East Surrey CCG, Guildford & Waverley CCG, North West Surrey CCG, Surrey Downs CCG, Surrey Heath CCG, Crawley CCG, Horsham & Mid-Sussex CCG

Evidence review for Prescribing Clinical Network

Medicine details	
Name, brand name	Alimemazine, syn. trimeprazine , brand name Valergan – discontinued
Manufacturer	Zentiva, Concordia Int.
Proposed indication	Urticaria (licensed)
Requested by	Surrey PCN in light of price increase

SUMMARY

Clinical Effectiveness

The purpose of this paper is to evaluate the evidence for the use of alimemazine in therapy of urticaria in children and adults. This was requested by the Surrey Prescribing Clinical Network (PCN) as this specific indication has not been appraised and it is desirable to have a complete evidence review of all UK licensed indications.

Alimemazine is a first-generation H1-antihistamine and phenothiazine derivative with hypnotic, antihistamine, antiemetic and week antipsychotic activity (1, 2). Alimemazine is licensed in the UK for the management of urticaria, but its use in this indication is not supported on local formulary.

Antihistamine drugs, specifically H1 antihistamines, are the mainstay of treatment for urticaria, although they control the condition rather than cure it (3).
The Cochrane Database of Systematic Reviews looked at the evidence of oral first- and second-generation H1-antihistamines in chronic spontaneous urticaria. Although the results of the review indicate that at standard doses of treatment, several antihistamines are effective when compared with placebo, all results were gathered from a few studies or, in some cases, from single-study estimates. The duration of the intervention was up to two weeks (short-term) or longer than two weeks and up to three months (intermediate-term). The overall quality of the evidence found for most outcomes was low, owing to the small number of studies in each comparison and the small sample size for many of the outcomes (3).
No single H1-antihistamine stands out as most effective. Authors noted that older (or 'first-generation') H1-antihistamines are no longer recommended for use in chronic urticaria, as they are more sedating than the newer 'second generation' of antihistamines and carry a higher risk of side effects (3).

The evidence search returned further 2 systematic reviews of chronic spontaneous and inducible urticaria (Cornillier et al. (4), Dressler et al. (5)) and 1 evidence review of chronic urticaria (Kavosh and Khan (6)). These papers, however, assessed only the safety and efficacy of second-generation antihistamines.

Four further randomized control studies didn’t prove superiority of first- over second-generation antihistamines in patients with chronic urticaria (CU), but reported less favourable side effect profile of the former one (7-11).

Safety

Many medications, in particular those introduced before 1985 have not been optimally studied in RCTs and in their day, they received authorisation out of lack of regulation of the required specifications and they remain on the market because the pharmacovigilance systems have not detected enough ADRs requiring their withdrawal (12).
A good example of this is the case of the first-generation antihistamines such as alimemazine. There is widespread use of first-generation H1-antihistamines in children; they have been on the market for a long time and many of them have received over-the-counter status (e.g. promethazine), though these first-generation H1-antihistamines are known to have the most major side effects due to poor receptor selectivity for the H1 receptor (12).

The most important ADRs are related to anticholinergic and histamine-like properties of alimemazine. Common side effects include drowsiness, headache and dizziness (> 1/100), anticholinergic effects such as constipation, urinary retention and accommodation disturbances are less common (1/100 to 1/1000), while extrapyramidal effects such as parkinsonism, acute dystonia and tardive dyskinesia, malignant neuroleptic syndrome, blood pressure drop and tachycardia or hematopoietic effects were

reported rarely (<1/1000) (13).
A more recent study in the Netherlands has echoed the above side effect concerns associated with the use of antihistamines children (14).
The negative neurocognitive effect of antihistamines was described by Van Ruitenbeek et al (15).

Jaundice, usually transient, occurs in a very small percentage of patients. A premonitory sign may be a sudden onset of fever after one to three weeks of treatment followed by the development of jaundice. Neuroleptic jaundice has the biochemical and other characteristics of obstructive jaundice and is associated with obstructions of the canaliculi by bile thrombi; the frequent presence of an accompanying eosinophilia indicates the allergic nature of this phenomenon. Treatment should be withheld on the development of jaundice (16).
Hypotension or pallor may occur in children. Elderly or volume depleted subjects are particularly susceptible to postural hypotension (16). Cardiac arrhythmias, including atrial arrhythmia: A-V Block, ventricular tachycardia and fibrillation have been reported during therapy, possibly related to dosage. Pre-existing cardiac disease, old age, hypokalaemia and concurrent tricyclic antidepressants may predispose. ECG changes, usually benign, include widened QT interval, ST depression, U-waves and T wave changes. Respiratory depression is possible in susceptible patients (16).
A mild leukopenia occurs in up to 30% of patients on prolonged high dosage. Agranulocytosis may occur rarely; it is not dose related. The occurrence of unexplained infections or fever requires immediate haematological investigation (16).
Acute dystonias or dyskinesias, usually transitory are commoner in children and young adults and usually occur within the first 4 days of treatment or after dosage increases.
• akathisia characteristically occurs after large doses
• Parkinsonism is commoner in adults and the elderly. It usually develops after weeks or months of treatment
One or more of the following may be seen - tremor, rigidity, akinesia or other features of Parkinsonism (commonly just tremor)
• tardive dyskinesia. If this occurs it is usually, but not necessarily, after prolonged or high dosage. It can even occur after treatment has been stopped. Dosage should therefore be kept low whenever possible (16).

At least 13 cases of lethal overdose were reported after receiving therapeutic doses of alimemazine with blood concentrations 10-50 times higher than typical maximum plasma concentration. There have been several case reports of serious and in some cases lethal events after use of alimemazine in therapeutic doses (in the range of 3 mg / kg) in children, including hypotension, bradycardia, respiratory depression, seizures, malignant neuroleptic syndrome and malignant hyperthermia. Some older reports suggest an association between the use of phenothiazines, primarily alimemazine and promethazine, and sudden infant death syndrome (13).
Up to date a total of 224 reactions were reported to MHRA through the Yellow Card Scheme in the UK (period from 1967 to 04/2018). These included 102 ADR reports, 76 serious ADR reports and 6 fatal ADR reports.

The safety of alimemazine prescribing was reviewed by NPSA in 2007 concerning two medicine error incidents. One of which was when alimemazine was prescribed at 3ml of 7.5mg/5ml solution and overdose was given as the only strength available was 30mg/5ml solution (Low harm) (17).
Another medication error occurred when patient was prescribed ‘as required’ doses of both chlorphenamine and alimemazine, and nursing staff were unaware of antihistamine properties of alimemazine (No harm) (17).
The use of both strengths in paediatric settings raises safety concerns and measures should be taken to prevent medicines errors from occurring, e.g. by prescribing the dose in both milligrams and millilitres. Additional patient information of indication (‘for insomnia’) shall be considered alongside standard BNF warning label.

Patient factors

Alimemazine is considered as a non-formulary drug on the East Surrey CCG, Guildford & Waverley CCG, North West Surrey CCG, Surrey Downs CCG & Surrey Heath CCG and Crawley, Horsham & Mid-Sussex CCG traffic light system for urticaria and BLACK for pruritus in eczema and sleep disorders in children and adolescents following a recent review.

The available data shows a significant degree of alimemazine prescribing in primary care. A total number of 1150 prescription items of alimemazine were issued across East Surrey, Guildford & Waverley, North West Surrey, Surrey Downs & Surrey Heath CCG in current 12 months based on NHS business authority data from ePACT2. In the same time period this accounted for 228 prescription items in Crawley, Horsham & Mid Sussex CCG.

Before any changes in the colour status, it will be helpful to map the extent to which alimemazine is used by dermatology specialists and if alternative first- or second-generation H1-antihistamine could be considered as an alternative. Shared care agreement should be considered if alternative first generation H1-antihistamine is used long term in these patients to allow monitoring of treatment outcomes, dose adjustments and toxicity and ADRs monitoring.
Patients may have their therapy stopped or repatriated back to the initiating provider if they are unable to change to an alternative option. As the prescribing may have been on-going for many years, patient expectations would need to be managed and any repatriation may adversely affect the patient.

Cost implications

Drug tariff

Following discontinuation of the Vallergan® brand, over the last two years the NHS list price of alimemazine has increased by more than 1500% for both tablets and liquid. The lack of market competition is reflected in alimemazine listed as category A drug in Drug Tariff with current prices of £112.85 per pack of 28 x 10 mg tablets, £243.51 per 100 ml of 30mg/5ml oral and £179.55 per 100 ml of 7.5mg/5ml oral solution.

Cost implications to local health authority

Based on information from The NHS Business Authority (ePACT data) the annual spend on alimemazine in East Surrey, Guildford & Waverley, North West Surrey, Surrey Downs & Surrey Heath CCG accounted for £416,523 whilst the figure in Crawley, Horsham and Mid Sussex CCG was £96,175. This includes only prescriptions issued within Primary care. The total cost to the NHS will be much higher.

Cost of alimemazine and comparative treatments

The table below gives the overview of the costs of alimemazine and comparative treatment in first generation H1-atihistamines - chlorphenamine and hydroxyzine. Cost is calculated for age groups of two, six and twelve years as well as the adults

Tab 1. Annual treatment cost for children 2 years and over.

Age / Drug and dose	**2 years (12kg)**	**6 years (21 kg)**	**12 years (39 kg)**	**Adult**
Alimemazine	*3 mg QDS*	*5 mg QDS*	*100 mg/ day*	*100 mg / day*
7.5 mg/5 mL	£4,826	£8,044	£40,219	£40,219
30mg/5 mL	£1,636	£2,727	£13,637	£13,637
10 mg tablet	NA	£2,708	£13,542	£13,542
Hydroxyzine	*15 mg / day*	*40 mg / day*	*80 mg / day*	*100 mg / day*
10 mg tablet	£7	£19	£38	£48
25 mg tablet	£4	£11	£22	£30
oral solution	Discont.	Discont.	Discont.	Discont.
Chlor-phenamine	*6 mg / day*	*12 mg / day*	*24 mg / day*	*24 mg / day*
4 mg tablet	NA	£ 27	£ 53	£ 53
2 mg / 5 ml	£ 93	£ 186	£ 372	£ 372
Cetirizine	*2.5 mg BD*	*5 mg BD*	*10 mg OD*	*10 mg OD*
10 mg tablet	NA	£4	£9	£9
1mg/ml SF	£9	£19	£19	£19
Loratadine	*5 mg OD*	*5 mg OD (<31 kg)*	*10 mg OD*	*10 mg OD*
10 mg tablet	NA	£3	£5	£5
1mg/ml	£24	£24	£49	£49

Note: Prices are based on April 2018 Drug Tariff prices of alimemazine 7.5mg/5ml oral solution (100 ml = £179.55) and 30mg/5ml oral solution (100 ml= £ 243.51), alimemazine 10 mg tablets (28 = £ 112.85), hydroxyzine 10mg tablets (84 = £ 1.20) and 25 mg tablets (28 = £ 0.62), chlorphenamine 4 mg tablets (28 = £ 0.76), chlorphenamine 2mg/5 ml oral solution (150 ml = £2.62), Loratadine 10mg tablets (30 = £ 0.45), Loratadine 5mg/5ml oral solution (100 ml = £ 1.33), Cetirizine 10mg tablets (30 = £ 0.70), Cetirizine 1mg/ml oral solution SF (200 ml = £1.02)
Doses are based on Children BNF and BNF maximum daily doses (18, 19)

Relevant guidance / reviews

Based on extensive evidence from controlled trials, clinical guidelines universally recommend second-generation oral antihistamines as first-line monotherapy for chronic urticaria. Despite safety concerns, some guidelines and published expert opinions continue to recommend first-generation antihistamines as alternative therapy for patients with suboptimal responses to high-dose second-generation agents.(20).

The British Society for Allergy and Clinical Immunology (BSACI) guidelines on the management of chronic urticaria and angioedema recommend starting pharmacological treatment with a standard dose of a non-sedating H1-antihistamine (grade of recommendation = A). Updosing with a single antihistamine is preferable to mixing different antihistamines. The guidelines advise that chronic use of first-generation antihistamines in CU should be avoided where possible (21).
Non-sedating antihistamines are the mainstay of treatment for children with chronic urticaria (grade of recommendation = B). Children may become accustomed to the sedating effects of first-generation antihistamines; however, the risk of psychomotor impairment remains and this may impact on the child's safety and education (21).

The 2007 British Association of Dermatologists Therapy Guidelines on evaluation and management of urticaria in adults and children recommend that all patients should be offered the choice of at least two non-sedating H1 antihistamines (Strength of recommendation A). The use of sedating antihistamines as monotherapy is considered less common practice. Addition of a sedating antihistamine at night to a non-sedating antihistamine by day has little additional clinical effect on urticaria (22).

The European Academy of Allergy and Clinical Immunology (EAACI), the Global Allergy and Asthma European Network (GA2LEN), the European Dermatology Forum (EDF), and the World Allergy Organization (WAO) published The 2013 revised Guidelines for the definition, classification, diagnosis, and management of urticaria. They recommend that modern second generation H1-antihistamines are to be preferred over first generation H1-antihistamines in the treatment of urticaria (strong recommendation/high level of evidence).This recommendation is based on strong evidence regarding potential serious side-effects of old sedating antihistamines (lethal overdoses have been reported) and the availability of modern second- generation antihistamines worldwide at low costs, which not only lack these side-effects but also have a higher efficacy and duration of action (23).

The Clinical Knowledge Summary for urticaria (NICE) recommend a non-sedating antihistamine for up to 6 weeks for symptomatic management of acute urticaria, which reflects the duration of symptoms in acute urticaria. At least 1-4 weeks should be allowed to assess full effectiveness of a treatment before changing to an alternative treatment. An additional sedative antihistamine (such as chlorphenamine) at night can be considered (as an add-on therapy) if itch is interfering with sleep. Sedating first-generation antihistamines are not recommended for use in any other setting as their efficacy does not seem to be superior to non-sedating antihistamines and they have a higher degree of sedation and cognitive impairment (24) .

Likely place in therapy relative to current treatments

The clinical need to prescribe alimemazine in primary care is unclear as there are alternative first and second generation H1 -antihistamines that offer a more cost effective option. Available British and European guidelines recommend non-sedating antihistamines in preference to sedating antihistamines in the management of urticaria, and therefore any alimemazine prescribing initiated within secondary care should remain in this setting.

If the decision is made to **deprescribe** alimemazine in existing dermatology patients, alternative treatments (e.g. second generation H1-antihistamines) should be considered and discussed with initiating specialist where appropriate. The need for continuous treatment should be re-assessed and treatment discontinued where appropriate.

There is a possibility that any change will trigger a need for a follow-up specialist appointment.
If the decision is made to recommend this indication as BLACK, it would be advisable to review the alimemazine prescribing in all existing dermatology patients to assess the benefits of treatment in light

of the poor clinical evidence for its continuous use.

Recommendation to PCN

The recommendation to the PCN in regards to place of alimemazine in treatment of urticaria in children and adults:

To blacklist alimemazine for all new patients.
Existing patients should be allowed a 6- to 12-month grace period, where the treatment should be reviewed by specialist. The traffic light status should be changed to BLACK for all patients after this transitional period.

The lack of supporting evidence, safety concerns and increased costs do not support the use of alimemazine in any care setting.

Medicine details

Name and brand name	Alimemazine (non-proprietary), formerly Valergan brand – discontinued
Licensed indication, formulation and usual dosage	Licensed for urticaria and pruritus in adults (unlicensed in children) Alimemazine 10mg tablets Alimemazine 30mg/5ml oral solution Alimemazine 7.5mg/5ml oral solution Dosage dependent on age, in adults and children of 12 years and over: 10mg bd –tds; up to 100mg per day in intractable cases (16).
Summary of mechanism of action, and relevant pharmacokinetics	Pharmacotherapeutic group: Antihistamines, Sedating Antihistamines, ATC code: R06AD01 (1, 19, 25). Alimemazine is a first-generation H1-antihistamine in the phenothiazine chemical class (12). It possesses antipruritic and antihistaminic properties with anticholinergic and sedative side effects. Studies evaluating the antipruritic effects of alimemazine have concluded that the antipruritic effect is due to central sedative action rather than peripheral H1-blockade (25). Oral bioavailability of alimemazine tablet is 70%. The mean time to peak plasma level is 3.5 hours for the syrup and 4.5 hours for the tablets. The mean relative bioavailability for the tablets with respect to the syrup is approximately 70%. Alimemazine undergoes extensive liver metabolism. The listed metabolites of alimemazine are N-desalkyl metabolites, which activity is unknown. The elimination half-life of the parent compound is 4.78 to 8 hours (25). The rate of metabolism and excretion of phenothiazines decreases in old age (16).
Important drug interactions	The sedative effects of phenothiazines may be intensified (additively) by alcohol, anxiolytics & hypnotics, opiates, barbiturates and other sedatives. There may be increased antimuscarinic and sedative effects of phenothiazines with tricyclic antidepressants & MAOI's (including moclobemide). Respiratory depression may occur (16). The hypotensive effect of most antihypertensive drugs especially alpha adrenoreceptor blocking agents may be exaggerated by phenothiazines. The use of antimuscarinics will increase the risk of antimuscarinic side effects when in conjunction with antihistamines (16). The mild anticholinergic effect of phenothiazines may be enhanced by other anticholinergic drugs possibly leading to constipation, heat stroke, etc. The action of some drugs may be opposed by phenothiazines; these include amphetamine, levodopa, clonidine, guanethidine, and adrenaline. Anticholinergic agents may reduce the antipsychotic effect of phenothiazines (16). Some drugs interfere with absorption of phenothiazines: antacids, anti-Parkinson, and lithium. Increases or decreases in the plasma concentrations of a number of drugs, e.g. propranolol and phenobarbital have been observed but were not of clinical significance (16). High doses of phenothiazines reduce the response to hypoglycaemic agents, the dosage of which may have to be raised. Adrenaline must not be

	used in patients overdosed with phenothiazines (16). As with other neuroleptic phenothiazines, caution is advised with concomitant use of QT prolonging drugs or drugs that cause electrolyte imbalance (16).
Monitoring requirements	Nil
Prescribing considerations	Alimemazine is contraindicated for use in children less than 2 years of age due to the risk of marked sedation and respiratory depression (16). Alimemazine should be used with caution in: • Elderly or volume depleted patients who are more susceptible to orthostatic hypotension (16), • Elderly patients presenting chronic constipation (risk of paralytic ileus) (16), • Elderly patients with possible prostatic hypertrophy. Contra-indicated in confirmed prostatic hypertrophy (16), • Elderly patients in hot and cold weather (risk of hyper/hypothermia) (16), • Patients with certain cardiovascular diseases: alimemazine may cause arrhythmias due to the tachycardia-inducing and hypotensive effects of phenothiazines (16). Other considerations: Patients are strongly advised not to consume alcoholic beverages or medicines containing alcohol throughout treatment. The sedative effects of phenothiazines may be intensified (additively) by alcohol (16). Exposure to sunlight should be avoided during treatment. Contact skin sensitisation is a serious but rare complication in those frequently handling preparations of phenothiazines. Care must be taken to avoid contact of the drug with the skin. Skin rashes of various kinds may also be seen in patients treated with the drug. Patients on high dosage may develop photosensitivity in sunny weather and should avoid exposure to direct sunlight. Ocular changes and the development of a metallic greyish-mauve colouration of exposed skin have been noted in some individuals, mainly females, who have received chlorpromazine continuously for long periods (four to eight years) (16). Liquid formulations: The sugar content should be considered in patients with diabetes or on low-sugar diets. This medicine contains sulphites that may cause or exacerbate anaphylactic reactions (16). Please refer to the latest edition of the BNF for full details
Other considerations	Prescribe the dose in both milligrams and millilitres to prevent medication errors as two strengths are available.

Potential patient group (if appropriate to include)	
Brief description of disease	Urticaria, or hives (sometimes referred to as welts or wheals), is a common disorder, with a prevalence of approximately 20 % in the general population. A typical urticarial lesion is an intensely pruritic, erythematous plaque. Urticaria is sometimes accompanied by angioedema, which is swelling deeper in the skin. Urticaria (with or without angioedema) is commonly categorized by its chronicity. Urticaria is considered **acute** when it has been present for less than six weeks. Recurrent urticaria, with signs and symptoms recurring most days of the week for six weeks or longer is classified as **chronic** (26).
Potential patient	Urticaria affects up to 20 % of the population at some point in their lives

<table>
<tr><td>numbers per 100,000</td><td>and occurs across the age spectrum. Approximately two-thirds of cases of new-onset urticaria will be self-limited and resolve spontaneously (26).
Recent publications show a female-to-male predominance of 2:1 with a prevalence of between 0.5% and 1% (3).
As many as 50 percent of patients with CU have accompanying episodes of angioedema (27).</td></tr>
<tr><td>Outcomes required</td><td>Urticaria Activity Score (UAS)
The Urticaria Activity Score (UAS) is a composite score of itch severity and hive count. To assess disease severity in patients with chronic idiopathic urticaria (CIU), patients record the severity of their itch and the number of hives 2 times per day (AM & PM). Each component of the UAS is scored on a scale of 0 to 3; the 2 scores are added together for a daily total of 0 to 6 (28).

Tab.2 Daily scoring the urticaria activity score (UAS)
<table>
<tr><td>Score</td><td>Itch Severity</td><td>Number of Hives</td></tr>
<tr><td>0</td><td>None</td><td>None</td></tr>
<tr><td>1</td><td>Mild</td><td>1-6</td></tr>
<tr><td>2</td><td>Moderate</td><td>7-12</td></tr>
<tr><td>3</td><td>Severe</td><td>>12</td></tr>
</table>
Adapted from GPNotebook: Weekly Urticaria Activity Score (UAS) (28)

Average Urticaria Activity Score for 7 days (UAS7)
The UAS7 is the sum of the average daily UAS over 7 days. After 7 days, average daily scores from the morning and evening assessments are added together. Values can range between 0 to 21 for weekly itch severity, and 0 to 21 for weekly hive count. The UAS7 ranges from 0 to 42 (28).</td></tr>
</table>

Summary of current treatment pathway

The Clinical Knowledge Summary for urticaria (NICE) recommend a non-sedating antihistamine for up to 6 weeks for symptomatic management of acute urticaria (24).

The British Society for Allergy and Clinical Immunology (BSACI) guidelines on the management of chronic urticaria and angioedema recommend starting pharmacological treatment with a standard dose of a non-sedating H1-antihistamine (grade of recommendation = A). The guidelines advise that chronic use of first-generation antihistamines in CU should be avoided where possible (21).

The EAACI/GA2LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria recommend that modern second generation H1-antihistamines are to be preferred over first generation H1-antihistamines in the treatment of urticaria (strong recommendation/high level of evidence) (23).

Evidence review

The Cochrane review of H1-antihistamines for chronic spontaneous urticaria included 73 randomised studies with 9759 participants. Only RCTs that evaluated the effectiveness of H1-antihistamines for chronic urticaria compared with placebo or another active treatment (including another H1-antihistamine) and those that compared different doses were included. Participants were adults or were 12 years of age or older, and most were female (3).
The included studies had notable methodological limitations; only 12 were clearly adequately randomised, and the randomisation method used in the rest was unclear or at high risk. Overall, the quality of evidence in each comparison was rated as low in most studies. Although the authors included a large number of studies, only a few for each comparison reported outcome data that could be incorporated in meta-analyses (10/23). Thus most of the findings are based on results from individual trials (3).

Tab.3 Trials that provided outcome data for the comparisons identified in Cochrane review (narrowed down to comparisons of sedating antihistamines only)

Comparison	Included trials	No. of patients	Age (y)	Sex	Primary outcome	Trial Design	Dur. of intervention	Results
Loratadine 10 mg versus hydroxyzine 25 mg	Monroe 1992 (8)	59 total, 18 for urticaria	18 to 63	29% male ,71 % female	Proportion of participants with complete suppression of urticaria whilst taking H1-antihistamines	Randomised double-blind 3-arm trial of loratadine vs hydroxyzine vs placebo	1 wk (+1 wk follow-up)	Loratadine is as effective as hydroxyzine in the treatment of urticaria.
Cetirizine 10 mg versus hydroxyzine 25 mg	Breneman 1996 (10)	188 (60-cetirizine; 63-hydroxyzine; 65-placebo group)	over 12	32% male , 68% female	Efficacy (definite or complete improvement) on a 4-point scale including number of lesions, number of episodes longer than 1 hour apart, average lesion size (cm), average duration of lesion (hours) and the presence of pruritus	Randomised double-blind placebo-controlled multi-centred 3-arm study of cetirizine vs hydroxyzine vs placebo	4 wks	Cetirizine 10 mg was equivalent to hydroxyzine 25 mg in symptom control
	Kalivas 1990 (11)	219; (cetirizine: 69, hydroxyzine: 69, placebo: 73)	over 12	not stated	Daily diary with 4-point scale: measured number, size, duration of lesions and number of urticarial episodes, degree of pruritus.	Randomised multi-centre parallel-group 3-arm double-blind placebo-controlled study of cetirizine vs hydroxyzine vs placebo	4 weeks	Cetirizine and hydroxyzine have equivalent efficacy, and both are superior to placebo; no significant differences in adverse effects were noted, except for somnolence and nausea
Hydroxyzine 25 mg versus placebo	Breneman 1996	See above						
	Kalivas 1990	See above						
	Monroe 1992	See above						
Cetirizine 5 mg and hydroxyzine 25 mg versus placebo	Wan 2009	120	18 - 54	38% male , 62% female	Daily record for the preceding 24 hours of the numbers and sizes of skin weals, relative severity of itch, i.e. weekly aggregate urticaria activity score (UAS7). A response to medication was defined as a reduction in weekly UAS7 to < 25% of baseline, and a relapse as a return to > 75% of baseline UAS7)	Randomised single-blind 4-arm trial comparing a combination of sedating H1-antihistamine and non-sedating H1-antihistamine (hydroxyzine plus cetirizine), comb. of H1-antihistamine & H2-antihistamine (hydroxyzine plus famotidine); and combination of H1-antihistamine and LRA (hydroxyzine plus montelukast) vs placebo	4 weeks , 1-week 'run-in' period to wash out previous antihistamine used for treatment.	Only the H1-antihistamine combination and placebo arms were compared and no analysis was possible for this comparison.
Doxepin 10 mg versus pheniramine 22.5 mg	Ghosh 1990	56	18 to 59	67% female - doxepin gr., 60% female – phenir. gr.	Complete remission; partial remission; no improvement after 3 weeks; recurrence 7 days after cessation of treatment	Randomised controlled trial of doxepin 10mg thrice daily vs pheniraminemaleate 22.5 mg thrice daily	4 wks (follow up extended 1 week after cessation of therapy)	After 3 weeks of therapy, 8 (28.6%) participants in doxepin group and 3 (10.7%) in pheniramine group were symptom free (complete suppression)

Adapted from Sharma M, Bennett C, Cohen SN, Carter B. H1-antihistamines for chronic spontaneous urticaria. Cochrane Database Syst Rev. 2014;14. (3)

No study looked at a long-term response of three months and beyond. Chronic spontaneous urticaria (CSU) can persist for years, and it would be useful for future studies to address whether treatments are effective over a longer period (3).
This review has found limited quality evidence to establish the efficacy of H1-antihistamines compared with placebo in the treatment of CSU. Several antihistamines were found to be superior to placebo at standard (licensed) doses of treatment. The authors did not carry out subgroup analyses on the basis of first-generation ('sedating') and second-generation ('non-sedating') antihistamines, as included studies with relevant outcome data were too few to allow meaningful comparisons (3).
No difference in short-term treatment was noted between loratadine (10mg) and hydroxyzine (25mg) in terms of complete suppression (RR 1.00, 95% CI 0.32 to 3.10). The results from other comparisons were not included in the review as the efficacy was not reported in a form commensurate with the outcome measures of our review in either of the two studies that compared these interventions (comparison of cetirizine 10 mg versus hydroxyzine 25 mg) (3).
The quality of evidence for adverse events was low. The authors investigated the frequency with which adverse events led to withdrawal of treatment. No significant differences were observed in efficacy or adverse events compared with placebo in the intermediate term for cetirizine (doses from 5 mg to 20 mg), desloratadine (5 mg), or hydroxyzine (25 mg). For withdrawals in comparisons of two active interventions, no significant differences were noted between cetirizine 10 mg and hydroxyzine 25 mg and cetirizine 5 mg to 25 mg and hydroxyzine 25 mg (3).

Equity / Stakeholder views (if relevant)	
Decisions of local Trusts DTCs and neighbouring APCs	Alimemazine is non-formulary for the treatment of urticaria in Crawley, Horsham & Mid Sussex, Brighton & Hove and Coastal West CCG. Further afield, the traffic light position for alimemazine was recently reviewed in the following other localities: • Manchester- added to 'Do Not Prescribe' list • Derbyshire - blacklisted as not cost effective and not supported by high quality clinical evidence. • Nottinghamshire - extended as second line to promethazine for paediatric sedation (previously only for pruritus in dermatology settings) • SW London & St. George's- for disturbed behaviour in children & adolescents according to rapid tranquillisation protocol • Buckinghamshire - children sedation undergoing MRI or CT scan classified as RED and on recommendation of paediatric / haematology specialist with continuation in primary care (AMBER) • Hampshire- premedication, dermatology use and in children with severe behavioural insomnia.
Recommendations from national / regional decision making groups	The Clinical Knowledge Summary for urticaria (NICE) recommends a non-sedating antihistamine for up to 6 weeks for symptomatic management of acute urticaria (24). The British Society for Allergy and Clinical Immunology (BSACI) guidelines on the management of chronic urticaria and angioedema recommend starting pharmacological treatment with a standard dose of a non-sedating H1-antihistamine (grade of recommendation = A). The guidelines advise that chronic use of first-generation antihistamines in CU should be avoided where possible (21). The EAACI/GA2LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria recommend that modern second generation H1-antihistamines are to be preferred over first generation H1-antihistamines in the treatment of urticaria (strong recommendation/high level of evidence) (23).
Stakeholder views	There was a change in traffic light status of alimemazine from GREEN to RED at Frimley Health NHS Foundation Trust. It was highlighted not to switch the prescribing of existing alimemazine patients into the secondary care as this would just shift the costs and an alternative antihistamine should be considered if appropriate.
CCG priorities	The medicine expenditure in NHS hospitals is increasing at a rate of 15% per annum as more complex and specialised medicines enter the market. The need to manage the cost of medicines in the context of financial constraints is critical as identified in Carter review in 2016.

	Alimemazine is an obsolete first generation H1-antihistamine, where the price has increased exponentially in recent years. Significant number of prescribing items is in primary care with several CCGs now recognising its potential financial impact and considering deprescribing initiatives or switch programmes.

Health economic considerations

Cost per year per patient

The annual treatment costs below are based on April 2018 Drug Tariff and maximum daily doses in BNF and Children BNF for pruritus (18, 19).

Drug, dose / Age	2 years (12kg)	6 years (21 kg)	12 years (39 kg)	Adult
Alimemazine	*3 mg QDS*	*5 mg QDS*	*100 mg/ day*	*100 mg / day*
7.5 mg/5 mL	£4,826	£8,044	£40,219	£40,219
30mg/5 mL	£1,636	£2,727	£13,637	£13,637
10 mg tablet	NA	£2,708	£13,542	£13,542

Alternative treatments cost per patient per year

The annual treatment costs below are based on October 2017 Drug Tariff and maximum daily doses in BNF and Children BNF for pruritus (18, 19).

Drug, dose / Age	2 years (12kg)	6 years (21 kg)	12 years (39 kg)	Adult
Hydroxyzine	*15 mg / day*	*40 mg / day*	*80 mg / day*	*100 mg / day*
10 mg tablet	£7	£19	£38	£48
25 mg tablet	£4	£11	£22	£30
oral solution	Discont.	Discont.	Discont.	Discont.
Chlor-phenamine	*6 mg / day*	*12 mg / day*	*24 mg / day*	*24 mg / day*
4 mg tablet	NA	£ 27	£ 53	£ 53
2 mg / 5 ml	£ 93	£ 186	£ 372	£ 372
Cetirizine	*2.5 mg BD*	*5 mg BD*	*10 mg OD*	*10 mg OD*
10 mg tablet	NA	£4	£9	£9
1mg/ml SF	£9	£19	£19	£19
Loratadine	*5 mg OD*	*5 mg OD (<31 kg)*	*10 mg OD*	*10 mg OD*
10 mg tablet	NA	£3	£5	£5
1mg/ml	£24	£24	£49	£49

Other financial considerations (if relevant)	Nil
Health economic data (if available)	Nil

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Version	Date	Author	Status	Comment
v.1	*07.06.2018*	*Michal Mensa*		*Out for consultation*
v.2				