FLYNN PHARMA LTD
A THERAPEUTIC BULLETIN

Slenyto®

(Prolonged-release melatonin tablets 1mg and 5mg)

SUMMARY

In July 2018, the European Medicines Agency (EMA) recommended granting a Paediatric Use Marketing Authorisation (PUMA) for Slenyto®, paediatric-appropriate prolonged-release melatonin mini tablets. The approval was based on a paediatric investigational plan (PIP) containing a Phase III study demonstrating short- and long-term efficacy and safety (see section 4). The EMA opinion was formally adopted by the European Commission on September 20th, 2018 with UK Marketing Authorisations given on the same date.

The registration-seeking study provided evidence of significant improvements, over baseline, in total sleep time, sleep initiation (latency) and maintenance, child behaviours (externalising), caregivers' quality of life and resolution of their own sleep disturbance. Notably, improvements in total sleep time and sleep onset were not associated with earlier waking (i.e. sleep-phase shift).

In contrast to the difficulties with conventional formulations experienced by children with autism spectrum disorder, the authors reported excellent compliance, without the need to crush, sub-divide or dissolve the mini-tablet (which would negate the prolonged-release properties).[1] Slenyto 1mg and 5mg tablets are 3mm in diameter, odourless and flavourless. Slenyto is indicated for the treatment of insomnia in children and adolescents aged 2-18 with autism spectrum disorder and / or Smith-Magenis syndrome (SMS), where sleep hygiene measures have been insufficient.[2] The NHS list price for Slenyto 1mg tablets (60 tablet pack) is £41.20 and Slenyto 5mg (30 tablet pack) is £103.00.[3]

1. AUTISTIC SPECTRUM DISORDER AND COMORBID INSOMNIA IN CHILDREN

Autism spectrum disorder (ASD) is a developmental disorder characterised by impairments in social interactions and communication, in association with restricted and repetitive behaviours. Formerly ASD was subdivided into five distinct disorders, namely Autistic Disorder, Asperger's Syndrome (AS), Rett's Disorder, Childhood Disintegrative Disorder, and Pervasive Developmental Disorder (PDD)-Not Otherwise Specified.[4] More recently, ASD has come to be regarded as a continuum of psychological conditions, necessitating moderate to substantial support to cope with the deficits in social communication and restricted, repetitive behaviours.[4] This shift acknowledges the lack of distinct neurobiological profiles differentiating the different subtypes and the inconsistency in their use.[5] Autism spectrum disorders are now recognised to occur in up to 1% of the population and to be a major public health concern because of their early onset, lifelong persistence and high levels of associated impairment.[6]

Paediatric insomnia is a widespread problem, with an overall prevalence of 1% to 6%, but rising to 50% to 75% in children with neurodevelopmental or psychiatric comorbidities, and specifically ASD and neurogenetic disorders (e.g. Rett syndrome, Tuberous Sclerosis, Smith-Magenis syndrome and Angelman syndrome).[1] The sleep disturbances exacerbate both cognitive performance deficits and behavioural problems and subsequently entire-family distress.[1] Long-term sleep disorders, and the resulting day and night care difficulties, are among the main factors affecting parental decisions on whether, and when, to institutionalise their child as they grow older.[7]

Increasing evidence demonstrates the compounding effect of sleep problems on autism symptomatology. In toddlers, sleep difficulties are associated with lower developmental functioning. In children and adolescents, sleep disturbances, particularly reduced sleep duration, predict ASD symptom severity. Poor sleepers with ASD have higher problems with social interaction, increased affective (mood) problems, lower adaptive functioning and communication deficits. Shorter sleep duration and night-waking are associated with more communication problems, whereas bedtime resistance, screaming during the night, and fewer hours of sleep are linked to stereotypic behaviours. Additionally, sleep problems exacerbate externalising (aggressive, hyperactive, noncompliant and under-controlled) behaviours and internalising (anxious, depressive, and overcontrolled behaviours) problems.[4]

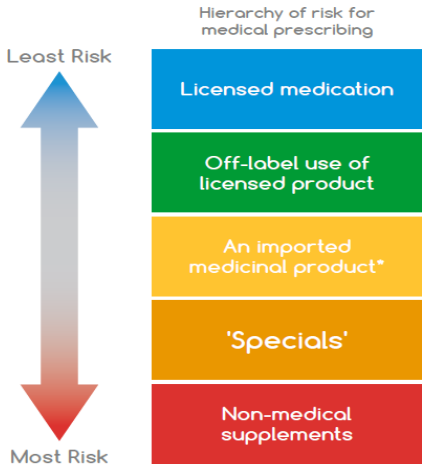
Poor sleep also predicts later anxiety difficulties both in neurotypical and ASD children. Conclusions that can be drawn from these studies/ findings are limited by possible bias in the relationships between sleep and symptom severity due to comorbid developmental disabilities. However, it is noteworthy that sleep onset delay, sleep duration, and parasomnias exacerbate autism severity in ASD children without any comorbid developmental disabilities. Night-waking is a strong predictor for social interaction deficits, whereas sleep onset delay predicts communication difficulties, stereotyped behaviour, and autism severity. Altogether, the available evidence indicates that sleep problems exacerbate ASD symptom severity. Interestingly, worsened ASD symptomatology appears to also increase the risk of sleep problems suggesting that the relationship between sleep and autism severity is bidirectional.[4]

Children with ASD who have greater overall presenting sleep problems are more likely to experience poorer health-related quality of life than ASD children who are good sleepers.[8] As well as the detrimental effect on the well-being of ASD children, sleep disturbances also negatively impact the mental health of family members.[4] Indeed, even after controlling for child behaviour, sleep problems in ASD children predict parental depressive symptoms and impaired sleep quality.[4] Neurotypical siblings are also more likely to present with sleep difficulties than siblings with no family history of autism.[4] Therefore, sleep intervention in people with ASD is an essential component of their management which should be embedded in a comprehensive approach to ASD.[4]

2. TREATMENT OF SLEEP PROBLEMS IN CHILDREN WITH ASD

Current practices recommend parent-directed behavioural sleep interventions as first-line management for paediatric insomnia in ASD/NGD (neurogenetic disorders), with reportedly a 25% response rate. Pharmacotherapy is often considered when the behavioural intervention fails.[1] Until now, however, there were no medications with regulatory approval for the treatment of chronic insomnia in children and adolescents and this was particularly problematic for children with ASD.[9] Consequently, physicians often prescribe drugs off-label. For example, Circadin® (2mg prolonged-release melatonin which is licensed for short-term treatment of primary insomnia in patients ≥55 years) is commonly used, albeit that to facilitate swallowing, the tablet is often sub-divided or crushed. In so doing, however, the intended release characteristics are destroyed, and the dose is effectively rendered immediate release.[9] Unlicensed liquid formulations of melatonin are also available; however, these are all immediate release, typically contain additives and preservatives, and require a willing patient for their effective administration. Moreover, unregulated melatonin preparations, or food supplements, are used despite concerns over their provenance, quality, potential safety hazards and lack of evidence for long-term efficacy and safety. Other medications are used outside of license including antihistamines, alpha-adrenergic agonists (clonidine), antidepressants, and antipsychotics, for their sedative side effects, but in absence of proven safety or efficacy.[10]

Current Pharmacological Practices for the Treatment of Insomnia in Children with ASD



*Licensed in the country of origin

Adapted from MHRA Guidance Note 14 (2014)

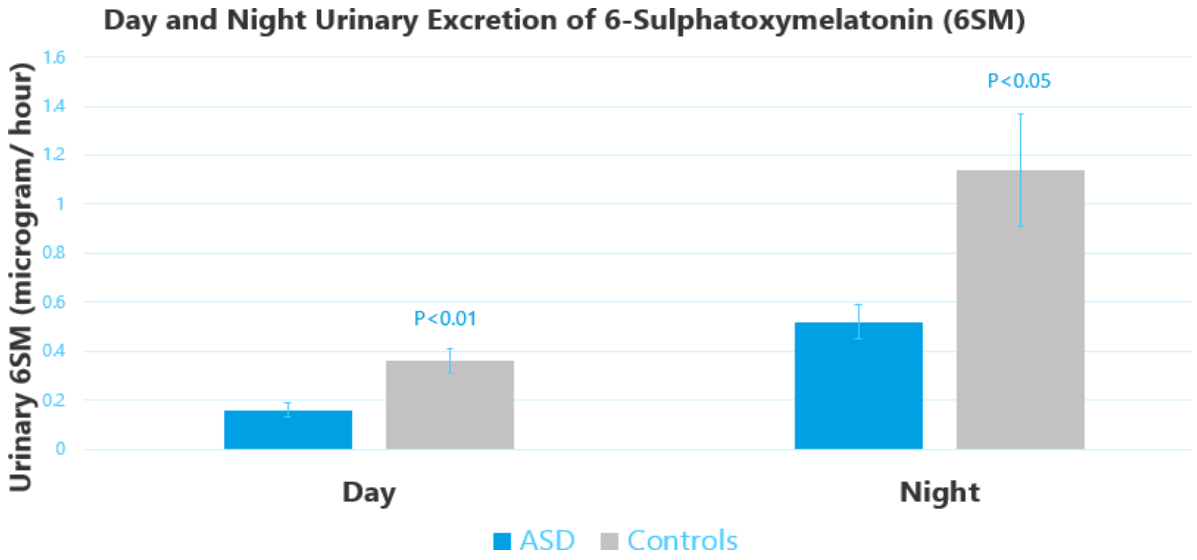
The General Medical Council (GMC) advises prescription of licensed medicines in accordance with their licence and that, before prescribing an unlicensed medication, prescribers should be satisfied that an alternative, licensed medicine would not meet and better serve the patient's need.[11]

Melatonin is a powerful antioxidant, involved in the regulation of circadian and seasonal rhythms and immune function. It is released mainly by the pineal gland during the night and is produced by the conversion of serotonin to N-acetyl serotonin followed by the conversion of N-acetyl serotonin to melatonin by
ASMT (acetyl serotonin methyltransferase). [12]

Melatonin secretion is highly heritable in humans, modulates neuronal plasticity and regulates circadian gene expression. Abnormal melatonin concentrations can have a dramatic effect on human behaviour, as shown in patients with Smith–Magenis syndrome, who exhibit an inverted melatonin circadian rhythm and display autistic behaviours. In ASD, low melatonin levels have been reported by three independent groups, but the underlying cause of the deficit and its relationship to susceptibility to ASD is unknown.[12]

The physiological increase in melatonin secretion during the night is well established with a peak around 2 am and night-time values usually at least three times greater than daytime values. Pineal melatonin production is powerfully suppressed by light acting through the retinohypothalamic tract. In addition to light, and consequently seasonal affects, pineal melatonin secretion can also be influenced by endogenous factors including sex, age and pubertal stage. The measures of melatonin concentration in plasma and saliva, or of the urinary excretion of its predominant metabolite, 6-sulphatoxymelatonin (6-SM), are considered the best peripheral indices of human circadian timing.[13]

Figure 1



Adapted from Tordjman et al., 2012[13]

Melatonin is of interest in autism due to its apparent role in neurodevelopment, reports of sleep-wake rhythm disturbances in individuals with autism, and its beneficial effects when administered to individuals with autism and sleep problems.[13] In addition, central and peripheral alterations in serotonin in autism have been widely reported and it is noteworthy that melatonin is synthesised in only two steps from serotonin in the pineal gland and the gut. Prior studies of melatonin production in ASD were often limited by small sample sizes and were equivocal, but all reported abnormalities in melatonin production.[13] However, given the limitations of the available data, it is not possible to conclude if there is a general decrease in melatonin secretion during the whole 24-h cycle, or if the melatonin circadian rhythm is altered or inverted in ASD.[13]

More recently, Tordjman et al., (2012) reported a night and daytime deficit in melatonin production in a substantial proportion of individuals with autism (see Figure 1).[13] The authors hypothesised that the small intra-individual night time-daytime differences, and the significant absence of melatonin variation found in autism, might be a reflection of the lower day and night time levels, or an indication that there exists a subgroup of individuals with autism that have a dysregulation of their circadian rhythm, and more precisely an absence of circadian rhythm.[13]

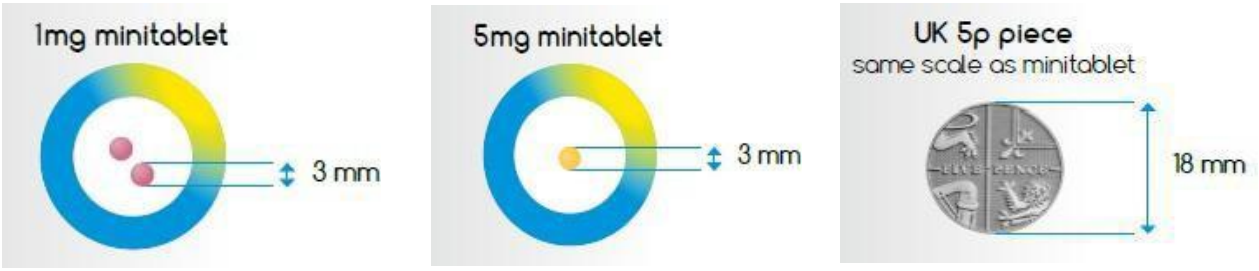
The use of melatonin for treating chronic sleep–wake cycle disorders of children with ASD/NGD is increasing. A recent meta-synthesis concluded that melatonin, behavioural interventions, and parent education interventions appear to be the most effective at ameliorating multiple domains of sleep problems.[1]
In a study of children who failed to improve on behavioural intervention alone, immediate release (IR) melatonin demonstrated beneficial effects on sleep latency (time to fall asleep) and, to a lesser extent, on total sleep time. The authors concluded, however, that children gained little additional sleep when taking melatonin since although they fell asleep significantly faster, waking times were earlier (phase shifting). Child behaviour and family functioning outcomes did not significantly improve.[14]

3. SLENYTO®

In September 2018 the European Medicines Agency (EMA) granted Marketing Authorisations (MAs) for Slenyto®, an age 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. The product development, and approval, under the Paediatric Regulations, followed the EMA's refusal to consider Circadin® (prolonged-release melatonin 2mg indicated for insomnia in patients ≥55) as a potential licensed indication extension. The EMA took the view that Circadin was not an appropriate product for this patient population.

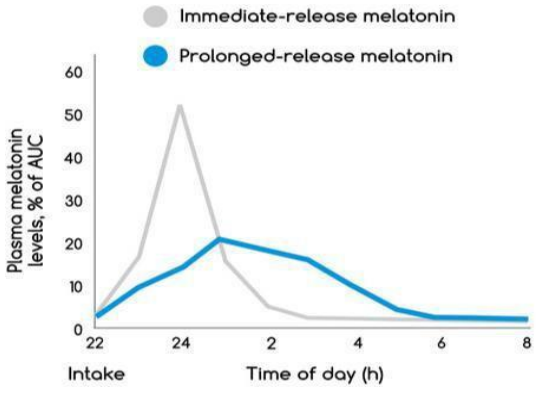
The MA for Slenyto is in fact a Paediatric- Use Marketing Authorisation (PUMA), since Slenyto is formulated to be both condition-(ASD) and age (2-18 years) appropriate. Slenyto minitablets (1mg and 5mg) are 3mm in diameter (see Figure 2- not actual size), flavourless and odourless and the strengths are differentiated by colour. The Summary of Product Characteristics also provides further information on co-administration with foodstuffs to facilitate swallowing and improve compliance.[3]

Figure 2. Slenyto® (prolonged-release melatonin minitablets) 1mg and 5mg

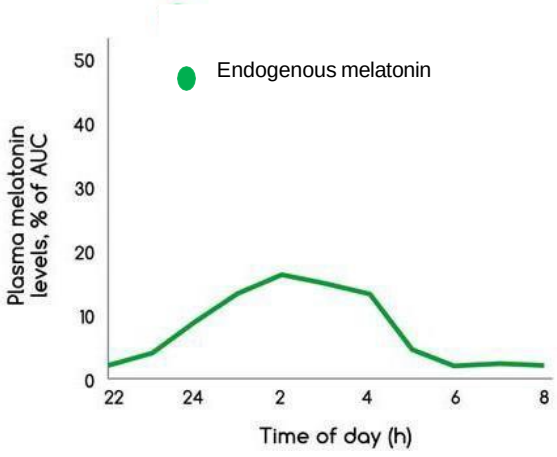


Slenyto is formulated to mimic the endogenous profile, by releasing melatonin throughout the night.

Figure 3. Pharmacokinetic Profiles of Immediate, Prolonged-Release and Endogenous Melatonin*



Graph adapted from Zisapel 2010[15]



Graph adapted from Zisapel, 2018[16]

*Data presented in Figure 3 derived from studies in adults

4. SLENYTO® - THE EVIDENCE BASE

The Paediatric Investigational Plan (PIP) included a Phase III study demonstrating the product's short, and long- term efficacy and safety. The study, in patients who had not previously responded to behavioural intervention, comprised a 2-week, single-blind placebo run-in, followed by a randomised double-blind study of 13 weeks active or placebo treatment (Gringras et al., 2017)[1], and a further open-label extension comprising 13 weeks of active treatment at final double-blind phase dose (or placebo equivalent dose), and a further 78 weeks treatment with an optional dose escalation to 10 mg, and concluded with a 2-week single-blind placebo period (to examine withdrawal effects). Data for the entire study formed part of the EMA assessment; data for 52 weeks have been published[10] and will be presented here; and publication of the full two-year data is pending.

Efficacy and safety of Paediatric Prolonged-Release Melatonin for Insomnia in Children with Autistic Spectrum Disorder[1]

In the double-blind period 125 children (2–17.5 years; 96.8% ASD, 3.2% SMS) with insomnia and without a documented history of sleep behavioural intervention at screening underwent 4 weeks of advice booklet– assisted, basic, parent-led sleep behavioural intervention based on a previously studied and standardised sleep behaviour treatment. This period ensured that children whose sleep disorder was amenable to non-pharmacological management were not randomised, and also served as wash-out from any hypnotics.

Eligible children entered a 2-week, single-blind, placebo run-in period after which, if they still had impaired sleep (defined as ≤6 hours of continuous sleep and/or ≥0.5 hour sleep latency (SL), from lights-off in 3 of 5 nights in the last 2 weeks, based on a parent-reported Sleep and Nap Diary (SND), they were randomised (1:1), to receive active or placebo for the 13-week double-blind treatment period. The starting dose of active (or placebo) was 2 mg once daily 30-60 minutes before habitual bedtime and with or after food.

After 3 weeks of double-blind treatment, sleep variables were reassessed. If the patient did not improve from baseline by at least 1 hour, as measured by a shortening of sleep latency (SL) and/or increase in total sleep time (TST), the dose was escalated to 5 mg. Patients continued double blind on 2 or 5 mg of active or placebo for the remaining 10 weeks, with an efficacy assessment by the end of the 13-week double-blind treatment period (see Figure 4).

Figure 4. Study Algorithm - Efficacy and Safety of Slenyto for Insomnia in Children with ASD

The primary efficacy outcome in the 13-week study was the change from baseline in mean TST and a secondary outcome was change from baseline in mean SL. Other secondary sleep variables were the change from baseline in duration of wake after sleep onset, number of awakenings, and longest (uninterrupted) sleep episode (LSE), change from baseline in Composite Sleep Disturbance Index (CSDI) score and subscores, and number of dropouts during the 13-week double-blind treatment period. The CSDI is a validated tool scoring the frequency and duration of sleep problems reported by parents.

Safety was monitored throughout the study using standard clinical trial methods and definitions and standard age-appropriate methods were used to assess the child development and health status.

After 13 weeks of treatment with Slenyto, children slept on average 57.5 minutes more per night and went to sleep on average 39.6 minutes earlier. Using the definition of clinical response as an increase in TST of ≥45 mins and/ or reduction in SL by ≥ 15 mins versus baseline, 68.9% of participants responded to Slenyto by 13 weeks (versus 39.3% with placebo; p=0.001) corresponding to a number needed to treat (NNT) of 3.38. Thus 2 of 3 children with ASD are expected to have a clinically meaningful response to a 2/5 mg dose.

Besides shortening of SL, the observed increase in TST could be best explained by a greater improvement (increase) in the LSE compared to placebo. This is especially important for caregivers and families since a child who sleeps for 5 hours but wakes twice every hour is more disruptive to parents than a child who sleeps for 5 hours but wakes 10 times in the first hour. By the end of the 13-week double-blind period, the mean LSE increased on average by 77.9 minutes in the Slenyto treated group i.e. the LSE improved by over an hour.

Importantly, and unlike IR melatonin, Slenyto did not result in earlier waking. In an earlier study of IR melatonin, a proportion of children fell asleep more quickly (i.e. SL was reduced) but also started to wake earlier (phase shifting).[14] Slenyto improved both sleep initiation and sleep maintenance since it has been developed to mimic the endogenous profile and releases melatonin throughout the night.

Slenyto 2 mg/5 mg treatment resulted in a significant improvement over placebo in the child's externalising behaviours (hyperactivity/inattention and conduct scores) as assessed by the Strength and Difficulties Questionnaire (SDQ) after 13 weeks of double-blind treatment (p=0.021)[1] – see Figure 5. Using improvement (i.e. decrease) in externalising behaviours score by 1 unit or more as a criterion of clinical response, the percentage of responders after 13 weeks of double-blind treatment in the Slenyto group was 53.7% compared to 27.7% in the placebo-treated group (Odds ratio 3.0; p = 0.008), providing evidence for the clinical meaningfulness of the treatment effect.[17] The 26% difference in percentage between the groups corresponds to an NNT of 3.8. For the total SDQ score after 13 weeks of double-blind treatment, there was a trend to benefit in favour of Slenyto (p=0.077). [17]

Figure 5. SDQ Externalizing Behaviour During the Double-blind Period [17]

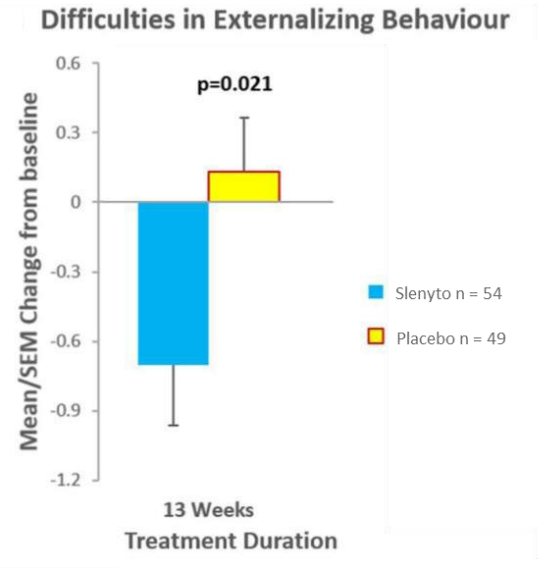
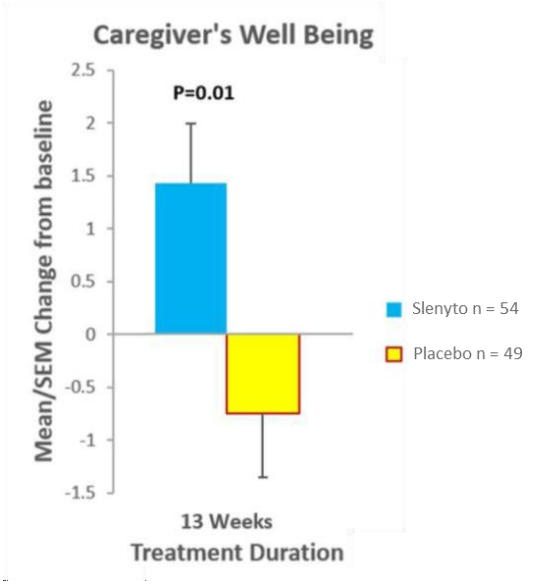


Figure 6. WHO-5 Caregiver's Well-being and Quality of Life During the Double-Blind Period [17]



The treatment effects on sleep variables were associated with improved caregivers' well-being assessed by the World Health Organisation scale (WHO-5) after 13 weeks double-blind treatment (p=0.01) – see Figure 6.

It is pertinent to ask whether the improvement in parents' quality of life, subsequent to the improvement in a child's sleep, might provide a "positive bias" on the parent-completed rating scales of patient behaviour or influence parenting and, therefore, behaviour of children. Yet, the change in caregivers' quality of life seems strongly related to the improvements in daytime behaviour (total SDQ) rather than to the improvements in child's sleep (TST, SL, or longest

duration of uninterrupted sleep). Of note, caregivers' quality of life had already improved significantly with the Slenyto-treated compared to the placebo-treated groups after 3 weeks; by that time the hyperactivity/inattention scores also improved significantly in the Slenyto compared to the placebo treated groups. Furthermore, caregivers' own sleep did not improve significantly with a Slenyto treated child compared to a placebo treated child and improved further only months later in the open-label study (Maras et al. 2018). These findings could be interpreted as improvement of wellbeing of parents is mediated by improvement of daily behaviour in the child and not directly by sleep improvement in the child or parent. It is, therefore, most likely that the improvement in sleep in the subjects led to the improvement in behaviour and that this improvement is more valuable to the caregivers' quality of life than the improvement in child sleep per se.[17]

The relevance of improvements in sleep to the observed improvements in behavioural attributes was demonstrated by the significant correlations between the changes in TST and duration of uninterrupted sleep with the changes in total SDQ and less so for SL. The impact of sleep duration on behaviour can thus be explained, at least in part, by the improvement in duration of uninterrupted sleep rather than the improvement in sleep latency. This is of note because the prolonged release formulation which releases melatonin throughout the night appears to be effective in improving both sleep onset and sleep maintenance whereas immediate release melatonin formulations are reportedly as effective in sleep induction but less so with sleep maintenance.[17]

Of the randomised participants, 28.8% had comorbid ADHD and 12.8% had comorbid epilepsy, as determined by patient medical history. Importantly, sub-group analyses demonstrated that Slenyto was similarly effective in children with or without ADHD comorbidity. No unexpected safety issues were reported and there was no increase in or new onset of seizures.

Adverse effects were few and mild, with only headaches and daytime somnolence increased in the treatment group relative to placebo group. There was no increase in, or new onset of, seizures. In contrast to the usual difficulties with tablet formulations experienced by children with ASD, compliance was excellent.

Long-Term Efficacy and Safety of Paediatric Prolonged-Release Melatonin for Insomnia in Children with Autism Spectrum Disorder[9]

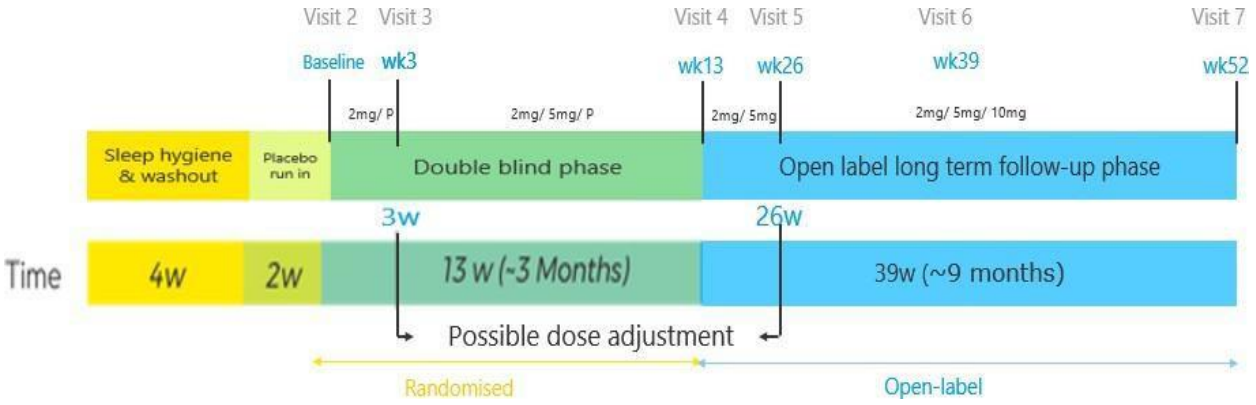
A total of 95 participants who completed the 13-week double-blind phase entered the 39-week, open-label follow-up phase. Accordingly, patients who received 2mg placebo in the double-blind phase received 2mg Slenyto, and those who were escalated to 5mg placebo received 5mg active. Of the 95 patients in the follow-up phase, 51 had been assigned to active and 44 to placebo in the double-blind phase.

After the first 13 weeks of follow-up sleep variables were assessed, and if the patient did not improve from baseline by at least 1 hour in sleep latency (SL) and/or total sleep time (TST) in the double-blind or follow-up phases, the dose was escalated from 2 to 5 mg/day and from 5 to 10 mg/day. An optional decrease in dose was also allowed at all times during the study, based on the evaluation of excessive drowsiness, behavioural changes, or ceasing to respond to study drug. Children then continued open label on 2, 5, or 10 mg for the remaining period, with efficacy assessment after 26 and 39 weeks of follow-up (see Figure 7, below).

Improvements in TST (increase), SL (decrease), and LSE (increase) observed in the double-blind phase were maintained or enhanced throughout the follow-up. After 52 weeks of continuous treatment, children slept on average 62 minutes longer ($p = 0.007$), went to sleep on average 49 minutes earlier ($p<0.001$) without earlier wakening.

Children also experienced an increase in the longest uninterrupted sleep episode by 89.1 minutes ($p = 0.001$), a reduced number of night-time awakenings by 53% ($p=0.001$) and quality of sleep improved significantly ($p < 0.001$) compared with baseline values.

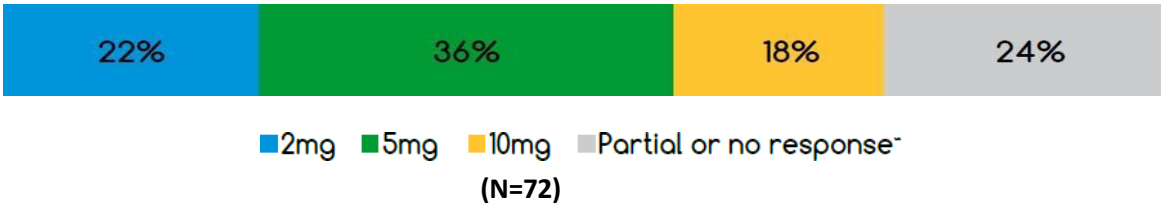
Figure 7. Study Algorithm – Long-Term Efficacy and Safety of Slenyto for Insomnia in Children with ASD



After 52 weeks of continuous treatment 76% of patients achieved a clinically meaningful response (i.e. overall improvement ≥1 hour in TST, SL or both over baseline). Of the 55 responders, 22% (16 patients) used 2mg/day, 36% (26 patients) used 5mg and 18% (13 patients) used 10mg~. Seventeen subjects (24%) had partial, or no measurable, response compared with baseline even at the highest (10mg) dose. The average daily dose after 1 year of treatment in patients who satisfied this criterion was 5.3mg. Diagnosis (ASD with/ without ADHD or SMS) and co-medication (e.g. stimulants) did not affect Slenyto efficacy outcomes.

Observations of the 2mg treatment group provide clinically important insights: (a) about lack of attrition of effects and (b) evidence of a substantial group of children responding to, and maintaining the benefit of, the lower dose. Patients remaining on a 2mg Slenyto dose had the same or greater benefits over time without dose escalation.

Figure 8. Clinically Meaningful Response to Slenyto by Dose After 52 Weeks#



*Response = overall improvement ≥1 hour in TST, SL or both over baseline, and did not require dose escalation
Dosage split, and response rate include participants taking placebo for the first 13 weeks of the clinical trial
~29% x55/72 =22%, 47% x55/72 =36%, 24% x55/72 =18%

Of note, in the double-blind phase, approximately 80% of patients in the placebo group were escalated to the 5mg (placebo) dose and, therefore, entered the open-label follow-up on a starting dose of 5mg. It is postulated that if these patients had started 2mg Slenyto treatment, a comparable number (up to 40%) would have stayed on the 2mg dose, as was seen in the Slenyto-assigned group.[10]

Importantly, as sleep disturbances in children with ASD can negatively impact not only the quality of life and daytime functioning of the child, but also the family, caregiver outcomes were also assessed. By the end of the follow-up, caregivers of children who had been randomised to Slenyto and treated continuously for 52 weeks showed significant improvements in sleep quality (mean change from baseline in Pittsburgh Sleep Quality Index score), quality of life (mean change from baseline in WHO-5 score) and CSDI-assessed satisfaction with their child's sleep patterns. Forty- nine percent of caregivers attained complete remission of their own insomnia and approximately the same percentage experienced a clinically relevant improvement in quality-of-life.

The most commonly reported treatment emergent adverse events (TEAEs) were fatigue (18.9%), vomiting (17.9%), somnolence (16.8%), cough (13.7%), mood swings (13.7%), upper respiratory tract infection (10.5%), headache and rash (8.4% each), dyspnoea (7.4%), constipation, nausea and pyrexia (6.3% each), rhinorrhoea, aggression and agitation (5.3% each). Only in 17.9% of patients were the TEAEs considered to be definitely, probably, or possibly related to study medication. There were small increases in Body Mass Index (BMI) and Z-scores* in the Slenyto and placebo groups, with no clinically significant difference between the groups.

*Z-score, standard deviation classification system of childhood growth indices (World Health Organisation)

CONCLUSION

Given the prevalence, and the known negative correlates with child and caregiver well-being, investigating and treating insomnia should be at the forefront of therapeutic interventions for children with ASD. Children with ASD can, however, present special challenges for drug administration and may present with unusual feeding difficulties, restrictive diets, dysphagia and tactile sensitivities/defensiveness.

Until now, there were no licensed insomnia medications for this population thus necessitating off-label use of medicines or use of wholly unlicensed preparations.

In September 2018, on the basis of robust evidence of long-term (2 years) efficacy and safety, Slenyto was licensed by EMA for the management of insomnia in children (2-18 years) with ASD and/ or SMS. Slenyto is formulated to be both condition-(ASD) and paediatric-(2-18 years) appropriate and the minitablets (1mg and 5mg) are 3mm in diameter, flavourless and odourless.

Slenyto makes an important, contribution to a previously unmet need and, addition to the clinician's armamentarium.

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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