cost-effective brand is selected as the costs vary significantly and when certain strengths and brands/formulations have much higher costs associated.

Aim: To use the most cost-effective preparations across NEL

Recommendations:

- **No prescribing** of melatonin for short-term treatment of **jet lag** in adults
- Switch patients to **tablet** formulation.
    - All melatonin capsules will be considered non-formulary as they are associated with significant higher costs and no clinical advantage.
- Where an immediate preparation is required, - Initiate all patients on first line branded generic:
    - **Adaflex® Tablets (immediate release tablets [IR])** where appropriate. This is because it is a licensed preparation for the clinical cohorts it is to be used in and comes in a range of strengths. And Adaflex® licensing covers the drug being used in a crushed form.
    - Cyesto® - second line as not available in full range of strengths
- If a modified release (MR) preparation is required, adopt first line preference:
    - **Generic MR tablet** OR
    - **Circadian® MR tablet** (where patients are already stabilised on this)
    - **Slenyto®** 1mg and 5mg is appropriate if for insomnia aged 2-18 with Autism Spectrum Disorder (ASD) and / or Smith-Magenis syndrome,
- If a patient requires a liquid preparation consider initially **Adaflex® IR tablet crushed and mixed with water prior to administration.**

- This includes children who were previously using oral liquids but if appropriate as they get older can consider switch to oral solid tablet form.

- Where a liquid formulation is required, preferred **choices are Kidmel® and Ceyesto®** as they meet the excipient requirements and more cost-effective choices
  - **NB: Colonis® 1mg/ml liquid is unlicensed for children 5years and under**

The table below highlights the cost-savings that can be generated if all capsules and prescribing for immediate release preparations are switched to corresponding Adaflex® brand based on NEL ICB prescribing data for these preparations for the financial year 2022-23.

Current Products Prescribed in 2022-23	**Sum of Cost 2022-23**	**Proposed recommended product: Adaflex®** [1mg, 2mg, 3mg,4mg 5mg IR Tablet]	**Potential Cost-Saving**
Melatonin 1mg, 2mg, 3mg, 5mg & 10mg IR Capsules	£217,718	£88,155	£129,563
Melatonin 1mg/ml oral solution The 1mg/ml has been chosen to calculate savings as it represents the largest denominator of all liquid strengths prescribed	£461,158 with unit average cost of £0.99 Total cost of all liquids = £488,950.68	Adalfex® tab unit cost £0.6 which is 39% cheaper	£179,851

* As doses used for liquids are unknown, applying average unit cost
There will be additional savings on other strengths of liquids if they are switched to Adaflex® tablets.

However, not all patients will be suitable, and 100% switch cannot be assumed.
Thus, assumption made that 20% of patients switched from liquid to crush tablets or able to transfer from liquid to swallowing tablets, presents further opportunity of £15K savings.

The selected recommended brands are based on the ones with lower NHS indicative price when compared to other brands in the market, but also most appropriate in terms of licensing, clinical and safety. available in most of the strengths. The recommendation includes more than one brand as to avoid potential issues such as shortages.

Action for practices

The ask is for practices to identify and review all patients across NEL ICB who have been prescribed either generic or branded melatonin capsules, IR or MR tablets or liquid preparations. If patients are clinically indicated to remain on these medications without any contraindication to the recommended brands, switch to the recommended cost-effective brands as per QIPP initiatives.

Practices are encouraged to work closely with their local community pharmacies to ensure there are stock available and able to obtain these products from wholesalers before making any switches.
The aim is to achieve 50% of capsules to tablets to release £65k and minimum 20% switch of liquid preparations to Adaflex® tablets to release £15k.

Resources and information packs will be provided to primary care upon approval from FPG.

Ask of practices:

1. Run a search on clinical system to identify patients who are currently receiving prescriptions for all strengths of melatonin capsules and tablets prescribed generically or any alternative brands. NB: many liquid preparations are unlicensed and may have varying excipient content.

2a. Review and assess the ongoing clinical need for patients to remain on these products in line with local and national guidance.

2b. New patients, or existing patients requiring an alternative formulation/dose review: the most cost-effective clinically suitable product from the table above should be prescribed.

- Existing patients:
  - o where patient is prescribed a formulation that is not listed above, specialists should consider a switch to one of the preferred options (especially where high-cost, unlicensed products are prescribed)
  - o where patient is stable on a formulation listed above, treatment can continue until a review of the dose or formulation is needed. At this point, the most cost-effective clinically suitable product from the table above should be prescribed.

3. Review the quantity prescribed on repeat and frequency of issues
4. Check whether patient has had previous intolerance or contraindications to the recommended brands before switching (this includes allergies status). See under exclusion criteria for full information.
5. If patient is not suitable for switches, please consider adding consultation note with rationale for remaining on non-preferred brand
6. If melatonin continues to be clinically indicated and your patient is suitable for switches, please consider switching to the specific generic brands below:

Formulation	Product name	Formulary position	Licensing	Notes
Immediate release preparation required	**Adaflex®** IR tablets 1mg, 2mg, 3mg, 4mg and 5mg tablet Cyesto® IR 3mg tablets	**First line formulary choice of melatonin** When an IR form is preferred: ▪ in patients where initiation of sleep is difficult and may be helped by a shorter onset of action ▪ those with a swallowing difficulty ▪ where a daily dose of melatonin MR is increased above 2mg daily (Adaflex® is more cost effective at doses of 4mg daily and above, & requires fewer tablets per dose) ▪ if a lactose free preparation is needed	• Insomnia in children and adolescents aged 6-17 years with ADHD, where sleep hygiene measures have been insufficient Use< 6yrs (off-label) • Use in other age groups is off-label • Insomnia in children and adolescents aged 6-17 years with ADHD, where sleep hygiene measures have been insufficient • Use< 6yrs (off-label)	Tablets can be crushed and mixed with water directly before administration (licensed use – see SPC). Lactose free Available in range of strengths 1mg-5mg. Off-label use for administration via PEG enteral feeding tubes.

			• Use in other age groups is off-label	
Modified release preparation required	Generic melatonin MR 2mg or Circadin®(where already established on this).	Formulary choice where a MR preparation is required e.g. maintaining sleep	Licensed >55yrs short term primary insomnia	Crushing the MR tablet render the modified release properties making it immediate release (IR) and off-label use. Unlicensed use for administration via PEG enteral feeding tubes.
Modified release preparation required	Slenyto® MR 1mg and 5mg	Formulary choice where patients on high (10mg) doses only	Licensed for insomnia 2-18yr with Autism Spectrum Disorder (ASD) and / or Smith-Magenis syndrome, (first line preparation for these patients)	Formulated as a microtab to facilitate Adherence.
Liquid formulation required	Crushed and dispersed Adaflex® immediate release tablets	First line formulary choice of melatonin where a liquid preparation is required.	Licensed in use 6-17yrs Off-label in other populations	See SPC for directions In glass with a small amount of plain water (30 – 50mls), add an Adaflex tablet. The tablet should breakdown in the water but can use a spoon to crush the tablet. Once crushed, mix the tablet into the water and administer.
Liquid formulation (alternative) *NB: only to be considered where clinically excluded from using other products (e.g. PEG)	Kidmel® melatonin 1mg/1ml oral solution Ceyesto® 1mg/ml oral liquid (Branded generic - from Phoenix & Alliance)	2nd line formulary position and considered low content for sugar free, alcohol free and PEG Kidmel excipients: •12.66 vol % ethanol (alcohol) •210 mg sorbitol per mL •1.5 mg propylene glycol per mL Ceyesto excipients:	Unlicensed Special	Prescribe by brand so as to get the SF and alcohol-free product. Requires letter to demonstrate clinical need for community pharmacists to obtain. NB: Some products e.g. Colonisl® liquid

		Propylene glycol (E1520): 52 mg per 1 ml dose Benzyl alcohol: 6 mg per 1 ml dose		(licensed 6-17yrs) has a PEG content deemed unsafe in children <5yrs as per EMEA Other liquids are very High cost

7. Please consider having a consultation with patients prior switching to the recommending brands. A template letter (Appendix 1) has been attached in this document for use or adaption by the practice if needed.

Exclusion criteria:

- Allergy (hypersensitivity) to the active substance, or to any of the excipients in the recommended brands (see under SPCs).
- History of intolerance to the recommended brands.

Summaries of product characteristic: to attach SPCs

Adaflex SPC - https://www.medicines.org.uk/emc/search?q=adaflex
Circadin SPC - https://www.medicines.org.uk/emc/product/2809
Slenyto SPC - https://www.medicines.org.uk/emc/search?q=%22Slenyto%22

Key messages

- Use of tablets only. Switch patients who are on capsules to tablets.
- New patients to be initiated on first line choices.
- Where the MR preparation is being crushed or a liquid preparation is required consider using Adaflex®.
- Review children who were initially initiated on liquid but can consider tablets as they get older.
- When patients are being considered for switching, the opportunity should be used to review ongoing need for melatonin, particularly in young people approaching their 18th birthday.
- Consider de-prescribing in adults where use for insomnia (short term) >55yrs exceeds 3months.
- No prescribing for indications of jet-lag.

Other immediate release formulations of melatonin are considered non-formulary and not recommended due to licensing or cost:

- o Melatonin 1mg/1ml oral solution by Colonis Pharma® Ltd
- o All other strengths except 1mg/ml of unlicensed special solutions and suspensions of melatonin
- o All other strengths and brands of melatonin tablets (apart from listed above)
- o All strengths of melatonin capsules.

Available resources

Patient letter to inform of switch – Appendix 1
Template letter of clinical need for use of Kidmel® / Ceyesto® for community pharmacy (available from Available from Alliance and Phoenix) - Appendix 2
BNF Online - https://bnf.nice.org.uk/
SPC - https://www.medicines.org.uk/emc#gref
Prescqipp – Melatonin Jan 2023
https://www.prescqipp.info/umbraco/surface/authorisedmediasurface/index?url=%2fmedia%2f6400%2f318-melatonin-20.pdf

Searches from Prescqipp:
MIS Web: https://www.prescqipp.info/media/6424/melatonin-searches-emis.xml
SystemOne: https://www.prescqipp.info/media/6426/exported-reports.rpt

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Appendix 1 – Template letter to patients

This letter is for you to adapt for your patient(s). Please ensure that you customise the text highlighted in yellow so that the information is appropriate. Please also ensure that once you have made your amendments, any important information isn't split across two pages, or that an instruction to continue on to a second page is added.

Insert practice header or print to practice headed paper, or type address details below.

[Practice name]

[Address]

[Tel]

[Fax]

[Email]

[Date]

[Title_Initial_Surname]

[Patient Address Block]

Dear [Title] [Surname],

Your repeat prescription for melatonin

The practice has been reviewing its prescribing of **Melatonin.** This is to ensure our patients receive the best treatment offering the best value to the NHS. As a result, we have changed your future prescriptions to **Adaflex® / Melatonin MR 2mg® / Circadin® / Senyto® / Kidmel® liquid / Ceyesto® liquid * (*delete as appropriate).**

If you were previously taking capsules, this will be changed to tablets.
The strength and dose of **Adaflex® / Melatonin MR 2mg® / Circadin® / Senyto® / Kidmel® liquid / Ceyesto® liquid * (*delete as appropriate)** is the same and you should not notice any difference in effect.

Your medication will be changed automatically so please order your next prescription in the usual way. It would help the NHS save money if you would use up of your remaining melatonin product first.

It is important to help the NHS save money where it can be redistributed to deliver and improve other health services.

Refer to the dosage instructions which are written on the label when the medicine is dispensed and/or the patient leaflet for advice if you are unsure.
If you have any queries regarding this letter please contact the surgery.
All medicines should be safely stored out of the reach of children.

GP/Nurse/Pharmacist [delete as applicable]	[Add number]

Yours sincerely

Dr [insert name] and partners

Appendix 2 – template letter for Community Pharmacy where a Melatonin Liquid is required

The template letter below can be used by prescribers when requesting KidMel® for suitable paediatric patients.

Please refer to individual Summary of Product Characteristics for a list of excipients and suitability for individual patient.

This letter is for you to adapt for your patient(s). Please ensure that you customise the text highlighted in yellow so that the information is appropriate. Please also ensure that once you have made your amendments, any important information isn't split across two pages, or that an instruction to continue on to a second page is added.

Insert practice header or print to practice headed paper, or type address details below.

[Practice name]

[Address]

[Tel]

[Fax]

[Email]

[Date]

[Title_Initial_Surname]

Dear [Community Pharmacy

Request for a repeat prescription for melatonin liquid

Purpose of letter

Suppliers require justification for the supply of an unlicensed melatonin oral solution of KidMel® / Ceyesto® (***delete as appropriate**) where an equivalent UK licensed preparation is available due to concern of containing the following excipients which may be potentially problematic when used in children:

Name: <Patient Name>

NHS No: <NHS number>

DOB: <Date of Birth>

To whom it may Concern,

Request for use of melatonin 1mg in 1ml oral solution (KidMel®)

We are aware that there is a licensed pharmaceutical preparation of melatonin 1mg in 1mL oral solution; however, we are requesting supplies of Kidmel® / Ceyesto® (***delete as appropriate**) melatonin 1mg in 1mL alcohol free oral solution to meet the special clinical needs of this patient as we are more satisfied with the excipient profile of this product in terms of appropriateness for use in children. Yours sincerely

<Your Name>

<Your Details>