FLYNN PHARMA LTD

Slenyto®

(Paediatric Prolonged-Release Melatonin)

Treatment Goals and Therapy Optimisation

A Guide for Healthcare Professionals

Prescribing information can be found on the last page

AUTISTIC SPECTRUM DISORDER AND COMORBID INSOMNIA IN CHILDREN

Sleep plays a fundamental role in health[1], but in paediatric autism spectrum disorder (ASD) patients' insomnia is particularly problematic with a prevalence as high as 50%-75%.[2-4] Insomnia in children with ASD is perceived to be one of the most challenging health effects of autism[5] with a substantial negative impact on day-to-day functioning, behaviours, cognitive performance of the child and is a cause of family distress.[6,7] If left untreated, especially in children under 6 years of age, insomnia has the potential to exacerbate the core symptoms of ASD.[8] Identification and appropriate management is therefore key and can improve the quality of life of both the child and family.[9]

MEASURING SLEEP AND DEFINING TREATMENT GOALS IN CHILDREN WITH ASD AND INSOMNIA

There is little doubt that the investigation of sleep, or any other medical disorder, can be more challenging in this group of children, who may be disturbed by changes in the environment, or have sensory issues and poorly tolerate any monitoring.[10]

Sleep diaries are still the most commonly used subjective form of monitoring and, whether paper based or electronic (such as SNappD), are easily completed and understood.[10]

SNappD is a simple-to-use sleep and nap app that allows sleep statistics and the impact of poor sleep to be recorded. The app, which is based on a clinically validated questionnaire used by medical researchers and specialist sleep practitioners, can be downloaded from the iOS or GooglePlay app stores free of charge. Results from the app can be shared electronically with healthcare professionals to monitor progress.

Scan the QR codes to download SNappD.

SNappD

Download on the App Store

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A successful intervention needs to define realistic and agreed outcomes, in full partnership with the child's carers and the child, where possible, that can be systematically monitored.[5]

Part of the challenge is that there are multiple potential goals of treatment and multiple stakeholders. The clinician has to decide whether to address the sleep onset, continuity, total sleep time (TST), or combinations of them all. However, the greatest impact of a sleep intervention might be on a child's daytime mood and concentration. Is the clinician treating the child's sleep issues, or the sleep-deprived parents, or the older sibling whose sleep and school work are affected?[10]

Sleep continuity (LSE; the longest continuous sleep episode) is an important sleep measure. Less than 6 hours of uninterrupted sleep has been associated with negative behavioural outcomes in children with ASD; children with high irritability and high stereotypic behaviours had shorter continuous sleep periods, compared to children with lower irritability, or less stereotypies.[9] LSE correlates with changes in the child's behaviours and parent's quality of life.[10]

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Sleep fragmentation, or its converse, sleep efficiency, is sometimes used, but there is a lack of standardisation on how they are defined, what is normal for a child with ASD, and how much change matters.[10] Sleep efficiency (SE), commonly defined as the ratio of total sleep time to time in bed (TIB), plays a central role in insomnia research and practice.

Another common measure is TST. Importantly, lower total sleep time is associated with poorer total and psychosocial paediatric quality of life in children with ASD.[9]

Whilst night awakenings are common in children with ASD, capturing them in a meaningful way is more difficult. There is a huge difference between 10 awakenings between 22:30 and 23:30 hours and 10 awakenings that occur every hour of the night.

INTERVENTIONS FOR INSOMNIA IN CHILDREN WITH ASD

Behavioural sleep interventions provide parents with strategies they can implement to help their child "learn" healthy sleep behaviours and, if necessary, "unlearn" inappropriate sleep behaviours. Parent-directed behavioural interventions are effective and should precede use of medication.[10] However, the reported response rate to these interventions for paediatric insomnia in autistic children is low at 25%.[11]

Exogenous melatonin is most commonly used for sleep problems in ASD, related to the pathophysiology of insomnia in this population.[9]

In line with consensus recommendations that clinicians should offer pharmaceutical grade melatonin, if behavioural strategies have not been helpful, the development and regulatory approval of paediatric-appropriate prolonged-release melatonin mini-tablets, Slenyto®, has been welcomed. For this indication, (insomnia treatment in paediatric ASD and/or Smith Magenis Syndrome), Slenyto represents in-label use that provides the proof of quality, efficacy, dosing, and safety, including long-term efficacy, safety and acceptance needed for regulatory drug approval. The pharmacokinetic profile of Slenyto is of major importance for its ability to improve sleep onset, consolidation and duration in children and adolescents with ASD.[9]

Slenyto use is supported by 2-year data: its efficacy has been proven in both a 13-week randomised placebo-controlled study and a 91-week open-label trial. The trial demonstrated a clinically meaningful increase in total sleep time, reduction in sleep latency and an increase in the duration of uninterrupted sleep. By improving total sleep time and uninterrupted sleep, these outcomes underpinned improvements in day-to-day functioning, cognitive performance and externalising behaviours, positively impacting the wider family well-being and quality of life of patients' caregivers/family members.[11-14]

Examining the improvements in individual sleep parameters and child behaviour after 13 weeks, Slenyto treated patients:

- Slept 57.5 minutes longer on average per night (compared to 9.1 minutes with placebo) resulting in significantly improved behavioural aspects.[11,14] This is consistent with a causal link between diminished TST and worsening of externalising behaviour abnormalities and supports the role of better sleep in improving behavioural problems. Comorbid ADHD (28.8% of participants) did not affect response, regardless of stimulant use. The number of children with TST within the recommended sleep duration for their age more than doubled (from 19.2 to 42.3%) and the number of those with inappropriately low TST values for their age decreased significantly (from 36.5 to 13.4% of participants). There were no such changes (and even a slight deterioration) with placebo.[9] See Figure 1.[15]

cont. overleaf

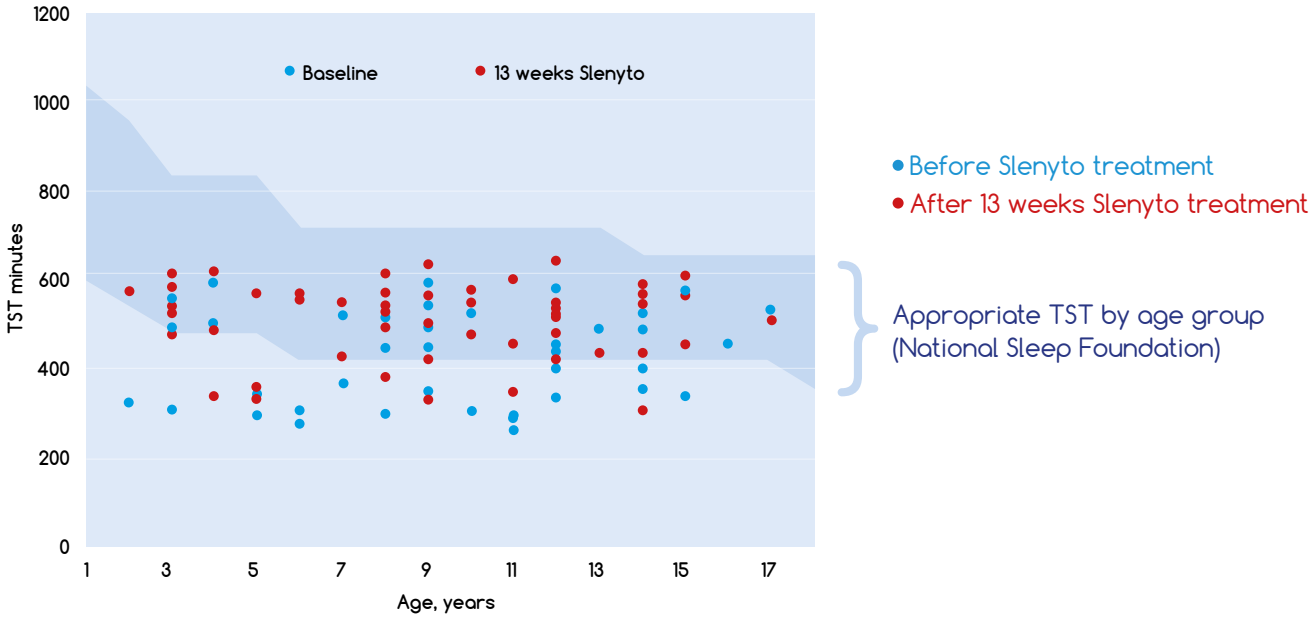
- Improved sleep onset latency (SOL) by a reduction of 39.6 minutes on average (compared with 12.5 minutes with placebo).[11] Of note, the undesired earlier awakening (i.e., phase shift) that may occur with immediate-release melatonin did not occur.[9]

- Increased LSE by 77.9 minutes on average (compared to 25.5 minutes with placebo). This improvement is approximately equivalent to 2 complete sleep cycles (REM and non-REM) in children (~ 45 minutes). Both REM sleep and non-REM sleep are related to children's growth and memory consolidation.[16-18]

- Displayed a significant and clinically-relevant improvement in externalising behaviour i.e., aggressive, hyperactive, noncompliant, and under-controlled behaviour, as measured by the Strengths and Difficulties Questionnaire, SDQ, (53.7% Slenyto versus 27.6% placebo). The change in total SDQ score correlated with the change in TST and specifically with LSE, but not with SOL.[9]

Compared to placebo, the beneficial effects of Slenyto treatment on the child's sleep were associated with significant improvements in parents' well-being and satisfaction with their child's sleep patterns that persisted throughout the 2-year follow-up. There was a significant correlation between the improvement in caregiver's quality of life (WHO-5) from baseline and the improvement (decrease) in child total SDQ score. These findings suggest that the improvement in parents' well-being is mediated by a noticeable improvement in children's daytime behaviour and further support the clinical benefits of improved sleep duration and continuity.[9] In contrast to the usual difficulties with tablet formulations experienced by children with ASD, compliance was excellent without the need to crush or dissolve Slenyto (which would negate the prolonged-release properties).[11] Slenyto tablets are flavourless and odourless and just 3mm in diameter.[9]

Figure 1. TST of Individual Patients Before and After 13 Weeks Slenyto Treatment[15]



The response to melatonin is seen rapidly (within 1 week) allowing fast evaluation of treatment success and dose optimisation. Because the pharmacokinetic and pharmacodynamic profiles of Slenyto are not predicted by age, body weight or puberty, the preferred dosing strategy is a personalised titration to optimal dose.[9]

The recommended starting dose of Slenyto for children who fail sleep hygiene/ behavioural intervention is 2 mg per day, with optional increase to 5 mg/day and then 10 mg/day. Dose adjustment is driven by the need to attain treatment success in one or more of the treatment success criteria (depending on the individual symptoms and severity).

Treatment Success Criteria[9]

1. TST within the recommended range for the subject's age
   - 10–13 hours for age 3–5 years
   - 9–11 hours for ages 6–13 years
   - 8–10 hours for ages 14–17 years
2. SOL <30 minutes
3. LSE >6 hours

For some people an additional hour or two on either side of a given range may be appropriate.

TST within the following range may be appropriate for the subject's age[19]

- *8–14 hours for age 3–5 years*
- *7–12 hours for ages 6–13 years*
- *7–11 hours for ages 14–17 years*

See algorithm overleaf for recommended treatment pathway

It should be noted that the recommended age-dependent TST range can vary due to genetically driven factors. In addition, child behaviour, parent satisfaction with child's sleep and safety should be considered in the decision to escalate or to continue the dose. If treatment success criteria are not achieved, despite a maximal dose of 10 mg, parental, or patient (if applicable), satisfaction should be considered before down-titration to a lower dose or stopping treatment.[9, 20]

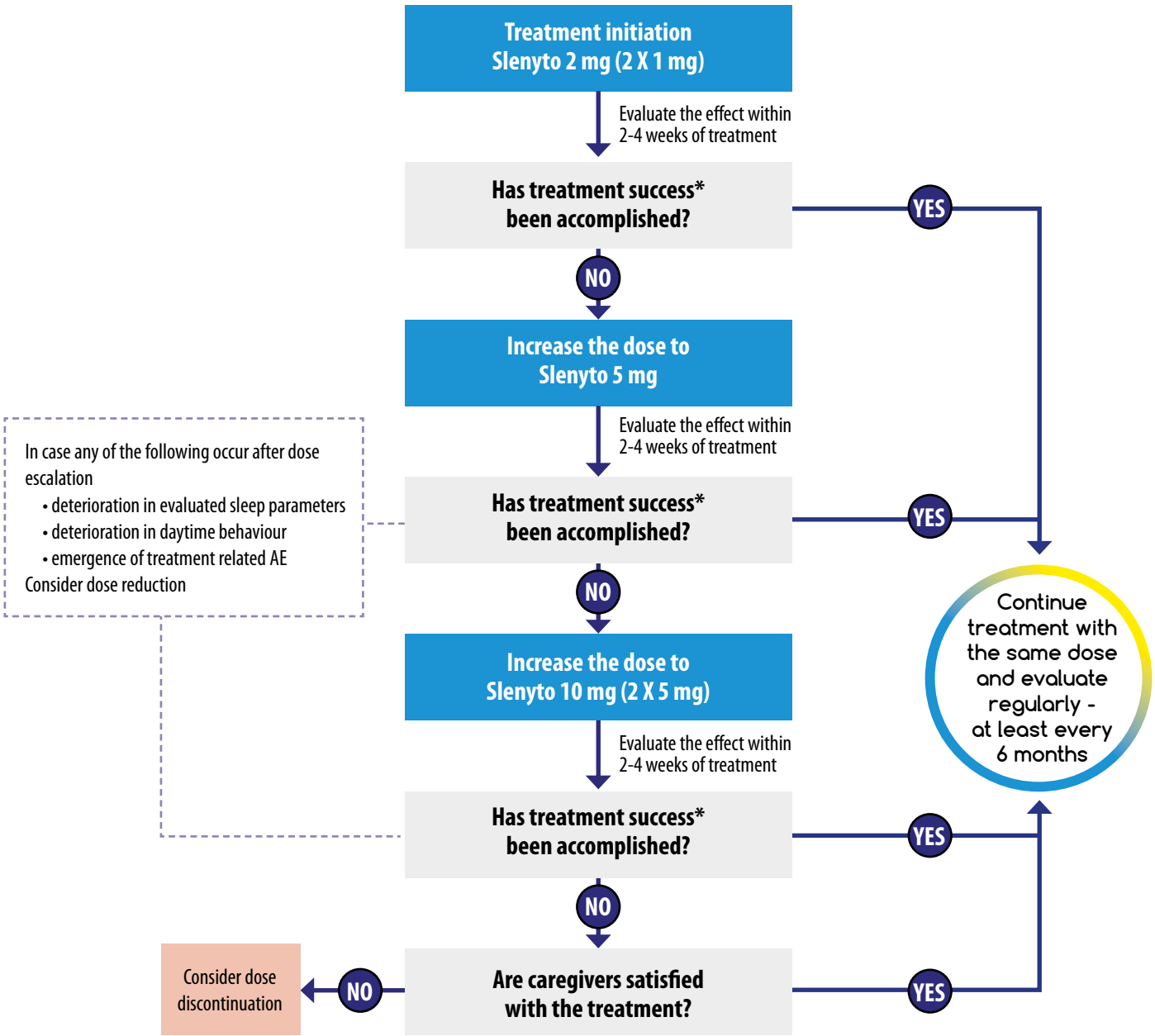
For children using other medication to treat insomnia, e.g., antihistamines, alpha adrenergic agonists (clonidine), anti-psychotics etc., it is advised to taper them off before starting Slenyto. In case such medications are used for an indication other than sleep disturbance they can be maintained without major drug interaction problems. Immediate release melatonin may be stopped just prior to starting Slenyto.[9]

If treatment effects are reduced, daytime behaviour deteriorates or adverse events related to the drug (e.g., daytime somnolence) appear after dose escalation, the prescriber should first consider a down-titration to a lower dose before deciding on a complete discontinuation of treatment. Gradual loss of effect of melatonin after initial positive effect may occur in subjects with slow CYP1A2 metabolism, resulting in excessively high melatonin levels. In such cases, efficacy could be reinstated by tapering down the dose.[9]

slenyto®
Prolonged-release melatonin

THERAPY OPTIMISATION

Slenyto Insomnia Treatment Algorithm[1]



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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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