Expert peer review on application for The 18th Expert Committee on the Selection and Use of Essential Medicines requested an evaluation for the use of chlorphenamine, the first generation histamine-1-receptor antagonist (FGAHs) currently on the EML versus diphenhydramine.

Given the broad use and favourable profile of 2nd generation systemic antihistamines (SGAHs), the review provides information on the efficacy, safety and cost information on two 1st generation antihistamines (FGAHs) chlorphenamine and diphenhydramine, plus an overview of efficacy, safety and cost of three over-the-counter, SGAHs: cetirizine, loratadine and fexofenadine and compares them to FGAHs.

The review was intended to answer the following questions.

1. Should Diphenhydramine replace Chlorphenamine on the Essential Medicines List?
2. Should a SGAH be on the WHO Essential Medicines List?
3. If so, should this be an addition or replacement to the FGAH currently on the list?

1. Assessment of efficacy
a. Have all relevant studies on efficacy been included
   Yes X  No (if no, please provide reference and information)

b. Summarize the data on efficacy, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

The evidence from five RCTs does show similar effectiveness and side effect profile of the two medications for both allergic rhinitis and urticaria. However, the review has shown significant evidence comparing efficacy and safety of SGAHs with FGAHs. Fifteen RCTs show similar efficacy between the two classes of medications in treating allergic rhinitis with significantly less side effects (in frequency and severity) resulting from use of SGAHs. For treatment of urticaria, nine RCTs showed similar efficacy between FGAHs and SGAHs, with lower incidence of side effects. Six RCTs, three retrospective studies and one systematic review provide evidence establishing superior safety profile of SGAHs over that of FGAHs. Significant sedation and psychomotor impairment is observed with FGAHs compared to SGAHs.

The review provides a detailed discussion on the use of antihistamines in anaphylaxis and concludes that there is no strong evidence recommending the use of antihistamines for this indication. There are no RCTs available that evaluate the use of antihistamines in anaphylaxis. The referenced guidelines strongly recommend the use of epinephrine as first line treatment for anaphylaxis and only recommend antihistamines as adjunct therapy for possible benefit in histamine mediated cutaneous reactions.

c. Please provide any additional relevant information with reference

2. Assessment of safety
a. Have all relevant studies on safety been included
   Yes X  No (if no, please provide reference and information)

b. Summarize the data on safety, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)
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The major distinction made between these medicine classes is on the basis of their side-effect of sedation. The FGAHs are referred to as ‘sedating’ while the SGAHs as ‘non-sedating’. This broad distinction is based on two primary differences between these medicine classes: 1) SGAHs are more specific to H-1 receptors compared to FGAHs. And 2) FGAHs are able to cross the blood brain barrier as opposed to the SGAHs. These differences in receptor specificity and lipophilicity cause FGAHs to display significant central nervous system, cardiovascular system, and gastrointestinal system side-effects.

FGAHs, in addition to their narrow therapeutic index leading to toxicity and implications in infant deaths (via accidental overdose and via homicides by caregivers) and suicides in teenagers and adults, are also responsible for cognitive impairment and disrupted sleep in children and adults.

Due to the anticholinergic side effects, the use of FGAHs in the elderly is strongly discouraged and SGAHs are recommended for use in allergic conditions. Evidence from 5 RCTs, two pharmacokinetic studies, a systematic review and guidelines conclude against the use of FGAHs in infants and children due to risk of sedation and death and establish safety of SGAHs.

c. Please provide any additional relevant information with reference

3. Assessment of cost and availability
   a. Have all relevant data on safety provided
      Yes X No (if no, please provide reference and information)

b. Summarize the data on cost and cost effectiveness, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

For cost and availability, using MSH pricing guide, the monthly treatment cost with loratadine is more economical than chlorphenamine.

The review concluded that due to the pharmacokinetics and clinical benefits of SGAHs, their use may pose an overall economic benefit. Furthermore, given the association of lost productivity with the use of FGAHs, use of SGAHs may prevent negative economic effects in the workplace.

c. Please provide any additional relevant information with reference

d. Is the product available in several low and middle income countries?

Ten of the fifteen countries surveyed had at least one formulation of chlorphenamine on the NEML, modeled after the WHO EML.

53% of the surveyed nations have included a SGAH on their respective NEMLs, indicating a growing trend and necessity for these agents for patient care, despite lack of WHO EML listing of these agents or class. However, not having an SGAH on the EML could be a disadvantage for many nations who primarily use WHO EML to establish their NEMLs.

4. Assessment of public health need
   a. Please provide the public health need for this product (1-2 sentences)
The World Allergy Association, an international umbrella organization for regional and national allergy and clinical immunology societies, in a 2011 report states that the prevalence of allergic conditions such as rhinitis, anaphylaxis, food and medicine allergies and urticaria is rising worldwide in both developing and developed nations. It is estimated that between 30-40% of the world’s population suffers from an allergic condition at any given time. However, many chronic allergic conditions are underdiagnosed and undertreated, possibly due to lack of awareness, therefore, underestimating the impact of allergic diseases on health and on the quality of life for the patients

b. Do guidelines (especially WHO guidelines) recommend this product? If yes, which ones? List 1 or 2 international preferable


SGAHs, specifically loratadine and fexofenadine, are preferred over FGAHs. Citing proven safety and effectiveness in children, WHO-collaborated guidelines, recommend use of SGAHs for treatment of allergic rhinitis in children and recommends against the use of FGAHs due to safety concerns, unless SGAHs are not available.

The same is true for urticaria, where the use of SGAH should be primary option in children.[113] An advantage, in addition to the low side effect profile, in the treatment of chronic urticaria SGAHs dose may be escalated up to four times in select patients if the standard dose is deemed ineffective; this cannot be done with FGAHs due to the possibility of fatal side effects.

5. Are there special requirements for use or training needed for safe/effective use?
If yes, please provide details in 1-2 sentences

No

6. Is the proposed product registered by a stringent regulatory authority?

Yes X  No

7. Any other comments

SGAHs have a better safety and tolerability profiles, and have at least similar efficacy compared with FGAHs.

8. What is your recommendation to the committee (please provide the rationale)

1. Delete Chlorphenamine from the EML c and EML and not include diphenhydramine. Based on the SRs , both are less safe and effective than SGAHs both in children and adults. I could not find any evidence to recommend leaving chlorphenamine in the EML.

2. Add to the EML: Loratadine, tablet and syrup formulations. A square box designation is recommended for loratadine, to indicate other medications in the second generation anti-histamine class are acceptable alternatives to loratadine.

3. Add to the EMLc: Loratadine, tablet and syrup formulations. A square box designation is recommended. Age restriction for loratadine is recommended for use against in children younger than 2 years of age.