SY ICB Shared Care Protocol

For

Alimemazine in the treatment of sleep disorders in Children

(Note – only for patients initiated on alimemazine by the Specialist Clinicians at Sheffield Children's NHS Foundation Trust Tertiary Sleep Service)

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Date approved: August 2024

South Yorkshire Integrated Medicines Optimisation Committee (IMOC)

Review Date: August 2029

Alimemazine for patients within Sheffield Children's Hospital tertiary sleep service*

***This shared care protocol applies to patients up to the age of 18 years. Beyond this age, primary care providers may choose to no longer be involved in prescribing, as the shared care agreement concludes. Patients will be informed of this transition at the initiation of treatment by the specialist initiating it.**

Specialists responsibilities (paediatrician and/or sleep consultant)

- Assess the patient and provide diagnosis; ensure that this diagnosis is within scope of this shared care protocol (section 2) and communicated to primary care.
- Use a shared decision making approach; discuss the benefits and risks of the treatment with the patient and/or their carer and provide the appropriate counselling (see section 11) to enable the patient to reach an informed decision. This is particularly important as alimemazine being prescribed is an unlicensed product /preparation being used off label. Its long-term effects are unknown. Obtain and document patient consent. Provide an appropriate patient information leaflet and inform patient it might not be continued beyond 18 years of age.
- To advise patients that exposure to sunlight should be avoided during treatment (see Alimemazine tartrate) or see ***Photosensitivity and alimemazine:**;
- Prior to initiating alimemazine sleep hygiene should be addressed followed by a trial of melatonin (see
- Appendix 1. Sleep Tips
- To explain to the patient / carer that alimemazine is intended as a short-term (6 months) intervention and must be used in line with sleep hygiene techniques. However, in children where Alimemazine is found to be beneficial it could be continued for longer duration after a review by paediatrician/sleep consultant.
- An attempt to withdraw/have a break in treatment should be made at least every 6 months (withdrawal may be tried earlier than 6 months if the clinician and parents decide it is appropriate).
- Assess for contraindications and cautions (see section 4) and interactions (see section 7).
- Conduct required baseline investigations and initial monitoring (see section 8).
- Initiate and optimise treatment as outlined in section 5. Prescribe the maintenance treatment for at least 12 weeks and until optimised.
- Once treatment is optimised, complete the shared care documentation and contact patient's primary care prescriber to request prescribing and monitoring under shared care detailing the diagnosis, current and ongoing dose, any relevant test results and when the next monitoring is required. Include contact information (section 13).
- Prescribe sufficient medication to enable transfer to primary care, including where there are unforeseen delays to transfer of care.
- Conduct the scheduled reviews and monitoring in section 8 and communicate the results to primary care. After each review, advise primary care whether treatment should be continued, confirm the ongoing dose, and whether the ongoing monitoring outlined in section 9 remains appropriate.
- Provide advice to primary care on the management of adverse effects if required.
- **The patient to remain under the consultant's care for the duration of prescribing (whilst under the care of SCH)**

Primary care responsibilities

- Prior to referral to specialist (paediatric clinic or sleep clinic) for sleep problems and consideration of alimemazine, parent-directed behavioural sleep interventions should be tried (See
- Appendix 1. Sleep Tips
- To agree/decline to prescribe for patients in line with the shared care protocol as advised by the consultant.
- If accepted, prescribe ongoing treatment as detailed in the specialists request and as per section 5, taking into account any potential drug interactions in section 7.
- Adjust the dose of Alimemazine as advised by the specialist.
- Conduct the required monitoring as outlined in section 9. Communicate any abnormal results to the specialist.
- To inform the consultant if the patient discontinues treatment for any reason or if patient fails to attend regular reviews/monitoring.
- If a patient fails to comply with the regular monitoring requested in primary care, the specialist should be informed and prescribing of Alimemazine then can be reverted to specialist care.
- If sleep issues are successfully resolved following a follow-up period and withdrawal from medication trials, and patients indicate no preference for further treatment, referral back to the sleep clinic may not be necessary. However, it remains necessary to inform the specialist as outlined in the preceding point.
- Manage adverse effects as detailed in section 10 and discuss with specialist team when required.
- Stop Alimemazine and make an urgent referral to the sleep specialist if Cardiovascular diseases (due to tachycardia-inducing and hypotensive effects of phenothiazines); exposure to sunlight should be avoided during treatment with high doses (please refer to ***Photosensitivity and alimemazine:** for further advice) ; pyloroduodenal obstruction; susceptibility to QT interval prolongation; urinary retention; volume depleted patients who are more susceptible to orthostatic hypotension.
- Stop treatment if/as advised by the specialist.

Patient responsibilities

- To be fully involved in, and in agreement with, the decision to move to shared care.
- To practice sleep hygiene alongside any alimemazine and other sleep medications that are prescribed.
- To take Alimemazine as prescribed and avoid abrupt withdrawal unless advised by the primary care prescriber or specialist.
- To read the drug information given to them.
- Attend regularly for monitoring and review appointments with primary care and specialist and keep contact details up to date with both prescribers. Be aware that medicines may be stopped if they do not attend.
- Report adverse effects to their primary care prescriber. Seek immediate medical attention if they develop any symptoms as detailed in section 11.
- Report the use of any over the counter medications to their primary care prescriber and be aware they should discuss the use of Alimemazine with their pharmacist before purchasing any OTC medicines.
- Patients of childbearing potential should take a pregnancy test if they think they could be pregnant and inform the specialist or GP immediately if they become pregnant or wish to become pregnant.

1. Background

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Alimemazine is a first-generation antihistamine that has a central sedative effect comparable to that of chlorpromazine but largely devoid of the latter's anti adrenaline action. It has powerful antihistamine and anti-emetic actions.

This shared care protocol (SCP) has been written to enable the continuation of care by primary care clinicians of patients (2*-16 years) initiated on **alimemazine** by the Specialist Clinicians at Sheffield Children's NHS Foundation Trust. Alimemazine preparations included within this SCP are not licensed to be used for sleep disorders in children and prescribing for this indication should be in line with the details within this SCP.

Insomnia in early childhood has diverse clinical presentations that vary from bedtime struggles to disturbing nocturnal awakenings.

The 4 main groups/ phenotypes of childhood behavioural insomnia consist of:

- sleep onset issues
- sleep maintenance/fragmentation issues
- early awakenings
- multiple other symptoms/ sleep issues across domains.

The identification of groups/phenotypes helps to optimise the assessment and treatment of symptoms of insomnia in young children. Within the SCH Sleep Service, the clinicians identify these phenotypes via a comprehensive clinical review and/or investigations such as sleep studies. Based on the identification of these different phenotypes, and exploration of other comorbidities that affect sleep, appropriate therapy is suggested.

Alimemazine is recommended as a 2nd line drug for treatment of behavioural insomnia if:

- there is poor response to maximum dose Melatonin (the patient would trial various formulations including instant release as well as prolonged acting depending on the phenotype of insomnia OR
- where the phenotype of chronic insomnia is associated with multiple night awakenings and difficulties falling asleep (often in children with an atopic background alluding to a histaminergic dysfunction suggesting a prominent role in this type of insomnia).

It is often used in combination with melatonin for synergistic action.

* Alimemazine is contraindicated for use in children less than 2 years of age due to the risk of marked sedation and respiratory depression.

2. Indications

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Alimemazine is licenced for treatment of urticaria and pruritus, please see Alimemazine tartrate, but in SCH it is used off licence (repurposed medication) for sleep disorders and retching in children.

3. Locally agreed off-label use*

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Alimemazine is recommended by tertiary sleep service in SCH specialists as a 2nd line drug (after melatonin) for treatment of behavioural insomnia in children if no response to maximum dose melatonin has been tried for 3-6 months or if there are side effects to melatonin/other sleep medications. The use of any medications is in conjunction with a sleep hygiene and parental education programme.

*It is proposed (subject to local formulary choices) that Alimemazine 7.5mg/5ml and 30mg/5ml solutions to be prescribed under the branded generic name of Alfresed® (sugar containing syrup) or Itzenal® (SF oral solution) 7.5mg/5ml and 30mg/5ml as these are more cost-effective options and they do not contain propylene glycol.

4. Contraindications and cautions

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This information does not replace the Summary of Product Characteristics (SPC) and should be read in conjunction with it. Please see BNFC & SPC for comprehensive information.

Contraindications:

Children under 2 years except on specialist advice (risk of respiratory depression); epilepsy; hepatic dysfunction; history of narrow angle glaucoma; hypothyroidism; myasthenia gravis; neonate (due to significant antimuscarinic activity) (in neonates); Parkinson's disease; phaeochromocytoma; renal dysfunction.

Cautions:

Cardiovascular diseases (due to tachycardia-inducing and hypotensive effects of phenothiazines); exposure to sunlight should be avoided during treatment with high doses*; pyloroduodenal obstruction; susceptibility to QT interval prolongation; urinary retention; volume depleted patients who are more susceptible to orthostatic hypotension.

***Photosensitivity and alimemazine:**

- Alimemazine, like most phenothiazines, is associated with drug-induced photosensitivity. Although specific literature on alimemazine-induced photosensitivity is lacking, research on phenothiazines can be extrapolated to alimemazine to some extent.

- Photosensitivity may occur at any dosage, but the risk and severity increase with higher doses. A specific dose for where the risk significantly increases has not been established.

- Reported cases of phenothiazine-induced photosensitivity typically involve high dosages during long-term therapy, resulting in slate-grey to violaceous hyperpigmentation on sun-exposed areas.

- Caution for co-administration with other drugs that induce photosensitivity.

- Please refer to the following resources:
    - Photosafety Screening of Phenothiazine Derivatives With Combined Use of Photochemical and Cassette-Dosing Pharmacokinetic Data | Toxicological Sciences | Oxford Academic (oup.com)
    - Drug-induced photosensitivity: Photoallergic and phototoxic reactions - ScienceDirect
    - Drug-induced photosensitivity: culprit drugs, potential mechanisms and clinical consequences (wiley.com)

- Management of drug-induced photosensitivity beyond using the minimum effective dose focuses on minimising UV exposure. The below summarises the Patient Education guidance for the management of drug-induced photosensitivity from the following paper Drug-Induced Photosensitivity: Clinical Types of Phototoxicity and Photoallergy and Pathogenetic Mechanisms - PMC (nih.gov):

- Sunscreen:
  - Use broad-spectrum sunscreens that protect against both UVB and UVA. A sun protection factor (SPF) of 50 or higher is recommended. Apply sunscreen before sun exposure and reapply within 1 hour.

- Clothing:
  - Opt for clothing with a high ultraviolet protection factor (UPF) of 40 or higher. Keep in mind that UV can still penetrate woven textiles.

- UV exposure apps:
  - Smartphone apps can help monitor UV levels and guide sun exposure behaviours. SunSmart Global UV App helps protect you from the dangers of the sun and promotes public health (who.int)

- Patient Education:
  - Educate patients about the photosensitising potential of drugs. Sun safety education programs can improve awareness and promote protective behaviours.

5. Initiation and ongoing dose regime

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Please note that the licensed doses for the indications of urticaria and pruritus differ from the unlicensed use for sleep. For more information, please refer to the Alimemazine section in the BNF: Alimemazine BNF

For the unlicensed use of Alimemazine for sleep disorders in children the recommended starting dose is 5mg. If inadequate response is seen an increase of the doses in steps by 2.5mg to 5 mg. The maximum dose is 60 mg.

- Transfer of monitoring and prescribing to primary care is normally after the patient's dose has been optimised and with satisfactory investigation results for at least 12 weeks.
- The duration of treatment & frequency of review will be determined by the specialist, based on clinical response and tolerability.
- All dose or formulation adjustments will be the responsibility of the initiating specialist unless directions have been discussed and agreed with the primary care clinician.

The specialist team will titrate any increase in dose needed and any change required will clearly be communicated to the primary care clinician.

6. Pharmaceutical aspects

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Route of administration:	Oral
Formulation:	Alimemazine 10mg tablets and 7.5mg/5ml and 30mg/5ml oral solutions. Liquid Alimemazine should be prescribed under the brands of Itzenal (which is a sugar-free solution) or Alfresed (contains sugar). Both of which come as 7.5mg/5ml liquid and 30mg/5ml liquid. Maximum dose for the unlicensed use of sleep in children is 60mg and for urticaria and pruritus is 100mg. Please refer to Alimemazine tartrate BNF
Administration details:	Alimemazine should be taken 30min before bedtime.

Other important information:	Give the medicine at the same time each day so that this becomes part of the child's daily routine.

7. Significant medicine interactions Back to top

The following list is not exhaustive. Please see Interactions BNFC or SPC for comprehensive information and recommended management.

The sedative effects of phenothiazines may be intensified (additively) by alcohol, anxiolytics and hypnotics, opiates, barbiturates, and other sedatives. There may be increased antimuscarinic and sedative effects of phenothiazines with tricyclic antidepressants and MAOI's (including moclobemide). Respiratory depression may occur.

8. Baseline investigations, initial monitoring and ongoing monitoring to be undertaken by specialist

Monitoring at baseline and during initiation is the responsibility of the specialist; only once the patient is optimised on the chosen medication with no anticipated further changes expected in immediate future will prescribing and monitoring be transferred to primary care. Back to top

Baseline investigations:

Baseline investigations include sleep studies and blood tests (ferritin) which would be undertaken by the specialists if indicated.

Initial monitoring:

The first follow up should be done by the specialist ideally within 3- 6 months of starting treatment.

Ongoing monitoring:

Once a response to treatment has been established, ongoing response to treatment, adherence to sleep hygiene advice and adverse effects should be monitored annually.

The specialist and the GP should both review the patient annually, rotating so the child is seen every 6-9 months by a health care professional. (Note in some cases the specialist may see the patient more frequently, however an annual review with the GP is still recommended).

When a patient is reviewed, advise primary care whether treatment should be continued, confirm the ongoing dose, and whether the ongoing monitoring outlined in section 9 remains appropriate.

9. Ongoing monitoring requirements to be undertaken by primary care Back to top

See section 10 for further guidance on management of adverse effects/responding to monitoring results.

Monitoring	Frequency
-Adherence to sleep hygiene (see Appendix 1) -Continued response to treatment. -Signs of adverse effects.	Annually
Regular breaks in treatment should be encouraged to assess continued need.	Every 2 years (This is typically managed by the specialist, but a GP may also consider it.)

Stopping or need for continued treatment should be discussed and documented.	

10. Adverse effects and other management

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Any serious adverse reactions should be reported to the MHRA via the Yellow Card scheme. Visit www.mhra.gov.uk/yellowcard

For information on incidence of ADRs see relevant summaries of product characteristics

Stopping treatment will be considered in the below scenarios:

- Sleep latency (time taken to fall asleep after getting into bed) - less than 60 minutes.
- Total sleep time – more than 8 hours if <10 years/ more than 6 hours if >10 years
- Evidence of non-engagement with sleep hygiene measures.

The general aim is to use alimemazine as a short-term treatment; this will be made clear to the parents and carers at initiation.

- An attempt to withdraw/have a break in treatment should be made at least every 6 months*.
- Sleep hygiene should be reinforced throughout treatment and prior to any attempt to stop.
- Treatment may be stopped by the GP or the specialist.
- For best success, mutually agree with the patient a suitable time to stop treatment, for example during school holidays, avoiding periods of stress e.g., during exams.
- A rebound worsening in sleep pattern may occur initially but this may improve over time. If after 7-14 days sleep has deteriorated significantly alimemazine can be restarted for another 6 months alongside sleep hygiene measures. Start at 5mg daily, increasing as per above. (This is typically managed by the specialist, but a GP may also consider it.)
- Total daily dose should not exceed 60mg daily or the maximum of previous dose agreed by specialist. (Please note that the dose for sleep issues is not age-dependent but primarily based on patient feedback).
- The GP should stop treatment immediately if a serious adverse drug reaction is experienced. This should be reported to the specialist and the MHRA using the yellow card.

*A trial of withdrawal may be tried earlier than 6 months if the clinician and parents decide it is appropriate. Also, a longer treatment period may be appropriate in some patients as advised by the specialist clinician.

11. Advice to patients and carers

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The specialist will counsel the patient with regard to the benefits and risks of treatment and will provide the patient with any relevant information and advice, including patient information leaflets on individual medicines.

The patients/carers should be advised to report any of the following signs or symptoms to their primary or secondary care prescriber without delay:

Cardiovascular symptoms like tachycardia and hypotension, skin reactions, pyloroduodenal obstruction (vomiting); urinary retention; orthostatic hypotension.

The patients/carers should be advised regarding their responsibilities as per above.

Please note:

The general aim is to use alimemazine as a short to medium-term treatment; this will be made clear to the parents and carers at initiation.

- An attempt to withdraw/have a break in treatment should be made at least every 6 months*.
- Sleep hygiene should be reinforced throughout treatment and prior to any attempt to stop.
- Treatment may be stopped by the GP or the specialist.
- For best success, mutually agree with the patient a suitable time to stop treatment, for example during school holidays, avoiding periods of stress e.g., during exams.
- A rebound worsening in sleep pattern may occur initially but this may improve over time. If after 7-14 days sleep has deteriorated significantly alimemazine can be restarted for another 3-6 months alongside sleep hygiene measures. Start at 5mg daily before bedtime, increasing dose as per above. Total daily dose should not exceed 60mg daily or the maximum of previous dose agreed by specialist.

*A trial of withdrawal may be tried earlier than 6 months if the clinician and parents decide it is appropriate. Also, a longer treatment period may be appropriate in some patients as advised by the specialist clinician.

Patient information: Below are some useful resources and links for patients/ to be signposted to.

12. Pregnancy, paternal exposure and breast feeding

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It is the responsibility of the specialist to provide advice on the need for contraception to male and female patients on initiation and at each review, but the ongoing responsibility for providing this advice rests with both the primary care prescriber and the specialist.

Please refer to BNFC and SPC for comprehensive information

Pregnancy:

There is inadequate evidence of the safety of alimemazine in human pregnancy, but it has been widely used for many years without apparent ill consequence.

Breastfeeding:

Phenothiazines may be excreted in milk: breast feeding should be suspended during treatment.

Paternal exposure:

Animal studies are insufficient with respect to effect on fertility. However, some phenothiazines show adverse effects on fertility.

13. Specialist contact information

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Alternative contact: *<scn-tr.respiratory.secretaries@nhs.net>*

Out of hours contact details: *01142717400, oncall registrar*

14. Additional information

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- Where patient care is transferred from one specialist service or GP practice to another, a new shared care agreement must be completed. Ensure that the specialist is informed in writing of any changes to the patient's GP or their contact details.

- Please prescribe most cost-effective branded generic according to place formulary.

15. References

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- Alimemazine, British National Formulary for Children available at Alimemazine tartrate | Drugs | BNFC | NICE accessed 6/12/23
- Alimemazine SPC, available from Search Results - (emc) (medicines.org.uk), accessed 14/3/24
- Quine L. Sleep problems in children with mental handicap. J Ment Defic Res1991 Aug;35 (Pt 4):269-90
- McDonald A, Joseph D. Paediatric neurodisability and sleep disorders: clinical pathways and management strategies. BMJ Paediatrics Open 2019;3:e000290
- Ramchandani P, Webb V V, Stores G. A systematic review of treatment of settling problems and night waking in young children. West J Med. 2000 Jul;173(1):33-8. doi: 10.1136/ewjm.173.1.33. PMID: 10903288; PMCID: PMC1070969.Wiggs L. Sleep problems in children with developmental disorders. J R Soc Med 2001 Apr;94(4):177-9, available from A systematic review of treatment of settling problems and night waking in young children - PMC (nih.gov)
- Sleep: a randomised, double-blind, placebo-controlled, parallel study (MENDS). Health Technol Assess 2012;16(40)

16. Other relevant national guidance

- Shared Care for Medicines Guidance – A Standard Approach (RMOC). Available from https://www.sps.nhs.uk/articles/rmoc-shared-care-guidance/
- NHSE policy – Responsibility for prescribing between primary & secondary/tertiary care. Available from https://www.england.nhs.uk/publication/responsibility-for-prescribing-between-primary-and-secondary-tertiary-care/
- General Medical Council. Good practice in prescribing and managing medicines and devices. Shared care. Available from https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/good-practice-in-prescribing-and-managing-medicines-and-devices/shared-care
- NICE NG197: Shared decision making. Last updated June 2021. https://www.nice.org.uk/guidance/ng197/.

The following are useful resources / websites / apps to support parents and children / adolescence with good sleeping habits

- Sleep and children | Sheffield (sheffielddirectory.org.uk)
- Encouraging good sleep habits in children with learning disabilities. | Research Autism Publications (informationautism.org)
- Sleep - Sheffield Children's NHS Foundation Trust (sheffieldchildrens.nhs.uk)
- Home - The Sleep Council

- Home - Teen Sleep Hub
- Children - The Sleep Charity
- Advice Sheets - The Sleep Charity
- Diet & Sleep - The Sleep Charity
- Relaxation Tips - The Sleep Charity
- Transform Your Sleep Sanctuary: Calming Bedroom Ideas Unveiled! - Children's Sleep Blog (thechildrenssleepcharity.org.uk)
- Bedtime Routines - The Sleep Charity
- NHS Healthy sleep tips for children - https://www.nhs.uk/live-well/sleep-and- tiredness/healthy-sleep-tips-for-children/
- NHS sleep and tiredness - Sleep and tiredness - NHS (www.nhs.uk)
- Every mind matters, understanding sleep problems - Sleep problems - Every Mind Matters - NHS (www.nhs.uk)
- Sleep diary for kids - Sleep Diary For Kids - The Sleep Charity
- Pzizz | Sleep at the push of a button (free to download, but some in- app purchases)
- Sleepio (six-week clinically proven programme used to treat insomnia, available free on the NHS) Onboarding Sleep Test - Sleepio

17. Local arrangements for referral

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Define the referral procedure from hospital to primary care prescriber & route of return should the patient's condition change.

The specialist will initiate and prescribe Alimemazine until a response to treatment has been confirmed and the optimal dose achieved (after a minimum of 3 months). If a positive response is observed, the specialist will send a comprehensive request letter to the primary care provider, detailing all pertinent patient information and proposed treatment protocols. Only then will the patient's GP be asked to consider continuing the prescription under the shared care arrangement.

However, if after 3–6 months of treatment with Alimemazine, the specialist determines that there is no clinically relevant treatment effect, discontinuation of Alimemazine will be considered.

Patients currently receiving Alimemazine who still experience any of the following symptoms should be referred back to the sleep clinic:

- Sleep initiation: Sleep latency (time taken to fall asleep after getting into bed) greater than 60 minutes.
- Sleep maintenance: Total sleep time less than 8 hours if under 10 years old or less than 6 hours if over 10 years old
- Early morning awakening
- Excessive daytime sleepiness
- Parasomnias
- Snoring or sleep-disordered breathing

Appendix 1. Sleep Tips

1. Have a consistent bedtime and wake-up time, even at weekends.
2. Plan a relaxing routine an hour before bedtime with, say, jigsaws, colouring or play dough.
3. Stop using screens an hour before bedtime and keep devices out of the bedroom overnight.
4. Avoid energy drinks and caffeine-based products from noon onwards.
5. Make the bedroom calm and comfortable, not stimulating
6. Keep the bedroom as dark and 'boring' as possible, if light is required ideally use a red light bulb to avoid inhibiting the production of melatonin.