# Shared Care Guideline for Melatonin for Sleep Disorders in Children (GP Summary).

It is essential that a transfer of care only takes place with agreement of the GP and when sufficient information has been received. If the GP does not agree to share care they will inform the Consultant responsible for the patient's care.

**Basingstoke, Southampton & Winchester District Prescribing Committee**

| **Specialist Contact Details** | **Patient ID Label** |
|---|---|
| **Name:**_____ | **Surname:**_____ |
| **Location:**_____ | **Forename:**_____ |
| **Date:**_____ | **NHS Number:**_____ |
| **Tel:**_____ | **Date of Birth:**_____ |

## Indications

**Melatonin is only indicated where non-pharmacological strategies have been tried, but sleep latency and maintenance remains a significant problem.**

**Melatonin may be considered for:**

- children and adolescents with chronic fatigue syndrome (CFS) or myalgic encephalomyelitis (ME) who have sleep difficulties in line with NICE CG53 (www.nice.org.uk/guidance/cg53).
- use in children ≥1 year of age with neurodevelopment disability, autism spectrum disorder, visual impairment or neuropsychiatric disorders and chronic sleep disturbance, including chronic fatigue syndrome, where both:
  - 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.
  - The sleep problem has been thoroughly evaluated, and a disorder of sleep that is likely to respond to melatonin has been diagnosed (e.g. sleep onset insomnia/delayed sleep phase syndrome, likely endogenous melatonin deficiency or phase reversal). Note: importantly disorders of sleep not responsive to melatonin should have been excluded (e.g. limb movement disorder in ADHD and sleep disordered breathing).

## Product choice, dose & response

Melatonin is classified as a prescription only medicine in the UK. A number of licensed products are available, although the majority are not licensed for use in children <18 years or for the indications detailed above. For details refer to the BNF or product SmPCs.

The choice of product should be in accordance with General Medical Council guidance on prescribing unlicensed medicines (in Good Practice in prescribing and managing medicines and devices 2013) and the MHRA guidance on the hierarchy for the use of unlicensed medicines (Appendix 2 The supply of unlicensed medicinal products).

A licensed product for licensed indication should always be considered first in all cases. But if there is no such product available, or if another product or formulation better suits the patient's needs, the next choice should be a licensed product used "off-label", and finally an unlicensed product (e.g. a UK manufactured "special", a nutritional supplement, or an imported product licensed abroad).
Risks versus benefits should be considered before switching patients already established on an unlicensed or off label product, and it may be more appropriate for them to continue taking that product if it has proved to be effective and well tolerated and they are comfortable with the formulation.

Where there are more than one licensed products for the same cohort of patients, the most cost-effective product should be considered. This applies particularly for use of Slenyto® outside of its licensed indications, i.e. off label (see table below). In this scenario prescribers should consider a more cost effective product for off label use, e.g. Circadin (prolonged-release) or Syncrodin (immediate-release) tablets.

The table below provides a summary of melatonin products supported for prescribing locally.
**Prescribers should also refer to the Melatonin pathway** (see Appendix) **to aid formulation choice:**



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| Product | Licensed indications | Cost per 30 days[4] |
|---|---|---|
| Melatonin 2mg prolonged-release tablets (Circadin®) | As monotherapy for the short-term (up to 13 weeks) treatment of primary insomnia in adult patients aged ≥ 55 years. | 2mg daily:£15.39<br>6mg daily: £46.17<br>10mg daily: £76.95 |
| Melatonin 3mg film-coated tablets[1] (Syncrodin®) **Prescribed by brand name.** | For short-term treatment (max 5 days) of jet lag in adults (≥18 years) - may be taken for a maximum of 16 treatment periods per year. | 3mg daily: £14.95<br>6mg daily: £29.90<br>9mg daily: £44.85 |
| Melatonin 1mg, 5mg prolonged-release tablets (Slenyto®) | Treatment of insomnia in children and adolescents aged 2 to 18 years with autism spectrum disorder (ASD) and/or Smiths-Magenis syndrome where sleep hygiene measures have been insufficient. Data available for up to 2 years' treatment. | 2mg daily: £41.20<br>5mg daily: £103.00<br>10mg daily: £206.00 |
| **Restricted use:** Melatonin 1mg in 1ml oral solution (Colonis Pharma Ltd)[2] | For short-term treatment (max 5 days) of jet lag in adults (≥18 years) - may be taken for a maximum of 16 treatment periods per year. | 2mg daily: £52.00<br>5mg daily: £130.00<br>10mg daily: £260.00 |
| **In exceptional circumstances only:** Melatonin liquid as an unlicensed special (varying strengths/formulations) [3] | Unlicensed | Variable.<br>Refer to Drug Tariff Part VIIIB |

[1] Melatonin 3mg film-coated tablets (Syncrodin®) must be prescribed by **brand name**. Generic prescriptions for melatonin 3mg tablets, or prescriptions for the Colonis Pharma brand of melatonin 3mg film-coated tablets will incur higher costs.

[2] Oral solution (Colonis Pharma Ltd) is **less preferred to tablets** due to content of excipients potentially harmful in children (e.g. propylene glycol, sorbitol), which is of particular concern for young children <5 years or those taking other liquid medicines, and also its higher cost. This preparation is supported for **restricted use only when tablets** (including crushed tablets) **are not suitable.**

[3] Other strengths and formulations of liquid melatonin are also available as **unlicensed specials**. These are not routinely recommended, but may be prescribed when other formulations are not tolerated or suitable (e.g. due to excipient content). Prices vary but may be lower cost than the licensed oral solution (refer to the Drug Tariff Part VIIIB for preferred options and current prices).

[4] Prices correct at time of writing but may be subject to change.

**Dose**

An initial dose of 2 to 3mg once daily is recommended. This may be increased by 2 to 3mg every 7 to 14 days depending on response. Usual maximum dose is 10mg once daily but additional benefits from doses above 6 mg are uncertain.

**Administration**

- Melatonin should be taken once a day, between 30 to 60 minutes before bedtime.
- Prolonged-release tablets should be taken with or after food, i.e. on a full stomach.
- Immediate release tablets and liquids are best taken on an empty stomach (≥2 hours before or after eating).

Note: split or crushed prolonged-release tablets should be treated as immediate release tablets.

**Swallowing difficulties/ enteral feeding tubes**

- Leaflets and videos for parents and carers on helping children to take tablets are available on the Medicines for Children website www.medicinesforchildren.org.uk .
- Slenyto® tablets are formulated as a mini tablet, specifically designed as smaller diameter (3mm) to



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| | facilitate swallowing in the ASD paediatric population. The SmPC also advises they can be mixed (whole) with food such as yoghurt, orange juice or ice cream and taken immediately.<br>• The practice of splitting (e.g. halving or quartering) or crushing melatonin tablets (immediate- or prolonged-release) is off label since the manufacturers recommend swallowing the tablets whole. However this practice is well established, particularly with Circadin® and Syncrodin® (formerly Melatonin PharmaNord/Bio-Melatonin) tablets, and is not associated with safety concerns. There is less experience with crushing Slenyto tablets, but since the formulation is very similar to Circadin, no problems are anticipated, although the presence of a film coating may make them more difficult to crush. This, along with cost considerations, makes Slenyto less preferred for crushing (see flow chart in Appendix below). The prescription should state if the medication is to be crushed prior to administration. The tablets should be crushed to a fine powder and mixed with water or a small amount of soft food such as jam or yoghurt, or added to 15-30ml of water for administration via enteral feeding tubes (flush with 30ml water before and after giving). Splitting or crushing will result in loss of prolonged-release properties resulting in a faster onset and shorter duration of effect.<br>• A liquid formulation may also be considered, but this is generally less preferred, mainly due to safety concerns with excipients but also higher cost. The licensed oral solution (1mg/ml; Colonis Pharma Ltd) contains 150.5mg/ml propylene glycol and 140mg/ml sorbitol, and caution is required to ensure use does not exceed safety limits in children, particularly children <5years or those taking other liquid preparations containing these excipients (further information available in PrescQIPP bulletin 245 or prescribers may contact the Southampton Medicines Advice Service: 023 8120 6908/9 or medicinesadvice@uhs.nhs.uk). Unlicensed liquid specials (listed in Drug Tariff Part VIIIB) may be considered if an excipient-free option is required and may be lower cost than the licensed oral solution (1mg/ml) or crushing Slenyto tablets.<br><br>**Response**<br>• Children should start to feel sleepy about 30 minutes after taking a dose of melatonin, possibly slightly longer (45 to 60 minutes) with a prolonged-release tablet.<br>• When swallowed whole, prolonged-release tablets release melatonin over at least 8 hours. Immediate-release tablets or liquids and crushed prolonged-release tablets will not last as long, possibly around 2 to 3 hours.<br>• Specialists will review patient's initial response after 4 weeks and continue prescribing until an effective dose is established.<br>• A drug holiday should be introduced at least annually to assess the continued need for treatment. Specialists should provide advice to patients, carers and GPs on how to instigate this. It could take place a month before the annual review, with the patient and/or the carer keeping a sleep diary/app. The outcome of any drug holiday must be recorded in the patient's notes. |
| Specialist's Responsibilities | Treatment with melatonin should be initiated by an experienced specialist in sleep medicine, CAMHS practitioner, paediatrician or learning disabilities specialist. Patients should remain under specialist supervision and should not be discharged to primary care for long-term management of melatonin.<br><br>• Establish a diagnosis and assess suitability of the patient for treatment, ensuring compatibility of melatonin with concomitant medication.<br>• Initiate treatment after discussion of the options available with the patient and carer(s).<br>• Discuss benefits and side effects of treatment with the patient/carer including that the medicine or administration method is unlicensed/off label (when applicable) and the lack of data pertaining to potential long-term side-effects of treatment and theoretical risks of delayed sexual maturation. Advise of the need for shared care (once dose stabilised), and obtain appropriate consent to treatment.<br>• Write to the GP when the melatonin is initiated, to ask the GP whether he/she is willing to participate in the ongoing prescribing and general care as outlined in this shared care agreement (published online at https://www.westhampshireccg.nhs.uk/shared-care-guidelines).<br>• Prescribe the initial supply (for at least 4 weeks treatment) and continue prescribing until the patient is stable on a particular dose and formulation.<br>• Once stable, provide the GP with: details of diagnostic information; dose and preparation of melatonin to prescribe (including clinical justification for the choice of preparation), and duration |



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| | of treatment before specialist review.<br>• Offer the patient outpatient appointments **at least annually** and regular appointments with the community teams or paediatric support team. At these appointments the efficacy and safety of melatonin should be reassessed, and treatment discontinued if appropriate. A drug holiday should be carried out at least annually, and actions required to achieve this communicated to all parties (patient, carer and GP), with the outcome documented in the patient's notes. The patient's height and weight should be checked. Pubertal development may also be checked if required (e.g. abnormal growth pattern), but routine monitoring is not necessary. Smoking status should be checked in older children. Reports of all outpatient consultations, including the outcome of any drug holidays, should be provided to the GP.<br>• Report any suspected adverse drug reactions (ADRs) to the Medicines and Healthcare products Regulatory Agency (MHRA) via the yellow card scheme.<br>• Promptly communicate any changes, recommendations, outcomes or other important information to the GP, and provide any other advice or information to the GP or patient if required. |
| GP Responsibilities | • Inform secondary care specialist immediately if unable to take on shared care.<br>• Prescribe melatonin once the patient is stable on a particular dose, continuing with the formulation selected by the specialist where clinical justification has been provided.<br>• Only continue to prescribe melatonin if there is some evidence of ongoing efficacy and benefit. Due to lack of long-term safety data, indefinite continuation of melatonin without specialist review is not recommended. Review the need for continuing melatonin at least every 6 months, referring back to the hospital specialist as appropriate. Seek/follow advice of specialists to facilitate patients having a drug holiday at least annually, and document this and the outcome in patient's notes. Counsel patients/carers on the importance of attending outpatient appointments regularly. Do not continue to prescribe melatonin beyond 2 years without specialist review.<br>• Ask patient/carer about side effects and general wellbeing, and check smoking status in older patients. Communicate any problems back to the specialist.<br>• If patient needs review, contact the initiating prescriber; CAMHS or paediatric team, but continue to prescribe until the reassessment has taken place (unless an adverse effect has occurred).<br>• Ask the specialist to take back the prescribing should unmanageable problems arise and allow an adequate notice period (4 weeks is a suggested minimum).<br>• Report any suspected adverse drug reactions (ADRs), including any concerns about height, weight or pubertal development, to the specialist and, when appropriate, to the Medicines and Healthcare products Regulatory Agency (MHRA) via the yellow card scheme. |
| Patient/Carer responsibilities | • Report to the specialist or GP if they do not have a clear understanding of their treatment<br>• Contact the GP to arrange supplies of melatonin, allowing sufficient time (usually at least 7 days) to ensure continuity of treatment<br>• Take/give the melatonin as advised.<br>• Attend all booked appointments with hospital and GP, bringing sleep diary/app (if issued).<br>• Share any concerns in relation to treatment with melatonin with the specialist, GP or pharmacist<br>• Report any side effects or warning symptoms to the specialist, GP or pharmacist whilst taking/giving melatonin.<br>• Report any use of over-the-counter medicines or complementary therapies (e.g. herbal medicines or supplements), illicit drugs and smoking to the specialist, GP or pharmacist whilst taking/giving melatonin. |
| Disease and drug monitoring | No routine tests required.<br>Specialists should monitor patient's weight and height annually.<br>The patient should be monitored at regular intervals (at least 6 monthly) to check melatonin is still the most appropriate treatment. |
| Contra-indications | Known hypersensitivity to melatonin or excipients. |
| Cautions | Refer to BNF or product SmPC/PIL (licensed formulations) published online at www.medicines.org.uk or www.mhra.gov.uk. |



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| | • Melatonin may cause drowsiness. After taking, children should not drive a vehicle, ride a bicycle or use machinery until completely recovered.<br>• Due to lack of clinical data, melatonin is not recommended for use in patients with autoimmune diseases.<br>• Circadin® and Slenyto® tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the LAPP lactase deficiency or glucose-galactose malabsorption should not take these formulations.<br>• Caution is required in hepatic impairment since the liver is the primary site of melatonin metabolism.<br>• Although caution is advised in product SmPCs, specialist texts advise melatonin can be dosed as normal in all stages of renal impairment. |

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| Important adverse effects & management | • Melatonin is generally well tolerated. Side effects are uncommon.<br>• For a complete list of side effects refer to BNF or product SmPC/PIL (licensed formulations) published online at www.medicines.org.uk or www.mhra.gov.uk).<br>• The most frequently reported adverse effects with melatonin (Slenyto) in children in clinical studies were somnolence, fatigue, mood swings, headache, irritability, aggression and hangover.<br>• Little is known about the long-term effects of melatonin, and the Slenyto SmPC cautions that data are only available for up to 2 years' treatment. Limited data from clinical studies so far do not suggest any effects over 2-3 years of treatment, but more long term, better quality safety data are needed.<br><br>Report adverse effects to specialist and to the Medicines and Healthcare products Regulatory Agency (MHRA) via the yellow card scheme. If adverse effect is clinically significant, discontinue melatonin and refer patient to specialist. |
| Important Interactions | Refer to BNF or product SmPC/PIL (licensed formulations published online at www.medicines.org.uk or www.mhra.gov.uk).<br>• Fluvoxamine, 5- or 8-methoxypsoralen, cimetidine, oestrogens, and quinolone antibiotics (e.g. ciprofloxacin, norfloxacin) may increase melatonin levels by inhibiting its metabolism resulting in increased risk of adverse effects.<br>• Enzyme inducers such as carbamazepine and rifampicin may reduce melatonin levels, requiring dose adjustment.<br>• Concomitant administration of other sedatives, e.g. benzodiazepines and "z"- drugs, and tricyclic antidepressants should be avoided due to increased risk of adverse effects.<br>• Non-steroidal inflammatory drugs (NSAIDS), e.g. ibuprofen, and beta-blockers may suppress night-time release of endogenous melatonin levels. Administration of these drugs should be avoided in the evening.<br>• Alcohol should not be taken with melatonin, because it reduces the effectiveness of melatonin on sleep.<br>• Smoking may reduce levels and efficacy of melatonin, while caffeine may increase levels and risk of adverse effects. |



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## Sources of Information/Contacts

| University Hospital Southampton Foundation Trust | Name / position | Telephone | Email |
|---|---|---|---|
| **Specialist / Consultant** | Dr Catherine M Hill<br>Children's Sleep Disorder Service<br>Southampton Children's Hospital | Secretary:<br>023 8120 5922 | Referral forms for the Southampton Children's Hospital sleep disorder service are available via the UHS website: Link here |
| **Hospital Pharmacy** | Southampton Medicines Advice Service<br><br>Kazeem Olalekan<br>Specialist Paediatric Pharmacist | 023 8120 6908/9<br><br>023 80777 222;<br>Bleep: 1033 | medicinesadvice@uhs.nhs.uk<br><br>kolalekan@nhs.net |

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| **Specialist / Consultant** | Dr Rebecca Macleod and Dr Paola Mirto, Consultant Community Paediatricians, Basingstoke and North Hampshire Hospital<br><br>Dr Rebecca Ferris, Paediatric Consultant, Royal Hampshire County Hospital, Winchester | 01256 313083<br><br>01962 824995 | Paediatric.SecretariesBNH@hhft.nhs.uk<br><br>Paediatric.SecretariesRHCH@hhft.nhs.uk |
| **Hospital Pharmacy** | Helen Leighs, Specialist Paediatric Pharmacist, Basingstoke and North Hampshire Hospital | 01256 473202 ext 3341<br>Bleep: 1560 | helen.leighs@hhft.nhs.uk |

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| **Specialist / Consultant** | Havant: Dr Asha Gowda (Consultant, Havant)<br>Dr Fiona Holden (Consultant, Fareham & Gosport) | 02392 224560<br><br>01329 822220 | |
| **Hospital Pharmacy** | Worthing Hospital<br><br>CAMHS Pharmacist | 01903 205111 (ext 85698)<br><br>07825 118323 | pharmacy@wsht.nhs.uk<br><br>graham.brown@wsht.nhs.uk |

| Solent NHS Trust | Name / position | Telephone | Email |
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| **Consultant** | Dr Julia Waine | 023 9268 4700 | |
| **CAMHS Portsmouth** | Falcon House, St James Hospital, Locksway Road, Portsmouth PO4 9EH | 023 9268 4700 | SNHS.CAMHS-general@nhs.net |
| **Pharmacy** | St Mary's Hospital Portsmouth | 023 92680280 | |



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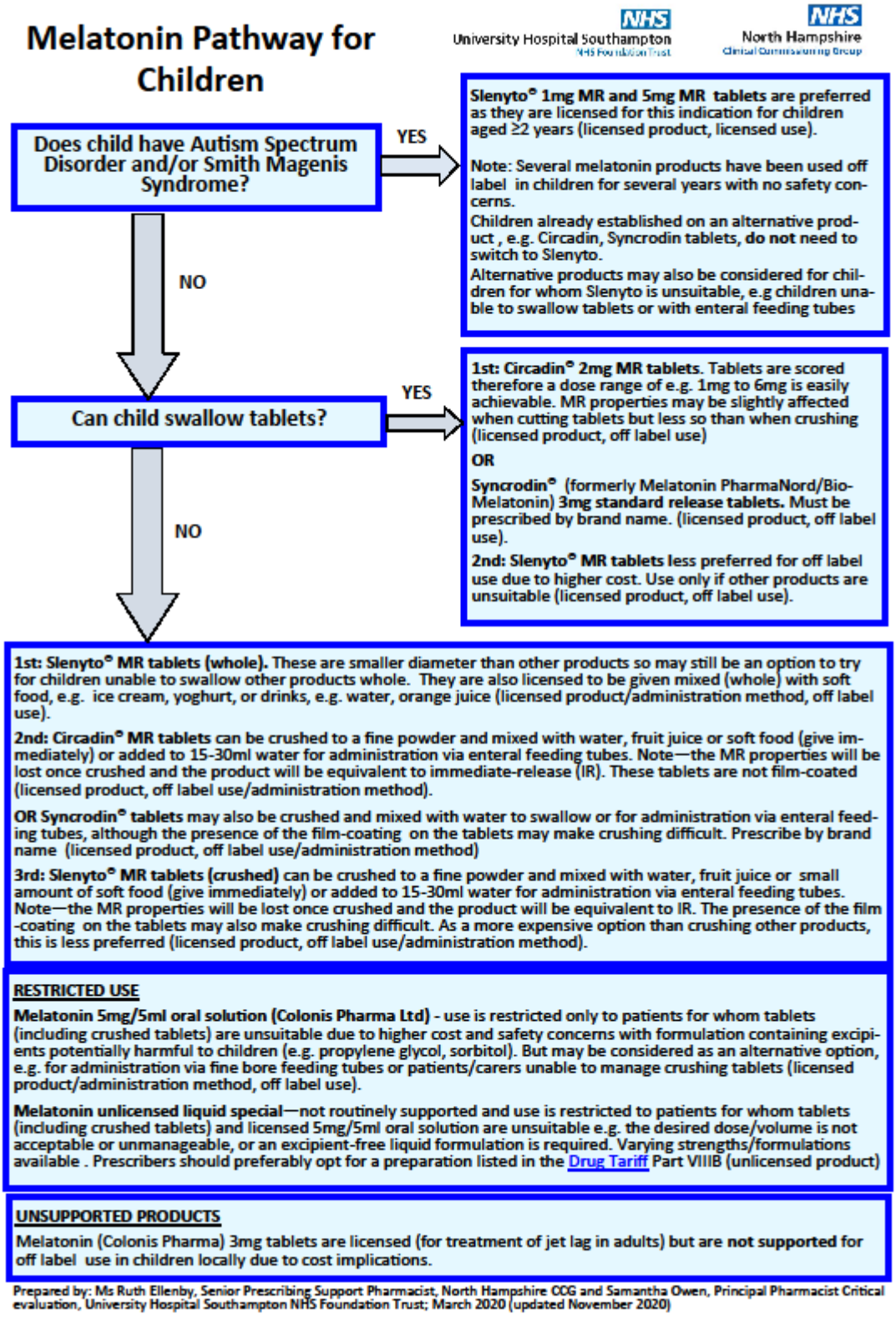
**Appendix:**



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