

Module 2.5 Clinical Overview

Melatonin 3 mg film-coated tablets

**Type II Variation to marketing authorisation
PL 20243/0004 (Melatonin 3 mg film-coated tablets)**

Applicant: Pharma Nord ApS

**Tinglykke 4-6
6500 Vojens
Denmark**

[Redacted]

[Redacted]

[Redacted]

Summary points of the clinical [REDACTED]

[REDACTED] Module 2.5 of PL 20243/0004 is divided into the following 7 distinct sections.

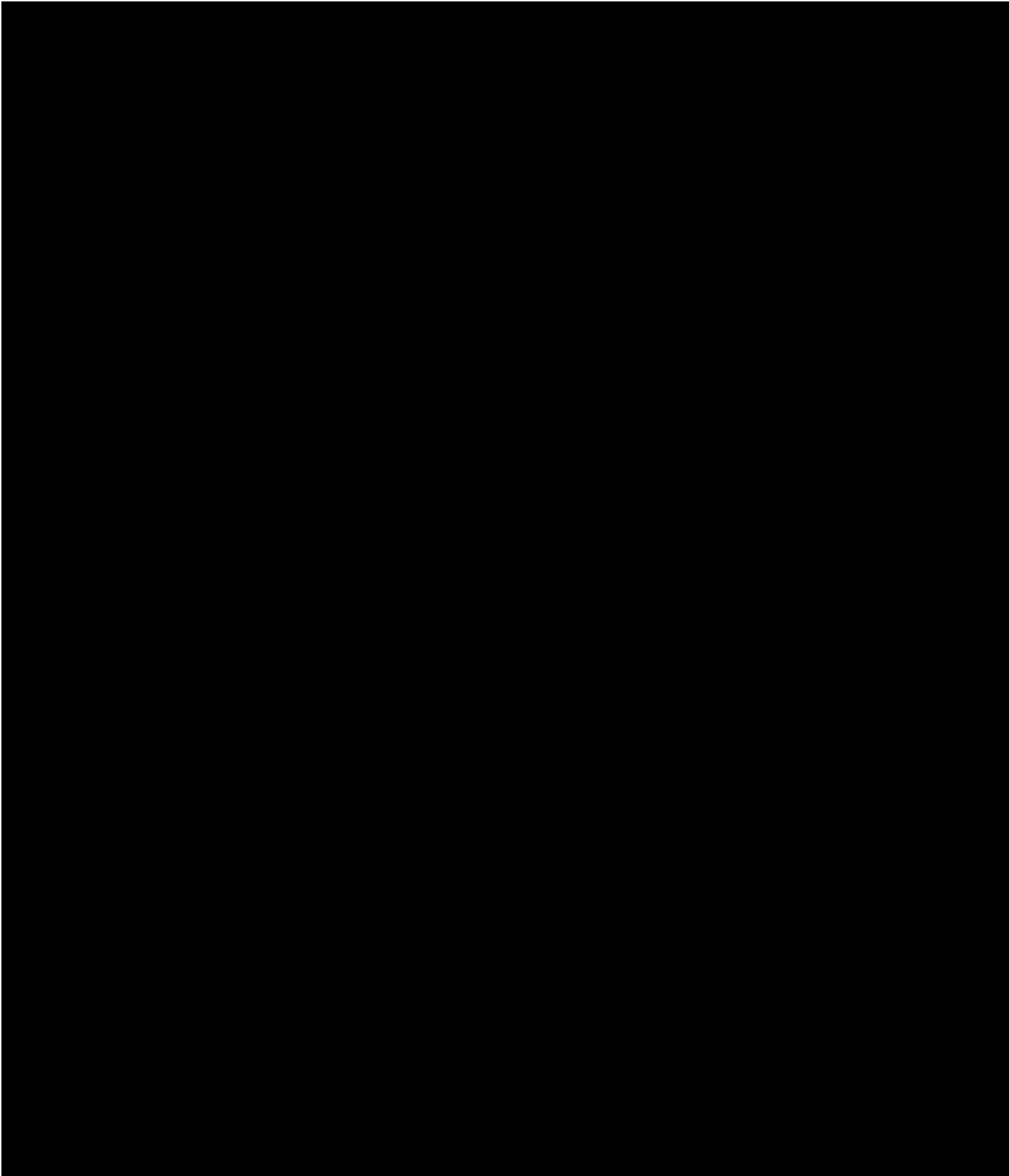
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[REDACTED]

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[REDACTED]

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Abbreviations

ADHD: attention deficit hyperactivity disorder

ASD: autism spectrum disorder

AUC: area under curve

CFS/ME: chronic fatigue syndrome/ myalgic encephalomyelitis

C_{max}: maximum plasma concentration

CR: controlled release

CYP1A2: cytochrome P450 enzyme isoform 1A2

DSPD: delayed sleep phase disorder

DLMO: dim light melatonin onset

EU: European union

FCT: film coated tablet

IR: immediate release

MAA: marketing authorisation application

NG: nasogastric tube

PK: pharmacokinetic

PEG: percutaneous endoscopic gastrostomy (tube)

SmPC: summary of product characteristics

SCN: suprachiasmatic nucleus

T_½: plasma half-life

T_{max}: time to maximum plasma concentration

5-HT: 5-hydroxytryptamine

WEU: well-established use

CLINICAL [REDACTED]

2.5.1 OVERVIEW OF THE PROPOSAL TO ADD A NEW INDICATION

This is an application for a Type II variation to the marketing authorization for Melatonin 3 mg film-coated tablets PL 20243/0004 currently approved for the short-term treatment of jet-lag in adults. [REDACTED]

[REDACTED]

The new proposed indication is:

[REDACTED]

This [REDACTED] provides additional evidence that supports the safety and efficacy of Melatonin 3 mg film-coated tablets for the new proposed indication.

The new proposed indication is supported by:

[REDACTED]

The following quotes provide a brief overview of clinical practice between 2007 and 2022.

Melatonin is used as a medicine for the treatment of sleep disorders for children [REDACTED]. Melatonin is used in children and adolescents for treating sleep onset insomnia and delayed sleep phase syndrome (DSPD) in children with conditions such as Visual impairment, Cerebral palsy, Attention deficit hyperactivity disorder (ADHD), Autism, Learning difficulties, Epilepsy and Neurodegenerative disorder [REDACTED]. Melatonin (immediate-release) is indicated for sleep onset insomnia and delayed sleep phase syndrome in children and adolescents and persistent sleep disorders in school-age children with neurodevelopmental disabilities [REDACTED]. Consider melatonin for children and young people with long-term sleep disturbances without a known cause or due to another illness and with reduced daytime function, where sleep hygiene measures have not had sufficient effect. [REDACTED]

[REDACTED]

The safety and efficacy of melatonin in the proposed patient population have been established by evidence of well-established use (WEU) [REDACTED]

[REDACTED]

[REDACTED] treatment of insomnia in children and adolescents that is associated with DSPD, ADHD, and ASD with or without neurological disorders (see [sections 2.5.1.4](#) and [2.5.1.5](#)). [REDACTED]

[REDACTED]

[REDACTED]

The proposed age range [REDACTED] for the use of Melatonin 3 mg film-coated tablets (PL 20243/0004) for the treatment of insomnia that is associated with DSPD, ADHD, and ASD in children and adolescents, with and without neurological disorders, is based on:

- 1- Data from relevant randomized controlled clinical trials [REDACTED]
[REDACTED] These trials have shown that melatonin is effective treatment in children and adolescents [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] for the use of Melatonin 3 mg film-coated tablets for the proposed indication.

Several clinical guidelines and recommendations have been followed regarding the proposed age range in the UK, Sweden, Denmark, and Norway in clinical practice. Some examples are provided below.

[REDACTED]	
[REDACTED]	Melatonin is used in children of <u>at least 1 year of age</u> with neurodevelopmental disability, autism, visual impairment or neuropsychiatric disorders and chronic sleep disturbance, including chronic fatigue syndrome, where Symptoms of sleep disturbance have been present for at least six months or sleep disturbance is so severe that it is causing significant family disturbance and after failure of sleep hygiene/ behavioural measures.
[REDACTED]	The Sussex Partnership NHS Foundation Trust has made a clinical decision to use immediate release melatonin to help achieve a new sleep pattern in our service users <u>under the age of 18</u>
[REDACTED]	Melatonin is used in children <u>over 3 years of age</u> with neuro-developmental disorders (including ADHD), Autism, visual impairment or neuropsychiatric disorders.
[REDACTED]	
[REDACTED]	The study titled "Paediatric use of prescribed melatonin in Sweden 2006 –2017" was conducted to investigate the prevalence and incidence of melatonin prescriptions dispensed to children and adolescents. The study population was comprised of children between 0 and less than 18 years of <u>age (0–17 years)</u> living in Sweden, between the years 2006 (number of children 1,934,080) and 2017 (number of children 2,099,005).
[REDACTED]	
[REDACTED]	Pharmacological treatment of sleep disorders in children and young people in Denmark primarily includes melatonin. From 2011-2020, the number of users of prescription melatonin among <u>0–17-year-olds</u> has more than doubled, as the number of users has increased from 4,630 per year in 2011 to 13,295 per year in 2020.
[REDACTED]	

	The prevalence of melatonin use among 4 to 17 years olds increased during the period of 2004–2012: three times among boys [from 3.4 (n = 1489) to 11.0 (n = 4913) per 1000 inhabitants] and five times among girls [1.5 (n = 612) to 7.7 (n = 3281) per 1000 inhabitants.
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2.5.1.2.

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Several clinical guidelines and recommendations have been followed regarding the proposed dosage

	The most commonly used formulation is 3 mg. Most patients will start on the standard release¹ capsules at a dose of 3 mg, given 30-60 minutes before the time of desired sleep onset. If there has been no beneficial response within 7-14 days, the dose can be increased in 3 mg steps every 7-14 days, up to a maximum of 9 mg daily.
	Recommended starting dose is 3 mg of melatonin 20-30 minutes before desired sleep time.

¹ Also known as immediate-release formulation (i.e. the applicant formulation)

	<i>From 1 month onwards, initially give 2 mg or 2.5 mg at night 30-60 minutes before bedtime. Increasing after 1 to 2 weeks 4 mg to 6 mg, if no response or partial response. Usually, maximum daily dose is 10 mg per day (though 12 mg /day has been used).</i>
	<i>If there is a problem getting to sleep, then the 3 mg immediate release tablets may be used: to be taken 30 minutes before going to bed.</i>
	<i>Melatonin for infants under 1-year of age should only be initiated by consultants. Initial starting dose of 2 mg or 3 mg given 30 to 60 minutes before bedtime. If no effect, dose can be increased to 4 mg or 6 mg after 7 to 14 days.</i>
	<i>Recommended dose of melatonin is 3 mg 20 - 30 mins before desired sleep time. The dose can be increased to 6 mg if insufficient response after 7-10 days up to a maximum daily dose of 12 mg.</i>
	<i>From 1 year onwards, an initial dose of 2-3 mg 30-60 minutes before bedtime. In the absence of improvement after 1 to 2 weeks, the dose is increased to 4 mg to 6 mg at night.</i>
	<i>Melatonin is used in children and adolescents in the age range from 1 month to 18 years. initially 2-3 mg daily before bedtime increased, if necessary, after 1-2 weeks to 4-6 mg daily before bedtime; maximum 10 mg daily. Doses higher than 10 mg are not considered to be of greater efficacy and may cause increased side-effects.</i>
	<i>Melatonin for infants under 1 year of age should only be initiated by consultants. Initial starting dose: 2 mg or 3 mg given 30 - 60 minutes before bedtime. Dose can be increased to 4 or 6 mg after 7 -14 days. Doses between 2 mg and 6 mg are generally effective. Maximum daily dose is 10 mg.</i>
	<i>Prescribe melatonin as a second line treatment option where non-pharmacological strategies such as provision of sleep hygiene advice (over 3-6 months) have failed, and underlying physical causes are managed. To prescribe melatonin where a parent or carer or an older adolescent has completed a sleep diary over 10 to 14 nights highlighting problems with sleep latency despite a trial of non-pharmacological strategies. Recommended dose of melatonin 3 mg tablets (Bio-Melatonin®) Initially 3 mg once daily taken half hour before bedtime. Increase to 6 mg depending on</i>

	<i>response after 7 - 14 days. Maximum daily dose is 12 mg but additional benefits from doses above 6 mg to 9 mg are uncertain.</i>																									
	<i>Initially 2 – 4 mg given 30 - 60 minutes before desired sleep time. If insufficient response after 7 - 10 days, increase to 6 mg. In some cases, doses of up to 10 mg may be tried.</i>																									
	<i>The average prescribed dose was lowest (3.1 mg) for the youngest age group and highest (4.0 mg) for the oldest age group, with a similar range in all age groups as shown below in the table.</i> <table><tr><th>Age groups (years)</th><th>Number of prescriptions</th><th>Average (SD)</th><th>Median dose (mg)</th><th>Range (mg)</th></tr><tr><td>0–4</td><td>200</td><td>3.1 (1.7)</td><td>2</td><td>0.5–10</td></tr><tr><td>5–9</td><td>200</td><td>3.6 (2.0)</td><td>3</td><td>0.5–12</td></tr><tr><td>10–12</td><td>200</td><td>3.7 (2.0)^a</td><td>4</td><td>1–12</td></tr><tr><td>13–17</td><td>200</td><td>4.0 (2.1)</td><td>4</td><td>0.5–15</td></tr></table>	Age groups (years)	Number of prescriptions	Average (SD)	Median dose (mg)	Range (mg)	0–4	200	3.1 (1.7)	2	0.5–10	5–9	200	3.6 (2.0)	3	0.5–12	10–12	200	3.7 (2.0) ^a	4	1–12	13–17	200	4.0 (2.1)	4	0.5–15
Age groups (years)	Number of prescriptions	Average (SD)	Median dose (mg)	Range (mg)																						
0–4	200	3.1 (1.7)	2	0.5–10																						
5–9	200	3.6 (2.0)	3	0.5–12																						
10–12	200	3.7 (2.0) ^a	4	1–12																						
13–17	200	4.0 (2.1)	4	0.5–15																						
	<i>A daily dose at around 3 mg or more throughout the year in half of the recurrent users seems, how-ever, to be within the range of what is recommended in recent clinical recommendations for melatonin use in children and adolescents. BNF for Children recommends a maximum daily dose at 10 mg.</i>																									

It is important to note that insomnia complaints in children and adolescents should be taken into account and appropriately investigated by the paediatrician, considering the association with several comorbidities, which must also be diagnosed. The main causes of insomnia and triggering factors vary according to age and development level. The therapeutic approach must include sleep hygiene and behavioural techniques and, in individual cases, pharmacological treatment

Before starting treatment with melatonin, sleep hygiene measures must be tested for a period of at least 4 weeks. Sleep hygiene measures are the first choice for treating sleep disorders in children and young people. Sleep hygiene measures can be described as an overall effort that is primarily aimed at counselling the parents/young person, where behaviour and lifestyle that inhibit sleep is avoided, and behaviour, habits, conditions and routines that stimulate better sleep are promoted

Limited data are available for treatment periods of up to 3 years. The long-term safety of melatonin supplementation in children has been addressed by [REDACTED]. A review on DSPD by [REDACTED] concluded no trial has ever documented any serious adverse effect from the use of supplemental melatonin, and studies documenting long term use (mean follow up of 3 years) in children have not identified any safety concerns.

It is worthwhile to note that the proposed indication is in line with the unlicensed indications recommended in the British National Formulary for Children (BNFc) for number of years, from which the following table is abstracted.

Indications	Recommended dose for Children
- Sleep onset insomnia - DSPD (delayed sleep phase syndrome) Note: Melatonin is used for sleep onset insomnia and delayed sleep phase syndrome but is not licensed for these indications.	Initially 2–3 mg daily for 1–2 weeks, then increased if necessary to 4–6 mg daily, dose to be taken before bedtime; maximum 10 mg per day.
Insomnia in patients with learning disabilities and behaviour that challenges (where sleep hygiene measures have been insufficient)	Initially 2 mg once daily, increased if necessary to 4–6 mg once daily, dose to be taken 30–60 minutes before bedtime; maximum 10 mg per day.
- Insomnia with autism spectrum disorder - Insomnia with Smith-Magenis syndrome	Initially 2 mg once daily, increased if necessary to 5 mg once daily, dose to be taken 30-60 minutes before bedtime; maximum 10 mg per day.

The listed action and use of melatonin in BP 2022 is for the treatment of sleep onset insomnia.

The proposed indication for the medicinal product (PL 20243/0004) is ‘Treatment of insomnia in children and adolescents aged [REDACTED] [REDACTED] with DSPD (delayed sleep phase disorder), ADHD (attention deficit hyperactivity disorder) and ASD (autism spectrum disorder), with or without neurological dysfunction where sleep hygiene measures have been insufficient.’

It should be noted that DSPD can occur in subjects with or without neurological dysfunction.

There is extensive information relating to insomnia, specifically DSPD which is also known as delayed sleep onset insomnia, delayed sleep-wake syndrome, delayed sleep-wake disorder, or delayed sleep wake cycle. As a sleep disorder it has been recognised for more than thirty years [1].

Insomnia associated with attention deficit hyperactivity disorder (ADHD)

ADHD is a chronic neurobehavioral disorder [REDACTED] [REDACTED] ADHD has a pattern of inattention and/or hyperactivity-impulsivity persisting for ≥ 6 months and present in ≥ 2 settings (home, school, play, or work) that is more frequent and severe than typically observed in individuals of comparable developmental level [REDACTED] ADHD is also known as attention deficit disorder (ADD), hyperkinetic syndrome, hyperkinetic disorder and hyperkinetic impulse disorder. Sleep disorders associated with ADHD in children may include sleep onset difficulties, night-time awakenings, difficult morning awakenings, daytime sleepiness, sleep disordered breathing, bedtime resistance and nocturnal enuresis [REDACTED]

[REDACTED]

Insomnia associated with autism spectrum disorder (ASD)

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by early-onset impairments in social communication and interaction, as well as by restricted, repetitive interests and behaviors [REDACTED]. ASD is also known as autism, autistic disorder, infantile autism, childhood autism and Kanner's syndrome. [REDACTED]

[REDACTED]

[REDACTED] of ASD. ASD may be associated with developmental, medical, or psychiatric conditions including intellectual and language disabilities, ADHD, tic disorders, and motor abnormalities, sleep disorders, and genetic syndromes. Two-thirds of children with autism are estimated to exhibit sleep problems at any one time [REDACTED]

[REDACTED]

[REDACTED] the application of good sleep hygiene practices; [REDACTED]

[REDACTED] Melatonin is a hormone synthesised by the pineal gland. It has a number of functions within the body, including the regulation of circadian rhythms, particularly the sleep-wake cycle. In humans, endogenous melatonin production starts soon after dark, peaks in the middle of the night and gradually declines during the second half of the night. The half-life of natural melatonin is approximately 40 minutes. Sleep disturbances are common in children

with ADHD, ASD and other neurodevelopmental disorders. The prevalence of circadian rhythm sleep disorders in children with neurodevelopmental disorders is higher than typically developing children due to an association with abnormal melatonin secretion. [REDACTED]

[REDACTED]

Clinical studies [REDACTED]

[REDACTED] have demonstrated that strategically timed administration of daily exogenous melatonin, typically in the dose range 2-10 mg, is effective in advancing circadian rhythm and sleep onset in children (normal or neurologically challenged) with DSPD/ADHD/ASD.

Melatonin to treat insomnia associated delayed sleep phase disorder (DSPD)

[REDACTED] “properly timed administration of melatonin is indicated as therapy for DSPD”. [REDACTED] suggested clinicians could treat children and adolescents with DSPD with strategically timed exogenous melatonin [REDACTED]

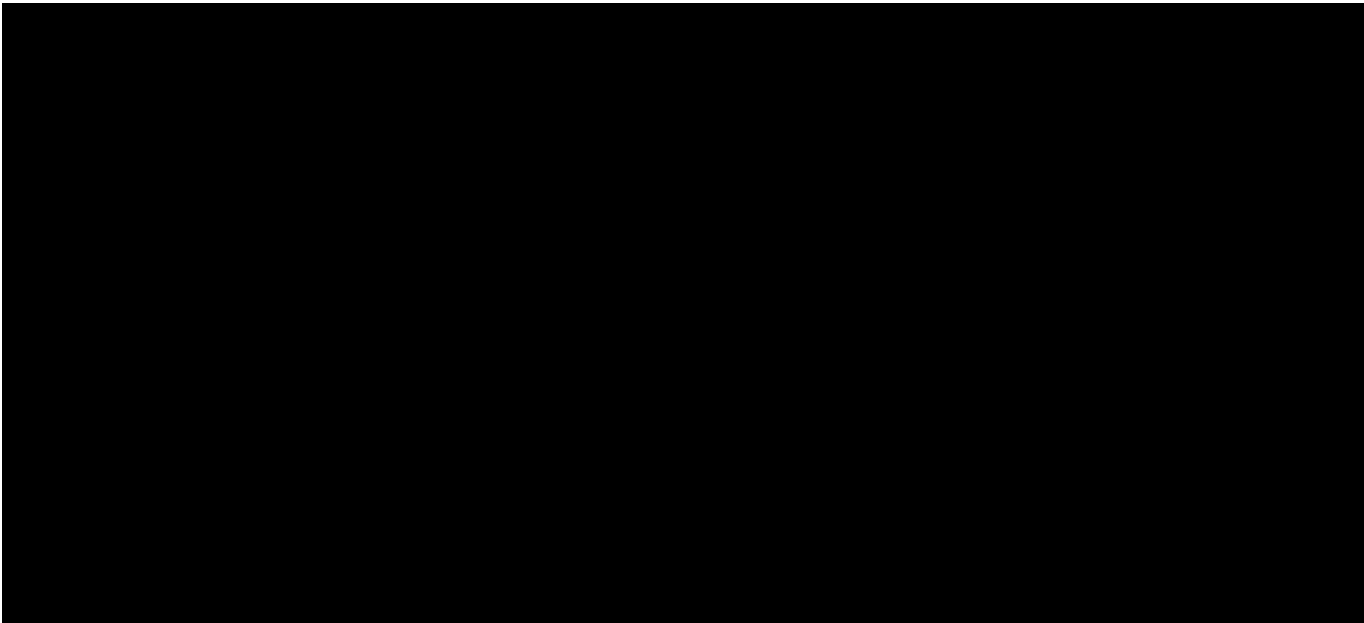
[REDACTED]

[REDACTED] The efficacy of melatonin for DSPD has been reported in a meta-analysis by [REDACTED] and the safety of melatonin administration (particularly in the short-term) in children with DSPD and a variety of other disorders has been extensively reported. [REDACTED]

[REDACTED]

Melatonin to treat insomnia associated with attention deficit hyperactivity disorder (ADHD)

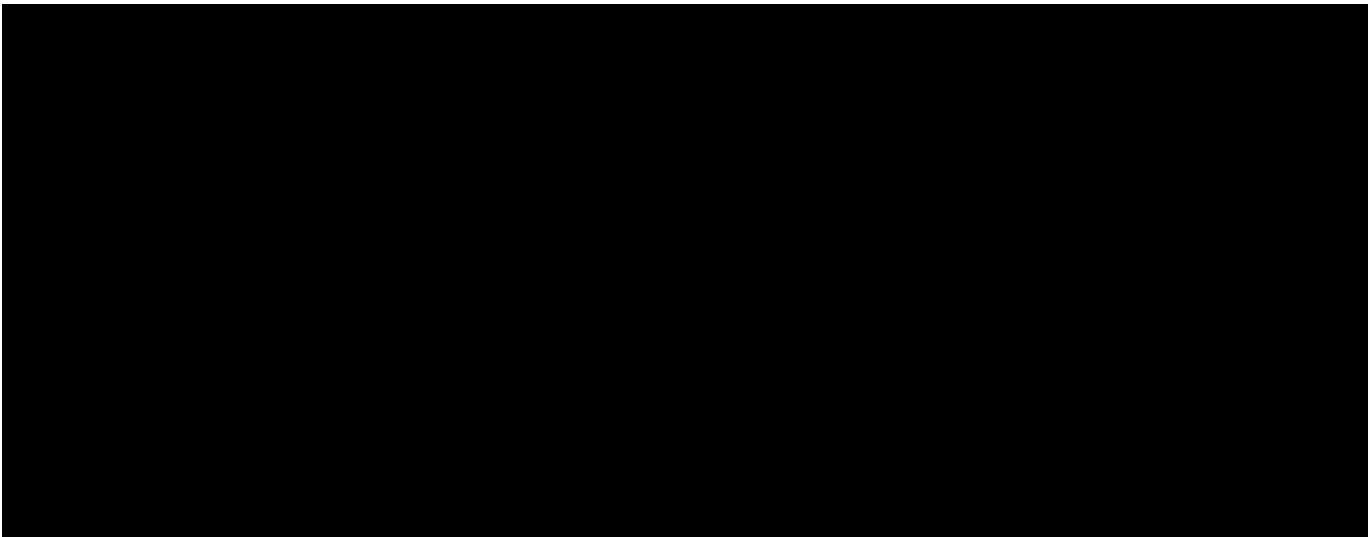
Children being evaluated for ADHD should be assessed for coexisting conditions, including sleep disorders [REDACTED]



ASD is a developmental disorder characterized by difficulties with social interaction and communication, and by restricted and repetitive behaviour. Parents often notice signs of ASD during the first three years of their child's life. ADHD is a mental health disorder that can cause above-normal levels of hyperactive and impulsive behaviours. Subjects with ADHD may also have trouble focusing their attention on a single task or sitting still for long periods of time. Both ASD and ADHD are relatively common disorders in children, with a prevalence of 1-2% and 3-5% respectively. ASD and ADHD in children are characterised by a high incidence (up to 80% of individuals) of sleep related problems. These include difficulty in falling asleep, difficulty maintaining sleep, problems with sleep quality, and behavioural problems relating to inadequate sleep. To date there have been 10 randomised controlled clinical trials to investigate the efficacy and safety of exogenous melatonin in children with ASD or ADHD

[Redacted text block]

[Redacted text block]



² Standard release means immediate release formulation (i.e., the applicant product)

[REDACTED]

Melatonin is a common name of N-acetyl-5-methoxy tryptamine, a biological active indole that is distributed widely in both animal and plant kingdoms. It is derived from the essential amino acid L-tryptophan and related chemically to its precursor the neurotransmitter 5-hydroxy tryptamine (5-HT) commonly known as serotonin.

[REDACTED] Anatomical Therapeutic Chemical (ATC) classification

Anatomical main group: Nervous system.
Therapeutic group: NO5 psycholeptics.
Pharmacological sub-group: NO5C hypnotics and sedatives.
Chemical sub-group: NO5CH melatonin receptor agonists.
Chemical substance: NO5CH01 melatonin.

[REDACTED] British National Formulary classification (BNF) classification

Chapter: Central Nervous System.
Sections: Sleep disorders: Insomnia, hypnotics and anxiolytics.

[REDACTED] Monthly Index of Medical Specialities classification (MIMS) classification

Chapter: Central Nervous System.
Sections: Insomnia, other hypnotics.

[REDACTED] Melatonin classification

The classification of melatonin as a food supplement or medicinal substance varies globally. [REDACTED]

[REDACTED]

In many European countries including [REDACTED], melatonin is classified as a medicinal substance and is a prescription only medicine (POM) often prescribed unlicensed or off-label.

In the UK, melatonin was classified as a medicinal substance by the Medicines and Healthcare products Regulatory Agency (MHRA) in 1995 and is therefore subject to the provisions of the Medicines Act 1968. Despite its classification as a food supplement prior to 1995 in the UK, Pharma Nord ApS (the applicant) supplied a pharmaceutical-grade melatonin formulation (Bio-Melatonin 3 mg film-coated tablets) as a food supplement to supply UK demand.

[REDACTED]

[REDACTED]

[REDACTED]

authorized melatonin products in the UK

Product	Licensed Indication	Age Licensed for	Dose, Treatment duration
Circadin® 2 mg prolonged release tablets (Flynn Pharma)	Monotherapy for short-term treatment of primary insomnia characterised by poor quality of sleep-in patients who are aged 55 or over	Adults aged 55 years and over. Not recommended under 18.	2 mg nightly 1-2 hours before bedtime for up to 13 weeks.
Slenyto® 1 mg and 5 mg prolonged release tablets (Flynn Pharma)	Treatment of insomnia in children and adolescents aged 2 to 18 years with ASD and/or Smith-Magenis Syndrome (SMS) where sleep hygiene measures have been insufficient.	Age 2 to 18 years. Not recommended under 2 years.	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.
Adaflex 1 mg, 2 mg, 3 mg, 4 mg, 5 mg Tablets (AGB – Pharma)	Short term treatment of jet lag in adults. Insomnia in children and adolescents aged 6-17 years with ADHD, where sleep hygiene measures have been insufficient.	Adults. children and adolescents aged 6-17 years.	Adults with jet lag The recommended dose is 1-5 mg for a maximum of 5 days. Children: Recommended starting dose of Melatonin tablet: 1-2 mg 30-60 minutes before bedtime. The dose of melatonin can be increased by 1 mg every week until effect up to a maximum 5 mg per day, independent of age. The lowest effective dose should be sought.
Syncrodin 3 mg Tablet (Pharma Nord UK Ltd)	Short-term treatment of jet lag in adults	Not recommended for under 18	3 mg daily for maximum five days. Dose can be increased to 6 mg daily. Maximum five-day course and 16 courses per year.
Melatonin 3 mg tablets (Colonis Pharma Ltd)	Short-term treatment of jet lag in adults	Adults (18 years and over)	3 mg daily for maximum five days. Dose can be increased to 6 mg daily. Maximum five-day course and 16 courses per year.
Ceyesto 3 mg Tablet (Alturix Ltd)	Short-term treatment of jet lag in adults. Insomnia in children and adolescents aged 6-17 years with ADHD, where sleep hygiene measures have been insufficient.	Adults. children and adolescents aged 6-17 years.	Adults - 3 mg daily for maximum four days. Children - Melatonin 3 mg dose is taken 30-60 minutes before bedtime. Ceyesto is suitable only when the lowest effective dose has been established to be 3 mg. Maximum dose: 3 mg.

Melatonin 2 mg, 3 mg, 5 mg Capsules (Colonis Pharma Ltd)	Short-term treatment of jet lag in adults.	Adults (18 years and over)	3 mg daily for maximum five days. Dose can be increased to 5 mg or 6 mg daily. 2 mg daily may be sufficient for some individuals. Maximum five-day course and 16 courses per year.
Melatonin 1 mg/ ml oral solution (Colonis Pharma Ltd)	Short-term treatment of jet lag in adults. Sleep onset insomnia in children and adolescents aged 6-17 years with attention- deficit hyperactivity disorder (ADHD) where sleep hygiene measures have been inadequate.	Adults, children and adolescents aged 6-17 years.	Adults: 3 mg daily for maximum five days Dose can be increased to 6 mg daily Maximum five-day course and 16 courses per year. Children - Recommended starting dose is 1-2 mg (1.0-2.0 ml) 30-60 minutes before bedtime. The dose of melatonin can be increased by 1 mg (1.0 ml) every week until effect up to a maximum 5 mg (5 ml) per day, independent of age. The lowest effective dose that controls symptoms should be given.
Melatonin Consilient Health 1 mg/ml oral solution. (Consilient Health Ltd)	Short-term treatment of jet lag in adults. The medicinal product is recommended to adult travellers flying across ≥5 time zones, particularly in an easterly direction, and especially if they have experienced jet lag symptoms on previous journeys. Travellers crossing 2-4 time zones can also use it if need be. Insomnia in children and adolescents aged 6-17 years with ADHD, where sleep hygiene measures have been insufficient	Adults, children and adolescents aged 6-17 years	Adults with jet lag The recommended dose is 1-5 mg one hour before bedtime at destination. Paediatric population with ADHD: Recommended starting dose: 1-2 ml (equivalent to 1-2 mg) 30 to 60 minutes before bedtime. The dose should be adjusted individually to a maximum of 5 ml (equivalent to 5 mg) daily regardless of age. The lowest effective dose should be sought. Maximal recommended daily dose: 5 ml (equivalent to 5 mg) Limited data are available for up to 3 years of treatment. After at least 3 months of treatment, the physician should evaluate the treatment effect and consider stopping treatment if no clinically relevant treatment effect is seen. The patient should be monitored at regular intervals (at least every 6 months) to check that Melatonin is still the most appropriate treatment. During ongoing treatment, especially if the treatment effect is uncertain, discontinuation attempts should be done regularly, e.g., once per year.
Melatonin 3 mg Tablet (Pharma Nord UK Ltd)	Short-term treatment of jet lag in adults	Not recommended for under 18	3 mg daily for maximum five days. Dose can be increased to 6 mg daily. Maximum five-day course and 16 courses per year.

[REDACTED]

The legal basis of this Type II variation of the UK National application to the Medicines and Healthcare products Regulatory Agency (MHRA) under Regulation 54 (previously Article 10a of Directive 2001/83/EC) is well-established use (WEU) of melatonin in the proposed indication.

[REDACTED]

The well-established use (WEU) of melatonin 3 mg as a medicinal product [REDACTED]

[REDACTED]

1. **Time Period:** Melatonin has been used in children and adolescents for over 10 years, providing a sufficient period of time to establish its well-established medicinal use (for detailed information see [section 2.5.1.9.1](#) below).

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] existing licensed product (Melatonin 3 mg film-coated tablets – PL 20243/0004) is supported by detailed references of published scientific literature from various databases, [REDACTED]. These references provide evidence of the safety and efficacy of melatonin in the proposed indication. The scientific literature includes randomized controlled trials, observational studies, meta-analyses, meta-reviews, case-series, case reports, systematic reviews, and guidelines. The references have been carefully selected from the scientific databases to demonstrate the WEU and safety of melatonin in children and adolescents.

[REDACTED]

██████████ proposed indication demonstrating quality, safety and efficacy of the product and a positive benefit-risk balance.

██████████ **WEU**

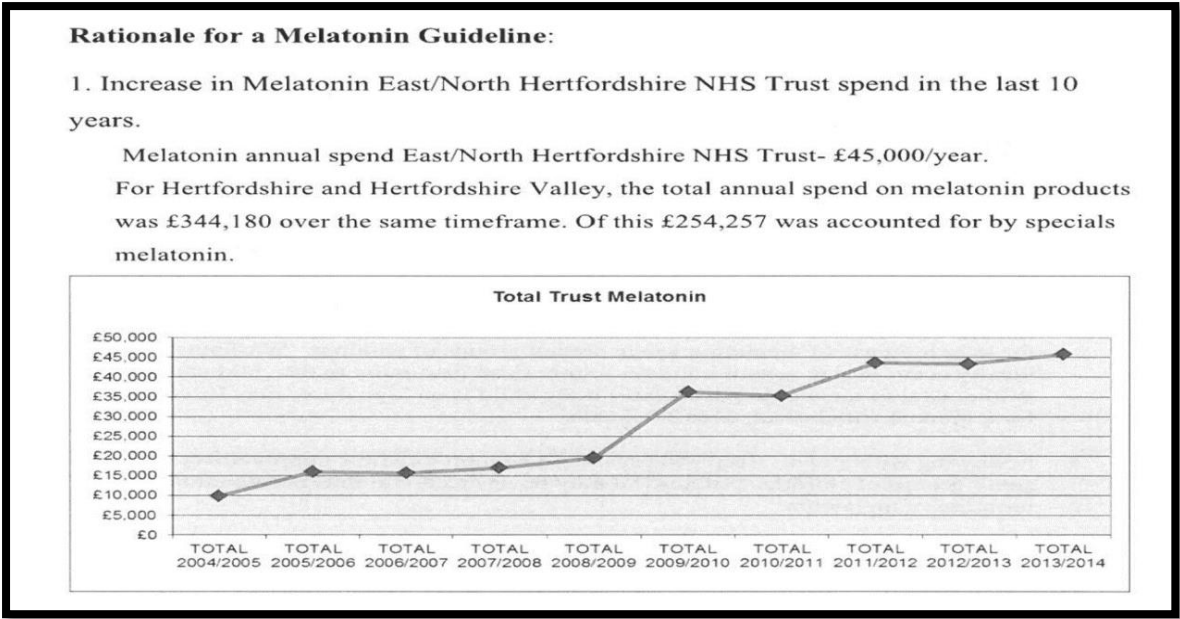
██████████ there have been 2 randomised controlled clinical trials (mentioned below) of relevance to this application, by ██████████ and ██████████ both studies reported clinically significant improvements in sleep latency, with no significant adverse events.

██████████ In a phase 3 randomized, placebo-controlled clinical trial, we administered 1-mg melatonin (n = 65), 4-mg melatonin (n = 65), or placebo (n = 66) to 196 children with ASD once daily before bedtime under adequate sleep hygiene interventions. The primary outcome was sleep onset latency (SOL) assessed with the electronic sleep diary. SOL shortened significantly in the 1- and 4-mg melatonin groups compared to the placebo group (- 22.0 - 28.0 and - 5.0 min, respectively; $p < 0.0001$ each).

██████████ This study was a double blind randomized clinical trial in the sleep clinic of Qods Hospital. Sixty healthy children between 7 and 12 years of age having sleep problems were chosen and randomly divided in interventional and placebo groups. Before the treatment, children's sleep habits questionnaire (CSHQ) was filled in both groups. Then, both groups were taught about sleep hygiene. Afterwards, the intervention group was treated with 3 mg nocturnal dose of melatonin for one month and the other group with a placebo. Then, CSHQ was filled again for both groups. The intervention was melatonin. The mean analysed results of the variants in pre-test and post-test were compared and $p < 0.05$ was regarded as significant. Results showed that melatonin with no side effect is effective in improving: 1- The initiation and maintenance of sleep, 2- Sleep onset delay, 3- Sleep duration, 4- Sleep anxiety, 5- Nightly awakenings 6- Parasomnias and 7- daily performance; but is ineffective in bedtime resistance and sleep disordered breathing. The results indicate that melatonin is more effective than placebo in improving the initiation and maintenance of sleep and most of its subscales in primary school aged children.

██████████ Use of melatonin in children and adolescents between ██████████

The following graphical data for 10 years (2004 -2014) is from the guideline for the safe prescribing of melatonin in children with neurodevelopmental disorders /neuro-disabilities



The utilization of melatonin in paediatric patients has been included in numerous regional and national hospital

Guideline	Date	Description
		In clinical settings, immediate release melatonin is used in children and adolescents who have problems with sleep onset. Melatonin is recommended for children with neurological or neurodevelopmental disorder suffering from severe sleep disturbances where the aim is to improve the onset and duration of sleep and to establish a regular nocturnal sleep pattern.
		The Maudsley Prescribing Guidelines is the most widely used guide to psychiatric prescribing in the UK and it mention that melatonin is used for the treatment of insomnia in children and adolescents.
		There is significant clinical experience with the use of melatonin for the treatment of paediatric sleep-wake cycle disorders. Results in terms of improved sleep patterns have been generally favourable and adverse effects minimal.

		Melatonin may be considered for children and young people with CFS/ME who have sleep difficulties, but only under specialist supervision because it is not licensed in the UK.
████████████████████	████	Melatonin is an endogenous hormone used in the treatment of persistent (initial) sleep onset disorders in school age children with a range of neuro-developmental problems, including attention deficit hyperactivity disorder.
████████████████████ ████████████████████	████	Melatonin briefing was produced by London New Drugs Group in 2008 for use of melatonin in paediatric sleep disorders.
██████████ █████ █████ ██████████ █████████ █████ ██████	████	The Children's BNF states that clinical experience suggests that melatonin may be of value for treating sleep disorders in children with conditions such as visual impairment, cerebral palsy, ADHD and autism. It's used for sleep difficulties and is also supported by NICE in the clinical guideline on the diagnosis and management of chronic fatigue syndrome/ myalgic encephalomyelitis in adults and children.
████████████████████ ████████████████████	████	Melatonin is effective in the treatment of sleep disorders in children with visual problems and learning difficulties, cerebral palsy and autistic spectrum disorders.
████ █████ █████ █████ ████████████████████	████	Melatonin is used to improve the onset and duration of sleep-in infants, children and adolescents with neurological and/or behavioural problems who have severe sleep disturbances. It can also be used to improve onset and duration of sleep in children and adolescents with congenital or acquired neurological/neurodevelopmental problems including conditions such as learning difficulties, autism spectrum disorders, cerebral palsy, visual impairment, epilepsy and neurodegenerative disorders.
██████████ █████ █████ ██████████ █████████ █████ ██████	████	Melatonin is effective in the treatment of sleep disorders in children with visual problems and learning difficulties, cerebral palsy and autistic spectrum disorders. It is also occasionally used in children, and particularly adolescents, who have a reverse sleep pattern in order to re-establish a normal one.

[REDACTED]	[REDACTED]	Melatonin is an endogenous hormone used in the treatment of persistent sleep onset disorders in children and adolescents (4-17 years inclusive) with a range of neurodevelopmental problems, including attention deficit hyperactivity disorder (ADHD).
[REDACTED]	[REDACTED]	Melatonin (Circadin, Flynn Pharma Ltd) is currently licensed in the UK for the short-term treatment of primary insomnia, characterised by poor quality of sleep, in adults who are aged 55 years or over. It is a prescription-only medication available as 2 mg prolonged-release tablets (also referred to as modified-release). Its use outside of this indication including use in children and young people under 18 years, is 'off-label'.
[REDACTED]	[REDACTED]	NICE guideline-using melatonin to treat sleep disorders in children and young people with ADHD states melatonin 3 hours before bedtime reduced the time it took the children to fall asleep (after lights out or when they were put to bed) by approximately 20 minutes. It also improved the total time they were asleep by an average of approximately 15 to 20 minutes.
[REDACTED]	[REDACTED]	Melatonin is indicated for treating sleep disorders in children and adults with neurodevelopment disorders and conditions such as visual impairment, cerebral palsy, attention deficit hyperactivity disorder and autism. It is also sometimes used before EEG investigations.
[REDACTED]	[REDACTED]	The licensed product melatonin 2 mg MR (Circadin®) is to be used first line, for an off-label indication, if clinically appropriate. Once stabilised, shared care is appropriate, in accordance with the Essential Shared Care Agreement (ESCA). It is worth noting that Circadin is a modified release tablet, which cannot be crushed. If an unlicensed product is clinically indicated, rather than the licensed product, e.g., because of swallowing difficulties, or because of the release characteristics, then Bio-melatonin 3 mg (Pharma Nord ApS – the applicant) is recommended for use wherever possible.
[REDACTED]	[REDACTED]	In Worcestershire, melatonin is recommended for the treatment of children and adults with neurological and/or behavioral problems, including attention deficit hyperactivity disorder (ADHD) and autism, treatment of older adults with dementia where alternative hypnotics have failed and in critical care where use of

		first line hypnotics has failed. As part of the sleep Electroencephalography (EEG) procedure at Worcestershire Trusts.
████████████████████	████	Melatonin is used in the treatment of persistent sleep onset disorders in children and adolescents (4-17 years inclusive) with a range of neurodevelopmental problems, including attention deficit disorder.
██████ █████ ████████████████████ ██████	████	Melatonin is used to improve the onset and duration of sleep-in infants, children and adolescents with neurological and/or behavioural problems who have refractory severe sleep disturbance. It can also be used to improve onset and duration of sleep-in children and adolescents with congenital or acquired neurological/neuro-developmental problems including conditions such as learning difficulties, Autistic Spectrum Disorders, Cerebral Palsy, visual impairment, epilepsy and neurodegenerative disorders.
██████ ████████████████████ ██ ██████ ████████████████████ ████████████████████ ██████	████	Melatonin is recommended for Sleep aid for children over 2 years of age with neurodevelopmental disorders and chronic sleep disturbance.
██ ██ ██ ██ ██████	████	Melatonin is recommended for the treatment of insomnia in children and sleep disturbances in children (under the age of 18 years) with a formal confirmed diagnosis of autism spectrum disorder (ASD) or a formal confirmed diagnosis of attention deficit hyperactivity disorder (ADHD). Melatonin is a pineal hormone which affects sleep. It is indicated for sleep disorders in children and young people between 1 - 18 years of age with neurodevelopmental disorders, e.g., attention deficit hyperactivity disorder (ADHD), ASD, visual impairment, learning difficulties, developmental delay or any other neurodevelopmental condition.
██ ██ ██ ██ ██████	████	Crushed melatonin MR tablets are not suitable for administration via enteral feeding tubes, and in these patients' melatonin oral solution should be prescribed by the specialist and dispensing retained within the hospital.
██ ██ ██ ██ ██	████	Circadin® can be prescribed off-label in children and is the preferred first line choice. For patients who cannot swallow solid oral dosage forms or where an immediate release effect is required, Circadin® tablets may be crushed. This removes the modified release properties and is a cost effective (though off-label) option.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

As mentioned earlier the categorization of melatonin as a dietary supplement or therapeutic agent varies among different regions worldwide. In the United States, it is recognized as a dietary supplement, whereas in Europe, its classification as either a dietary supplement or medication differs from country to country. Specifically, it holds a dual classification of both a medication and dietary supplement in several European nations, including France, Belgium, Poland, Latvia, and Portugal.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

In the UK, melatonin is classified as a prescription-only medication. The most recent information regarding prescription data in the UK can be obtained through WaveData [REDACTED] which has maintained records since the year 2000. [REDACTED]

[REDACTED]

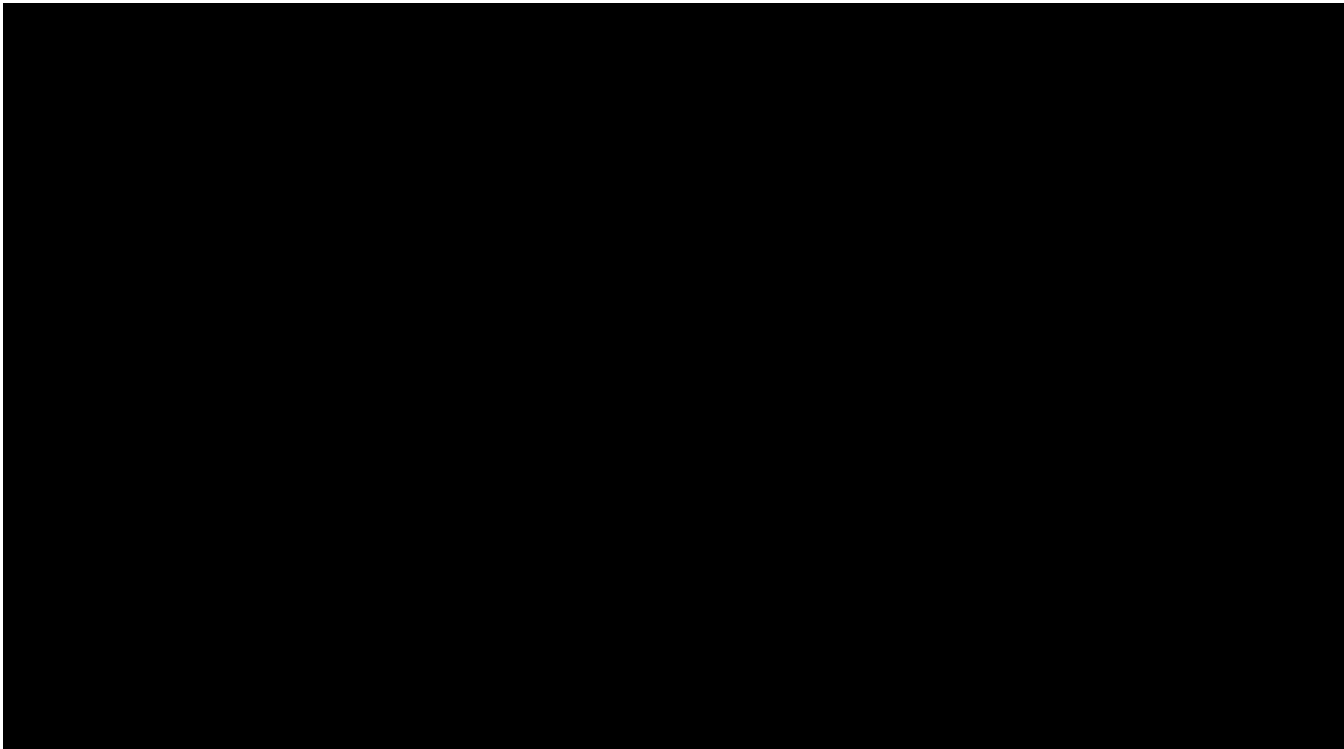
[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]



[Redacted]

Prescription Cost Analysis data of prescriptions dispensed in the community in England (one country data) show that in 2018, 974,122 items of melatonin were dispensed at a cost of approximately £36 million. These data relate to all melatonin preparations, including 'specials', for all indications [Redacted]

[Redacted]

[Redacted]

[Redacted]
[Redacted]
[Redacted]
[Redacted]
[Redacted]
[Redacted]

Document Name	Date	Description of Bio-Melatonin.
Melatonin Shared Care Guideline	[Redacted]	Bio-Melatonin recommended for immediate release preparation, as is licensed within EU. Launch of licensed modified release Circadin does not affect the clinical decision to prescribe immediate release Bio-Melatonin. Price is listed at £12.97. [Redacted] [Redacted]
Melatonin ADHD Shared Care Guideline	[Redacted]	Bio-Melatonin listed as unlicensed alternative to

		Circadin, which is recommended to use off-licence in children before suggesting Bio-Melatonin. ()
Alternatives to Prescribing “Specials” for adults		Bio-Melatonin listed as preferred brand in Shared Care Guideline with Sussex Partnership Trust, as is licensed within EU. State it can be crushed and mixed with water. ()
Melatonin Shared Care Agreement		As Bio-Melatonin is licensed within EU, it is listed as alternative choice to Circadin if modified release preparation is not suitable. States it can be crushed and mixed with food or liquids. Mentions requirement for Letter of Special Clinical Need. ()
Common Medicines & Unlicensed Uses		Bio-Melatonin listed as EU licensed preparation. Evidence for melatonin use in sleep disorders is inconclusive. Improves sleep in blind patients, neurologically disabled children, and the elderly. ()
Common Medicines & Unlicensed Uses		Bio-Melatonin listed as EU licensed preparation. In October 2012, NICE Evidence Summaries: Unlicensed and Off-label Medicines shows limited evidence for melatonin for sleep disorders in children and young people with ADHD. ()
Central Nervous System		Bio-Melatonin listed in formulary as a hypnotic, and central nervous system stimulant and drug used for ADHD. Circadin not approved for insomnia by Scottish Medicines Consortium and should not be prescribed routinely. ()
A-Z List of Specials		Bio-Melatonin licensed within EU and is preferred preparation in paediatric formulary. Shared Care Protocol states it can be crushed and mixed with food or liquids and can be used in NG or PEG tubes. Is included in Part 7S of Scottish Drug Tariff ()
Formulary & Prescribing Guidance		Bio-Melatonin listed in formulary as only unlicensed brand used for treatment of ADHD. Shared Care Guidelines with GPs apply in West Sussex and

		[REDACTED] [REDACTED]
Abbreviated Formulary List	[REDACTED]	Bio-Melatonin listed in formulary as a hypnotic, and a central nervous system stimulant and drug used for ADHD. ([REDACTED])
A-Z List of Specials	[REDACTED]	Bio-Melatonin licensed within EU, and is preferred preparation in paediatric formulary. Shared Care Protocol states it can be crushed and mixed with food or liquids, and can be used in NG or PEG tubes. Is included in Part 7U of Scottish Drug Tariff. ([REDACTED])
Abbreviated Formulary List	[REDACTED]	Bio-Melatonin listed in formulary as a hypnotic, and a central nervous system stimulant and drug used for ADHD. ([REDACTED])
Melatonin Information Sheet	[REDACTED]	Bio-Melatonin can only be used in secondary care, whereas Circadin can be used by GPs. ([REDACTED])
Abbreviated Formulary List	[REDACTED]	Bio-Melatonin listed in formulary as a hypnotic, and a central nervous system stimulant and drug used for ADHD. ([REDACTED])
A-Z List of Specials	[REDACTED]	Bio-Melatonin licensed within EU and is preferred preparation in paediatric formulary. Shared Care Protocol states it can be crushed and mixed with food or liquids and can be used in NG or PEG tubes. Is included in Part 7U of Scottish Drug Tariff. ([REDACTED])
A-Z List of Specials	[REDACTED]	Bio-Melatonin licensed within EU and is preferred preparation in paediatric formulary. Shared Care Protocol states it can be crushed and mixed with food or liquids and can be used in NG or PEG tubes. Is included in Part 7U of Scottish Drug Tariff. ([REDACTED])
Formulary & Prescribing Guidance	[REDACTED]	Bio-Melatonin and Ramatonin listed in formulary as only unlicensed brands used for treatment of ADHD

		by CAMHS only. Shared Care Guidelines with GPs apply in Coastal West Sussex. (N [REDACTED]) [REDACTED]
Shared Care Guideline – Melatonin for Children with Severe Sleep Disorders	[REDACTED]	Circadin and Bio-Melatonin preferred for off-label use in line with MHRA guidance. Bio-Melatonin can be crushed and mixed with food or used via a PEG tube. Price listed as approx. £38.00 for 30 tablets. (N [REDACTED]) [REDACTED]
A-Z List of Specials	[REDACTED]	Circadin preferred for insomnia in 55+ patients, but unlicensed immediate release preparations may be more suitable for children. Bio-Melatonin included in Part 7U of Scottish Drug Tariff, but Shared Care Agreement recommends Melatonin 3 mg Capsules. [REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

[REDACTED]

F

[REDACTED]

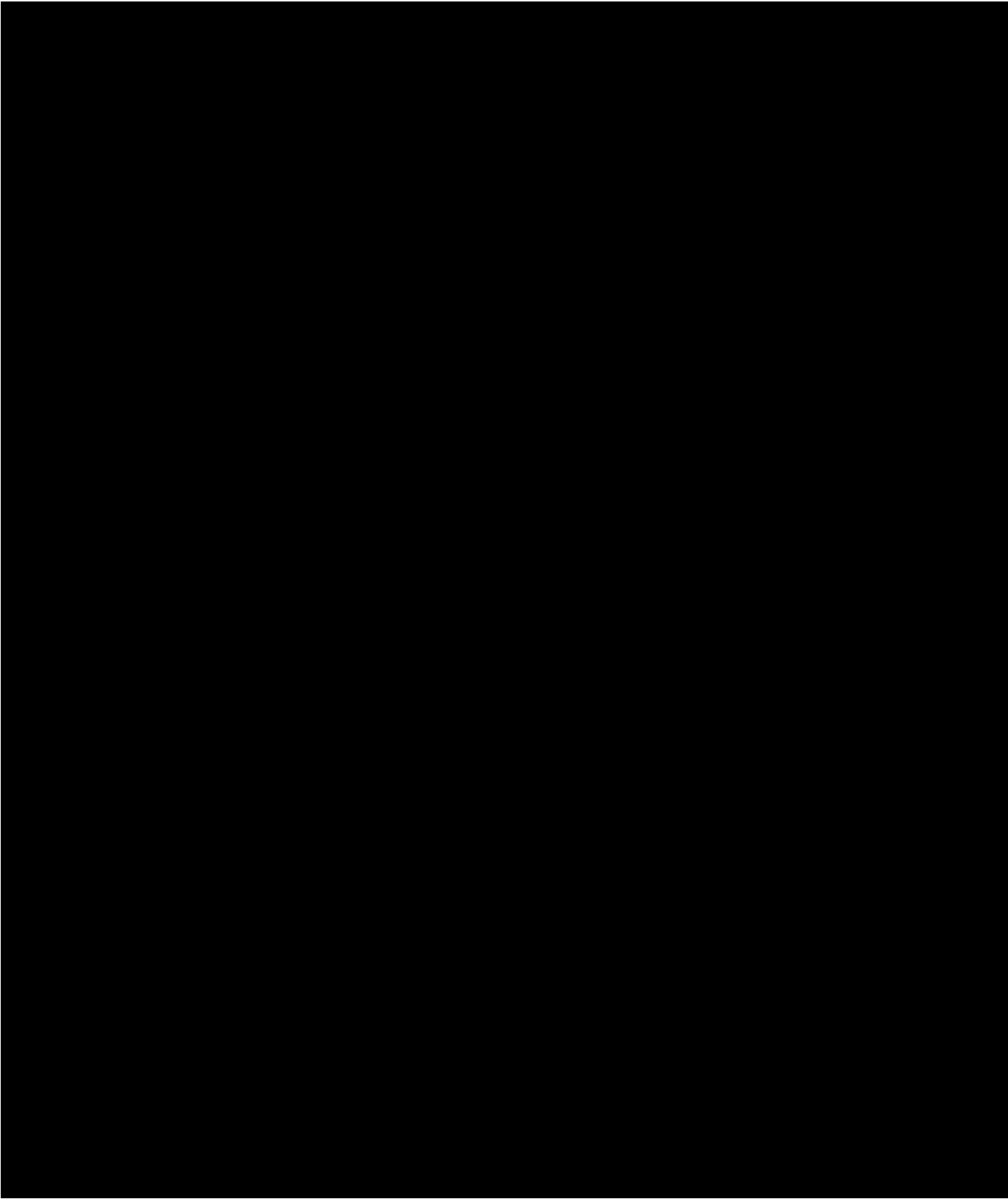
[REDACTED]

[REDACTED]

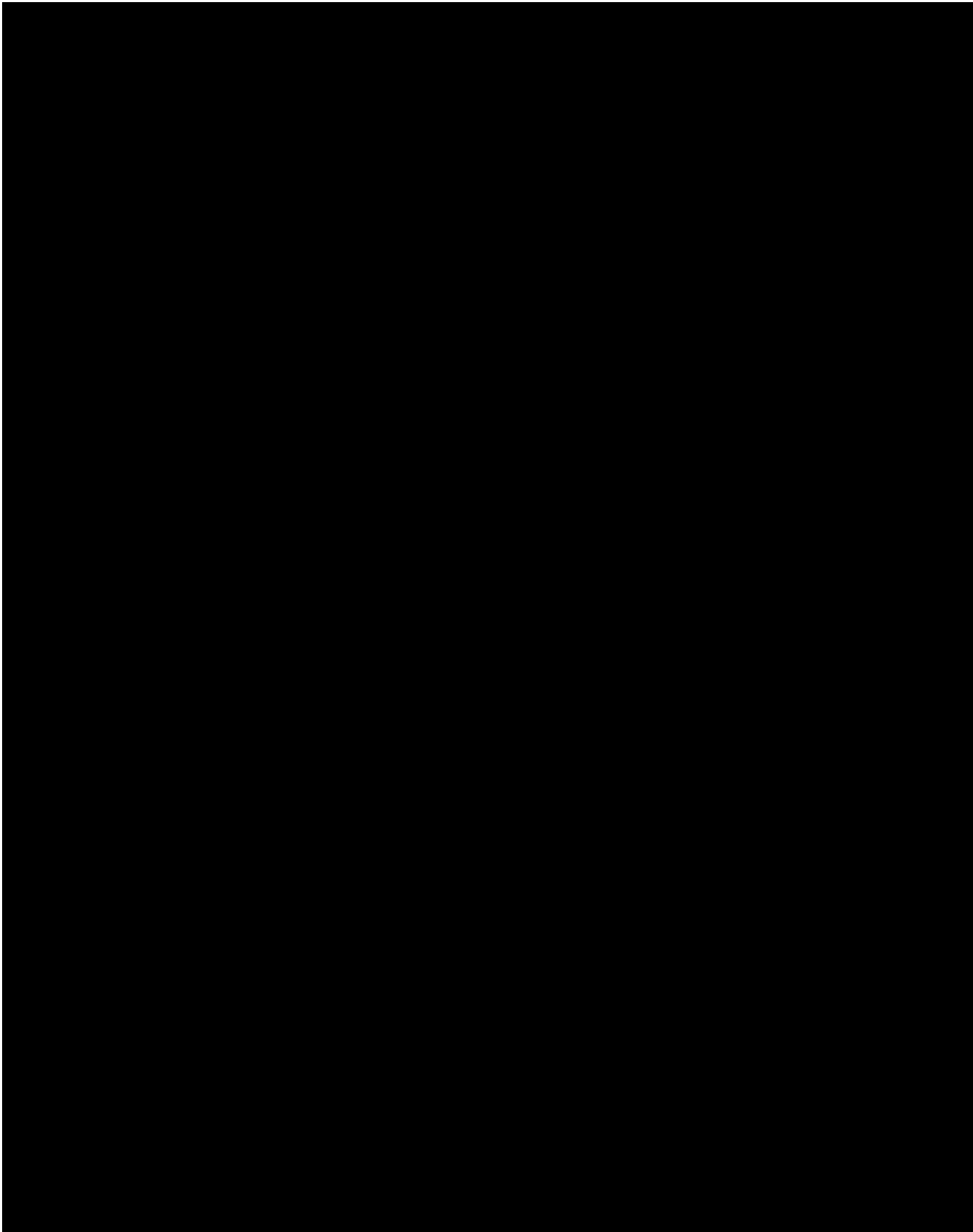
[REDACTED]

[REDACTED]

[REDACTED]



[Redacted text block]



[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

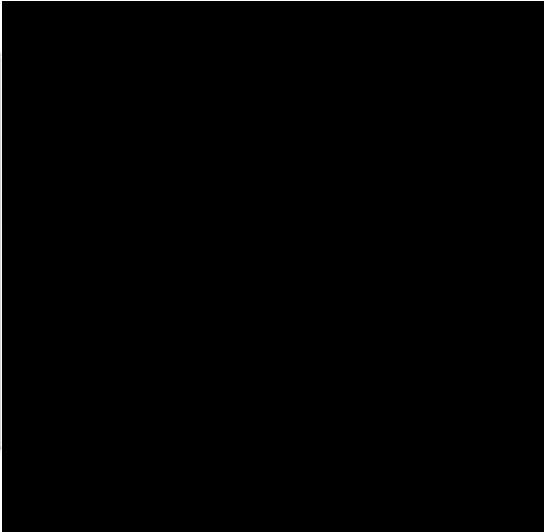
[REDACTED]

[REDACTED]

There has been a great deal of renewed interest in melatonin, its mechanism of action and its therapeutic effects. The degree of scientific interest in the use of melatonin is increasing day by day.

[REDACTED]

[REDACTED]

[REDACTED]	[REDACTED]	
[REDACTED]	[REDACTED]	
[REDACTED]	[REDACTED]	
[REDACTED]	[REDACTED]	
[REDACTED]	[REDACTED]	
[REDACTED]	[REDACTED]	
[REDACTED]	[REDACTED]	
[REDACTED]	[REDACTED]	
[REDACTED]	[REDACTED]	
[REDACTED]	[REDACTED]	
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[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

2.5.2 OVERVIEW OF BIOPHARMACEUTICS

Immediate release (IR) melatonin may have a role in the treatment of paediatric insomnia disorder with unknown cause or with known illnesses including DSPD, ADHD and ASD. [REDACTED]

Please note that the formulation of Melatonin 3 mg film coated tablets (PL 20243/0004) listed below in the [table 2.5.2.1](#) is an immediate release formulation. [REDACTED]

[REDACTED] Formulation of Melatonin 3 mg film coated tablets (PL 20243/0004)

Description

White film coated biconvex tablet containing 3 mg of the active substance melatonin. The tablets contain conventional excipients [REDACTED]

Active Ingredient:

Melatonin

Other Ingredient

Cellulose, microcrystalline [REDACTED]

Cellulose, microcrystalline [REDACTED]

Maltodextrin [REDACTED]

Silica colloidal, anhydrous

Magnesium stearate

Croscarmellose Sodium

Core tablet:

Coating:

Hypromellose [REDACTED]

Tablet weight:

[REDACTED] Product characteristics:

The concept of patient centered healthcare is a crucial aspect for all healthcare and social care professionals, which has been widely integrated into healthcare policies throughout the UK. The core themes of this policy emphasize the importance of treating patients with respect, recognizing them as

individuals, and involving them as equal partners in decisions about their care. This includes prioritizing patient preferences and choices.

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

Active Ingredient: Melatonin

Melatonin as a chemical substance is not classified as a hazardous pursuant to the provisions set forth in EC Regulation 1272/2008 (CLP) (and subsequent amendments and supplements). None of the excipients are classified as hazardous.

Excipients:

1. Magnesium stearate: [REDACTED]
[REDACTED]
[REDACTED]
2. Colloid silica, anhydrous: [REDACTED]
[REDACTED]
3. Maltodextrin: - [REDACTED]
[REDACTED]
4. Microcrystalline cellulose: [REDACTED]
[REDACTED]

5. Croscarmellose sodium: [REDACTED]
[REDACTED]

6. Hypromellose: [REDACTED]

Melatonin 3 mg film coated tablets [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

[REDACTED]
[REDACTED]

Study	Melatonin supplier	Melatonin formulation/principal excipients
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[REDACTED]		
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[REDACTED]

In conclusion, the melatonin formulations used in referenced controlled clinical studies listed in above [REDACTED] indicate that the vast majority of formulations used in clinical trials are immediate release formulations.

[REDACTED]

2.5.3 OVERVIEW OF CLINICAL PHARMACOLOGY IN ADULTS, CHILDREN AND ADOLESCENTS

[REDACTED]

2.5.3.1 Pharmacokinetics

No formal pharmacokinetic (PK) studies have been made with the applicant's product (Melatonin 3 mg film coated tablets PL 20243/0004).

The pharmacokinetic data given in [REDACTED] is derived from the clinical studies ([REDACTED] [REDACTED] 2 of [REDACTED] support the [REDACTED] (see [REDACTED] of [REDACTED] in which melatonin formulation (immediate release) and dosage (3 mg to 9 mg) are considered to be relevant ([REDACTED]

Detailed pharmacokinetic (PK) data relating to administration of exogenous melatonin in adults covering absorption, distribution, metabolism, excretion, linearity, intrinsic factors, extrinsic factors and pharmacokinetic drug interactions have [REDACTED]

The question of how the pharmacokinetics of melatonin may be altered in children is now addressed. [REDACTED] noted that of the various factors (absorption, protein binding, hepatic metabolism, renal clearance) potentially affecting the pharmacokinetics of melatonin in children, increased enzyme activity of CYP1A2 in the liver of children aged 1-12 years is the most significant issue; an

increased dosage of melatonin (on a weight basis compared to adults) is therefore predicted to have an effect on sleep.

The pharmacokinetics of melatonin in children compared to adults, was reported by [REDACTED] [REDACTED] who investigated the effect of melatonin infusion (0.5 mcg/kg) in 9 pre-pubertal subjects (mean age 8.4 yr), 8 pubertal subjects (mean age 13 yr), and 16 adults (mean age 27 yr); the respective mean values for pre-pubertal, pubertal and adults were 0.67, 0.78 and 0.79 h for $T_{1/2}$, and 251, 300 and 376 pg/ml for AUC respectively. In very young children, [REDACTED] investigated the oral administration (via nasogastric tube) of melatonin (dose range 0.5-5 mg/kg) in 5 new born infants; depending on dosage, mean values for C_{max} varied from 0.44-7.0 mcg/ml, T_{max} 4.3-4.7 h, $T_{1/2}$ 10.9-7.9 h, and AUC 10.5-119 mcg/ml/h.

Cross-over studies using immediate release formulations in the dose range 0.1-5 mg by [REDACTED] [REDACTED] and [REDACTED] indicate a linear dose-response relationship for serum/plasma melatonin levels (C_{max} , AUC) for melatonin in the dose range 1-5 mg. In children with DSPD a dose finding study by [REDACTED] reported that melatonin dose of 0.05 mg/kg reduced sleep onset latency by 35 min, with no further dose-response for 0.1 mg/kg and 0.15 mg/kg doses.

With regard to extrinsic factors mentioned [REDACTED] [REDACTED] since exogenous melatonin is administered prior to bedtime with the objective of inducing sleep, the potential interaction with food (particularly caffeine) is not considered to be an issue. Similarly, the potential role of alcohol consumption or cigarette smoking are not considered to be of relevance in children.

Endogenous melatonin plasma concentrations in children are generally higher than in adults, due to the fixed size of the pineal gland in humans during development, while the body volume increases [REDACTED] However, children metabolize endogenous/exogenous melatonin more quickly than adults, primarily due to increased CYP 1A2 enzyme activity in the liver. Thus, the metabolism of melatonin in post-pubertal adolescents is comparable to that in adults, whilst in younger children the metabolism of melatonin is more rapid than in adults, resulting from increased CYP1A2 activity in the liver.

In a review article, [REDACTED] identified the route of administration (IV administration, oral administration), formulation type (immediate release, controlled release), timing of administration and dosage as factors affecting outcome in both normal subjects and children/adolescents with ASD.

Pharmacokinetic summary

[REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] Exogenous melatonin is efficiently absorbed from the digestive tract, but has a low bioavailability (<15%) due to extensive first-pass hepatic metabolism. In adults, a 3-6 mg dose of immediate release melatonin results in a T_{max} value of approximately 50 minutes and C_{max} of approximately 3400 pg/ml, with both values subject to considerable inter-individual variation. C_{max} and AUC are linear in the dose range 0.5-5 mg, whilst T_{max} and $T_{1/2}$ are constant. The main difference between children and adults in the pharmacokinetics of exogenous melatonin is the increased rate of clearance in younger (pre-pubertal) children, resulting from increased enzymic activity of CYP1A2 (the principal metaboliser of melatonin) in the liver; this in turn may require a higher dose of melatonin to induce sleep than would be required in adults. There is no physiological rationale why intrinsic or extrinsic factors potentially affecting melatonin pharmacokinetics reported in adults could be different in children, and this is reflected in the relevant sections of the proposed SmPC (e.g., caution advised in patients with hepatic or renal dysfunction). Depending on individual liver CYP1A2 activity, a melatonin dose substantially less than 3 mg may be sufficient to induce sleep; however, since there is no ethical means of discriminating between fast and slow melatonin metabolisers, a dose of 3 mg (with potential

increase up to 9 mg if required) is recommended to encompass both fast and slow melatonin metabolising children.

Pharmacodynamics

[REDACTED], which concerns the original indication jet-lag in adults, in which a comprehensive discussion including safety pharmacology, mechanism of action and pharmacodynamic effects of melatonin in both paediatric and adult populations is given in detail.

The following information is listed as it is relevant to children and adolescents.

Primary pharmacodynamics

Effect on sleep: [REDACTED] for general updates and updated information related to already approved indication short-term treatment of jet-lag in adults. It is noteworthy that no evidence suggests a disparity in the physiological action of melatonin between children and adults. [REDACTED]

Secondary pharmacodynamics

Cardiovascular function

Please refer to [REDACTED] for general updates and updated information related to already approved indication short-term treatment of jet-lag in adults. Of note to children is that increased plasma levels of endogenous melatonin are considered to be a compensatory mechanism in children with heart failure [REDACTED]

Sexual development

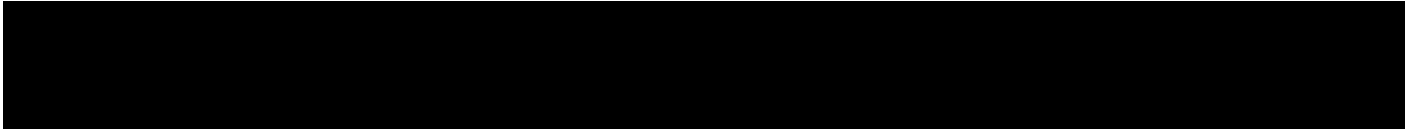
With regard to sexual development, a study by [REDACTED] of pubertal development in children with long-term (1-5 years) melatonin treatment (mean dose 3 mg) did not find any significant deviation compared to the general Dutch child population, as measured by the Tanner score. [REDACTED] conducted a longitudinal study of melatonin treatment in 44 children with neurodevelopmental disorders and treatment-resistant circadian rhythm sleep disorders. Precocious puberty was present in five children with severe neurodevelopmental disability, most of whom experienced it prior to the melatonin treatment. In the remaining children, pubertal timing was considered within normal limits. A meta-analysis by [REDACTED] found no evidence for adverse effects of exogenous melatonin administration on the levels of hypothalamic-pituitary-adrenal or hypothalamic-pituitary-gonadal hormones. No literature reports were identified indicating exogenous melatonin affects the hypothalamo-pituitary-gonadal axis pathways in any manner different to those normally occurring when melatonin is produced endogenously.

2.5.4 OVERVIEW OF EFFICACY IN CHILDREN AND ADOLESCENTS

The relevance of melatonin supplementation to improving sleep (particularly sleep latency) has been previously discussed in the pharmacokinetic (2.5.3.1) and pharmacodynamic (2.5.3.2) sections of this clinical [REDACTED]. Evidence for the efficacy of melatonin supplementation in children with insomnia is derived principally from randomised controlled trials, as summarised below.

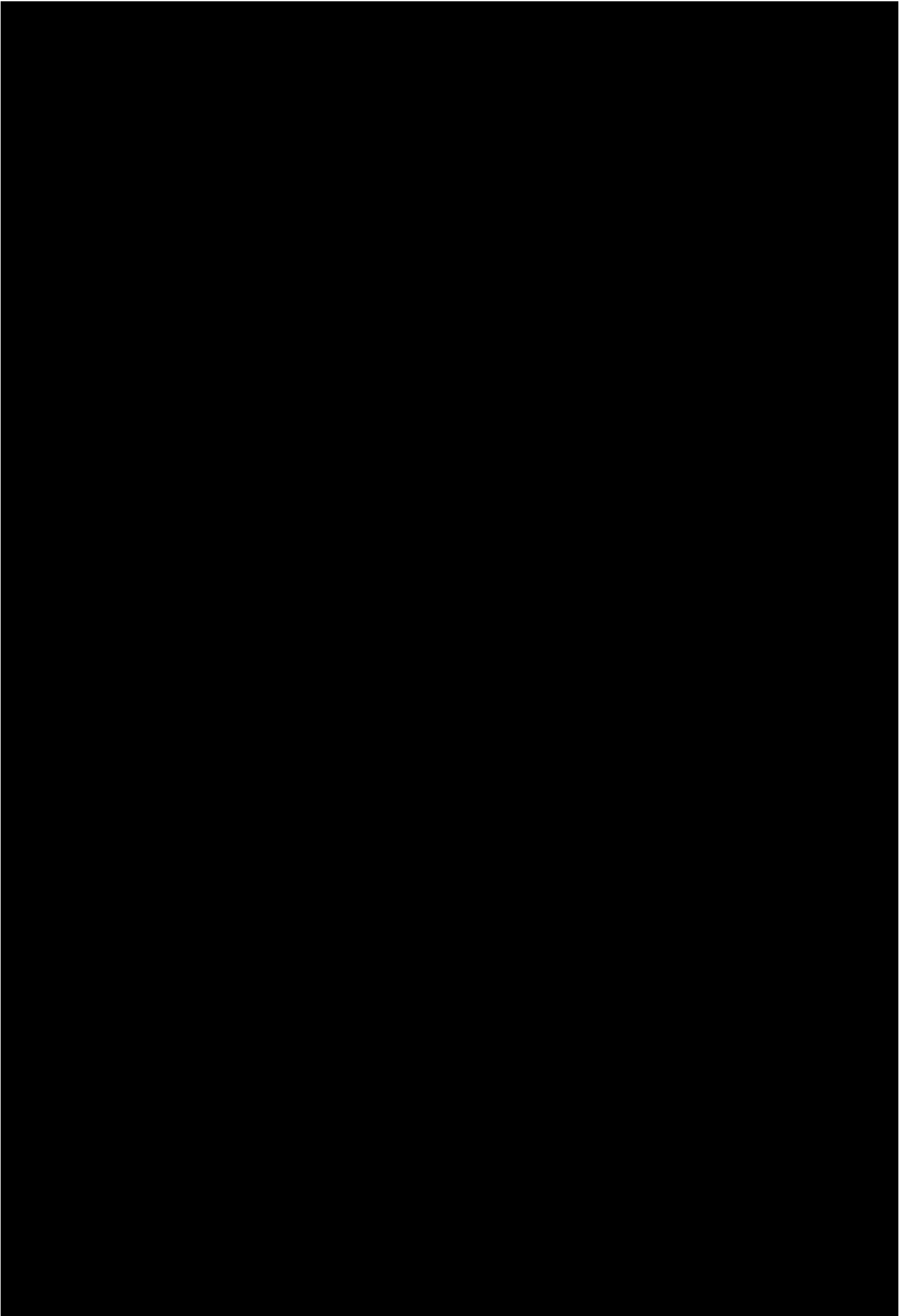
Study narratives.

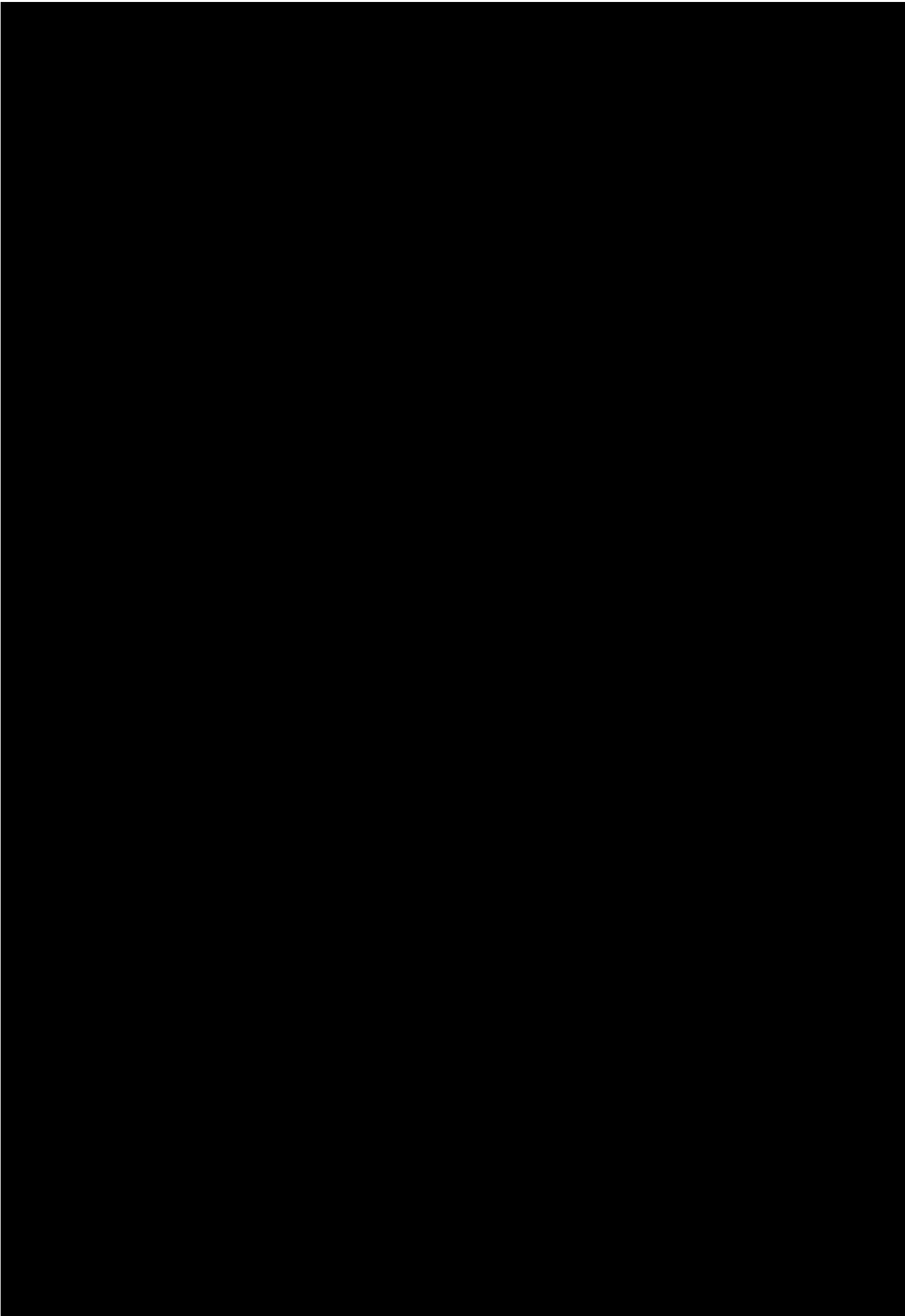
Summary of controlled clinical trial studies supplementing melatonin for insomnia in children are listed in [Table 2.5.4.1.1.1](#), and details of uncontrolled studies in [Table 2.5.4.1.1.2](#) respectively. Summary narratives are based on the abstracts from the respective publications.



Study/location	Study design	Patient details (disease category, number, ages)	Melatonin (formulation, dose/duration, manufacturer)	Outcome (as significant mean difference)
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[Redacted content]				
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Randomised controlled studies (1998 – 2017):

██████████ Nine girls with Rett syndrome (mean age, 10.1 years) were monitored 24 hours a day over a period of 10 weeks using wrist actigraphy. Baseline sleep-wake patterns were assessed for 1 week. Subsequently, patients underwent a 4-week melatonin treatment period in a double-blind, placebo-controlled, crossover protocol that employed a 1-week washout between treatment trials. ██████████

██████████ ██████████ Melatonin significantly decreased sleep-onset latency to (mean $\pm$ SE) 19.1 $\pm$ 5.3 minutes ($P < 0.05$) during the first 3 weeks of treatment. Finally, a 4-week administration of melatonin appears to be a safe treatment as no adverse side effects were detected.

██████████ A double blind randomised placebo controlled study comprising 40 children aged 6-12 yrs with chronic sleep onset insomnia (lasting more than one year).. The children were randomly assigned to receive either 5-mg melatonin (immediate release) or placebo. ██████████

██████████ The results show that melatonin, 5 mg at 6 PM, was relatively safe to take in the short term and significantly more effective than placebo in advancing sleep onset and dim light melatonin onset and increasing sleep duration in elementary school children with chronic sleep onset insomnia.

██████████ A double blind randomised placebo controlled trial comprising 20 children with development disabilities with sleep onset insomnia. Patients received either melatonin or placebo over a six week period. ██████████

██████████ The effect of melatonin on sleep latency was significant ($P < .05$). The duration of sleep while receiving melatonin was significantly greater than baseline ($P < .007$) but was not significantly different from placebo, and no difference in the number of awakenings was noted. No side effects were reported. Eleven of 18 parents (61%) correctly identified the weeks their child received melatonin. This study indicates that synthetic melatonin reduces sleep latency in children with developmental disabilities.

██████████ A randomized, double-blind, placebo-controlled trial comprising 62 children aged 6-12 yrs with chronic sleep onset insomnia (lasting more than one year). Patients received either 5 mg melatonin (immediate release) or placebo at 7 pm. ██████████

██████████ improved significantly more during melatonin treatment compared to placebo. The magnitude of change was much higher in the melatonin group than in the placebo group, with standardized response means for the RAND-GHRI of 0.69 versus 0.07 and for the FS-II of 1.61 versus 0.64. Melatonin treatment also significantly advanced sleep onset by 57 minutes, melatonin onset by 82 minutes, and decreased sleep latency by 17 minutes. Lights-off time and total sleep time did not change. A follow-up study to ██████████

The aim of this study was to verify the clinical efficacy of melatonin (MLT) in children, adolescents and young adults with wake-sleep disorder and mental retardation, most of them on chronic anticonvulsant therapy for epileptic seizures, by means of a randomized, double-blind, placebo-controlled cross-over trial.

██████████ A randomized, double-blind, controlled, crossover trial investigating the response to oral melatonin using two dose regimens in patients with sleep disorders associated with tuberous sclerosis complex. ██████████ ██████████

██████████ This double-blind, randomized, placebo-controlled study in epileptic children, aged 3 to 12 years, evaluated the effect of add-on melatonin on the sleep behaviour of these children on sodium valproate monotherapy using a parental questionnaire. ██████████

██████████ A randomised double blind placebo-controlled study comprising 22 children aged 6-14 yrs with ADHD and sleep onset Insomnia. Patients received 5mg melatonin or placebo for 30 days on a cross-over basis. There was a significant reduction in initial insomnia of 16 minutes with melatonin compared to placebo.

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██████████ A randomised double-blind placebo controlled study comprising 105 children aged 6-12 years with ADHD and sleep onset insomnia. Patients were given 3 or 6 mg melatonin (depending on bodyweight) or placebo for 4 weeks. ██████████

██████████ Total time asleep increased with melatonin (19.8 +/- 61.9 minutes) as compared to placebo (-13.6 +/- 50.6 minutes; $p = .01$). There was no significant effect on behaviour, cognition, and quality of life, and significant adverse events did not occur.

██████████ A randomized double-blind, placebo-controlled crossover trial of controlled release melatonin (5 mg) followed by a 3-month open-label study was conducted during which the dose was gradually increased until the therapy showed optimal beneficial effects. ██████████

██████████ Recordings of total night-time sleep and sleep latency showed significant improvement of approximately 30 min. Similarly, significant improvement was observed in clinician and parent ratings. There was additional improvement in the open-label somnology measures of sleep efficiency and the longest sleep episode in the open-label phase. Overall, the therapy improved the sleep of 47 children and was effective in reducing family stress. Children with neurodevelopmental disabilities, who had treatment resistant chronic delayed sleep phase syndrome and impaired sleep maintenance, showed improvement in melatonin therapy.

██████████ The effectiveness of melatonin for the treatment of chronic sleep disturbance was assessed in a randomized double-blind placebo-controlled trial with 51 individuals with intellectual disabilities. ██████████

██████████ Compared with placebo, melatonin significantly advanced mean sleep onset time by 34 min, decreased mean sleep latency by 29 min, increased mean total sleep time by 48 min, reduced the mean number of times the person awoke during the night by 0.4, decreased the mean duration of these night waking periods by 17 min and advanced endogenous melatonin onset at night by an average of 2.01 h. Lights off time, sleep offset time and the number of nights per week with night waking did not change. Only few minor or temporary adverse reactions and no changes in seizure frequency were reported.

██████████ To assess the efficacy of melatonin, a randomized placebo-controlled study was conducted in 8 children with Angelman syndrome with idiopathic chronic insomnia. ██████████

██████████ Melatonin significantly advanced sleep onset by 28 minutes, decreased sleep latency by 32 minutes, increased total sleep time by 56 minutes, reduced the number of nights with wakes from 3.1 to 1.6 nights a week, and increased endogenous salivary melatonin levels.

██████████ To determine the efficacy of melatonin on sleep problems in children with autistic spectrum disorder (ASD) and fragile X syndrome (FXS), a 4-week, randomized, double blind, placebo-controlled, crossover design was conducted following a 1-week baseline period. Either melatonin, 3 mg, or placebo was given to participants for 2 weeks and then alternated for another 2 weeks. Sleep variables, including sleep duration, sleep-onset time, sleep-onset latency time, and the number of night awakenings, were recorded using an Actiwatch and from sleep diaries completed by parents. All participants had been thoroughly assessed for ASD and also had DNA testing for the diagnosis of FXS. Data were successfully obtained from the 12 of 18 subjects who completed the study (11 males, age range 2 to 15.25 years, mean 5.47, SD 3.6). Five participants met diagnostic criteria for ASD, 3 for FXS alone, 3 for FXS and ASD, and 1 for fragile X premutation. Eight out of 12 had melatonin first. The conclusions from a nonparametric repeated-measures technique indicate that mean night sleep duration was longer on melatonin than placebo by 21 minutes ($p = .02$), mean sleep-onset latency was shorter by 28 minutes ($p = .0001$), and mean sleep-onset time was earlier by 42 minutes ($p = .02$).

██████████ Children with chronic sleep onset insomnia (CSOI; $n = 72$) received either melatonin 0.05, 0.1, and 0.15 mg/kg or placebo for 1 week. ██████████

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██████████ This study demonstrates that melatonin for treatment of CSOI in children is effective in a dosage of 0.05 mg/kg given at least 1 to 2 h before DLMO and before desired bedtime.

██████████ Twenty-two children with autism spectrum disorders who had not responded to supported behaviour management strategies for severe dysomnias entered a double blind, randomised, controlled crossover trial involving 3 months of placebo versus 3 months of melatonin to a maximum dose of 10 mg. 17 children completed the study. There were no significant differences between sleep variables at baseline. Melatonin significantly improved sleep latency (by an average of 47 min) and total sleep (by an average of 52 min) compared to placebo, but not number of night awakenings. The side effect profile was low and not significantly different between the two arms.

██████████ The study comprised children with neurodevelopmental problems aged from 3- 15 years who did not fall asleep within 1 hour of lights out or who had < 6 hours of continuous sleep. Sleep was measured using sleep diaries and actigraphy. Melatonin or placebo capsules in doses of 0.5 mg, 2 mg, 6 mg and 12 mg were given for a period of 12 weeks. ██████████

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██████████ The primary outcome was total night-time sleep time (TST) calculated using sleep diaries at 12 weeks compared with baseline. ██████████

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██████████ There were no significant differences between the two groups in terms of the reporting of adverse events. The results of other

secondary outcomes favoured melatonin but were not statistically significant. On average, the children treated with melatonin slept 23 minutes longer than those in the placebo group; however, the upper limit of the confidence interval was less than 1 hour, the minimum clinically worthwhile difference specified at the outset of the trial. Melatonin is effective in reducing SOL in children with neurodevelopmental delay by a mean of 45 minutes; a value of 30 minutes was specified a priori to be clinically important.

One hundred and sixty children with autism spectrum disorders, aged 4-10 years, suffering from sleep onset insomnia and impaired sleep maintenance, were assigned randomly to either (1) combination of controlled-release melatonin and cognitive-behavioural therapy; (2) controlled-release melatonin; (3) four sessions of cognitive-behavioural therapy; or (4) placebo drug treatment condition for 12 weeks in a 1 : 1 : 1 : 1 ratio. Children were studied at baseline and after 12 weeks of treatment. Treatment response was assessed with 1-week actigraphic monitoring, sleep diary and sleep questionnaire. Main outcome measures, derived actigraphically, were sleep latency, total sleep time, wake after sleep onset and number of awakenings. The active treatment groups all resulted in improvements across all outcome measures, with moderate-to-large effect sizes from baseline to a 12-week assessment. Melatonin treatment was mainly effective in reducing insomnia symptoms, while cognitive-behavioural therapy had a light positive impact mainly on sleep latency, suggesting that some behavioural aspects might play a role in determining initial insomnia. The combination treatment group showed a trend to outperform other active treatment groups, with fewer dropouts and a greater proportion of treatment responders achieving clinically significant changes (63.38% normative sleep efficiency criterion of >85% and 84.62%, sleep onset latency <30 min). This study demonstrates that adding behavioural intervention to melatonin treatment seems to result in a better treatment response, at least in the short term.

A randomized, double-blind, placebo-controlled, crossover study to identify the effects of melatonin on sleep and seizure control in children with epilepsy.

The primary outcomes were sleep onset latency and wakefulness after sleep onset (WASO) measured on polysomnography. The secondary outcomes included seizure frequency, epileptiform spike density per hour of sleep on electroencephalogram (EEG), and reaction time (RT) measures on psychomotor vigilance task (PVT).

Additionally, slow-wave sleep duration and rapid eye movement (REM) latency were increased with melatonin and REM sleep duration was decreased. These changes were statistically significant.

This randomized clinical trial used a double-blind, placebo-controlled crossover design to study 73 children and adolescents aged 1 to 18 years with physician-diagnosed atopic dermatitis involving at least 5% of the total body surface area.

The primary outcome was AD severity evaluated using the Scoring Atopic Dermatitis (SCORAD) index, with scores ranging from 0 to 103 and greater scores indicating worse symptoms. Secondary outcomes included sleep variables measured by actigraphy, subjective change in sleep and dermatitis, sleep variables measured by polysomnography, nocturnal urinary levels of 6-sulfatoxymelatonin, and serum IgE levels. After melatonin treatment among the 48 children included in the study, the SCORAD index decreased by 9.1 compared with after placebo (95% CI, -13.7 to -4.6; $P < .001$), from a mean (SD) of 49.1 (24.3)

to 40.2 (20.9). Moreover, the sleep-onset latency shortened by 21.4 minutes after melatonin treatment compared with after placebo (95% CI, -38.6 to -4.2; $P = .02$). The improvement in the SCORAD index did not correlate significantly with the change in sleep-onset latency ($r = -0.04$; $P = .85$). No patient withdrew owing to adverse events, and no adverse event was reported.

██████████ In this study, the effects of melatonin and bright light treatment with a placebo condition in children with chronic sleep onset insomnia and late melatonin onset were studied. Eighty-four children (mean age 10.0 years, 61% boys) first entered a baseline week, after which they received melatonin ($N = 26$), light ($N = 30$), or placebo pills ($N = 28$) for 3 to 4 weeks. Sleep was measured daily with sleep diaries and actigraphy. Before and after treatment children completed a questionnaire on chronic sleep reduction and Dim Light Melatonin Onset (DLMO) was measured. Results were analyzed with linear mixed model analyses. Melatonin treatment and light therapy decreased sleep latency (sleep diary) and advanced sleep onset (sleep diary and actigraphy), although for sleep onset the effects of melatonin were stronger. In addition, melatonin treatment advanced DLMO and had positive effects on sleep latency and sleep efficiency (actigraphy data), and sleep time (sleep diary and actigraphy data). However, wake after sleep onset (actigraphy) increased with melatonin treatment. No effects on chronic sleep reduction were found.

██████████ To assess the efficacy and safety of novel paediatric-appropriate, prolonged-release melatonin minitablets (PedPRM) versus placebo for insomnia in children and adolescents with autism spectrum disorder (ASD), with or without attention-deficit/hyperactivity disorder (ADHD) comorbidity, and neurogenetic disorders (NGD), ██████████

██████████ Overall sleep disturbance (CSDI) tended to decrease. PedPRM was generally safe; somnolence was more commonly reported with PedPRM than placebo.

[REDACTED]

In addition to the above, there have been a number of open studies supplementing melatonin for sleep onset in children based on small numbers (<5) or single individuals that have not been included in [Table 2.5.4.1.1.2](#)

[REDACTED]

Uncontrolled studies (1996 – 2012):

[REDACTED] A group of Vancouver health professionals, including the authors, have studied the use of oral melatonin in the treatment of chronic sleep disorders in children with disabilities since the Fall of 1991. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] Melatonin, which benefited slightly over 80% of our patients, appears to be a safe, inexpensive, and a very effective treatment of sleep-wake cycle

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[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] In the present study, 12 young healthy volunteers, free of sleep disturbances, received 0.3 or 1.0 mg of melatonin or placebo at 2100 hours, 2-4 hours prior to their habitual bedtime. Polysomnographic recording of overnight sleep began at 2200 hours and continued until 0700 hours the following morning, when subjects were awakened. Sleep onset latency and latency to stage 2 sleep were significantly decreased as a result of melatonin treatment. Neither dose of melatonin significantly altered sleep architecture. [REDACTED]

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These observations provide additional evidence that nocturnal melatonin secretion has a sleep-promoting function. They also indicate that an increase in serum melatonin concentrations, within the

normal physiologic range, does not significantly alter sleep architecture in subjects with normal sleep who receive the treatment several hours prior to their habitual bedtime.

During the last 5 years our research group has used melatonin to successfully treat chronic sleep disorders in more than 90 children. Approximately half of these were visually impaired, and most were multi-disabled and of low intellect. The most effective dose of fast release melatonin was consistently greater than 2.5 mg, most usually between 5 and 10 mg.

The efficacy and side effects of melatonin at bedtime were evaluated in 50 children and young adults with sleep disorders (3-28 years old, 41 males and 9 females, autism [AU] in 27 patients, mentally retardation [MR] in 20 patients, and severe motor and intellectual disability [SMID] in 3 patients).

There was almost no change in contrariness, stereotyped behavior and in school/workshop refusal. Melatonin at bedtime was efficacious in 42 of the 50 patients with sleep disorders. In 17 patients, there were side effects (residual drowsiness on the next morning, awakening in the middle of sleep, excitement after awakening and before going to sleep, etc.). But these side effects were not serious. The effects of melatonin were influenced by the type of sleep disturbances, the factors of the environment and the mental conditions. Taking side effects into account, melatonin was judged to be useful in 34 patients.

The effects of low dose melatonin therapy on sleep behaviour and serum melatonin levels were studied in Angelman syndrome (AS) children suffering from insomnia.

Analysis of the group data revealed a significant decrease in motor activity during the total sleep period following melatonin treatment, and an increase in the duration of the total sleep period. Endogenous peak nocturnal melatonin values ranged from 19 to 177 pg/ml.

These data suggest that a moderate increase in circulating melatonin levels significantly reduces motor activity during the sleep period in Angelman syndrome children and promotes sleep.

In this open clinical trial, the effectiveness of melatonin was studied in a sample of 15 children with Asperger disorder (13 boys, 2 girls) aged 6-17 years using several questionnaires and actigraph measurements.

The sleep patterns of all the children improved, and half of them displayed excellent responses to melatonin.

This retrospective study describes the effects of long-term treatment with melatonin in 33 adolescents (age range, 10-18 years) with delayed sleep phase syndrome (DSPS).

Patients were treated with oral melatonin, 3 to 5 mg/day for an average period of 6 months. During the treatment, sleep onset was advanced. Treatment was also associated with a decrease in the proportion of patients reporting school difficulties. No adverse effects of melatonin were noted. This study indicates that long-term treatment with melatonin can be beneficial for adolescents with DSPS in terms of sleep-wake schedule and school performance.

Long-term effectiveness of controlled-release melatonin in 25 children, aged 2.6-9.6 years with autism without other coexistent pathologies was evaluated openly. Sleep patterns were studied using Children's Sleep Habits Questionnaire (CSHQ) and sleep diaries at baseline, after 1-3-6 months melatonin treatment and 1 month after discontinuation. Sleep diary and CSHQ showed a more problematic sleep in autistic children compared with controls. During treatment sleep patterns of all children improved. After discontinuation 16 children returned to pre-treatment score, readministration of melatonin was again effective. Treatment gains were maintained at 12 and 24-month follow-ups. No adverse side effects were reported. In conclusion, controlled-release melatonin may provide an effective and well-tolerated treatment for autistic children with chronic sleep disorders.

One hundred seven children (2-18 years of age) with a confirmed diagnosis of autism spectrum disorders who received melatonin were identified by reviewing the electronic medical records of a single paediatrician. All parents were counselled on sleep hygiene techniques. Clinical response to melatonin, based on parental report, was categorized as (1) sleep no longer a concern, (2) improved sleep but continued parental concerns, (3) sleep continues to be a major concern, and (4) worsened sleep. The melatonin dose varied from 0.75 to 6 mg. After initiation of melatonin, parents of 27 children (25%) no longer reported sleep concerns at follow-up visits. Parents of 64 children (60%) reported improved sleep, although continued to have concerns regarding sleep. Parents of 14 children (13%) continued to report sleep problems as a major concern, with only 1 child having worse sleep after starting melatonin (1%), and 1 child having undetermined response (1%). Only 3 children had mild side-effects after starting melatonin, which included morning sleepiness and increased enuresis. There was no reported increase in seizures after starting melatonin in children with pre-existing epilepsy and no new-onset seizures. The majority of children were taking psychotropic medications. Melatonin appears to be a safe and well-tolerated treatment for insomnia in children with autism spectrum disorders.

Twenty-four children with ASD, free of psychotropic medications, completed an open-label dose-escalation study to assess dose-response, tolerability, safety, feasibility of collecting actigraphy data, and ability of outcome measures to detect change during a 14-week intervention. Supplemental melatonin improved sleep latency, as measured by actigraphy, in most children at 1 or 3 mg dosages. It was effective in week 1 of treatment, maintained effects over several months, was well tolerated and safe, and showed improvement in sleep, behaviour, and parenting stress.

Patient age: The age range in children covered by the above studies was 2-18 yrs.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] Efficacy of melatonin in other disorders

DSPD in adults: A number of randomised controlled studies have reported significant clinical benefit of exogenous melatonin in advancing sleep latency in adults with DSPD; these have been summarised in the meta-analysis by [REDACTED]. A scientific opinion by the European Food Safety Authority considered a cause-and-effect relationship to be established between the consumption of melatonin and a reduction in sleep latency. It was stated that in order to obtain an effect in the target general population, 1mg of melatonin should be consumed close to bedtime.

Primary sleep disorders: Meta-analyses by [REDACTED] and [REDACTED] concluded that exogenous melatonin was not effective in treating most primary sleep disorders (i.e. non-circadian rhythm sleep disorders). However, [REDACTED] noted a clinically important improvement in sleep latency (mean value 39 mins) in individuals with DSPD.

Secondary sleep disorders: A meta-analysis by [REDACTED] found no evidence of benefit for melatonin supplementation in patients with non-circadian rhythm secondary sleep disorders.

The above studies demonstrate the efficacy of exogenous melatonin for significant clinical benefit in patients with circadian rhythm type sleep disorders (principally DSPD), and lack of efficacy of supplemental melatonin in non-circadian rhythm type sleep disorders.

Recommendations for melatonin administration for insomnia in children and adolescents with or without neurological dysfunction

Supplemental melatonin is suitable for advancing sleep latency in children in the age range 2-18 years with or without neurological problems, for whom improvement in sleep hygiene practices proved

ineffective. The recommended formulation/dosage is 3 mg per day of immediate release melatonin given 30-60 minutes prior to bedtime, for a period of 4 weeks in the first instance to a maximum of 9 mg per day, subject to clinical review.

2.5.5 OVERVIEW OF SAFETY IN CHILDREN AND ADOLESCENTS

The safety outcomes of randomised controlled studies of exogenous melatonin for insomnia in children are listed in [Table 2.5.5.1.1](#); summary narratives of these studies are given in [section 2.5.4](#).

As noted from the [REDACTED] most randomised controlled trials of exogenous melatonin for the treatment of insomnia in children reported no adverse effects, irrespective of dose up to 10 mg/day, or IR/CR formulation type; studies were typically of 4 weeks duration, although some studies extended to 3 months. The safety of melatonin for the treatment in children with insomnia was confirmed in the meta-analysis by [REDACTED] A meta-analysis by [REDACTED] concluded that supplemental melatonin was effective and safe (in the short term) for individuals (primarily children) with intellectual disability. A meta-analysis by [REDACTED] concluded supplementation with melatonin was safe and effective for improving sleep in children with neurodevelopment disorders. Brief narratives of the latter studies have been given following [Table 2.5.5.1.1](#).

[REDACTED]

[REDACTED]

Key to abbreviations: IR=immediate release; CR= controlled release; MR= mixed release

Summary narratives of the above studies have been given in [REDACTED]
[REDACTED] The following comments have been taken verbatim from the full versions of the respective papers.

Randomised controlled trials (1998 – 2021):

[REDACTED] No adverse effects reported during 4 week administration of melatonin.

[REDACTED] Mild headache occurred in 2 children during the first 2 days of melatonin treatment.

[REDACTED] No side effects were reported.

[REDACTED] Only a few relatively minor adverse events were reported. In the melatonin treated group, 7 patients reported feeling cold, decreased appetite or minor dizziness after first intake of melatonin; in the placebo group 3 patients reported headache, nausea or dizziness. These possible adverse events recovered within 3 days of the start of the trial.

[REDACTED] Melatonin was well tolerated in all patients and no side effects were reported.

[REDACTED] No adverse effects were noted following melatonin administration.

[REDACTED] No adverse event warranting discontinuation of melatonin therapy was reported.

[REDACTED] Adverse events were generally mild and not different from those recorded with placebo treatment.

[REDACTED] The number of adverse events did not differ significantly between melatonin and placebo treatment groups. There were no discontinuations or withdrawals caused by adverse events, and none of the adverse events required treatment.

[REDACTED] The incidence of adverse effects was similar in the melatonin and placebo treated groups. There was no evidence of adverse effects specific to melatonin, and in particular there was no increase in the frequency or severity of seizures.

[REDACTED] Only few minor or temporary adverse reactions and no changes in seizure frequency were reported.

[REDACTED] No adverse events reported, no occurrence of seizures during study.

[REDACTED] No adverse effects were reported throughout the study.

[REDACTED] The most common adverse events were red cheeks, red earlobes and red eyelids (n=15), pale looks, dizziness and coldness (n=8), headache (n=2), headache and nausea

(n=1). Most of the adverse effects wore off during the treatment week. Three participants reported increased incidence of diuresis.

██████████ The side effect profile was low and not significantly different between the melatonin and placebo study arms.

Adverse events were mild; there was no significant difference in the frequency of adverse events in the melatonin or placebo treatment groups.

██████████ Melatonin was well tolerated, and no adverse effects were reported or observed; blood tests and urinalysis showed no abnormalities and no one had to discontinue the study because of side effects.

██████████ Four subjects reported adverse events while taking melatonin compared to two subjects taking placebo. One subject taking melatonin with a history of migraine hasd increased severity of headache.

██████████ No adverse effect of melatonin medication was reported throughout the study.

██████████ One child dropped out of study due to headaches following melatonin administration.

██████████ Adverse effects were few and mild, with only headaches and daytime somnolence increased in the melatonin treatment group compared to placebo, and there was no increase in or new onset of seizures.

██████████ Melatonin treatment was generally safe; the most frequent treatment-related adverse events were fatigue (6.3%), somnolence (6.3%), and mood swings (4.2%). There were no observed detrimental effects on children's growth and pubertal development and no withdrawal or safety issues related to the use or discontinuation of the drug.

The long-term safety of melatonin supplementation in children has been addressed by

Summary narratives of these studies are given below. A review on DSPD by ██████████ concluded no trial has ever documented any serious adverse effect from the use of supplemental melatonin, and studies documenting long term use (mean follow up of 3 years) in children have not identified any safety concerns.

██████████ This study reports data from a prospective follow-up study of 44 children with neurodevelopmental disabilities and treatment-resistant circadian rhythm sleep disorders (CRSD) who had participated in a placebo controlled, double blind cross-over trial of sustained-release melatonin. ██████████

At the end of the study, the parental comments regarding the effectiveness of long-term melatonin therapy were highly positive.

██████████ This study assessed long-term melatonin treatment course, effectiveness and safety in children with attention-deficit/hyperactivity disorder (ADHD) and chronic sleep onset insomnia (CSOI). ██████████

██████████ It was concluded that melatonin remains an effective therapy on the long term for the treatment of CSOI in children with ADHD and has no safety concerns regarding serious adverse events or treatment related co-morbidity. Discontinuation of melatonin treatment usually leads to a relapse of sleep onset insomnia and in resuming melatonin treatment, even after several years of treatment.

██████████ To investigate the efficacy of melatonin in treating sleep problems in individuals with intellectual disabilities, a meta-analysis of placebo-controlled randomized trials of melatonin in individuals with intellectual disabilities and sleep problems was carried out. ██████████

██████████ Melatonin decreases sleep latency and number of wakes per night, and increases total sleep time in individuals with intellectual disabilities. Three of the included studies gave no information on side effects, otherwise adverse effects were minor and their incidence similar in both melatonin and placebo phases.

██████████ A meta-analysis of data of randomized controlled trials involving individuals with delayed sleep phase disorder that were published in English, compared melatonin with placebo, and reported 1 or more of the following: endogenous melatonin onset, clock hour of sleep onset, wake-up time, sleep-onset latency, and total sleep time. ██████████

██████████ Of those studies reporting adverse events, 6-7% of subjects reported having headaches during melatonin treatment. Other adverse events during melatonin treatment, and not during placebo included feeling cold ██████████ and dizziness ██████████

██████████ The objective of this study was to establish whether long-term use of melatonin influences pubertal development, sleep quality and mental health development in children as compared with the normal Dutch population of the same age. ██████████

In this study several adverse events were reported: nausea at the start of the study (1 child), weight gain (one child), nocturnal diuresis (3 children), short temper during high dose (10mg) therapy (1 child). Specifically with regard to headache, 21 children reported regular (once per week to once per month) headaches, 11 children seldom, and 23 children never experiencing headaches.

██████████ The objective of this study was to determine the efficacy and safety of melatonin as therapy for sleep problems in children with neurodevelopmental disorders. ██████████

██████████ Melatonin was reported to be safe and effective in improving sleep in the studied children.

timing, sleep quality, adverse events, reasons for cessation of therapy, and patient characteristics with regard to therapy regimen, chronotype and lifestyle factors possibly influencing sleeping behavior were assessed. With an online survey using questionnaires (Pittsburgh Sleep Quality Index, Insomnia Severity Index, Morningness-Eveningness Questionnaire, and Munich Chronotype Questionnaire), outcomes were measured and compared with age-related controls. These controls were extracted from published epidemiological research programs applying the same questionnaires. At the moment of the survey, melatonin was still continued by 27.3% of the patients, with a mean treatment duration of 10.8 years. The overall average treatment duration was 7.1 years. Sleep quality of both discontinued and persistent melatonin users did not deviate from controls. Sleep timing and chronotype scores indicated evening type preference in all responders. Adverse events were scarce but the perceived timing of pubertal development suggested a tendency towards delayed puberty in former and current users of melatonin. This study may underestimate the number of children that are able to stop using melatonin due to the response rate (47.8%) and appeal for continuing users. Sleep timing parameters were based on self-reported estimates. Control populations were predominantly students and were of varying nationalities. The statistical power of this study is low due to the limited sample size. Melatonin therapy sustained for 7.1 years does not result in substantial deviations of sleep quality as compared to controls and appears to be safe. The evening type preference suggests a causal relation with CSOI. This study shows that ten years after initiation of treatment with melatonin for CSOI,

approximately 75% of the patients will have normal sleep quality without medication. Adverse events were scarce and of an acceptable nature.

██████████ A prospective, open-label efficacy and safety follow-up of nightly 2, 5, or 10 mg PedPRM (see Gringras et al, 2017) in subjects who completed the 13-week double-blind trial (51 PedPRM; 44 placebo). Measures included caregiver-reported Sleep and Nap Diary, Composite Sleep Disturbance Index (CSDI), caregiver's Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale, and quality of life (WHO-5 Well-Being Index). Ninety-five subjects (74.7% males; mean [standard deviation] age, 9 [4.24]; range, 2-17.5 years) received PedPRM (2/5 mg) according to the double-blind phase dose, for 39 weeks with optional dose adjustment (2, 5, or 10 mg/day) after the first 13 weeks. After 52 weeks of continuous treatment (PedPRM-randomized group) subjects slept (mean [SE]) 62.08 (21.5) minutes longer ($p = 0.007$); fell asleep 48.6 (10.2) minutes faster ($p < 0.001$); had 89.1 (25.5) minutes longer uninterrupted sleep episodes ($p = 0.001$); 0.41 (0.12) less nightly awakenings ($>50\%$ decrease; $p = 0.001$); and better sleep quality ($p < 0.001$) compared with baseline. The placebo-randomized group also improved with PedPRM. Altogether, by the end of 39-week follow-up, regardless of randomization assignment, 55/72 (76%) of completers achieved overall improvement of ≥ 1 hour in total sleep time (TST), sleep latency or both, over baseline, with no evidence of decreased efficacy. In parallel, CSDI child sleep disturbance and caregivers' satisfaction of their child's sleep patterns ($p < 0.001$ for both), PSQI global ($p < 0.001$), and WHO-5 ($p = 0.001$) improved in statistically significant and clinically relevant manner ($n = 72$) compared with baseline. PedPRM was generally safe; most frequent treatment-related adverse events were fatigue (5.3%) and mood swings (3.2% of patients). PedPRM, an easily swallowed formulation shown to be efficacious versus placebo, is an efficacious and safe option for long-term treatment (up to 52 weeks reported here) of children with ASD and NGD who suffer from insomnia and subsequently improves caregivers' quality of life.

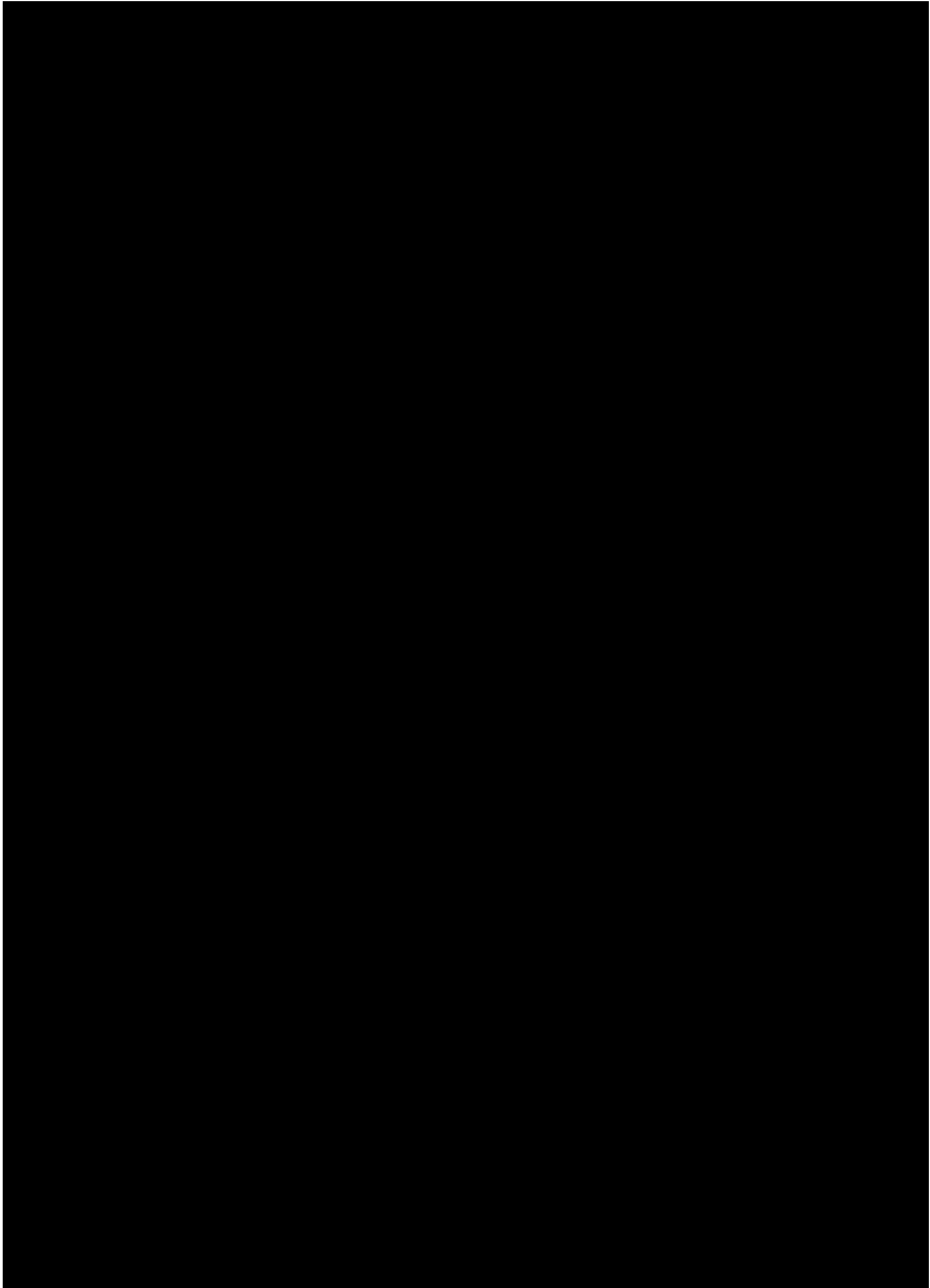
██████████ Eighty children and adolescents (2-17.5 years of age; 96% with autism spectrum disorder) who completed the double-blind, placebo-controlled trial were given 2 mg, 5 mg, or 10 mg PedPRM nightly up to 104 weeks, followed by a 2-week placebo period to assess withdrawal effects. Improvements in child sleep disturbance and caregiver satisfaction with child sleep patterns, quality of sleep, and quality of life were maintained throughout the 104-week treatment period ($p < .001$ versus baseline for all). During the 2-week withdrawal placebo period, measures declined compared with the treatment period but were still improved compared with baseline. PedPRM was generally safe; the most frequent treatment-related adverse events were fatigue (6.3%), somnolence (6.3%), and mood swings (4.2%). Changes in mean weight, height, body mass index, and pubertal status (Tanner staging done by a physician) were within normal ranges for age with no evidence of delay in body mass index or pubertal development. Nightly PedPRM at optimal dose (2, 5, or 10 mg nightly) is safe and effective for long-term treatment in children and adolescents with autism spectrum disorder and insomnia. There were no observed detrimental effects on children's growth and pubertal development and no withdrawal or safety issues related to the use or discontinuation of the drug.

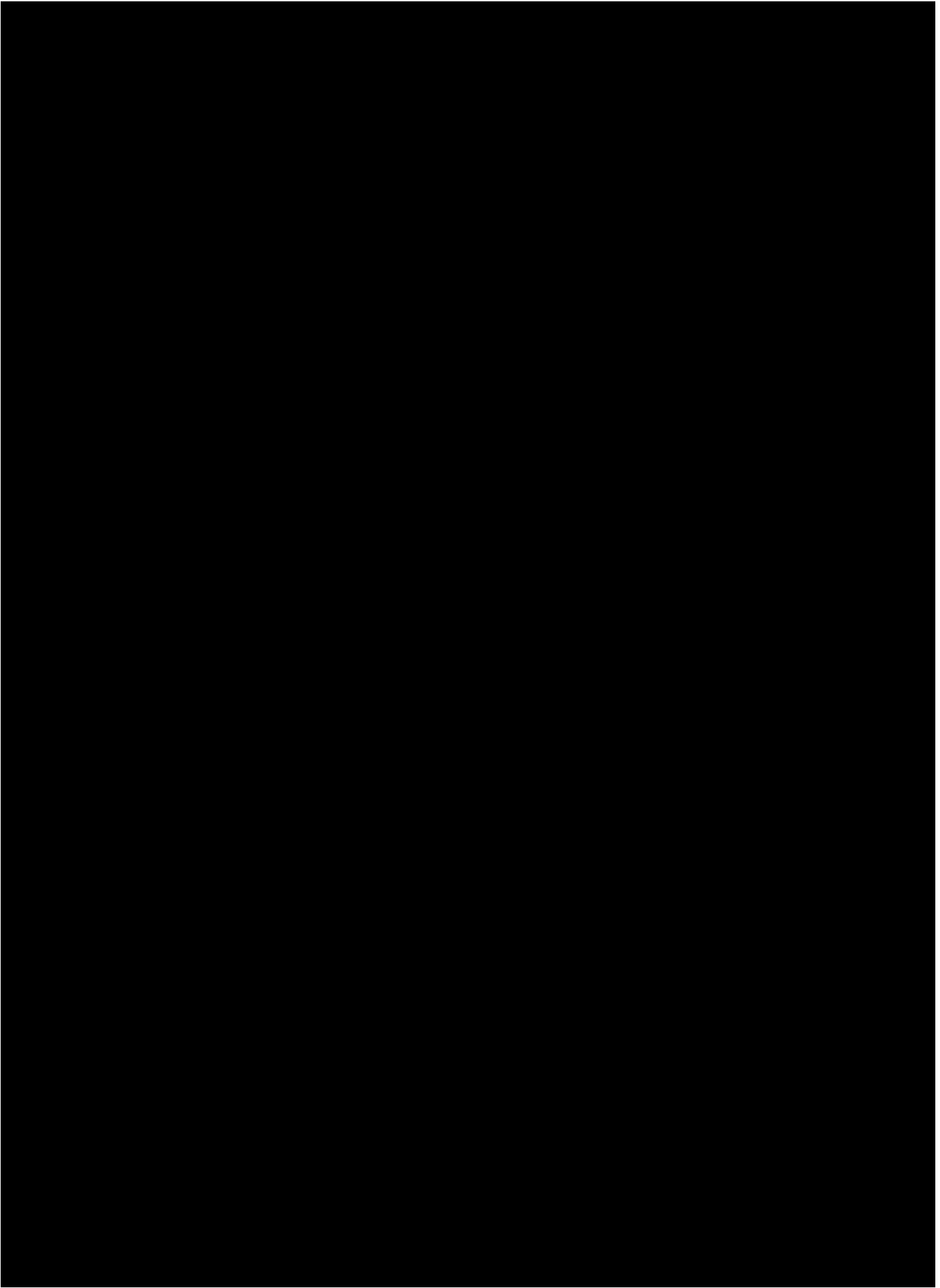
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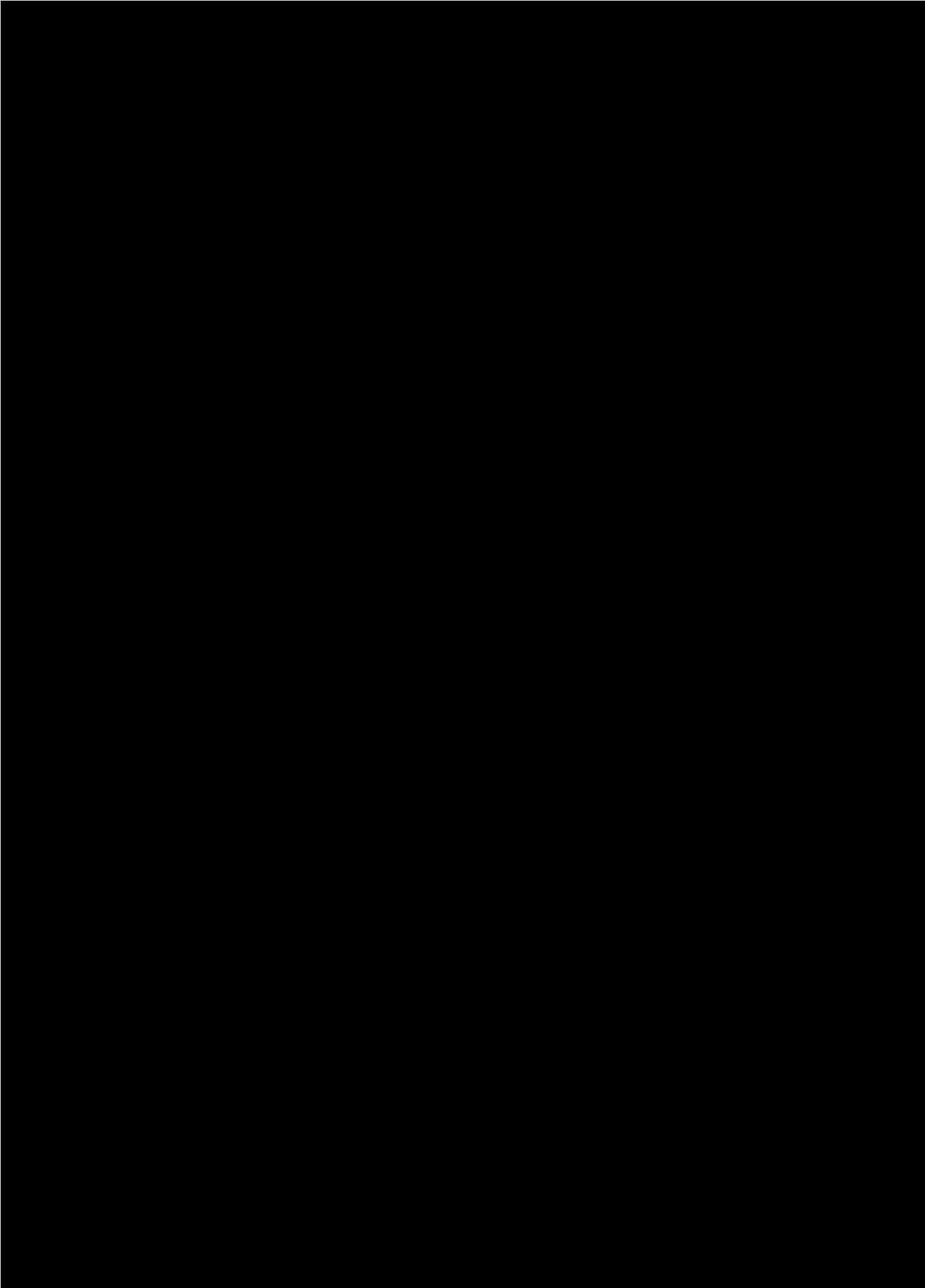
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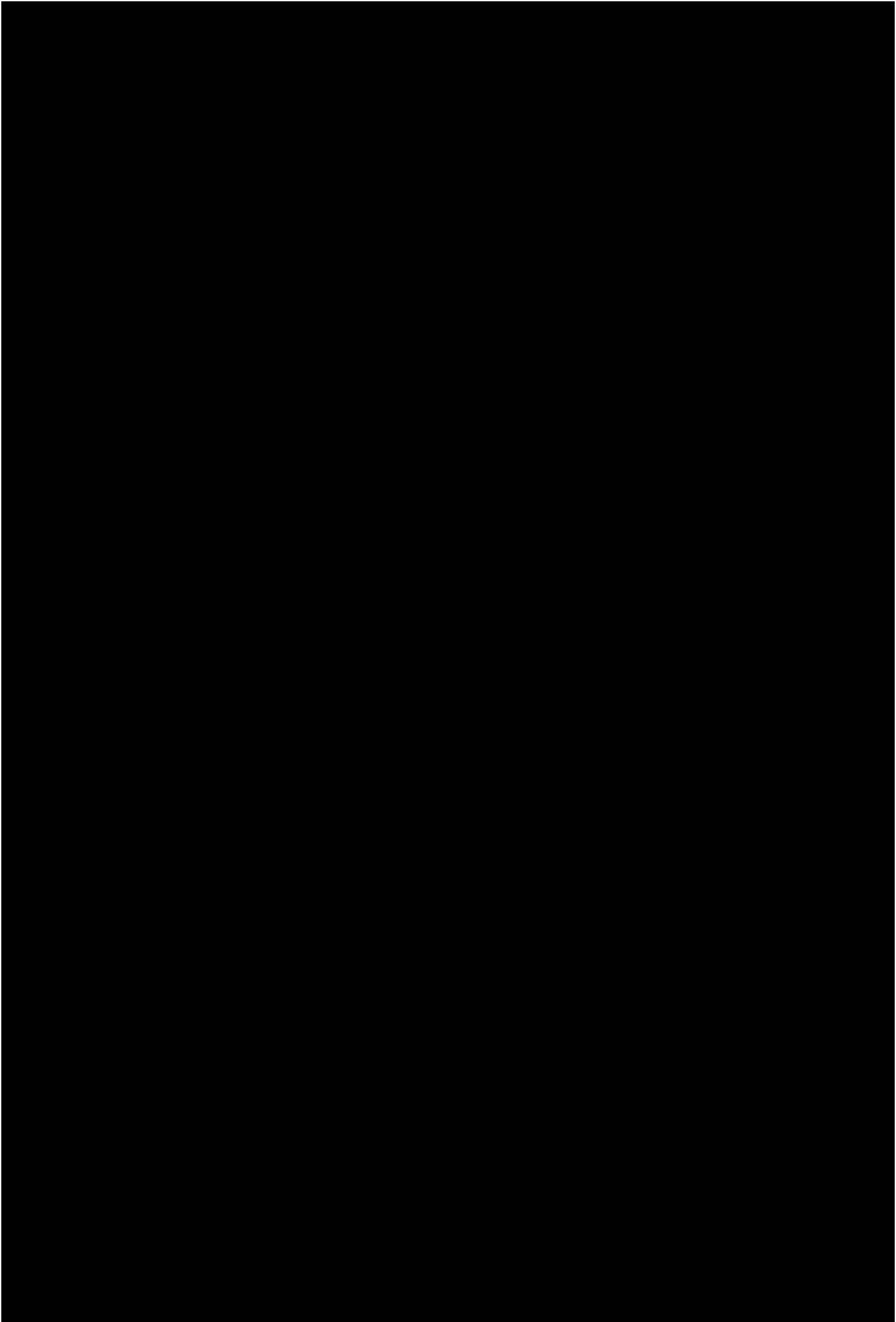
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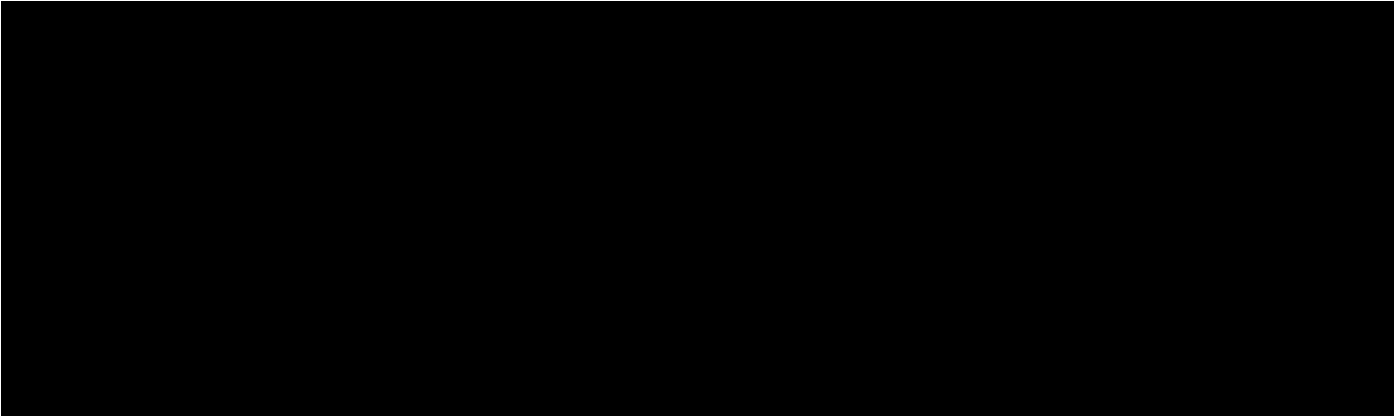
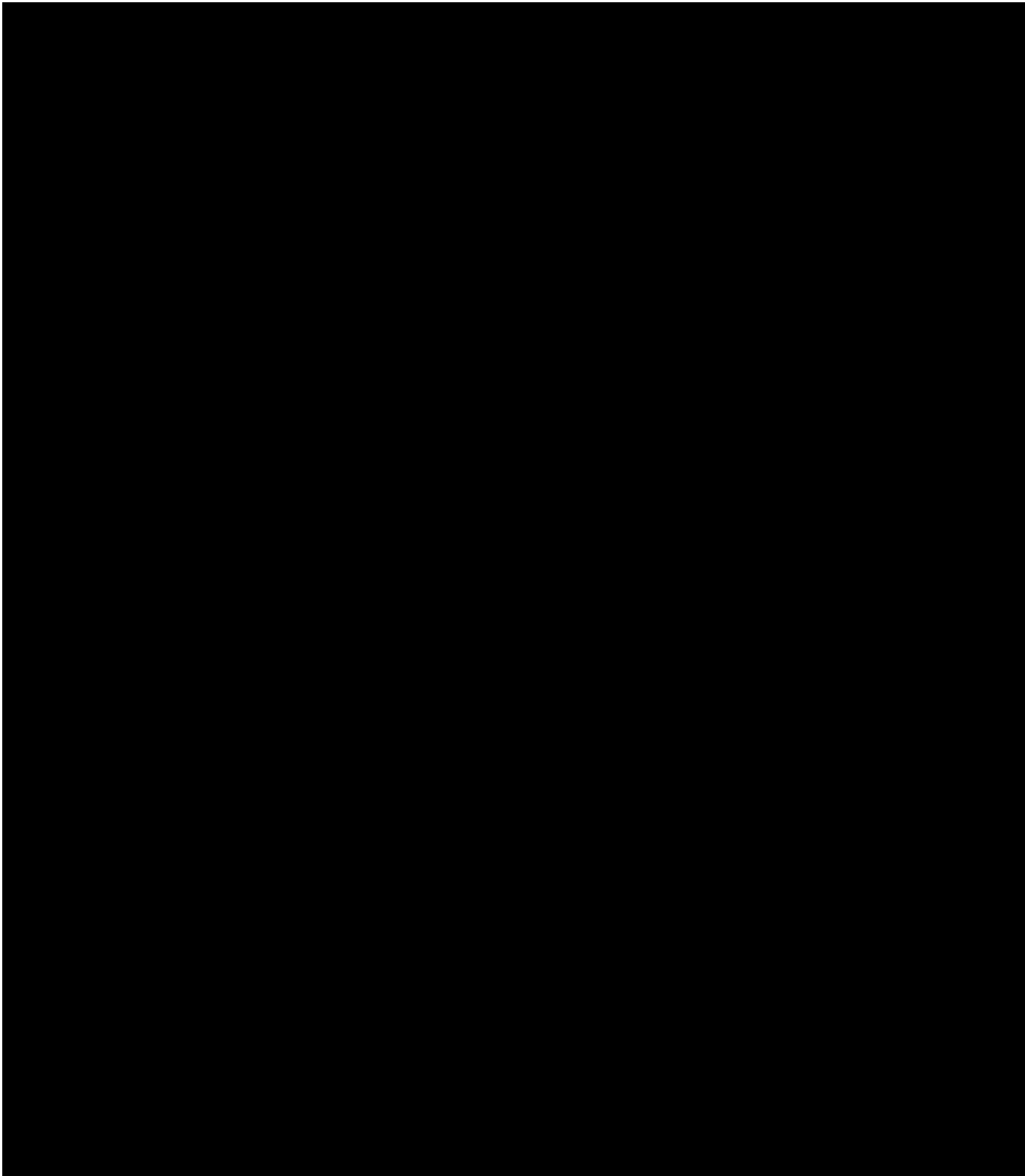
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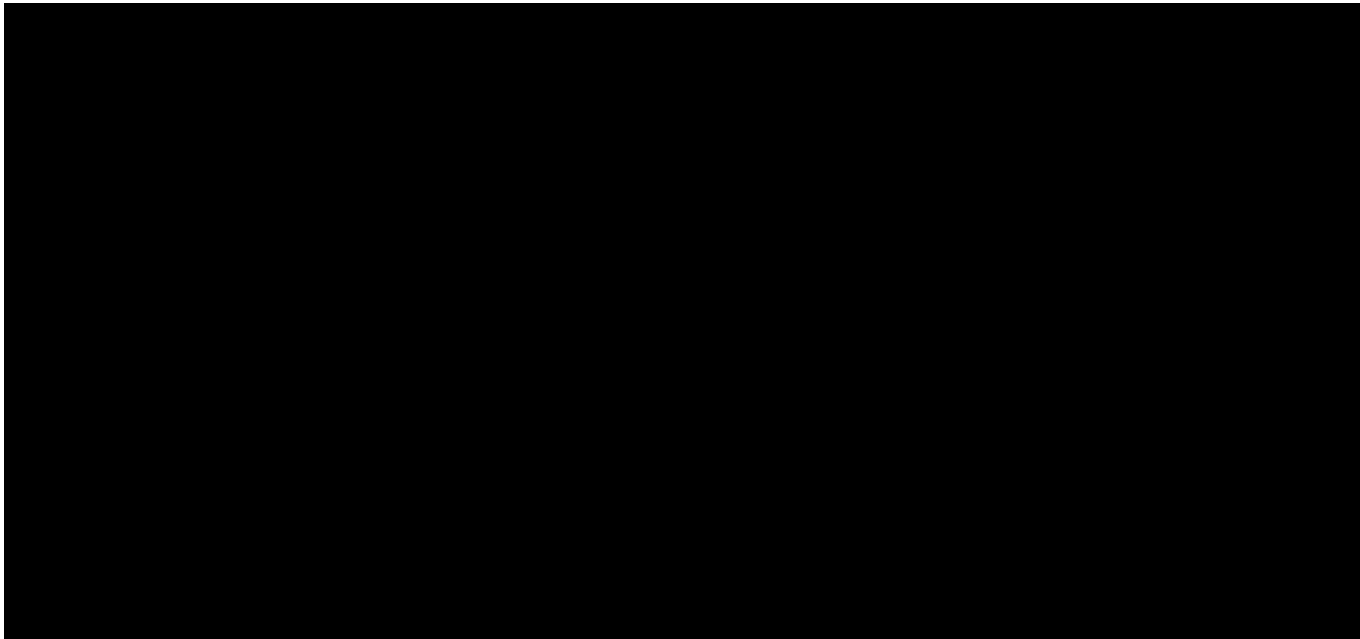
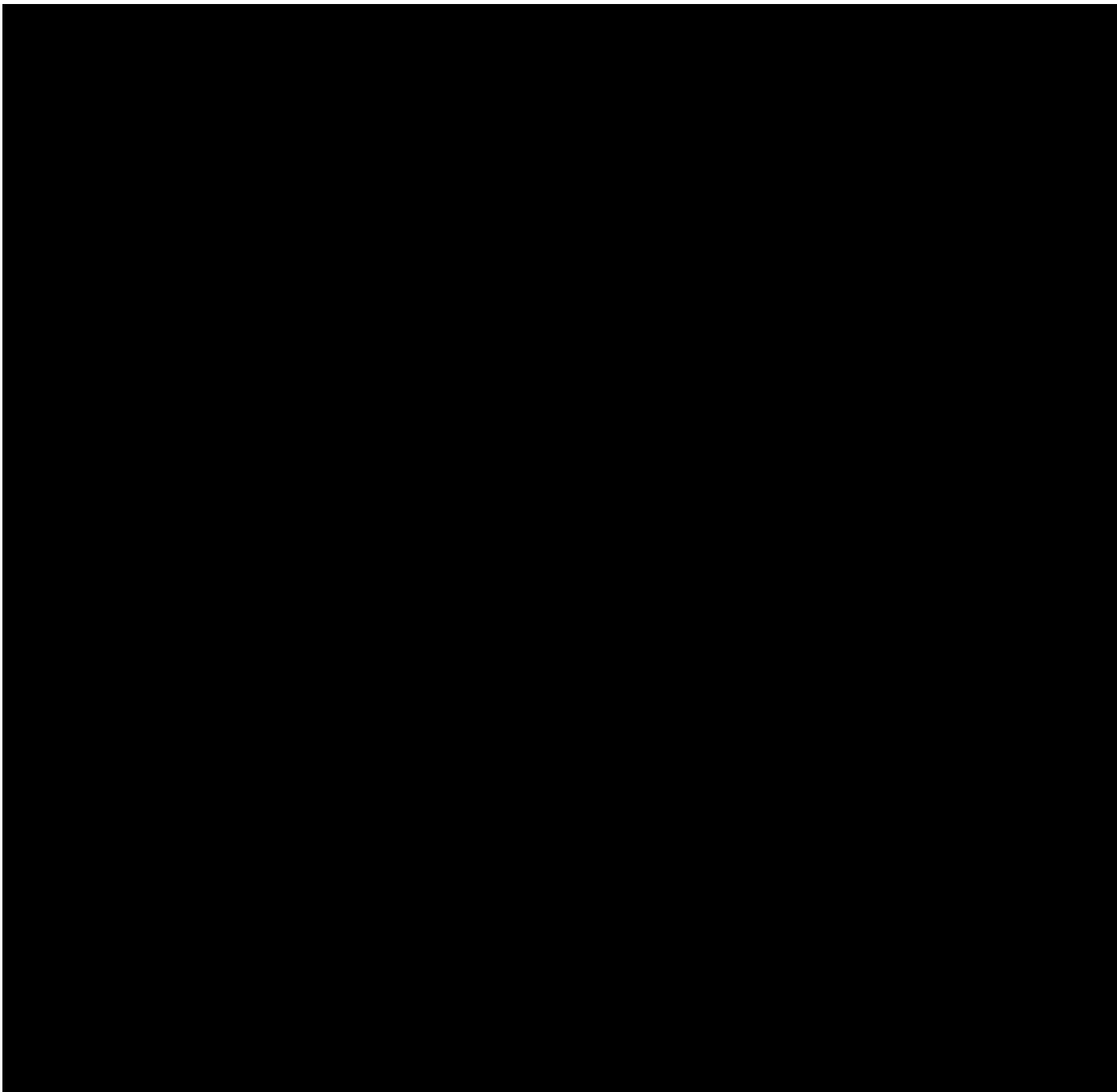


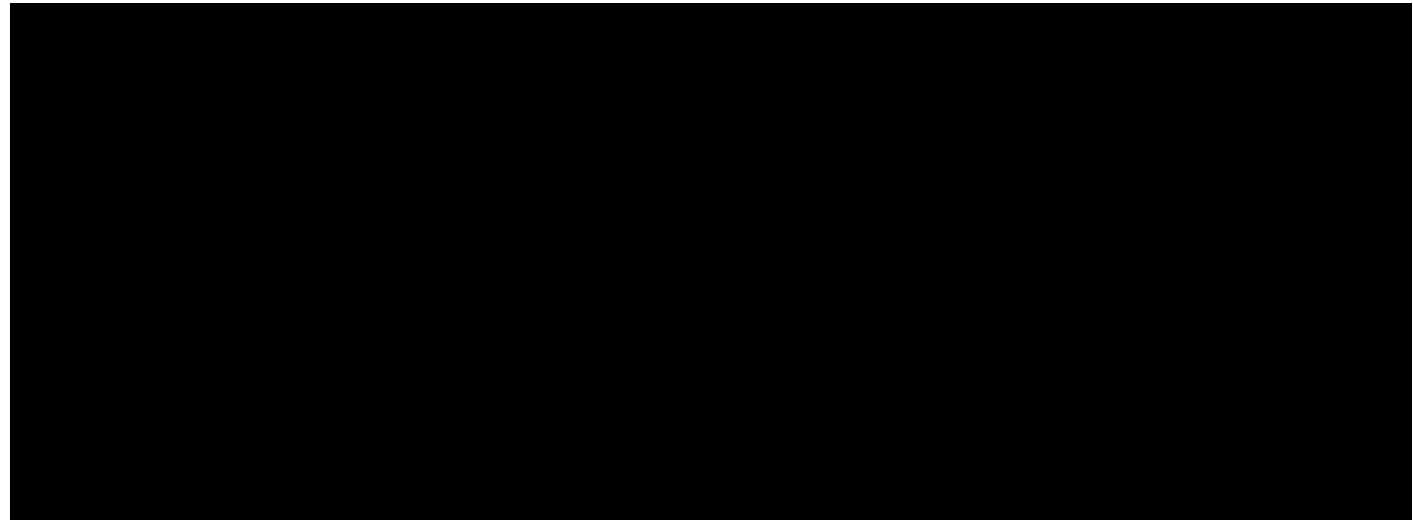
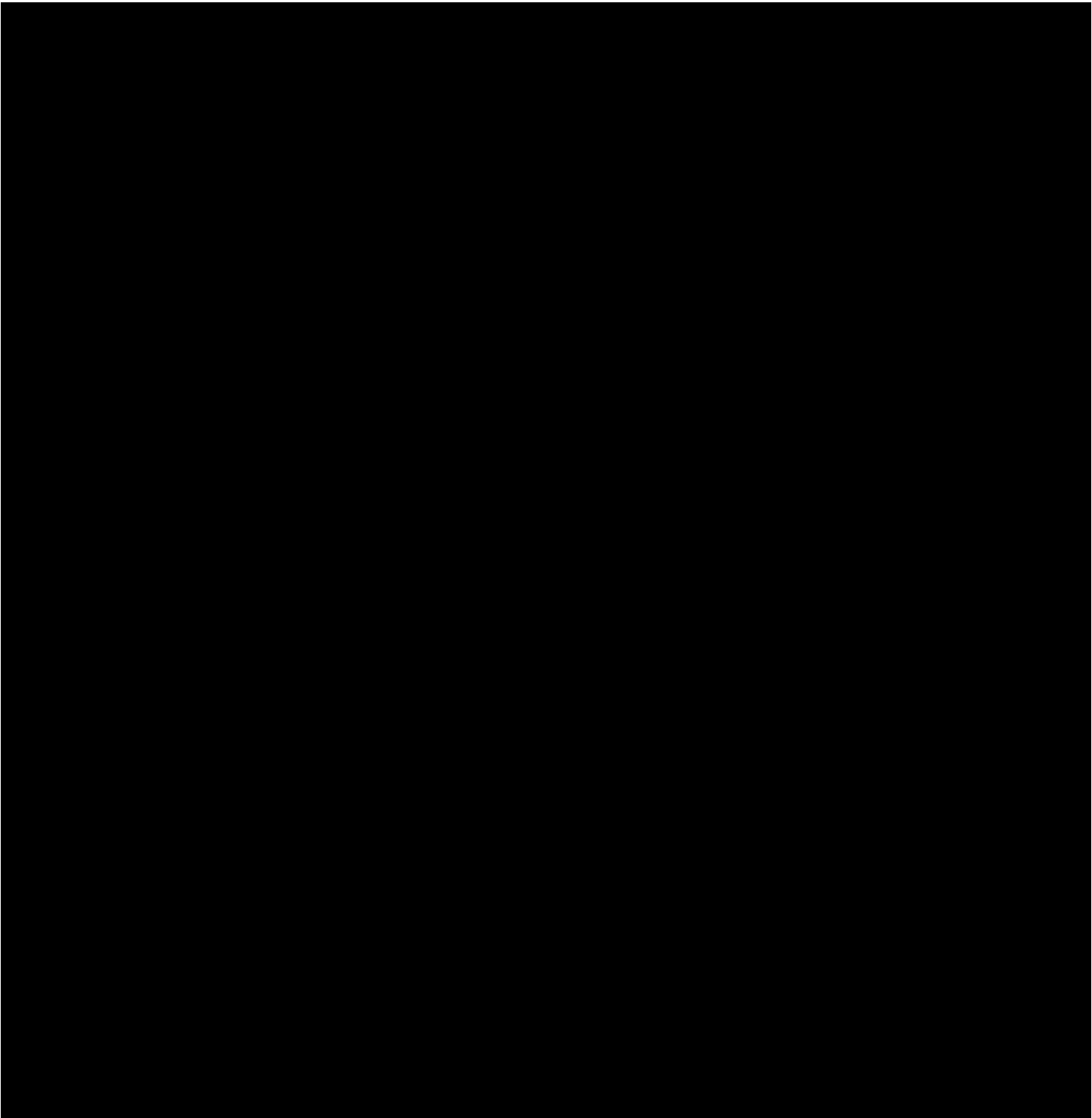












[REDACTED]

[REDACTED] Conducted a systematic review of randomized clinical trials (RCTs) on [REDACTED] and included six studies that met our inclusion criteria. RCTs were conducted in patients from two to 18 years of age with a diagnostic and statistical manual of mental disorders (DSM)-IV diagnosis of autism spectrum disease (ASD) and/or attention-deficit hyperactivity disorder (ADHD) in both short-term and long-term RCTs ranging from eight-week to 52-week studies. The mean difference in the children's sleep disorder showed statistically significant improvement in sleep duration and sleep latency onset compared to the placebo. Overall, a high response rate was observed in the melatonin group compared to the placebo in treating sleep problems in children. Melatonin is a well-tolerated and safe medication in the dose range of 2-10 mg/day in the child and adolescent population.

[REDACTED]

Reviews:

[REDACTED] A large proportion of paediatric patients with attention-deficit/hyperactivity disorder (ADHD) have associated sleep problems which not only affect the child's wellbeing but also impact family functioning. Management of sleep problems is consequently an important aspect of overall ADHD management in paediatric patients. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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The following information is listed as it is relevant to children and adolescents.

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No literature reports from clinical studies of melatonin in children were identified indicating exogenous melatonin affects the hypothalamo-pituitary-gonadal axis pathways in any manner different to those normally occurring when melatonin is produced endogenously.

11/11/2016

The study by ██████████ in children followed for up to 3.8 years found no evidence of tolerance with long-term use. No studies were identified in the literature describing development of dependence in children supplemented with melatonin.

11/11/2016

Periodic benefit-risk evaluation reports covering the period 2020-2022 (appended) concluded that no potential safety issues caused by melatonin were identified. It was concluded that the

recommendations provided in the reference safety information concerning sleep disturbance related to the impact of melatonin remain satisfactory. No updates to the reference safety information are recommended. Risk evaluation concluded that Melatonine Pharma Nord is safe and well tolerated in the doses recommended in the safety information.

2.5.6 BENEFITS AND RISKS CONCLUSION FOR THE NEW PROPOSED INDICATION

2.5.6.1 Therapeutic indication

As evidenced by clinical trials cited in [section 2.5.4](#), oral melatonin supplementation, given at the right time in a suitable dosage under the guidance of a physician skilled in treating DSPD, ADHD, ASD and/or paediatric sleep disorders, can effectively reduce sleep onset latency in children and adolescents [REDACTED] with insomnia associated with DSPD, ADHD and ASD with or without neurological dysfunction where sleep hygiene measures have been insufficient.

[REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

[REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

[REDACTED]

[REDACTED] Efficacy [REDACTED]

A total of 23 double-blind, randomised placebo-controlled clinical studies of melatonin supplementation for insomnia in children with DSPD, with or without neurological conditions (comprising >1000 individuals) including ADHD and ASD, were identified in [REDACTED]. The age range was [REDACTED] with typical dose of 3-6 mg/day for 4 weeks. Of these, 17 studies used immediate-release melatonin, [REDACTED] controlled-release, and [REDACTED] a mix (immediate/controlled release formulation). All of the studies listed reported a clinically meaningful improvement in sleep latency of approximately 30 minutes or more.

Safety

Clinical published literature

Short-term Safety: Several randomized clinical studies as [REDACTED] have investigated the short-term safety of exogenous melatonin for the treatment of insomnia in children reported no adverse effects, irrespective of dose up to 10 mg per day.

Long-term Safety: The long-term safety of melatonin supplementation in children has been addressed by [REDACTED]
[REDACTED] A review on DSPD by [REDACTED] concluded no trial has ever documented any serious adverse effect from the use of supplemental melatonin, and studies documenting long term use (mean follow up of 3 years) in children have not identified any safety concerns.

Based on the available evidence, it appears that melatonin is safe for short-term use in children. However, further research is needed to determine the long-term safety of melatonin in children. No serious adverse effects have been associated with ingestion of typical therapeutic doses of melatonin in individual studies nor in reviews addressing melatonin safety. These findings are supported by pharmacovigilance data showing a very low number and severity of reported adverse effects. Safety outcomes from the clinical trials are summarised in [REDACTED] The frequency of adverse events in children was generally comparable with placebo; a few individuals were subject to increased headaches which usually dissipated within the first week of treatment. None of these studies reported any incidence of serious adverse events. Whilst these studies are typically of short duration (e.g., 4 weeks), several follow-up studies have confirmed the safety of melatonin administration in children in the longer-term. Additional randomised controlled studies were identified in which melatonin was administered to children for indications other than DSPD (e.g., surgical pre-medication); again, none of these studies reported any incidence of serious adverse events. Melatonin is metabolised primarily by the liver enzyme CYP1A2, and pharmacokinetic interactions with other drugs primarily metabolised by this enzyme are possible; however, these have been recognised as documented under Pharmacokinetics in [REDACTED] Melatonin has limited potential for tolerance, dependence and withdrawal. Warnings relating to drowsiness and driving or operation of machinery are included in the SmPC.

Non-clinical published literature

As described in [section 2.4.4.8 “Overall conclusion on toxicology”](#) of the non-clinical overview melatonin treatment at the recommended dose is considered safe based on results from various animal models. No studies were identified in which exogenous melatonin was implicated as a toxic factor; non-clinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential. No information was identified from non-clinical studies which impacted negatively on the efficacy and safety of melatonin for the proposed indication.

Pharmacovigilance data

[REDACTED]														
[REDACTED]					[REDACTED]									
[REDACTED]														
[REDACTED]														
[REDACTED]														
[REDACTED]														
[REDACTED]														
[REDACTED]														
[REDACTED]		[REDACTED]		[REDACTED]		[REDACTED]		[REDACTED]						
[REDACTED]														

Information from the Interactive Drug Analysis Profile (iDAP) by the MHRA, from Eudravigilance - European database of suspected adverse drug reaction reports and from the FDA adverse events reporting system (FAERS) have not contributed further to our assessment of effect and safety of melatonin for the proposed indication in children and adolescents [REDACTED]

Risk Management Plan (RMP)

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Based on the updated Risk Management Plan (RMP) for Melatonin 3 mg film-coated tablets listed in section 1.8 of module 1, an important potential risk and missing information have been identified in relation to the proposed indication in children and adolescents [REDACTED] and are included in the list of safety concerns in the RMP. It is considered that routine pharmacovigilance activities are currently sufficient to characterise these risks and monitor the benefit-risk profile of the product. Based on the review of the available evidence, and the information presented in the SmPC with respect to the new target population, Pharma Nord ApS (the applicant) considers that the current product labelling, in conjunction with routine monitoring, is an acceptable method of risk minimisation for this product and no additional risk minimisation measures are required.

[REDACTED] Conclusion

Supplemental melatonin has been extensively prescribed for managing sleep disorders including insomnia in children, with or without neurological disorders. Pertaining to WEU, compelling evidence has been presented, corroborating the extensive utilization of supplemental melatonin for the proposed indication, adhering to the recommended dosage, for over a decade worldwide, including Europe and the UK. [REDACTED]
[REDACTED]

In conclusion, no information was identified which impacted negatively on the efficacy and safety of melatonin for the new proposed indication. Following a thorough review of the proposed therapeutic indication, unmet clinical need, quality of the applicant product, risk management plan, pharmacovigilance data, and comprehensive supporting material to support the safety and efficacy, it has been determined that the benefits of this new indication outweigh the potential risks. The quality of the applicant product, with its long clinical use history, is also reassuring. Multiple factors have been considered in reaching this conclusion that this proposed indication can provide a valuable treatment option for patients with unmet clinical needs. The benefit-risk balance is favourable.

2.5.7 LITERATURE REFERENCES (ALPHABETICALLY)

