Medicines Optimisation Programme Board (MOPB)

Drug	Alimemazine Tablets/Oral Solution
Licenced Indication	• Uritcaria • Pruritis • Alimemazine may be used in pre-medication as a sedative before anaesthesia in children aged between 2 to 7 years. • Alimemazine tartrate 30 mg / 5ml syrup can be used for the specific indication of pre-anaesthesia sedation in children
Other off-label uses	Allergic Rhinitis; sedation prior to CT/MRI or other imaging scans (in paediatric patients)
Decision	NHS West Essex Clinical Commissioning Group **does not** commission Alimemazine for Urticaria, Pruritus or Allergic Rhinitis. The use of Alimemazine as a sedative before anaesthesia or imaging scans is approved for secondary care only (**RED** status).
Date	25th July 2019
Evidence	Alimemazine belongs to the group of 'first generation' histamines receptor antagonists, alongside chlorphenamine, hydroxyzine and promethazine, which are known to be relatively non-selective and therefore, block not only histamine receptors (H1, H2, H3 and H4) but also, muscarinic, adrenoreceptors and dopaminergic receptors. Due to this, they are known to elicit adverse effects on the body's cardiovascular, urinary and gastrointestinal system. The first generation antihistamines are known to be highly lipophilic, therefore readily cross the blood-brain barrier, resulting in sedation. They are known to display a relatively short half-life, thus require multiple doses per a day. 'Second generation' antihistamines, such as cetirizine and loratadine have an increased affinity for H1 receptors (which are known to play the most important role in histamine-dependent allergic diseases) making them effective at reducing symptoms of allergic rhinitis and urticaria. Their lower affinity for non-specific antihistamine receptors as well as adrenergic, muscarinic and dopaminergic receptors, results in a better safety profile and their lipophobic nature means they are less likely to penetrate the blood brain barrier, thus reduces the occurrence of sedation. Alimemazine was previously marketed under the brand name Vallergan®. However, following discontinuation, it is only available as non-proprietary branded tablets (10mg strength) and also as liquid preparations (7.5mg/5ml, 30mg/5ml).

Recommendation to MOPB

Position Statement:

NHS West Essex Clinical Commissioning Group does not commission Alimemazine for Urticaria, Pruritus or Allergic Rhinitis.

- Commence all new patients requiring a sedating antihistamine on either chlorphenamine or hydroxyzine.
- Any existing patient should be reviewed and switched to an alternative sedation antihistamine if appropriate (e.g. Chlorpheniramine or hydroxyzine). Please refer to the WECCG formulary for choice of products. There is little evidence that any of these are more superior to the other.
- **Do not** prescribe hydroxyzine to people with a prolonged QT interval or risk factors for QT interval prolongation. The MHRA recommends that the maximum adult daily dose of hydroxyzine is 100mg.[1]
- **Do not** use sedating antihistamines long term unless clinically indicated.

The use of Alimemazine as a sedative before anaesthesia or imaging scans is approved for secondary care only (**RED** status).

Rationale for recommendation

Effectiveness

Urticaria

NICE Clinical Knowledge Summaries (CKS) Urticaria

- For people with mild urticaria with an identifiable and avoidable cause/trigger, advise that urticaria is likely to be self-limiting without treatment.
- For people with symptoms requiring treatment:
    - Offer a non-sedating antihistamine (for example cetirizine, fexofenadine, or loratadine) for up to 6 weeks (use clinical judgement to determine the duration of treatment).
- A Cochrane systematic review (search date: June 2014) assessed the effects of H1-antihistamines for chronic spontaneous urticaria (CSU, n = 9759) and found that cetirizine, desloratadine, and levocetirizine are effective when compared with placebo. Loratadine showed no significant difference when compared with placebo [Sharma, 2014]. Adverse effects, such as headache and dry mouth, were tolerable with most antihistamines, but the evidence was less clear for improvement in quality of life (for example reduction in sleep disturbance from itching and less distress from the appearance of hives) as many studies did not address this.
  There was no strong evidence that one non-sedating antihistamine was more effective than the other.
  The authors pointed out that all results were gathered from a few studies or, in some cases, from single-study estimates. The quality of the evidence was affected by the small number of studies in each comparison and the small sample size for many of the outcomes.
- If there is an inadequate response to the first-line antihistamine treatment, consider the following options, using clinical judgement:
    - In adults, gradually increase the dose of the first-line antihistamine to up to four times the standard licensed dose (off-label use). Consider seeking specialist advice if this approach is being considered in a child.
    - Switch to an alternative non-sedating antihistamine.
    - Prescribe a topical antipruritic treatment (such as calamine lotion or topical menthol 1% in aqueous cream) to relieve itch.
    - Prescribe an additional sedative antihistamine (such as chlorphenamine) at night, if itch is interfering with sleep.
    - Refer the person to a dermatologist or immunologist.

BSACI guideline for the management of chronic urticaria and angioedema (2015)

- All antihistamines are licensed for use in chronic urticaria, but the chronic use of first-generation antihistamines, such as chlorphenamine, should be avoided where possible because of sedation and interference with psychomotor performance.

Allergic rhinitis

NICE Clinical Knowledge Summaries (CKS) Allergic Rhinitis

- If the person has mild-to-moderate intermittent, or mild persistent symptoms:
    - Advise on the 'as-needed' use of an intranasal antihistamine first-line, or a second-generation, non-sedating oral antihistamine, depending on the person's age and personal preference.
    - Advise that intranasal antihistamines (azelastine) have a faster onset of action and are more effective than oral preparations. See the section on Intranasal antihistamines in Prescribing information for more information on intranasal antihistamines and intranasal spray and drop technique.
    - Oral antihistamine options include loratadine or cetirizine, which may be available over-the-counter. See the section on Oral antihistamines in Prescribing information for more information.

BSACI guideline for the diagnosis and management of allergic and non-allergic rhinitis (Revised Edition 2017; First edition 2007)

- Antihistamines are available as oral, intranasal and ocular preparations.
- All demonstrate clinical efficacy. It is important to use a drug with the least adverse effect and that is considered safe for the current situation (i.e such as pregnancy, breastfeeding).
- Second-generation antihistamines are long acting and are largely non-sedating and have no clinically significant anti-cholinergic activity at therapeutic doses, although there is variation in individual susceptibility to such effects.

Adverse effects

- First-generation antihistamines are less useful due to sedation and cognitive impairment, which can worsen driving

and examination results already impaired by rhinitis. Their use is not recommended. Antihistamines with an anticholinergic effect are associated with development of dementia.

Sedation

Sedation in under 19s: using sedation for diagnostic and therapeutic procedures (2010)

- For children and young people who are unable to tolerate a painless procedure (for example, during diagnostic imaging) consider one of the following drugs, which have a wide margin of safety:
    - chloral hydrate for children under 15 kg
    - midazolam.
- For children and young people undergoing a painful procedure (for example suture laceration or orthopaedic manipulation), when the target level of sedation is minimal or moderate, consider:
    - nitrous oxide (in oxygen) and/or
    - midazolam (oral or intranasal)
- For all children and young people undergoing a painful procedure, consider using a local anaesthetic, as well as a sedative.
- For children and young people undergoing a painful procedure (for example, suture laceration or orthopaedic manipulation) in whom nitrous oxide (in oxygen) and/or midazolam (oral or intranasal) are unsuitable consider:
    - ketamine (intravenous or intramuscular), or
    - intravenous midazolam with or without fentanyl (to achieve moderate sedation).
- For children and young people undergoing a painful procedure (for example suture laceration or orthopaedic manipulation) in whom ketamine (intravenous or intramuscular) or intravenous midazolam with or without fentanyl (to achieve moderate sedation) are unsuitable, consider a specialist sedation technique such as propofol with or without fentanyl

BNF
Sedation of children during diagnostic and therapeutic procedures is used to reduce fear and anxiety, to control pain, and to minimise excessive movement. The choice of sedative drug will depend upon the intended procedure and whether the child is cooperative; some procedures are safer and more successful under anaesthesia.

Midazolam and chloral hydrate are suitable for sedating children for painless procedures, such as imaging. For painful procedures, alternative choices include nitrous oxide, local anaesthesia, ketamine, or concomitant use of sedation with opioid or non-opioid analgesia.

Safety

Side-effects[2]
Frequency not known
Agitation; agranulocytosis; amenorrhoea; atrioventricular block; autonomic dysfunction; bile thrombus; consciousness impaired; drug fever; dry mouth; eosinophilia; erectile dysfunction; eye disorder; galactorrhoea; gynaecomastia; hepatic disorders; hyperprolactinaemia; hyperthermia; hypotension; insomnia; leucopenia (on prolonged high dose); movement disorders; muscle rigidity; nasal congestion; neuroleptic malignant syndrome; pallor; parkinsonism; photosensitivity reaction; postural hypotension (more common in the elderly or in volume depletion); QT interval prolongation; respiratory depression; seizure; skin reactions; tardive dyskinesia (more common after long term high doses); tremor; ventricular fibrillation (increased risk with hypokalamia and cardiac disease); ventricular tachycardia (increased risk with hypokalamia and cardiac disease)

Further information
- Drowsiness may diminish after a few days.
- Patients on high dosage may develop photosensitivity and should avoid exposure to direct sunlight.
- Children and elderly patients are more susceptible to side-effects.

Patient factors

Urticaria, Pruritus
By mouth

For Child 2–4 years: 2.5 mg 3–4 times a day.
For Child 5–11 years: 5 mg 3–4 times a day.
For Child 12–17 years: 10 mg 2–3 times a day, in severe cases up to maximum daily dose has been used; maximum 100 mg per day.

For Adult: 10 mg 2–3 times a day, in severe cases up to maximum daily dose has been used; maximum 100 mg per day.

For Elderly: 10 mg 1–2 times a day.

Resource implications

Drug	Quantity	DT Price [23.5.19]	Dose in adults	Max. Price/day
Alimemazine Tart_Oral Soln 30mg/5ml	100ml	£243.51	10 mg 2–3 times a day, in severe cases up to maximum daily dose has been used; maximum 100 mg per day.	£12.17
Alimemazine Tart_Oral Soln 7.5mg/5ml	100ml	£179.55		n/a
Alimemazine Tart_Tab 10mg	28	£112.85		£12.09
Chlorphenamine 2mg/5ml oral solution	150ml	£2.78 (Piriton) £2.21 (Allerief)	4 mg every 4–6 hours; maximum 24 mg per day.	£1.12 £0.88
Chlorphenamine 4mg tablets	28	£0.76		£0.16
Hydroxyzine 10mg tablets (Atarax)	84	£1.65	Initially 25 mg daily, dose to be taken at night; increased if necessary to 25 mg 3–4 times a day.	£0.20
Hydroxyzine 25mg tablets	28	£0.85		£0.12

References

1. MHRA Drug safety update (2015) Hydroxyzine (Atarax, Ucerax): risk of QT interval prolongation and Torsade de Pointes
2. BNF Alimemazine [accessed 24.5.19]

With Thanks to Hertfordshire Medicines management Committee