

Guidance to support use of lowest cost melatonin product options for the treatment of insomnia in adult and paediatric patients with learning disabilities.

Background: National Institute for Health and Care Excellence (NICE) guidance [NG11](#): ‘Challenging behaviour and learning disabilities: prevention and interventions for people with learning disabilities whose behaviour challenges’ advises to consider use of melatonin to aid sleep if behavioural support has failed to work in patients with learning disabilities. However, it recognises melatonin is not licensed for the management of insomnia in patients with learning disabilities, therefore if used, treatment would be considered off-label¹.

Herts and West Essex (HWE) Area Prescribing Committee have approved use of melatonin for patients with learning disabilities as follows:

- **Approved for use for children and adults under specialist care (e.g. a paediatrician, psychiatrist or a specialist involved in the patient’s care) – AMBER initiation status with initiation and stabilisation by specialists with continuation in primary care (see Prescribing Support Document for further details).**

*In recent years there has been a significant increase in different formulations, strengths, specials liquids and corresponding costs, necessitating guidance on product choice. **Product choice should be based on the most cost-effective and most clinically suitable product.** Please see page 3 for supporting information on selecting a suitable melatonin product for new and existing patients. The tables below provide information to support product selection. While other licensed melatonin products are available in the UK, the tables below provide information to support product selection based on the lowest cost products available.^a*

Lowest cost product option for modified-release (M/R) melatonin: The table below shows the lowest cost preparation of M/R melatonin currently available for use in the UK:

Preparation, strength, form, brand	Wording for prescription	Size (Diameter)	Able to crush?	Price*
Melatonin 2mg modified release tablets* (Generic)	Melatonin 2mg modified-release tablets	5.2x10 mm (oval)	Unlicensed, no information available in published practice guidance ²	£3.96 [#] /30 tablets

Source: *Electronic Medicines Compendium (emc)*, accessed 19th October 2022

* **NB: Licensed product, but not licensed in UK for patients with learning disabilities; treatment therefore ‘off-label’**

* Prices as per NHS dm+d and Drug Tariff, accessed 3rd April 2024

This is a Drug Tariff Category M product, therefore the price may fluctuate, but is likely to remain lower cost than the branded equivalent

- **Modified-release (M/R) melatonin: generic melatonin 2mg M/R tablets are first line choice** for all patients including when an M/R preparation is preferred:
 - in patients where maintaining sleep is the main difficulty, which may be helped by the longer duration of action, **and**
 - where maintaining a patient on a specific brand of melatonin 2mg M/R is not a concern

NB The Circadin® brand of M/R melatonin is no longer approved for use in HWE. M/R melatonin should be prescribed generically where possible as this is the most cost-effective option.

^a Slenyto – not recommendation by the East of England Priorities Advisory Committee (PAC) as the case for cost effectiveness has not been proved. See [LINK](#) for further details.

Lowest cost product options for immediate-release melatonin: The table below summarises the lowest cost preparations of immediate-release melatonin currently available for use in the UK:

Preparation, strength, form, brand	Wording for prescription	Size (Diameter)	Able to crush?	Price*
Melatonin 1mg tablets (Adaflex®)*	Adaflex 1mg tablets	9.5 mm	Can be crushed and mixed with water directly before administration [licensed use] ³	£10.89/30 tablets
Melatonin 2mg tablets (Adaflex®)*	Adaflex 2mg tablets			£10.89/30 tablets
Melatonin 3mg tablets (Adaflex®)*	Adaflex 3mg tablets			£10.89/30 tablets
Melatonin 4mg tablets (Adaflex®)*	Adaflex 4mg tablets			£10.89/30 tablets
Melatonin 5mg tablets (Adaflex®)*	Adaflex 5mg tablets			£10.89/30 tablets
Melatonin 3mg tablets (Ceyesto®)*	Ceyesto 3mg tablets	7 mm	Unlicensed, no information available in published practice guidance ²	£10.99/30 tablets
Melatonin 1mg/ml Oral Solution (Ceyesto®)*	Ceyesto 1mg/ml oral solution	N/A		£25.65/150ml £17.10/100ml

Source: *Electronic Medicines Compendium (emc)*, accessed 19th October 2022

* **NB: Licensed product, but not licensed in UK for patients with learning disabilities; treatment therefore 'off-label'**

*Prices as per NHS dm+d and Drug Tariff, accessed 28th March 2024

- **Generic melatonin 2mg M/R tablets are first line choice. Immediate-release melatonin: Adaflex® or Ceyesto® tablets** may be considered when an immediate release preparation is preferred:
 - in patients where initiation of sleep is the main difficulty, which may be helped by a shorter onset of action, **or**
 - if a lactose free preparation is required, as Adaflex® and Ceyesto® tablets are lactose free.
- Use **Adaflex® tablets** for those with a **swallowing difficulty** (Adaflex® tablets can be crushed and mixed with water directly before administration [licensed use]³)
- Use **Ceyesto® 1mg/ml oral solution** for children 3 years and over with a swallowing difficulty only if Adaflex® tablets are not suitable.
- **Ascomel® liquid** is no longer recommended in HWE as it is an unlicensed product, making it complex to prescribe on GP clinical systems to send via the Electronic Prescription Service EPS, and feedback from both community pharmacies and patients/carers suggests they have to overcome several barriers to source this product. As a licensed product (Ceyesto® oral solution) is now available, this will remove the need to overcome the barriers faced with Ascomel®.

Supporting information

- **Unlicensed use:** there are no melatonin products licensed in the UK for the treatment of insomnia in patients with learning disabilities. Where used, treatment would therefore be considered off-label¹.
- **New patients, or existing patients requiring an alternative formulation/dose review:** the most cost-effective clinically suitable product from the tables above should be prescribed.
- **Existing patients:**
 - 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)
 - 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 tables above should be prescribed.
 - where patient is 3 years and over on Ascomel[®] liquid, switch to Ceyesto[®] oral solution immediately and then consider whether Adaflex[®] tablets may be suitable at the next specialist review (i.e. if using crushed tablets may be a suitable alternative).
 - **Please note**, switching from Ascomel[®] liquid to Ceyesto[®] oral solution, and from Circadin[®] to generic melatonin 2mg M/R tablets will be carried out by prescribers in primary care, as agreed with learning disability specialists.

Modified-release versus immediate-release melatonin: although the BNF currently recommends the use of melatonin modified-release (M/R) tablets for treatment of insomnia in patients with learning disabilities and behaviour that challenges, this is not specified in NICE NG11, and clinical trials conducted to date (of melatonin for patients with learning disabilities) have used both modified-release and immediate-release formulations with positive outcomes^{4 5}.

Ceyesto[®] oral solution:

- When considering liquid melatonin preparations, there are various excipients that may be present in quantities that are potentially harmful to babies and children. Please refer to [NPPG position statement](#) for further information.
- Ceyesto[®] oral solution is the liquid preparation of choice in HWE as a risk assessment has been undertaken and has identified two excipients that can have potential to harm when used outside of NPPG recommendations: propylene glycol (total content 52mg per ml dose) and benzyl alcohol (6mg per 1 ml dose)- see appendix 1 for further information. The risk assessment found that Ceyesto[®] oral solution is expected to be suitable for use in patients 3 years and over.
- Ceyesto[®] oral solution can be considered **sugar, sodium and ethanol free**.
- It is recommended that food is not consumed 2 hours before and 2 hours after intake of melatonin.
- Ceyesto[®] oral solution can be **administered via a silicone gastric, duodenal or nasal feeding tube**.
- Ceyesto[®] oral solution has a **1-month expiry** from opening and therefore the 100ml pack size should be prescribed for doses <3mg(3ml) per day to avoid wastage.

References:

- 1) National Institute for Health and Care Excellence (NICE) (2015). Challenging behaviour and learning disabilities: prevention and interventions for people with learning disabilities whose behaviour challenges. Available at: <https://www.nice.org.uk/guidance/ng11/chapter/Recommendations>. Last accessed 3rd December 2021.
- 2) The NEWT Guidelines. <https://access.newtguidelines.com/C.html> [accessed 07/12/2023- login required]
- 3) SPC Adaflex 3mg tablets. <https://www.medicines.org.uk/emc/product/13630/smpc#gref> [accessed 14/9/2022]
- 4) Braam W, Didden R, Smits M, Curfs L. Melatonin treatment in individuals with intellectual disability and chronic insomnia: a randomized placebo-controlled study. Journal of Intellectual Disability Research. 2008a;52:256-64. Available at <https://pubmed.ncbi.nlm.nih.gov/18261024/>
- 5) Sajith SG, Clarke D. Melatonin and sleep disorders associated with intellectual disability: a clinical review. J Intellect Disabil Res. 2007;51:2–13. Available at <https://pubmed.ncbi.nlm.nih.gov/17181598/>

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Superseded version	V2.0 Price of generic melatonin MR tablets updated & advice on use updated accordingly V3.0 Ascomel® oral solution removed and replaced with Ceyesto® oral solution V4.0 Circadin® tablets removed

Appendix 1 – risk assessment for Ceyesto® oral solution

As shown below, Ceyesto® meets the European Medicines Agency (EMA) and the NPPG recommendations for children aged 3 years and over:

Benzyl alcohol

The [EMA](#) recommend for products that contain benzyl alcohol ‘do not use for more than a week in young children (less than 3 years old), unless advised by your doctor or pharmacist’ as there is an ‘increased risk due to accumulation in young children (less than 3 years old).’ ‘Young children (less than 3 years old) may not be sufficiently mature to metabolise and eliminate benzyl alcohol as efficiently as adults.’ This risk of accumulation is in newborn babies (pre-and full-term) and is due to metabolic immaturity. It is therefore suggested that Ceyesto® oral solution is suitable for patients aged 3 years and over.

Regarding use in children aged 3 years and over, the [NPPG](#) advises a maximum acceptable daily intake of 5mg/kg of benzyl alcohol in children over 4 weeks of age. Therefore, for a 3-year-old (mean weight 14kg as per [BNFC](#)), the maximum acceptable daily intake of benzyl alcohol is 70mg. As each 1ml of Ceyesto® oral solution has 6mg benzyl alcohol, a maximum dose of 10mg melatonin per day will result in 60mg benzyl alcohol, which is less than the maximum acceptable daily limit for a 3-year-old child. This is for illustrative purposes only and dosing should follow BNFC.

Propylene glycol

The [EMA](#) threshold for propylene glycol is 50mg/kg daily for a child of 1 month – 4 years. The propylene glycol content of Ceyesto® oral solution is 52mg per ml, which is almost a third of that contained in other licensed melatonin formulations and almost half of that in Ascomel® (93.6mg per ml).

For a 3-year-old (mean weight 14kg as per [BNFC](#)), the maximum acceptable daily intake of propylene glycol is 700mg. As each 1ml of Ceyesto® oral solution has 52mg propylene glycol, a maximum dose of 10mg melatonin per day will result in 520mg propylene glycol, which is less than the maximum acceptable limit for a 3-year-old child. This is for illustrative purposes only and dosing should follow BNFC.

[BNFC](#) recommends a maximum melatonin dose of 10mg per day for insomnia in patients with learning disabilities and behaviour that challenges (where sleep hygiene measures have been insufficient).

Based on the benzyl alcohol and propylene glycol content of Ceyesto® oral solution (as outlined above), Ceyesto® oral solution is expected to be suitable for use in patients 3 years and over prescribed a daily dose of up to 10mg melatonin.