Health and Social Care Board

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To: Community Pharmacies
General Medical Practices

23rd December 2019

Dear Colleague

MELATONIN PREPARATIONS – PRESCRIBING AND SUPPLY

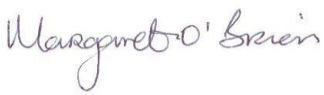
The evidence supporting the use of melatonin is limited, particularly in children, but it may be prescribed in certain circumstances. There is a range of products available which vary in their licensing and formulation. The purpose of this correspondence is to provide clarification, given recent issues around accessing particular formulations. The box below summarises the key considerations and these are explained further in the attached appendix:

Key Considerations for Prescribing and Supply of Melatonin:

- **Tablets should be the product of choice; liquids should only be considered for those who cannot swallow tablets**
- Any decision taken regarding prescribing or dispensing an unlicensed or off-label medication should be made on an individual patient basis
- If it is deemed necessary to prescribe melatonin liquid, please take account of the product's licensing status and excipient content
- Melatonin 1mg/ml oral solution (or liquid) sugar free is currently the only licensed liquid formulation. Other unlicensed formulations may be necessary to consider.
- It is important that the prescription is written correctly to allow the pharmacy to supply the correct product. This may require liaison between the prescriber and community pharmacist.
- If there are any doubts about the melatonin product to be supplied, or its suitability for an individual patient, the original prescribing clinician should be contacted for advice.

Yours sincerely,

Joe Brogan
Assistant Director of Integrated Care
Head of Pharmacy and Medicines Management



Dr Margaret O'Brien
Assistant Director of Integrated Care
Head of General Medical Services

Appendix to HSCB Correspondence of 20th December 2019: Melatonin Preparations - Prescribing and Supply (Information checked December 2019)

1. CONSIDER IF A LIQUID PREPARATION IS ACTUALLY REQUIRED

Melatonin as a liquid formulation should only be considered for those who are unable or unwilling to swallow tablets. Further information is provided in the tables in Section 5 on the available tablet and liquid preparations.

2. CONSIDER THE LICENSING OF THE PRODUCT

Although the MHRA does not recommend "off-label" (outside the licensed indications) use of products, they advise that if a UK licensed product can meet the clinical need, even off-label, it should be used in preference to an unlicensed product.[1] The steps below should be considered in terms of licensing when deciding on an appropriate melatonin product for children.

Step 1	Is there a licensed product that could be used **within** its licence?
Step 2	Is there a licensed product that could be used **outside** its licence (off-label)?
Step 3	If the answer is 'no' to steps (1) and (2), an unlicensed manufactured 'special' could be considered.

3. CONSIDER THE EXCIPIENTS (OTHER INGREDIENTS) IN THE LIQUID PREPARATION

There are 3 notable excipients that are included at varying levels in the liquid preparations available: propylene glycol, sorbitol and alcohol. When prescribing or supplying a liquid product, the total daily dose of the excipients should be given careful consideration.

Younger children's ability to metabolise propylene glycol (under 5) and alcohol (under 6) has not fully developed therefore the suggested limits in these age groups are substantially lower than in older children. Further information is provided below on the excipient content of liquid preparations.

Propylene glycol (PG) content

The following oral limits, expressed in terms of maximum daily dose, are considered to be safe[2] and with no noticeable effects whatever the duration and the route of administration

Age group	Oral Safety Limits
1 month (29 days) up to 4 years and 364 days	50mg /kg
5 years up to adult	500mg /kg

[1] https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/373505/The_supply_of_unlicensed_medicinal_products__specials_.pdf

[2] https://www.ema.europa.eu/en/documents/scientific-guideline/questions-answers-propylene-glycol-used-excipient-medicinal-products-human-use_en.pdf

For the purposes of this document only, a product exceeding 100mg/ml of Propylene Glycol should not generally be considered under 5 years. This is a pragmatic approach, because although starting doses may be within limits, titration or inadvertent overdosing may subsequently occur.

Sorbitol content

Excessive sorbitol levels may cause gastrointestinal side effects and may accumulate. The proposed safety limit is **140mg/kg/day** with no specific age differentiation. **Please take into account the sorbitol content of other medications and diet.**

Ethanol content

European Medicines Agency (EMA) proposed safety thresholds for alcohol in children ≤12 years of age:

- Children aged 2-6 years: a maximum dose of 6mg/kg
- Children aged ≥6 years: a maximum dose of 75mg/kg

NB: There is no guidance for patients younger than 2 years[3]

4. PRESCRIPTION REQUIREMENTS IF A LIQUID PREPARATION IS REQUIRED

GP Practices:

1) **Melatonin 1mg/ml oral solution (or liquid) sugar free (SF) is the licensed product, used off-label. In EMIS it is listed as Melatonin 5mg/5ml oral solution sugar free.**
2) **Other strengths and formulations in suspension or containing sugar are unlicensed at this time. If a licensed product is not clinically appropriate, the desired formulation should be indicated on the prescription and endorsed "unlicensed special to be dispensed"**
3) **Some companies who supply unlicensed medicines may require the prescriber to complete a letter of clinical need to comply with MHRA requirements.**

Community Pharmacists:

4) **Clinically check the prescription as per normal processes, in particular, taking account of any issues such as excipient content in young children.**
5) **If necessary contact the prescriber for both clarification of the product required, and patient prescription record amendment if necessary**.

Note: For payment purposes, prescriptions written for Melatonin 1mg/ml oral solution sugar-free will be reimbursed at the Part 1 Drug Tariff price (i.e. for the licensed but off-label product), unless endorsed 'unlicensed preparation to be dispensed' by the prescriber.

[3] https://www.ema.europa.eu/en/documents/scientific-guideline/questions-answers-ethanol-context-revision-guideline-excipients-label-package-leaflet-medicinal_en.pdf

5. PREPARATIONS AVAILABLE

Note – the following tables provide information on the known preparations at the time of development (correct at December 2019).

MELATONIN TABLETS – further information at https://www.medicines.org.uk/emc/	
	Market Authorisation (Licensed indications)
Circadin® 2mg prolonged release tablets	Licensed for the short-term treatment of primary insomnia characterised by poor quality of sleep in patients who are aged 55 or over. **Per Melatonin - Paediatric Shared Care Guideline may be prescribed off-label in children and is the current preferred first line choice in Northern Ireland.** Tablets may be crushed to aid swallowing or for immediate release- see shared care guideline for further information.
Slenyto® **1mg or 5mg prolonged release tablets**	Licensed for treatment of insomnia in children and adolescents aged 2-18 with Autism Spectrum Disorder and / or Smith-Magenis syndrome, where sleep hygiene measures have been insufficient.
Melatonin 3mg tablets	Examples include Colonis Pharma Ltd which is licensed in adults for short-term treatment of jet-lag (should not be prescribed on HS21 for this indication).

Appendix to HSCB Correspondence of 20th December 2019: Melatonin Preparations - Prescribing and Supply (Information checked December 2019)

MELATONIN LIQUID PREPARATIONS (use only if tablets not an option)

Please refer to manufacturer for further details and full excipient content

Increasing Excipient Content ➡

	Product	Licensed status	Excipients to consider clinically and other notes	Recommended GP Rx endorsements
	Martindale Melatonin 1mg/ml oral solution SF	Unlicensed 'Special'	Contains propylene glycol 48mg/ml	*"Unlicensed special to be dispensed- Martindale"*
	Kidmel (melatonin) 1mg/ml oral solution SF	Unlicensed 'Special'	Contains propylene glycol 52mg/ml Also contains aspartame	*"Unlicensed special to be dispensed - Kidmel "*
	The following products have an excipient content which may make them unsuitable for use in under 5s			
	Melatonin Oral Solution 5mg/5ml (Quantum Pharmaceuticals)	Unlicensed 'Special'	Contains propylene glycol 142mg/ml Contains sorbitol 132mg/ml	*"Unlicensed special to be dispensed – Quantum"*
	Melatonin 1mg/ml oral solution sugar-free (Colonis Pharma Ltd)	Licensed product; **'off-label' use in children***	Contains propylene glycol 150mg/ml; sorbitol 140mg/ml; also contains ethanol at levels unlikely to be clinically significant Licensed in **adults** for short-term treatment of jet-lag (should not be prescribed on HS21 for this indication).	Should state only : *Melatonin 1mg/ml oral solution sugar-free*** No further endorsements required
	The following products have excipient content that makes them generally unsuitable for use in children			
	Neomel 1mg/ml oral solution SF	Unlicensed 'Special'	Contains propylene glycol 150mg/ml Contains sorbitol 210mg/ml	*"Unlicensed special-Neomel"*
	Kidnaps 1mg/ml oral solution SF	Unlicensed 'Special'	Contains propylene glycol 1.5 mg/ml Contains sorbitol 210mg/ml Contains alcohol 100mg/ml	*"Unlicensed special-Kidnaps"*

Notes on table:

*SPC for Colonis Product states "Melatonin 1mg/ml oral solution should not be used in children and adolescents aged 0 – 18 years due to safety concerns. Specifically, this is due to the fact that interference with the function of endogenous melatonin on the development of the hypothalamic-pituitary-gonadal axis cannot be excluded". Unlicensed products do not have a published SPC available, as they have not gone through the licensing process.

**Listings vary on GP systems. For prescription payment purposes the words "liquid" and "solution" are interchangeable, as are the strengths "5mg/5ml" and "1mg/ml".
However "Suspension" is a separate formulation and is not interchangeable with "liquid" or "solution".

Propylene Glycol Limits considered to be safe: Age 1 month> 5 years: 50mg/kg Age 5yrs and older: 500mg/kg

Sorbitol: The proposed safety limit is 140mg/kg/day with no specific age differentiation. Please take into account the sorbitol content of other medications and diet.

Ethanol: European Medicines Agency (EMA) proposed safety thresholds for alcohol in children ≤12 years of age:

- Children aged 2-6 years: a maximum dose of 6mg/kg
- Children aged ≥6 years: a maximum dose of 75mg/kg

NB: There is no guidance for patients younger than 2 years

Important: See main body of this document for further details on licensing, excipients and reference sources.
Note: This document is accurate only at the point of issue.