

## Melatonin Prescribing for Paediatric Patients (Formulation Choice)

### Recommendation to prescribers

- Review all prescribing of melatonin for adult patients. Cambridgeshire and Peterborough does not currently support prescribing of melatonin for adults in primary care. Where this has been recommended by a secondary care doctor prescribing should remain with the hospital / community service, until a business case and pathway associated with the defined cohort of patients is presented to CPJPG for consideration.
- Do not prescribe melatonin for the management of jetlag on the NHS within Cambridgeshire and Peterborough (adults or children).
- Review all paediatric prescribing of melatonin for continued need. Patients who have been prescribed melatonin continuously for more than 6 months should have a discussion with their clinician regarding a trial discontinuation or dose reduction, to assess for on-going need.

### Immediate release formulation

- The current practice is crushing and dispersing of Circadin prolonged release tablets (off-label) making it equivalent to an immediate release product. An immediate release licensed preparation, Adaflex, for use in children and adolescents has recently become available.
- Adaflex immediate release tablets is licensed in children and adolescents aged 6-17 years old with attention-deficit hyperactivity disorder (ADHD), where sleep hygiene measures have been insufficient. Adaflex tablets can be crushed and mixed with water directly before the administration (licensed). Adaflex is available in the following strengths; 1mg, 2mg, 3mg, 4mg and 5mg.
- Patients (6 – 17 years) who require an immediate release formulation should be reviewed and switched to Adaflex tablets. Adaflex is also the preferred immediate release formulation for children under 6 years (off-label).
- Licensed melatonin 1mg/1ml oral solution (manufactured by Consilient Health) is available for patients who are unable to tolerate crushed tablets (this may include patients with learning difficulties / autism and issues with texture).
- All other immediate release formulations of melatonin are considered non-formulary and not recommended for prescribing including:
  - *Melatonin 1mg/1ml oral solution by Colonis Pharma Ltd*
  - *All strengths of unlicensed special solutions and suspensions of melatonin*
  - *All strengths and brands of melatonin tablets (apart from Adaflex)*
  - *All strengths of melatonin capsules.*

### Prolonged release formulation

Patients requiring prolonged release melatonin, should be reviewed on an individual basis and the decision as to whether the patient remains on their current formulation (generic modified release formulation is preferred, off-label) or switched to the licensed formulation (Slenyto) should be made in conjunction with the patient / guardian considering:

- Slenyto should only be considered for children who meet the indications covered by the license specifically a confirmed diagnosis of Autism Spectrum Disorder and / or Smith-Magenis syndrome) and require a modified release formulation.

- Generic melatonin prolonged release should be prescribed for all children who are receiving melatonin for an indication which is not covered by the Slenyto license or where the dose currently prescribed does not fall within the license of Slenyto. Noting, Slenyto is licensed at doses of 2mg, 5mg and 10mg only. Patients must be able to swallow the preparation whole as breaking or crushing will result in loss of the modified release properties.
- Tablet burden to the patient (4mg MR dose prescribed as 2 x 2mg melatonin tablets or 4 x 1mg Slenyto tablets)

**All children being prescribed melatonin should be reviewed against the principles above.**

#### Background

- Melatonin is only recommended to be prescribed in primary care for children and adolescents on the advice of a paediatric specialist.
- Until recently there were no immediate release licensed preparations of melatonin for use in children and adolescents. Adaflex immediate release tablets (licensed in children and adolescents aged 6-17 years old with ADHD, where sleep hygiene measures have been insufficient) is the first line formulary choice of melatonin across Cambridgeshire and Peterborough. Adaflex tablets can be crushed and mixed with water directly before the administration (licensed).

#### Slenyto prolonged release tablets

- Flynn Pharma Ltd, who manufacturer Circadin, launched Slenyto prolonged release tablets (1mg and 5mg) 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. [2]
- Slenyto is a 3mm diameter, prolonged release (1mg and 5mg strength) film coated tablet, which should be swallowed whole. The manufacturer recommends that tablet should not be broken, crushed or chewed because it will lose the prolonged release properties. Tablets can be put into food such as yoghurt, orange juice or ice-cream to facilitate swallowing and improve compliance. [2]
- 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. [2]

#### Licensed Immediate Release formulations: Melatonin tablets (Adaflex), Melatonin 1mg/1ml oral solution and Melatonin 3mg film coated tablets (off-label in children)

- In May 2022, AGB-Pharma AB launched an immediate release formulation of melatonin (Adaflex 1mg, 2mg, 3mg, 4mg, 5mg tablets) indicated for children and adolescents aged 6-17 years old with ADHD, where sleep hygiene measures have been insufficient. **Adaflex tablets can be crushed and mixed with water directly before the administration (licensed).** Food can enhance the increase in plasma melatonin concentration. Intake of melatonin with carbohydrate-rich meals may impair blood glucose control for several hours (see section 4.4). It is recommended that food is not consumed 2 hours before and 2 hours after intake of Adaflex tablets.
- Melatonin 1mg/1ml oral solution manufactured by Consilient Health (propylene glycol free and alcohol free) is licensed for insomnia in children and adolescents aged 6-17 years with ADHD,

where sleep hygiene measures have been inadequate. This formulation should be reserved for patients who are unable to tolerate crushed tablets (this may include patients with learning difficulties / autism and issues with texture). Melatonin 1mg/1ml oral solution (Consilient Health) is the formulary choice of liquid melatonin. The prescription should state 'Consilient Health brand' to ensure the correct formulation is supplied to the patient. Use in children under 6 years of age would be considered 'off-label'.

- Melatonin 1mg/1ml oral solution is also manufactured and licensed by Colonis however this formulation contains the following excipients with known effect: sorbitol 140 mg per 1 ml dose and propylene glycol 150.50 mg per 1 ml dose. *The addition of these excipients makes this formulation less suitable for use in children in particular those under 6 years of age, and therefore melatonin 1mg/1ml oral solution (Colonis) is not recommended for prescribing in Cambridgeshire and Peterborough.*

#### Unlicensed / Off-label use of Medicines

Unlicensed medicines have not been subject to the same stringent scrutiny by the MHRA and so the same assumptions regarding product quality, safety and efficacy that accompany licensed products cannot be made.

"Guidance Note 14 – the supply of unlicensed relevant medicinal products for individual patients" - issued by the MHRA provides guidance on the prescribing, procurement, manufacture and distribution of unlicensed medicines. It states that unlicensed medicinal products may only be placed on the market (and by implication purchased) when no pharmaceutically equivalent licensed product is available for use. Products are considered pharmaceutically equivalent if they contain the same amount of the same active substance in the same dosage form and meet the same standards, when considered in the light of the clinical needs of the patient at the time of its use.[10]

However, it is recognised that licensed indications for a product will not always meet the clinical needs of an individual patient in every situation. Therefore, to ensure that the patient's requirements for a medicine are met, and to preserve the prescriber's clinical freedom, the legislation provides an exemption to allow the manufacture, supply and administration of unlicensed medicines (i.e. medicines without a Marketing Authorisation) when necessary. In addition, provision is also made for licensed medicines (i.e. medicines with full Marketing Authorisation) to be prescribed for unlicensed indications or in unlicensed dosages i.e. "off label".

Appendix 2 of Guidance Note 14 'Guidance on the hierarchy for the use of unlicensed medicines' states [10]:

1. An unlicensed product should not be used where a product available and licensed within the UK could be used to meet the patient's special need.
2. Although MHRA does not recommend "off label" (outside of the licensed indications) use of products, if the UK licensed product can meet the clinical need, even "off-label", it should be used instead of an unlicensed product. Licensed products available in the UK have been assessed for quality safety and efficacy. If used "off-label" some of this assessment may not apply, but much will still be valid. This is better than the use of an unassessed, unlicensed product. The fact that the intended use is outside of the licensed indications is therefore not a reason to use an unlicensed product. It should be understood that the prescriber's responsibility and potential liability are increased when prescribing off-label.

3. If the UK product cannot meet the special need, then another (imported) medicinal product should be considered, which is licensed in the country of origin.
4. If none of these options will suffice, then a completely unlicensed product may have to be used, for example, UK manufactured "specials", which are made in GMP inspected facilities, but which are otherwise un-assessed (GMP inspection of "specials" manufacturers is not product specific). There may also be other products available which are unlicensed in the country of origin.

The MHRA state [10] that a prescriber must:

- Before prescribing an unlicensed medicine, be satisfied that an alternative, licensed medicine would not meet the patient's needs
- Before prescribing a medicine off-label, be satisfied that such use would better serve the patient's needs than an appropriately licensed alternative
- Before prescribing an unlicensed medicine or using a medicine off-label:
  - Be satisfied that there is a sufficient evidence base and/or experience of using the medicine to show its safety and efficacy
  - Take responsibility for prescribing the medicine and for overseeing the patient's care, including monitoring and follow-up
  - Record the medicine prescribed and, where common practice is not being followed, the reasons for prescribing this medicine; you may wish to record that you have discussed the issue with the patient

#### Review and deprescribing

If treatment is successful, a trial reduction in the dose should be attempted after 6 months as some patients would have settled into a regular sleep pattern and may not need to continue at the same dose or may even be able to maintain sleep with no medication. If sleep patterns are maintained, dosing can be reduced by 2mg every 4-6 weeks. If the difficulties recur the original dose should be reinstated, but a further trial reduction should be attempted 6 months later.

Some clinical experience from the National Child and Adolescent Learning Disability Psychiatry Network suggests that the efficacy may be lost if melatonin is prescribed for longer than two years continuously. It suggests that if the melatonin is withdrawn prior to this, sensitivity may be re-established, and melatonin successfully re-introduced at a lower dose.

Table of comparative costs (Drug Tariff October 2022):

| Licensed formulation                                                 | NHS List Price  | Per 2mg dose | Per 4mg dose |
|----------------------------------------------------------------------|-----------------|--------------|--------------|
| Adaflex 2mg tablets<br>(can be crushed)                              | £15.30 (30)     | £0.51        | £1.02        |
| Adaflex 4mg tablets<br>(can be crushed)                              | £20.23 (30)     | N/A          | £0.67        |
| Melatonin 1mg/1ml oral solution<br>manufactured by Consilient Health | £155.57 (150ml) | £2.07        | £4.15        |
| Generic melatonin 2mg prolonged release<br>tablets                   | £15.39 (30)     | £0.51        | £1.03        |
| Slentyto 1mg prolonged release tablets                               | £41.20 (60)     | £1.37        | £2.75        |
| Slentyto 5mg prolonged release tablets                               | £103.00 (30)    | N/A          | N/A          |

## References

1. Summary of Product Characteristics. Circadin®. Flynn Pharma Limited. Available at: [www.medicines.org.uk](http://www.medicines.org.uk) Accessed 01/05/19.
2. Summaries of Product Characteristics. Slenyto® 1mg and 5mg tablets. Flynn Pharma Limited. Available at: [www.medicines.org.uk](http://www.medicines.org.uk) Accessed 01/05/2019.
3. Personal communication. Flynn Pharma Ltd. 15/05/2019
4. Summary of Product Characteristics. Melatonin 3mg film-coated tablets. Colonis Pharma Limited. Available at: [www.medicines.org.uk](http://www.medicines.org.uk) Accessed 29/06/2019.
5. Summary of Product Characteristics Melatonin 1mg/ml oral solution. Colonis Pharma Limited. Available at: [www.medicines.org.uk](http://www.medicines.org.uk) Accessed 15/06/2020.
6. Arthur S, Burgess A. How to identify and manage problem excipients in medicines for children. The Pharmaceutical Journal 2017; 299 (7903) online | DOI: 10.1211/PJ.2017.20203121. Available at: <https://www.pharmaceutical-journal.com/learning/learning-article/how-to-identify-and-manageproblem-excipients-in-medicines-for-children/20203121.fullarticle?firstPass=false> Accessed 01/07/2019.
7. European Medicines Agency. Background review for the excipient propylene glycol in the context of the revision of the guideline on 'Excipients in the label and package leaflet of medical products for human use' (CPMP/463/00 Rev. 1) Draft; Nov 2014. Available at: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Report/2014/12/WC500177937.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Report/2014/12/WC500177937.pdf) Accessed 03/07/2019.
8. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP): Questions and answers on ethanol in the context of the revision of the guideline on 'Excipients in the label and package leaflet of medical products for human use' (CPMP/463/00) Draft; Jan 2014. Available at: [https://www.ema.europa.eu/en/documents/scientific-guideline/questions-answers-ethanolcontext-revision-guideline-excipients-label-package-leaflet-medicinal\\_en.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/questions-answers-ethanolcontext-revision-guideline-excipients-label-package-leaflet-medicinal_en.pdf) Accessed 03/07/19.
9. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP): Information in the package leaflet for fructose and sorbitol in the context of the revision of the guideline on 'Excipients in the label and package leaflet of medicinal products for human use' (CPMP/463/00 Rev. 1) Draft; April 2016. Available at: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2016/05/WC500206001.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/05/WC500206001.pdf) Accessed 03/07/19.
10. MHRA Guidance Note 14. The supply of unlicensed medicinal products ("specials"). 2014. Available: [https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\\_data/file/373505/The\\_supply\\_of\\_unlicensed\\_medicinal\\_products\\_specials.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/373505/The_supply_of_unlicensed_medicinal_products_specials.pdf) Accessed 05/07/2019.
11. Summary of Product Characteristics. Adaflex®. AGB-Pharma AB. Available at: [www.medicines.org.uk](http://www.medicines.org.uk) Accessed 14/10/22.
12. Summary of Product Characteristics. Melatonin 1 mg/ml oral solution. Consilient Health. Available at: [Hqrdtemplatecleanen v10.1 \(consilienthealth.co.uk\)](http://Hqrdtemplatecleanen v10.1 (consilienthealth.co.uk)) Accessed 02/12/22.

## Document ratification details

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