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	Pruritus in eczema (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 pruritus in eczema in children and adults.

The available evidence looked at pruritus associated with eczema as the evidence associated with pruritus in other indications is scarce and it was identified by the Surrey Prescribing Clinical Network (PCN) that the majority of non-formulary prescribing of alimemazine takes place in dermatology. It would also be inappropriate to compare efficacy of alimemazine across all indications associated with pruritic symptoms due to large heterogenicity and different pathological mechanisms.

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 and pruritus, but its use in this indication is not supported on local formulary.

The Cochrane Database of Systematic Reviews looked at the evidence of oral H1-antihistamines as a monotherapy in eczema. The review of antihistamines as 'add-on' therapy to topical treatment for eczema is in development (3).
The review by Apfelbacher et al. 2013 concluded that there is currently no high-level evidence to support or refute the efficacy or safety of oral H1 antihistamines used as monotherapy for eczema. No H1-antihistamine study matched the inclusion criteria. As most of the studies allowed the use of concomitant medications and involved multi-therapeutic approaches, meaningful assessments of the individual effects of oral H1 antihistamines on eczema were not feasible. This does not mean that such antihistamines could not be useful as an add-on therapy to the main topical treatments (3).
Although antihistamines are often used in the treatment of eczema, little objective evidence exists to demonstrate relief of either pruritus or skin lesions. Many studies are flawed in terms of sample size and study design. Further evaluation of the efficacy of antihistamines in eczema is necessary (4).

As part of a comprehensive health technology assessment of treatments available for atopic eczema, randomised controlled trials investigating the effects of antihistamines in atopic eczema were summarised in an HTA report by Hoare et al 2000. (5). Studies that have evaluated sedating antihistamines against placebo did not show any benefit for pruritus or global improvement. (6)

A systematic search of the literature was undertaken by Sidbury et al 2014 to inform the guideline of care for the management of atopic dermatitis by the American Academy of Dermatology (AAD). It concluded that the short-term, intermittent use of sedating antihistamines may bring some benefit in the case of sleeping problems arising as a consequence of itch (5).

The British Association of Dermatologists published an information leaflet, in which sedating H1-antihistamines are not generally recommended in the management of pruritus (7).

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 (8).
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 (8).

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) (9).

A more recent study in the Netherlands has echoed the above side effect concerns associated with the use of antihistamines children (10).
The negative neurocognitive effect of antihistamines was described by van Ruitenbeek et al. (11).

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 (12).

Hypotension or pallor may occur in children. Elderly or volume depleted subjects are particularly susceptible to postural hypotension (12). 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 (12).

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 (12).

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 (12).

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 (9).
Up to date a total of 217 reactions were reported to MHRA through the Yellow Card Scheme in the UK (period from 1967 to 07/2017). These included 99 ADR reports, 73 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) (13).
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) (13).

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.

NHS England has called for an action to tackle the over-prescribing of psychotropic drugs to people with learning disabilities after three separate reports highlighted the need for change. Research commissioned by the health body and delivered in three reports from the Care Quality Commission, Public Health England and NHS Improving Quality has found that:

- There is a much higher rate of prescribing of medicines associated with mental illness amongst people with learning disabilities than the general population, often more than one medicine in the same class, and in the majority of cases with no clear justification;
- Medicines are often used for long periods without adequate review, and;
- There is poor communication with parents and carers, and between different healthcare providers (14).

Patient factors

Alimemazine is considered as a non-formulary drug on the North West Surrey traffic light system for pruritus in eczema. It is considered as a RED drug on the North West Surrey traffic light system for sleep disorders in children and adolescents.

The available data shows a significant degree of alimemazine prescribing in primary care. A total number of 841 prescription items of alimemazine were issued across East Surrey, Guildford & Waverley, Surrey Downs and Surrey Heath CCG in current 12 months based on NHS business authority data from ePACT. In the same time period this accounted for 307 prescription items in Crawley, Horsham & Mid Sussex CCG.

In clinical practice, antihistamines are often used as 'add-on' therapy to topical treatment in the management of eczema, although little objective evidence exists to demonstrate any benefit from their use.

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 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, Surrey Downs and Surrey Heath CCGs accounted for £268,557 whilst the figure in Crawley, Horsham and Mid Sussex CCG was £115,390. 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

Note: Prices are based on October 2017 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).
Doses are based on Children BNF and BNF maximum daily doses (15, 16)

Relevant guidance / reviews

The British Association of Dermatologists published an information leaflet, in which sedating H1-antihistamines are not generally recommended in the management of pruritus. Some patients may benefit from non-sedating antihistamines (7).

The 2014 Guideline on the Treatment of Atopic Eczema (Atopic Dermatitis) of European Dermatology Forum concluded that there is not enough evidence to support the general use of both first and second generation H1-antihistamines for treatment of pruritus in atopic eczema (1b, A) (17).

The Clinical Knowledge Summaries (NICE) recommend a 2-week trial of sedating oral H1-antihistamine, such as hydroxyzine 25 mg at night or chlorphenamine 4 mg at night in the management of widespread pruritus (18). Conversely, for the management of severe pruritus in eczema NICE recommends a one-month trial of a non-sedating antihistamine (such as cetirizine, loratadine, or fexofenadine) (19).

Likely place in therapy relative to current treatments

The clinical need to prescribe alimemazine in primary care is unclear as there are alternative first generation H1 -antihistamines that offer a more cost effective option. The British Association of Dermatologists doesn't recommend sedating antihistamines in the management of pruritus, and therefore any 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. third generation H1-antihistamines, topical steroid or calcineurin inhibitors) 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.

Formulary alternatives:
If short term hypnotic in the group of sedating antihistamine is required in adults, promethazine should be used as first line if appropriate.

Chlorphenamine is first line sedating antihistamine for pruritus and allergic conditions in children and adults over 1 year of age (12).
Hydroxyzine is second line on Crawley, Horsham and Mid Sussex (CHMS) CCG formulary for pruritus (licensed from 6 months over), it is also licensed for anxiety in adults only (12). In April 2015 MHRA issued a safety alert on new maximal doses of hydroxyzine, its QT-prolonging potential and unsuitability in elderly patients (20).
N.B. All sedating antihistamines should not be used long term unless clinically indicated (21).

Recommendation to PCN

The recommendation to the PCN in regards to place of alimemazine in treatment of pruritus in eczema 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 (12).
Summary of mechanism of action, and relevant pharmacokinetics	Pharmacotherapeutic group: Antihistamines, Sedating Antihistamines, ATC code: R06AD01 (16, 22). Alimemazine is a first-generation H1-antihistamine in the phenothiazine chemical class (8). It possesses antipruritic and antihistaminic properties with anticholinergic and sedative side effects. Studies evaluating the antipruritic effects of trimeprazine have concluded that the antipruritic effect is due to central sedative action rather than peripheral H1-blockade (23). 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 (23). The rate of metabolism and excretion of phenothiazines decreases in old age (12).
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. 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. 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. 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. 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. As with other neuroleptic phenothiazines, caution is advised with concomitant use of QT prolonging drugs or drugs that cause electrolyte imbalance (12).
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 (12). Alimemazine should be used with caution in: • Elderly or volume depleted patients who are more susceptible to orthostatic hypotension (12), • Elderly patients presenting chronic constipation (risk of paralytic ileus) (12), • Elderly patients with possible prostatic hypertrophy. Contra-indicated in confirmed prostatic hypertrophy (12), • Elderly patients in hot and cold weather (risk of hyper/hypothermia) (12), • Patients with certain cardiovascular diseases: alimemazine may cause

	arrhythmias due to the tachycardia-inducing and hypotensive effects of phenothiazines (12). 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 (12). 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) (12). 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 (12). 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	Eczema (a unifying term for 'atopic eczema', 'atopic dermatitis', and 'neurodermatitis') is a common skin disease. Although the majority of cases of eczema occur before the age of five years and often resolve during childhood or adolescence, it can also persist into adulthood. Itch (pruritus) is the most important aspect of eczema, often impacting significantly on the quality of life of an affected individual. It is defined as an unpleasant sensation eliciting the urge to scratch. It is such an important aspect of eczema that the diagnosis "cannot be made if there is no history of pruritus". This sensation is not constant but comes in attacks, which can be very severe and disruptive to a person's quality of life. Two recent studies reported that pruritus occurred on a daily basis in 87% to 91% of people with eczema (3).
Potential patient numbers per 100,000	Data on the prevalence of Chronic Pruritus (CP) is very limited. The prevalence of CP seems to increase with age (24), but epidemiological studies are missing. It is estimated that about 60% of the elderly (above 65 years of age) suffer from mild to severe occasional pruritus each week (25), entitled senile pruritus or pruritus in the elderly. Recent surveys indicate a point-prevalence of CP to be around 13,5% in the general adult population (26, 27). Multivariate analysis revealed eczema, dry skin, asthma, and liver diseases, an elevated body mass index and higher anxiety scores as determinants of prevalent CP (27) . There are no epidemiological studies assessing the prevalence of CP in children (28, 29). Differential diagnosis of CP in children has a wide spectrum but is dominated by atopic dermatitis. The cumulative prevalence of atopic dermatitis is between 5 to 22% in developed countries (28).
Outcomes required	Reduction of subjectively perceived itch, as determined by validated rating scales (e.g. visual analogue scales).

Summary of current treatment pathway

The Clinical Knowledge Summaries (NICE) recommend a 2-week trial of sedating oral H1-antihistamine, such as hydroxyzine 25 mg at night or chlorphenamine 4 mg at night in the management of widespread pruritus (18).
Conversely, for the management of severe pruritus in eczema NICE recommends a one-month trial of a non-sedating antihistamine (such as cetirizine, loratadine, or fexofenadine). Treatment can be continued, while symptoms persist, and should be reviewed every 3 months. This recommendation is based mainly on clinical experience, as there is only very limited evidence from controlled trials on the effectiveness of antihistamines for the treatment of atopic eczema (19).

The British Association of Dermatologists published an information leaflet, in which sedating H1-antihistamines are not generally recommended in the management of pruritus (7).

The 2014 Guideline on the Treatment of Atopic Eczema (Atopic Dermatitis) of European Dermatology Forum concluded that there is not enough evidence to support the general use of both first and second generation H1-antihistamines for treatment of pruritus in atopic eczema (1b, A) (17).

Evidence review

The first systematic review on the use of antihistamines in atopic dermatitis was performed in 1999 (30). Sixteen studies were included, but 13 of these lacked randomisation, had no placebo group or had fewer than 20 participants per group. Of the three remaining studies (grade B), two trials refuted and one trial supported the use of antihistamines in relieving pruritus in atopic dermatitis (5).
No specific trials of alimemazine were identified. One of the three remaining studies by Wahlgren et al compared terfenadine (non-sedating H1-antihistamine) and clemastine fumarate (sedating H1-antihistamine). The study was randomized with a double-dummy protocol, with each patient receiving 3 courses in random order: 1/ active terfenadine and placebo clemastine fumarate; 2/ placebo terfenadine and active clemastine fumarate; and 3/ placebo terfenadine and placebo clemastine fumarate. Patients were permitted to use topical hydrocortisone and emollients during the study. The authors found no significant difference in the intensity of itch between the 3 treatment groups. The sedative effect of clemastine fumarate was significantly greater than terfenadine or placebo, yet its antipruritic effect did not differ (30).
As part of a comprehensive health technology assessment of treatments available for atopic eczema, randomised controlled trials investigating the effects of antihistamines in atopic eczema were summarised in an HTA report (Hoare 2000). The authors identified 21 RCTs of any oral antihistamines for the treatment of atopic eczema. Of these, studies investigating sedating antihistamines or studies investigating H2 antihistamines (alone or combined with H1 antihistamines) were unable to demonstrate a clear benefit of the intervention. Generally, the authors of the HTA report state that study reporting was poor, rendering it difficult to draw firm conclusions (5).
Those studies that have evaluated sedating antihistamines against placebo did not show any benefit for pruritus or global improvement. The number of study participants was also relatively small (6).

Tab.2 Patient characteristics and interventions of included studies of antihistamines (narrowed down to sedating H1-antihistamines)

Study	Design	No. of patients	Age (years)	Duration	Severity	Treatment	Comparator	Co-treatments	Withdrawals and drop-outs
Foulds & MacKie, 1981	Multip. crossover RCT	21	14–29	3 × 2 weeks	Life-long atopic eczema	Cimetidine + placebo vs Sedative H_1 + placebo vs Cimetidine + H_1	Placebo Placebo H_1	Ichthammol + emulsifier + 25 mg promethazine hydrochloride	One loss to follow-up
Frosch et al., 1984	Multiple crossover RCT	18 179 OSR	14–43	3 × 4 weeks	3-year history of atopic eczema	Cimetidine + chlorpheniramine vs Chlorpheniramine + Placebo vs Placebo + placebo	Placebo	Bland greasy ointment 0.1% betamethasone	Two personal reasons
Klein & Galant, 1980	Parallel RCT	20	2–16	1 week	Acute exacerbations of at.ezma	Hydroxyzine 1.25 mg/kg/day	Cyproheptadine 0.25 mg/kg/day	Lubriderm lubricating cream	*
Monroe, 1992	Parallel RCT	41 out of 59	18–65	1 week	*	10 mg loratadine o.d. placebo b.d. 25 mg hydroxyzine t.d.s.	Placebo t.d.s.	Topical treatment but not specified	None

Savin et al., 1979	Unclear if parallel or crossover RCT	12	23–38	3 nights over 4 week	Severe atopic eczema	Trimeprazine tartrate 20 mg Trimeprazine tartrate 50 mg	Placebo	Yes but not specified	*
Simons, 1984	Crossover RCT	12	1–14	4 days	Severe widespread	Hydroxyzine 1.4 mg/kg	Hydroxyzine 0.7 mg/kg	*	Unclear
Wahlgren et al., 1990	Crossover RCT	25	17–42	3 days	Persistent atopic eczema	Terfenadine 60 mg b.d. Clemastine 2 mg b.d.	Placebo	1% hydrocortisone	None
Zuluaga de Cadena *et al.*, 1989 (Colomb. Translat)	Parallel RCT	52	2–6	4 weeks	Not specified	Hydroxyzine 25 mg daily in three divided doses Terfenadine 10 mg daily in two divided doses vs Astemizole 5 mg daily in one dose	Three active treatments	Emollients only	8 total (6 on hydroxyzine & 2 on astemizole treatm.)

Adapted from Hoare C, Li Wan Po A, Williams H. Systematic review of treatments for atopic eczema. Health Technol Assess. 2000;4(37):1-191. (6)

Explanations: - No data; o.d., once daily; b.d., twice daily; t.d.s., three times daily

Savin et al. admitted twelve men with severe and long-standing atopic eczema to a double-blind trial to establish the effects of trimeprazine tartrate, trimipramine maleate, and placebo on nocturnal scratching. Neither of the drugs altered the likelihood of a scratching bout beginning in wakefulness or in any stage of sleep (31).

A systematic search of the literature was undertaken by Sidbury et al 2014 to inform the guideline of care for the management of atopic dermatitis by the American Academy of Dermatology (AAD). It concluded that the short-term, intermittent use of sedating antihistamines may bring some benefit in the case of sleeping problems arising as a consequence of itch (5).

Sher et al. 2012 undertaken a meta-analysis on randomized controlled trials of topical therapies compared against their vehicles, and systemic therapies compared against their placebos in relieving the pruritus of atopic dermatitis. Only 10 studies (of a total of 647 study subjects) met the inclusion criteria for oral treatment. Oral anti-histamine was included in only one RCT that tested the effectiveness of cetirizine. The pooled relative risk of treatment effect of the anti-histamine versus placebo was 0.71 (95% CI, 0.49–1.01 [p = 0.058]). The evidence of heterogeneity in a random effects model was not found to be significant. The use of the anti-histamine as a therapeutic agent did not significantly reduce the pruritus of AD in patients compared to the use of placebo (32).

Fischer et al. 1968 studied the antipruritic effect of trimeprazine and cyproheptadine in double blind RCT. Forty-six patients with a variety of chronic pruritic dermatoses which has been present not less than six months, were studied for a period of one month. During this time, no other medications were prescribed (33). No significant difference could be found among the antipruritic effect of trimeprazine, cyproheptadine, and a placebo. However, a highly significant difference was demonstrated between taking any one of the three and nothing at all (33).

Equity / Stakeholder views (if relevant)

Decisions of local Trusts DTCs and neighbouring APCs	Alimemazine is non-formulary in Crawley, Horsham & Mid Sussex, Brighton & Hove, Coastal West and East Sussex 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 2014 Guideline on the Treatment of Atopic Eczema (Atopic Dermatitis) of European Dermatology Forum concluded that there is not enough evidence to support the general use of both first and second generation H1-antihistamines for treatment of pruritus in atopic eczema (1b, A) (17). The British Association of Dermatologists published an information leaflet, in which sedating H1- antihistamines are not generally recommended in the management of pruritus (7). The Clinical Knowledge Summaries (NICE) recommend a 2-week trial of sedating oral H1-antihistamine, such as hydroxyzine 25 mg at night or chlorphenamine 4 mg at night in the management of widespread pruritus (18). Conversely, for the management of severe pruritus in eczema NICE recommends a one-month trial of a non-sedating antihistamine (such as cetirizine, loratadine, or fexofenadine) (19).
Stakeholder views	No responses were received from dermatology consultants or clinicians to support or refute the use of alimemazine in this setting. The Clinical Commissioners requested a clarification on the narrow indication of this review, which were enlightened in the first part of this review. If the recommendation is made by PCN to blacklist alimemazine, this should be considered for all indications to avoid any ambiguity. A transitional period was suggested in case of a change to BLACK traffic light status to minimise any negative impact on existing patients. Also additional safety evidence was included in this review.
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 October 2017 Drug Tariff and maximum daily doses in BNF and Children BNF for pruritus (15, 16).

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 (15, 16).

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

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

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