

Melatonin Liquid Formulary Review

Introduction

In November 2019, DTC approved an update to the formulary to include off-label use of the newly licensed product, Colonis liquid® in accordance with the MHRA hierarchy for use of unlicensed medicines. Discussions were had at the time about the suitability for use in children, due to the levels of propylene glycol being above EU recommended levels for children under 5 years old, the warning in the leaflet *not to be used in children* and the higher cost. It was decided that children under 5 years old would continue to receive the unlicensed special made by Martindale and the off-label use of Colonis liquid would only be for children over 5 years old.

Current Position

We are now reviewing our formulary choice for melatonin liquid, with a view to only having one liquid preparation, due to:

- an identified risk of dispensing the wrong product to children under 5 years old, that remains despite measures implemented to mitigate the risk
- to mirror the choices made by neighbouring Trusts and Children's Hospitals

Available Options

Supplier	Licensed product?	Strength 1mg/ml	Pack Size	Excipients (including amounts)			Cost	Storage
				PEG	Alcohol	Sorbitol		
Colonis*	Yes	☒	150ml	150mg/ml	-	140mg/ml	£125.95	2 months
Martindale	No	☒	200ml	49mg/ml	-	-	£19.67	4 weeks
Kidmel Kidnaps	No	☒	200ml	52mg/ml	- 9-11%	-	Unclear if currently available; Oxford have switched to Kidnaps [9-11% alcohol]	
Rosemont	No	☒	200ml	-	-	200mg/ml	£60	4 weeks

*See Appendix A for details of age limitations of excipients (from PrescQIPP, May2020)

Rationale to Support Change

MHRA Guidance about Use of Unlicensed Specials MHRA Guidance Note 14, 2014

Find out more

assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/373505/The_supply_of_unlicensed_medicinal_products_specials.pdf

The MHRA rightly provide guidance to discourage the use of unlicensed medicines, where there is an equivalent licensed medicinal product that can meet the special needs of a patient. For melatonin liquid, the licensed product is not pharmaceutically equivalent due to the excipients contained, and so use of an unlicensed special is justifiable in children.

Complaint Upheld About Promotional Material Used Marketing Colonis® Liquid

A complaint was made to the Prescription Medicines Code of Practice Authority (PMCPA) in 2019 [AUTH/3221/6/19] by a Medicines Information pharmacist about the promotional letter sent to Healthcare Professionals being poorly referenced and misleading. A full review was conducted, and the complaint was upheld by the PMCPA (See Appendix B for details).

Formulary Choices of other Trusts reviewed

Oxfordshire CCG Formulary	Kidmel and Martindale ONLY
Buckinghamshire CCG Formulary	'Colonis liquid is not licensed and not recommended in children'
Southampton Children's Hospital	Colonis branded Melatonin liquid will not be prescribed or kept in stock. Unlicensed liquid specials preferred in infants or children with allergy/intolerant of excipients or in those where the amount of excipient(s) are deemed unsuitable.
Great Ormond Street Hospital	Kidmel
Leeds Children's Hospital	Melatonin 5mg in 5ml Oral Solution – this can be prescribed as an 'alcohol free' special. However, in all cases of prescribing, add 'special order product, propylene glycol and alcohol free' to the dosage section of the prescription. Note this is unlicensed use of an unlicensed product however there are safety concerns with using the licensed product in children.
Sheffield Children's Hospital	Colonis brand only for use in children with a feeding tube. If child is under 5 and has a feeding tube contact Medicine Information for advice RE: Propylene Glycol content.
Alder Hey Children's Hospital	The melatonin 1mg/ml liquid has been assessed and the quantities of propylene glycol may be excessive for some children. Other unlicensed melatonin preparations or melatonin food supplements remain RED due to the variation in quality, cost to primary care and lack of evidence regarding suitability of excipients in children. For certain patients, unlicensed melatonin may be required i.e., patients with feeding tubes.
Colonis liquid not approved for Prescribing	NHS Essex CCG, March 2021, NHS Basildon and Brentwood CCG, NHS Thurrock CCG, July 2020, NHS Hertfordshire and Worcester CCG, December 2020, NHS Eastern Cheshire Clinical Commissioning Group NHS South Cheshire Clinical Commissioning Group NHS Vale Royal Clinical Commissioning Group East Cheshire NHS Trust Mid Cheshire NHS Foundation Trust Cheshire and Wirral Partnership NHS Foundation Trust, September 2019

PrescQIPP Review May 2020 245. Melatonin 2.2 (prescqipp.info)

Find out more

prescqipp.info/umbraco/surface/authorisedmediasurface/index?url=%2fmedia%2f4920%2f245-melatonin-22.pdf

Melatonin 1mg/ml oral solution (Colonis Pharma Ltd) should not be used in children and adolescents due to safety and efficacy concerns. Melatonin 1mg/ml oral solution (Colonis Pharma Ltd) contains the following excipients which may be potentially problematic when used in children: Propylene glycol 150.37 mg per 1ml dose, Sorbitol 140 mg per 1ml dose

The total daily dose of excipients needs to be calculated and checked whether they are within the safety limits for the age and weight if melatonin 1mg/ml oral solution (Colonis Pharma Ltd) is being considered for use in a child.

Consider:

- EU safety limits for PEG assumes a healthy child, where low weight is not a concern – medical monitoring is advised in children with renal or hepatic dysfunction even at 50mg/kg Q&As propylene glycol used as an excipient in medicinal products(europa.eu)

Find out more

ema.europa.eu/en/documents/scientific-guideline/questions-answers-propylene-glycol-used-excipient-medicinal-products-human-use_en.pdf

- total daily dose should content from any liquid preparations (including food)

Options

1. Remove Colonis liquid from the formulary and use Limit formulary choice of liquid to Martindale unlicensed special for all children (as per current choice for under 5 years, and in keeping with Oxfordshire and Buckinghamshire).
2. Do nothing

Appendix A

Table 2. Melatonin 1mg/ml oral solution (Colonis Pharma Ltd) excipient quantities and safety limit (maximum daily dose) checks when used in children^{3,8,26,27}

Excipient	Amount in melatonin 1mg/ml oral solution (Colonis Pharma Ltd)	Child's age group	Safety limit (maximum daily dose)	Example calculations and checks
Propylene glycol	150.37mg per 1ml	Children aged 1 month - 4 years	50mg/kg	<p>The maximum daily dose of propylene glycol for a two year old weighing 16kg is 800mg. This is contained in 5.3ml of melatonin 1mg/ml oral solution (Colonis Pharma Ltd). The safety limit would be exceeded in doses of melatonin over 5.3mg.</p> <p>The maximum daily dose of propylene glycol for a four year old weighing 23kg is 1150mg. This is contained in 7.65ml melatonin 1mg/ml oral solution (Colonis Pharma Ltd). The safety limit would be exceeded in doses of melatonin over 7.65mg.</p>
		Children aged 5- 17 years	500mg/kg	<p>The maximum daily dose of propylene glycol for a five year old weighing 27kg is 13.5g. This is contained in 89.8mls melatonin 1mg/ml oral solution (Colonis Pharma Ltd). The safety limit would not be reached at melatonin doses of 10mg and under.</p>

Excipient	Amount in melatonin 1mg/ml oral solution (Colonis Pharma Ltd)	Child's age group	Safety limit (maximum daily dose)	Example calculations and checks
Sorbitol	140 mg per 1ml	All ages of children	<p>An oral dose of greater than 140mg/kg/day may result in gastrointestinal symptoms.</p> <p>The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly.</p>	<p>Melatonin 1mg/ml contains 140mg of sorbitol per ml. A 10kg child may have gastrointestinal symptoms with doses of sorbitol over 1400mg. 1400mg of sorbitol is contained in 10ml of melatonin 1mg/ml oral solution (Colonis Pharma Ltd).</p> <p>It is important to consider the additive effects of sorbitol from other medicines or dietary sources.</p>

Appendix B

Complaint Upheld About Promotional Material Used Marketing Colonis® Liquid

A complaint was made to the Prescription Medicines Code of Practice Authority (PMCPA) [AUTH/3221/6/19] by a Medicines Information pharmacist about this letter being poorly referenced and misleading, a review was conducted, and the complaint was upheld that the letter breached clauses:

- 7.2 Information claims and comparisons must be accurate, balanced, fair, objective, and unambiguous and must be based on an up-to-date evaluation of all the evidence and reflect that evidence clearly. They must not mislead either directly or by implication, by distortion, exaggeration, or undue emphasis. Material must be sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicine
- 7.4 Any information, claim, or comparison must be capable of substantiation
- 9.1 High standards must be maintained at all times

AUTH/3221/6/19 – Medicine’s information pharmacist v Colonis (pmcpa.org.uk)

Find out more

pmcpa.org.uk/cases/completed-cases/auth3221619-medicines-information-pharmacist-v-colonis/

“The Panel noted its comments above and considered that it was misleading to cite general advice about the principles of using unlicensed medicines or ‘Specials’ in a way which implied that such documents specifically discussed the preferential use of Melatonin 1mg/ml Oral Solution over ‘Specials’. Together the cited references implied to the reader that the claim ‘Specials should not be supplied on the basis of cost or convenience if Melatonin 1mg/ml Oral Solution satisfies the patient’s clinical need’ was based on robust, product specific advice which was not so. The Panel considered that the claim was misleading in this regard and ruled a breach of the Code. The Panel did not consider that the named CCG document, the Royal Pharmaceutical Society document, or the email trail with the MHRA substantiated the claim which was specifically about Melatonin 1mg/ml Oral Solution and a breach was ruled. A further breach was ruled as Colonis had failed to maintain high standards.”

Regarding the 'data on file' referenced in the letter:

The Panel noted that the data on file was correspondence between Colonis and the MHRA in relation to Melatonin 3mg Tablets and made no reference to Melatonin 1mg/ml Oral Solution. **In the correspondence, the MHRA stated that it was important for marketing authorization holders to understand that there may still be reasons for using an unlicensed product after a licensed equivalent has become available.**