4 reasons to **STOP** prescribing liquid melatonin for children

slenyto®

Prolonged-release melatonin

a tablet that is a solution

UK/SLY/2022/2022(v3) | November 2022

Melatonin 1mg/mL oral solution:

- Contains excipients (Propylene glycol, sorbitol, and ethanol) which may be potentially problematic when used in children[2]

Slenyto®

- An age (2-18 years) and condition-appropriate paediatric formulation of prolonged-release melatonin for the treatment of insomnia in children with Autistic Spectrum Disorder and/or Smith Magenis Syndrome[3]
- Use supported by published evidence and approved licence particulars[3]
- No excipients which may be potentially problematic when used in children[3]
- No 'very common' (≥1/10) adverse reactions[3]
- 'Common' (≥ 1/100 to < 1/10) adverse reactions are somnolence, fatigue, mood swings, headache, irritability, aggression, hangover, sinusitis, and sudden onset of sleep[3]

EFFICACY

Liquid melatonin preparations:

- Are all immediate-release formulations with poor night-time cover resulting in poor sleep maintenance[4]

Immediate-release melatonin:

- Children gain little additional sleep - they fall asleep earlier but wake earlier[4]
- Child behaviour and family functioning outcomes do not significantly improve[4]

Slenyto®

- A paediatric formulation of prolonged-release melatonin designed to mimic endogenous melatonin production[5]
- When used to treat insomnia in children with Autistic Spectrum Disorder and/or Smith Magenis Syndrome for an initial period of 13 weeks[6]:
  - Over **two thirds** had a clinically meaningful# improvement in their sleep*
  - Improvements in Total Sleep Time (TST) and Sleep Latency (SL) did not result in earlier awakening
  - Mean Longest (uninterrupted) Sleep Episode (LSE) improved by over **an hour** (78 minutes)
  - Externalising behaviours (hyperactivity/inattention and conduct scores) improved significantly^
  - The treatment effects on sleep variables were associated with improved parents' well-being[3]

Clinically meaningful improvement = increase in TST ≥ 45 mins versus baseline and/or reduction in SL ≥ 15 mins versus baseline
* Versus 39.3% with placebo; p=0.001
^ Versus placebo; p=0.021

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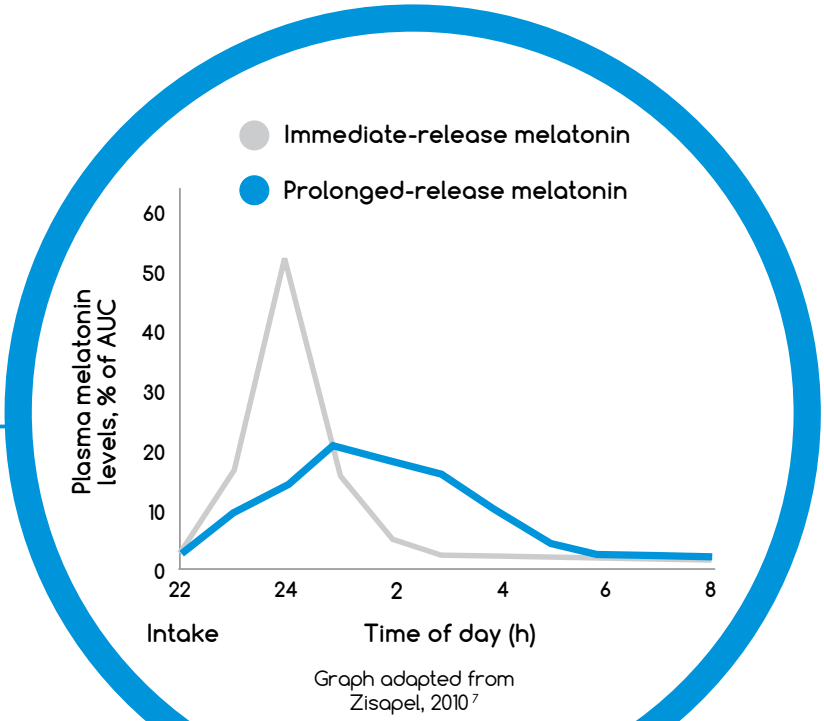
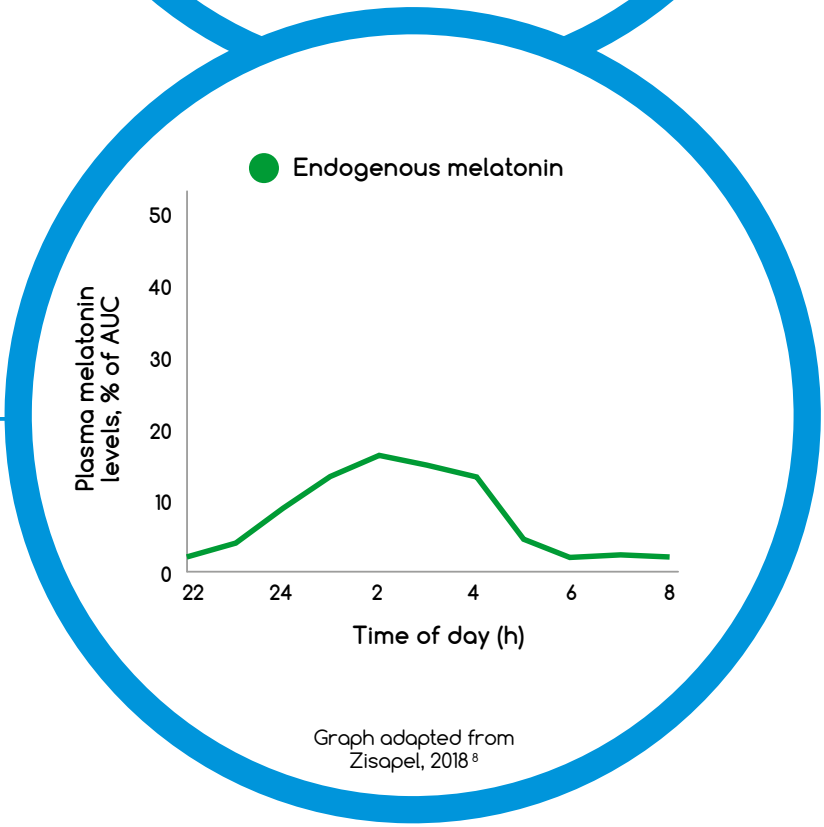
2 EFFICACY

Figure 1.
Pharmacokinetics of immediate-release versus prolonged-release melatonin+



Graph adapted from Zisapel, 2010 [7]

Figure 2.
Endogenous production of melatonin+



Graph adapted from Zisapel, 2018 [8]

+ Data presented derived from studies in adults[7,8]

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ADHERENCE

Melatonin 1mg/mL oral solution:

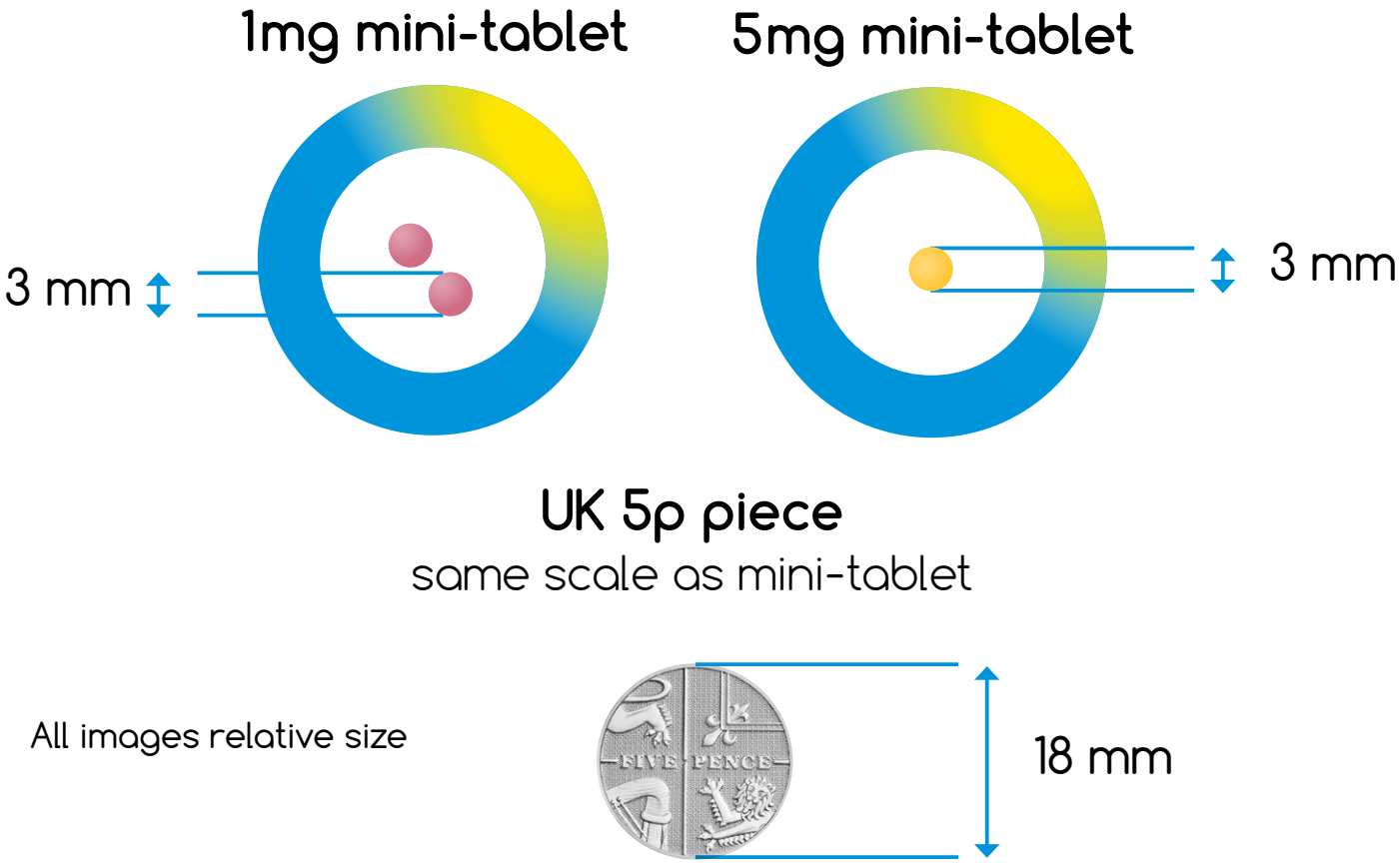
- Colourless to yellowish solution with a characteristic strawberry odour[1]
- Children with Autism Spectrum Disorder have documented tactile sensitivities, including issues with swallowing and excessive reactions to taste, smell, texture, or appearance of food[9, 10]
- There is general acceptance of the benefits of solid dosage forms over liquid dosage forms for stability, dosing, and administration issues[11]

Slenyto®

- Mini-tablets (1mg and 5mg) are odourless, flavourless, and just 3mm in diameter – easy to swallow, no need to crush[3] (Figure 3)
- Helps to overcome potential administration challenges associated with administration of liquid melatonin to children with ASD and/or SMS[14]
- Developed to meet the needs of children with swallowing difficulties (young age) and/or sensitivities to touch, odour or taste (due to autistic core symptoms)[6]
- Offers the functional benefits of a liquid in terms of ease of administration[14]
- Helps avoid palatability issues, high levels of dosing errors and unacceptable excipients associated with some liquid formulations of melatonin[1,4,6,10]
- Slenyto should be taken once daily, 0.5-1 hour before bedtime and with, or after, food[3]
- Tablets can be put into food such as yoghurt, orange juice or ice-cream to facilitate swallowing and improve compliance[3]
- All licensed doses achievable with a maximum of two mini-tablets[3]

3 ADHERENCE

Figure 3.



"In contrast to the usual difficulties experienced by children with autism, compliance was excellent without the need to crush or dissolve." [6]

Melatonin liquid 1mg/1mL added to Drug Tariff in July 2019:

- At a cost of £130/150ml which has continued to rise to £157/150ml (as of November 2022)[12]
- This has resulted in an increased spend on liquid melatonin from £4m to approximately £19.5m per annum (to date)[2,12]
- Liquid melatonin is 52% more expensive than Slenyto (comparative cost £1.05 /mg versus £0.69/mg)[12]

Slenyto® (prolonged-release melatonin) mini-tablets:

- Average daily dose after 1 year of treatment in patients who responded~ was 5.3mg[5]
- Choosing to prescribe Slenyto rather than liquid melatonin preparations could save £3.1 million per year in England and Wales or £5,009 per 100,000 population[2]

Product	NHS List Price	Pack Size
Slenyto 1mg	£41.20*	60 tablets
Slenyto 5mg	£103.00*	30 tablets

~ Response = overall improvement ≥1 hour in TST, SL or both over baseline, and did not require dose escalation
* NHS list prices are before and subject to an approved Patient Access Scheme (PAS) rebate

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REFERENCES AND PRESCRIBING INFORMATION

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4. Gringras, P. et. al. 2012 'Melatonin for sleep problems in children with neurodevelopmental disorders: randomised double masked placebo controlled trial', British Journal of Pharmacology. 345.
5. Maras, A. et. al. 2018 'Long-Term Efficacy and Safety of Pediatric Prolonged-Released Melatonin for Insomnia in Children with Autism Spectrum Disorder', Journal of Child and Adolescent Psychopharmacology. Volume 28, No 10, 699-710.
6. Gringras, P. et. al 2017 'Efficacy and Safety of Pediatric Prolonged-Release Melatonin for Insomnia in Children with Autism Spectrum Disorder', Journal of the American Academy of Child & Adolescent Psychiatry. Volume 56, Issue 11, 948-957.
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8. Zisapel, N. 2018 'New perspectives on the role of melatonin in human sleep, circadian rhythms and their regulation', British Journal of Pharmacology. Volume 175, Issue 16, 3190-3199.
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10. NICE Clinical guideline CG170, Autism spectrum disorder in under 19s: support and management. Published August 2013
11. European Medicines Agency, Guideline on pharmaceutical development of medicines for paediatric use [Accessed November 2022]
12. Drug Tariff https://www.nhsbsa.nhs.uk/pharmacies-gp-practices-and-appliancecontractors/drug-tariff [Accessed November 2022]
13. NHS Business Services Authority [Accessed November 2022]
14. Zuccari, G. et al. 2022. 'Mini-Tablets: A Valid Strategy to Combine Efficacy and Safety in Pediatrics', Pharmaceuticals. 15(1)

SLENYTO® PROLONGED-RELEASE TABLETS 1mg and 5mg

PRESCRIBING INFORMATION: Please refer to Summary of Product Characteristics (SmPC) before prescribing.

ACTIVE INGREDIENT: Melatonin 1mg or 5mg.

INDICATIONS: Insomnia in children and adolescents aged 2-18 years with Autism Spectrum Disorder and / or Smith-Magenis syndrome, where sleep hygiene measures have been insufficient.

DOSAGE AND ADMINISTRATION:

Dose titration: Recommended starting dose is 2mg once daily. If an inadequate response is observed, increase the dose to 5 mg, with a maximal dose of 10 mg. Data are available for up to two years treatment. Monitor at regular intervals (at least every 6 months) to check that Slenyto is still the most appropriate treatment. After at least 3 months, evaluate treatment effect and consider stopping if no clinically relevant treatment effect is observed. If a lower treatment effect is seen after titration to a higher dose, consider a down-titration to a lower dose before deciding on a complete discontinuation of treatment.

Administration: Once daily 0.5-1 hour before bedtime with or after food. Swallow whole, do not crush, break or chew. To facilitate swallowing, tablets may be put into food such as yoghurt, orange juice or ice-cream and then taken immediately.

CONTRAINDICATIONS: Hypersensitivity to the active substance or to any of the excipients.

SPECIAL WARNINGS AND PRECAUTIONS: Use caution in patients with renal insufficiency. Not recommended in patients with hepatic impairment. Children under 2 years: not recommended. Slenyto may cause drowsiness, therefore use with caution if the effects of drowsiness are likely to be associated with a risk to safety. Not recommended in patients with autoimmune disease. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

INTERACTIONS: Concomitant use with fluvoxamine, alcohol, thioridazine, imipramine, benzodiazepines and non-benzodiazepine hypnotics should be avoided. Use caution with 5- or 8-methoxypsoralen, cimetidine, oestrogens, CYP1A2 inhibitors, CYP1A2 inducers, NSAIDs, beta- blockers and with smoking.

FERTILITY, PREGNANCY, LACTATION: Avoid use of melatonin during pregnancy. Consider discontinuation of breastfeeding or discontinuation of melatonin therapy taking account of the benefit of breastfeeding for the child and the benefit of therapy for the woman. No known effects on fertility.

DRIVING: Melatonin has a moderate influence on the ability to drive and use machines.

UNDESIRABLE EFFECTS: Very common: None. Common: Mood swings, aggression, irritability, somnolence, headache, sudden onset of sleep, sinusitis, fatigue, hangover. Consult SmPC in relation to other adverse reactions.

PHARMACEUTICAL PRECAUTIONS: Do not store above 30°C.

LEGAL CATEGORY: POM

MARKETING AUTHORISATION HOLDER: RAD Neurim Pharmaceuticals EEC SARL, 4 rue de Marivaux, 75002 Paris, France . Marketed in the UK by Flynn Pharma Limited, Hertlands House, Primett Road, Stevenage, Herts, SG1 3EE, Tel: 01438 727822, E-mail: medinfo@flynnpharma.com.

Product	NHS List Price	Pack Size	Marketing Authorisation Number
Slenyto 1mg	£ 41.20	60 tablets	PLGB 52348/0003 EU/1/18/1318/001
Slenyto 5mg	£ 103.00	30 tablets	PLGB 52348/0004 EU/1/18/1318/003

Adverse events should be reported. Reporting forms and information can be found at https://yellowcard.mhra.gov.uk/. Adverse events should also be reported to RAD Neurim Pharmaceuticals EEC Limited Medical Information e-mail: regulatory@neurim.com

DATE OF REVISION OF PRESCRIBING INFORMATION: June 2021

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