Comments on Chlorphenamine from Expert Member

3. ANTIALLERGICS AND MEDICINES USED IN ANAPHYLAXIS

| ☐ chlorphenamine | Injection: 10 mg (hydrogen maleate) in 1-ml ampoule. |
|                | Oral liquid: 2 mg/5 ml. |
|                | Tablet: 4 mg (hydrogen maleate). |
|                | ≥ 1 year. |
|                | Review of diphenhydramine to assess comparative efficacy and safety with chlorphenamine as a possible preferable alternative. |

**Comment 1:** Regarding the comparative efficacy and safety between chlorphenamine and diphenhydramine, if there are any, will not be sufficient for recommending a preferable choice. Safety data is likely to be a class effect with anticholinergic activities as a major factor along with somnolence effects, of which diphenhydramine seems to have a disadvantage.

**Discussion:**

1. Micromedex 2007 search. There was no comparison between chlorpheniramine and diphenhydramine published in the database.

2. Pubmed search. Using the term chlorpheniramine AND diphenhydramine and limited the search to clinical trials i.e. (("chlorpheniramine"[MeSH Terms] OR chlorpheniramine[Text Word]) AND ("diphenhydramine"[MeSH Terms] OR diphenhydramine[Text Word])) AND Clinical Trial[ptyp], only 12 articles were found (appendix 1) with the following retrievable relevant summaries. The only accountable difference between the two is that diphenhydramine is more sedating than chlorphenamine.


The antihistamines **(chlorpheniramine, diphenhydramine)** had lowest abuse liability profiles, while the antidepressants (amitriptyline, fluoxetine, trazadone) and non-benzodiazepine hypnotics (zolpidem, zopiclone) had similar profiles.

The general rank order of (soporific) effects was diphenhydramine (50 mg), followed by diphenhydramine (25 mg), followed by chlorpheniramine (4 mg). Greater soporific effects from diphenhydramine relative to chlorpheniramine ($P < .05$) was observed.


The antihistamine products in order of increasing frequency of significant side effects were: trimeprazine, chlorpheniramine, hydroxyzine, diphenhydramine, and tripelennamine. The order of antihistamine preference by the patients was chlorpheniramine (27%), diphenhydramine (22%), tripelennamine (20%), hydroxyzine (16%), and trimeprazine (14%).

The suppression of skin test reactivity by single doses of six antihistamines was measured before and after a period of daily antihistamine ingestion in 18 subjects. Single doses of hydroxyzine, 50 mg; chlorpheniramine, 16 mg; and promethazine, 50 mg; induced significant suppression of skin test reactivity at 2 hr, whereas the suppression produced by tripelennamine, 100 mg; diphenhydramine, 50 mg; and cyproheptadine, 16 mg; did not differ significantly from that produced by placebo.

**Note.** DDD of chlorpheniramine and diphenhydramine are 12 mg. and 200 mg. respectively. For single dose test, should 4 mg of chlorpheniramine (instead of 16 mg.) be compared with 50 mg. of diphenhydramine?

**Comment 2:** The Subcommittee requested a review of diphenhydramine to assess the comparative efficacy and safety with chlorphenamine, as it may be applicable to a broader age range of children than chlorphenamine. After reviewing available data, it was found that the age limit of diphenhydramine injection and chlorphenamine injection was the same i.e. 1 month. Additionally, diphenhydramine liquid in an elixir form may contain as much as 14% of alcohol (PAI Pharmaceutical Associates, Inc.) and 52 elixir products (not all of them contain alcohol) are available in the US. (Micromedex 2007). In contrast, only 8 products of chlorphenamine liquid in an elixir form are available in the US, and none of them are single ingredient chlorphenamine (Micromedex 2007).
Discussion:

1. In the US, diphenhydramine injection is recommended to be used for infant age > 1 month, while oral form is used in children age > 2 years.

**Pediatric Patients**

**Other than premature infants and neonates:** 5 mg/kg/24 hr or 150 mg/m²/24 hr. Maximum daily dosage is 300 mg. Divide into four doses, administered intravenously at a rate generally not exceeding 25 mg/min, or deep intramuscularly. Source PDR for diphenhydramine Injection USP.

2. In the UK, chlorphenamine injection is licensed for use in infant age > 1 month, while oral form is licensed for use in infant age > 1 year.

Chlorphenamine injection, SPC from the eMC

**Link Pharmaceuticals Ltd**

Horsham
West Sussex
RH12 1AH

**Chlorphenamine injection**

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
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</thead>
<tbody>
<tr>
<td>1 month to 1 year</td>
<td></td>
<td>0.25mg/kg</td>
</tr>
<tr>
<td>1 to 5 years</td>
<td>2.5mg to 5mg</td>
<td>0.20mg/kg</td>
</tr>
<tr>
<td>6 to 12 years</td>
<td>5mg to 10mg</td>
<td>0.20mg/kg</td>
</tr>
<tr>
<td>12 to 18 years</td>
<td>10mg to 20mg</td>
<td>0.20mg/kg</td>
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</tbody>
</table>

![Piriton Syrup](piriton-syrup.png)
Comment 3: Regarding the square box listing of chlorphenamine. The Subcommittee recommended that these medicines be reviewed as chlorphenamine is not registered for children under 1 year of age and may not be the best indicative drug for this class. After reviewing available data, when compared approval indications for each of the medicines in this class, chlorphenamine has the most coverage, is available in both oral and parenteral form and approved to be used in infant age 1 month for parenteral route (chlorphenamine injection – Link Pharmaceutical Ltd.). Should the square box be lifted off from chlorphenamine?

1. US FDA and UK approval indications for each of the medicines in this class are listed in the Table below. Dimetindene (R06AB03), Pheniramine (R06AB06), Dextromethorphan (R06AB06) and Talastine (R06AB07) are not included in the table because of poor availability, especially outside of the EU. Data scarcity is also a problem.

<table>
<thead>
<tr>
<th>R06AB Substituted alylaminés</th>
<th>Age</th>
<th>AC</th>
<th>AR</th>
<th>AP</th>
<th>AE</th>
<th>DR</th>
<th>DS</th>
<th>HF</th>
<th>IN</th>
<th>UR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brompheniramine (R06AB01) US PD</td>
<td>2 yr¹</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
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<td>✔️</td>
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<tr>
<td>Brompheniramine (R06AB01) UK</td>
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<td>Not available</td>
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<tr>
<td>Dextromethorphan (R06AB02) US</td>
<td>2 yr²</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
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<td></td>
<td>✔️</td>
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<tr>
<td>Dextromethorphan (R06AB02) UK</td>
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<td></td>
<td></td>
<td></td>
<td>Not available</td>
</tr>
<tr>
<td>Chlorphenamine (R06AB04) US</td>
<td>2 yr³</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
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<td>τ</td>
</tr>
<tr>
<td>Chlorphenamine (R06AB04) UK PD</td>
<td>1 mo⁴</td>
<td></td>
<td>✔️</td>
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<td>✔️</td>
<td>✔️</td>
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<td>✔️</td>
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</tr>
</tbody>
</table>

US = The United State of America, UK = The United Kingdom, PD = Parenteral Dose,
¹ For oral drops, approval age is 1 month.
² No parenteral dose is available in the US.
Oral dose. For subcutaneous route dosage is available for children age > 6 and IM or IV routes dosages are available only for adults and adolescents.

For oral syrup, approval age is 1 year.

AC = Allergic Conjunctivitis, AR = Allergic Rhinitis, AP = Anaphylaxis, AE = Angioedema, DR = Desensitisation reactions, DS = Drug and Serum reactions, HF = Hay Fever, IN = Insect bites and stings, UR = Urticaria,

✓ = approved indications  ✘ = not-FDA-approved indications  Blank = not mentioned

Source: Gold Standard. Clinical Pharmacology CD-ROM. 2007 and Medicines.org.uk (eMC)

### Comment 4:
When comparing licensed indications between chlorphenamine and diphenhydramine, it was found that diphenhydramine had been approved with fewer indications. Availability is more limited than chlorphenamine. Combining comment 3 and comment 4, chlorphenamine should still be listed in the EML.

### Discussion
1. Below is the Table summarizing licensed indications for diphenhydramine in the US.

<table>
<thead>
<tr>
<th>R06AA</th>
<th>Amino alkyl ethers</th>
<th>Age</th>
<th>AC</th>
<th>AR</th>
<th>AP</th>
<th>AE</th>
<th>DR</th>
<th>DS</th>
<th>HF</th>
<th>IN</th>
<th>UR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphenhydramine (R06AA02) US PD</td>
<td>1 mo¹</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diphenhydramine (R06AA02) UK</td>
<td>Not available</td>
<td></td>
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</tbody>
</table>

¹Diphenhydramine injection is recommended to be used for infant age > 1 month, while oral form is used in children age > 2 years.

### Comment 5:
The lowest dose recommended for chlorphenamine for children (1 month-2 years) in the BNF-C (2006) is 1 mg twice daily. The subcommittee endorsed the inclusion of chlorpheniramine liquid formulation in the EML. This is quite contradictory to the decision not to include ibuprofen liquid in the EML. The discussion below will show that ibuprofen suspension should be listed in the EML for children.

### Discussion:
1. Chlorphenamine tablets are usually scored, while ibuprofen tablet are rarely scored. Dividing ibuprofen tablets for use in small children is not practical.
2. Chlorphenamine is readily soluble in water, while ibuprofen does not dissolve in water at all. After dividing the tablet, preparing ibuprofen into solution is not possible, making it impractical.
3. The lowest dose recommended for chlorphenamine in children (1 month-2 years) in the BNF-C (2006) is 1 mg twice daily which is ¼ of a tablet, and this is do-able. The smallest tablet of ibuprofen listed in the EML is 200 mg. (almost always unscored, insoluble in water) and the dosage for infant is 5 mg/kg. Therefore, infants weighing less than 10 kgs should take less than 50 mg. of ibuprofen, which is smaller than ¼ of a tablet, actually for an infant who weighs 4 kgs the calculated dose is 20 mg. which is 1/10 of a tablet, this is undo-able.

4. In the area where parenteral ibuprofen is not available (such as Thailand), ibuprofen suspension has been used successfully to close the PDA. This is confirmed by the work of Aly et al. who compared oral ibuprofen suspension (OIS) at 5 mg/kg and IV indomethacin and concluded that oral ibuprofen could be an easy-to-administer and efficacious alternative in the treatment of PDA.


5. My suggestion. Ibuprofen suspension should be listed in the EML for children. A warning statement about improper use of ibuprofen suspension must be in place, such as “Paracetamol is the drug of choice for fever and pain in children. For young children, if deemed necessary, ibuprofen suspension should be used cautiously, especially in the area where hemorrhagic fever is endemic. Severe bleeding may occur.”
Appendix 1


1: Jaffe JH, Bloor R, Crome I, Carr M, Alam F, Simmons A, Meyer RE.
   A postmarketing study of relative abuse liability of hypnotic sedative drugs.
   PMID: 14756709 [PubMed - indexed for MEDLINE]

2: Simons FE, Fraser TG, Maher J, Pillay N, Simons KJ.
   Central nervous system effects of H1-receptor antagonists in the elderly.
   PMID: 10071518 [PubMed - indexed for MEDLINE]

3: Lang AE.
   Antihistaminics in idiopathic dystonia.
   PMID: 8624213 [PubMed - indexed for MEDLINE]

4: Witek TJ Jr, Canestrari DA, Miller RD, Yang JY, Riker DK.
   Characterization of daytime sleepiness and psychomotor performance following H1
   receptor antagonists.
   PMID: 7749974 [PubMed - indexed for MEDLINE]

5: Philpot EE, Brooker AE, Biegalski CS.
   Effects of sedating and nonsedating antihistamines on flying performance.
   PMID: 8264923 [PubMed - indexed for MEDLINE]

6: Grant JA, Bernstein DI, Buckley CE, Chu T, Fox RW, Rocklin RE, Schoenwetter
   Double-blind comparison of terfenadine, chlorpheniramine, and placebo in the
   treatment of chronic idiopathic urticaria.
   PMID: 3126220 [PubMed - indexed for MEDLINE]

7: Gaffey MJ, Gwaltney JM Jr, Sastre A, Dressler WE, Sorrentino JV, Hayden FG.
   Intranasally and orally administered antihistamine treatment of experimental
   rhinovirus colds.
   PMID: 3307567 [PubMed - indexed for MEDLINE]

8: Rumore MM, Schlichting DA.
   Clinical efficacy of antihistaminics as analgesics.
   PMID: 2872645 [PubMed - indexed for MEDLINE]

9: von Maur K.
   Antihistamine selection in patients with allergic rhinitis.
   PMID: 2864005 [PubMed - indexed for MEDLINE]


1. Chlorpheniramine (with square box listing)

Licensing status in children:

UK: Syrup not licensed for children under 1 year; tablets not licensed for use in children under 6 years; injection not licensed for use in neonates. Tablets indicated for use in allergy, injection for treatment of anaphylaxis (not in neonates).

Australia, US: not licensed for use in children (Cranswick review).

In Australia, dexchlorpheniramine is used (dextroisomer of chlorpheniramine) where oral liquid is used in children aged 2-6 years and tablets used in children 6-12 years for the treatment of allergic conditions (e.g. rhinitis, conjunctivitis, urticaria, contact dermatitis), pruritus and adjunctive treatment for anaphylactic and anaphylactoid reactions (AMH January 2007).

Specific safety issues in relation to use in children:

BNF-C (2006): Suggests sedating antihistamines should not be given to children under 2 years except on specialist advice, because safety of use has not been established. In addition, sedating antihistamines have significant anti-muscarinic activity and should not be used in neonates, and should be used with caution in children with urinary retention, glaucoma or pyloroduodenal obstruction.

Route of administration, appropriateness of dose form and strength:

BNF-C (2006) suggests usual doses in children under 12 years for symptomatic relief of allergy such as hayfever and urticaria are 1mg twice daily (1 month-2 years), 1 mg 4-6 hourly (children 2-6 years) and 2 mg every 4-6 hours (children 6-12 years). Therefore if chlorpheniramine is considered appropriate in children, there may be a need for a liquid formulation (2 mg/5 ml).

Current listing in 15th EML:
- Injection: 10 mg (hydrogen maleate) in 1-ml ampoule.
- Tablet: 4 mg (hydrogen maleate).

Other comments received on listing of this medicine:

FIP: Have deleted chlorpheniramine and suggested that diphenhydramine injection 50 mg/ml and tablets 25 mg be added to the Model List.

HW Seyberth (German perspective): Comments that chlorpheniramine appears popular in the UK but is unknown in Germany, apart from use in a combination flu
medication. Notes that if the additional sedative effect of an older antihistamine is appreciated, dimetindene (Fenestil) is of widespread use on the Continent for decades, licensed for children >1 year and available in most age appropriate formulations including droplets. Otherwise, cetirizidine is preferred antiallergic agent. Provides some more recent references for dimetindene.
Reviews of this Section were prepared by Dr Coelho and Dr Peterson. Comments were received as listed in Annex 6. No applications for additional medicines for this Section were submitted. The Subcommittee considered that allergic disorders (e.g. rhinitis, conjunctivitis, urticaria and contact dermatitis) are a common problem in children and therefore medicines for their treatment could be considered essential. Epinephrine was endorsed as essential for treatment of anaphylaxis. The question of inclusion of antihistamines was more difficult. The value of sedating versus non-sedating antihistamines needs to be assessed, and there are national preferences for particular medicines within these classes. Different dosage forms need to be available, and it was noted that if, for example, oral liquid forms of antihistamines were recommended, these might not be appropriate for use in children under 2 years. In the absence of a formal review of comparative effectiveness and safety, the Subcommittee decided to endorse the inclusion of chlorphenamine injection and tablets with a square box on the Model List, noting that the choice of medicine within the class of sedating antihistamines would be a national one, depending upon availability and cost. The Subcommittee recommended that these medicines be reviewed as chlorphenamine is not registered for children under 1 year of age and may not be the best indicative drug for this class. The Subcommittee requested a review of diphenhydramine to assess the comparative efficacy and safety with chlorphenamine, as it may be applicable to a broader age range of children than chlorphenamine. It also noted the need for a review of the use of non-sedating antihistamines in children for its next meeting.