## Antimalarials in the WHO Essential Drugs List for Children

### Reviewer No.1

#### Part I: Evaluation of the current list

### Proposed grouping from the March 2007 meeting

#### 6.5.3 Antimalarial medicines

<table>
<thead>
<tr>
<th></th>
<th>'Green'</th>
<th>'Yellow'</th>
<th>'Red' and 'Pink'</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>6.5.3.1 For curative treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Artemether-lumefantrine tablet</td>
<td>amodiaquine tablet</td>
<td>artemether oily injection</td>
<td>none</td>
</tr>
<tr>
<td>Artemether oily injection</td>
<td>artesunate injection / tablet</td>
<td>chloroquine tablet / oral liquid</td>
<td></td>
</tr>
<tr>
<td>Artesunate injection / tablet</td>
<td>doxycycline capsule / tablet</td>
<td>mefloquine tablet</td>
<td></td>
</tr>
<tr>
<td>Chloroquine tablet / oral liquid</td>
<td>primaquine tablet</td>
<td>quinine injection / tablet</td>
<td></td>
</tr>
<tr>
<td>Proguanil tablet</td>
<td>sulfadoxine-pyrimethamine tablet</td>
<td></td>
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</tr>
</tbody>
</table>

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<tbody>
<tr>
<td><strong>6.5.3.2 For prophylaxis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>chloroquine tablet / oral liquid</td>
<td>doxycycline capsule / tablet</td>
<td>none</td>
</tr>
<tr>
<td>None</td>
<td>mefloquine tablet</td>
<td>proguanil tablet</td>
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</tbody>
</table>

For proposed 'yellows': Are these essential medicines for children? Yes, with one exception (see below),
- Do these medicines meet a public health need? Yes
- Are they registered for use in children? Yes
- Are there any unanswered/unexpected clinical issues with respect to effectiveness or safety? Yes

See below:

### My proposed revised grouping

#### 6.5.3 Antimalarial medicines

<table>
<thead>
<tr>
<th></th>
<th>'Green'</th>
<th>'Yellow' (should only be used in combination with another antimalarial)</th>
<th>'Pink' (not indicated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artemether-lumefantrine* tablet</td>
<td></td>
<td>amodiaquine tablet</td>
<td>proguanil tablet</td>
</tr>
<tr>
<td>Artemether oily injection</td>
<td></td>
<td>artemesunate tablet</td>
<td></td>
</tr>
<tr>
<td>Artesunate injection / tablet</td>
<td></td>
<td>doxycycline² capsule / tablet</td>
<td></td>
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<tr>
<td>Quinine injection / tablet</td>
<td></td>
<td>clindamycin</td>
<td></td>
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<tr>
<td>Mefloquine³ tablet</td>
<td></td>
<td>mefloquine³ tablet</td>
<td></td>
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<tr>
<td>Sulfadoxine-pyrimethamine tablet</td>
<td></td>
<td>sulfadoxine-pyrimethamine tablet</td>
<td></td>
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<tr>
<td>Chloroquine⁴ tablet / oral liquid</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Primaquine&quot; tablet</td>
<td></td>
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<td></td>
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</table>

* Not recommended for children <5 kg
² Not recommended for children < 8 years old
³ Not recommended for children <5 months old
∞ Do not use for falciparum malaria. Limit use to only central American regions.
⁴ Only for use to achieve radical cure/prevention of relapses of *P. vivax* and *P. ovale* infections. Adjust dosing in moderate G6PD deficiency. Do not give in severe G6PD deficiency.
1. The list aims to present the minimum medicine needs for a basic health care system, thus inclusion of a sub-section on "antimalarial medicines for prophylaxis" (i.e. for travelers from a non-endemic site) is not appropriate. In resource-poor settings, since chemoprophylaxis is not generally carried-out, chemoprophylaxis cannot be considered as "essential". This is in contrast to intermittent preventive treatment, the administration of a full course of an anti-malarial treatment to a population at risk at specified time points regardless of whether or not they are known to be infected. Intermittent preventive treatment is now a recommended approach in the prevention of malaria in pregnancy and is being explored as a potential way of preventing malaria in infants and children.

2. The choice of antimalarial for curative treatment should be based on infecting species, resistance patterns in the community, and severity of disease.

3. Uncomplicated falciparum malaria should be treated with a combination of oral antimalarials with different mechanisms of action.
   a. The following artemisinin-based combination therapy are currently recommended by WHO:
      - artether-lumefantrine (Not recommended in children below 5 kg),
      - artesunate + amodiaquine,
      - artesunate + mefloquine, OR
      - artesunate + sulfadoxine–pyrimethamine
   b. Amodiaquine + sulfadoxine–pyrimethamine may be considered as an interim option where artemisinin-based combination therapy cannot be made available, provided that efficacy of both is high.
   c. The choice of artemisinin-based combination therapy in a country or region will be based on the level of resistance of the partner medicine in the combination:
      - in areas of multidrug resistance (South-East Asia), artesunate + mefloquine or artemether-lumefantrine
      - in Africa, artemether-lumefantrine, artesunate + amodiaquine; artesunate + sulfadoxine-pyrimethamine.
   d. Atovaquone-proguanil is safe and effective but is not recommended for deployment in endemic areas because of its very high cost. This fixed drug combination is currently not on the list.
   e. Dihydroartemisinin-piperaquine has been shown to be safe and effective for the treatment of uncomplicated malaria caused by multi-drug-resistant P.falciparum and P. vivax but an application for inclusion in the list has not been received (?).

4. Treatment of severe falciparum malaria.
   a. The following are recommended to be given parenterally:
      - artesunate,
      - artemether, OR
      - quinine
   b. Treatment is completed by giving a full course of oral combination therapy:
      - artemisinin-based combination therapy OR
      - quinine + doxycycline (doxycycline not recommended in children < 8 years old; use clindamicin instead).

5. Treatment of uncomplicated vivax malaria
   a. The following are recommended:
      - chloroquine + primaquine,
      - amodiaquine+ primaquine (for chloroquine–resistant), OR
      - artemisinin-based combination therapy (except artesunate + sulfadoxine–pyrimethamine)
6. Treatment of severe vivax malaria (same as for severe falciparum malaria)

7. The recommended treatment for malaria caused by *P. ovale* is the same as that given to achieve radical cure in vivax malaria, i.e. with chloroquine and primaquine. *P. malariae* should be treated with the standard regimen of chloroquine as for vivax malaria, but it does not require radical cure with primaquine.

8. Few fixed drug combinations exist and their development and rigorous testing is encouraged.

- **Action proposed for the Committee to take**
  - Endorse greens as essential.
  - Endorse yellows as essential but with caveats.
  - Pink should not be on the list of essential drugs.

**References:**

Part II: Evaluation of drugs to be added to the list:

There are 2 are resubmissions from the March 2007 meeting: rectal artesunate and an artemether/lumefantrine suspension.

1. rectal artesunate

Background: The application refers to a study (Barnes KI, et al.) that directly compared rectal artesunate and intravenous quinine in 144 people with moderately severe malaria: 109 children in Malawi and 35 adults in South Africa. It found that in children, artesunate significantly reduced fever clearance time and parasite clearance time compared with quinine. In adults, there was no significant difference in fever clearance time and parasite clearance time. An additional randomized study identified by the expert reviewer, compared rectal artesunate and intramuscular artemether in 79 children in Papua New Guinea. There were statistically significant differences in parasite clearance time with the rectal artesunate but this small study did not find differences in clinical outcomes (Harin A, et al.).

Evidence on safety of rectal and intravenous artesunate was provided. Generally, particularly in the context of severe malaria, artesunate preparations are well tolerated. The Committee noted the potential value of rectal dosage formulations and overall the evidence provided in the application supports the public health need, effectiveness and safety of artesunate formulations for emergency use in adults and children for treating severe malaria. However, the Committee noted that the regulatory status of the products, particularly the rectal capsule, was unclear. The Committee therefore recommended that artesunate ampoules, containing 60 mg anhydrous artesunic acid with a separate ampoule of 5% sodium bicarbonate solution be added to the core list of the 15th WHO Model List with the note: for use in the management of severe malaria. The Committee decided, given uncertainty about current rectal products, to refer review of the rectal form to the paediatric subcommittee meeting and recommended further research on rectal dosage forms.

Check list for application for addition: rectal artesunate

(1) Have all important studies that you are aware of been included?  
   No ☑  (See additional references below)
(2) Is there adequate evidence of efficacy for the proposed use?  
   Yes ☑
(3) Is there evidence of efficacy in diverse settings and/or populations?  
   Yes ☑
(4) Are there adverse effects of concern?  
   No ☑
(5) Are there special requirements or training needed for safe/effective use?  
   No ☑
(6) Is this product needed to meet the majority health needs of the population?  
   Yes ☑
(7) Is the proposed dosage form registered by a stringent regulatory authority?  
   No ☑
(8) What action do you propose for the Committee to take?  
   Accept addition.
(9) Additional comments, if any.  
   Although the parenteral route is preferred for treatment of severe malaria whenever facilities are available, these facilities are usually lacking in the rural tropical villages where most cases arise. In these circumstances, the intrarectal route for giving antimalarials could be used as an alternative to parenteral treatments.
2. **artemether /lumefantrine suspension**

Background: An application has been received from Dafra Pharma (Belgium) for a powder for paediatric suspension of artemether/lumefantrine to be included in the Model List. The powder for suspension contains 7.9mg $\beta$-artemether/47.4 mg lumefantrine per gram of powder. After reconstitution with water the mixture delivers:

- 60 ml fixed-dose combination of 180mg $\beta$-artemether and 1080 mg lumefantrine.
- 120 ml fixed-dose combination of 360mg $\beta$-artemether and 2160 mg lumefantrine, i.e. the same 1:6 ratio as is included in the tablet formulation. The recommended dosage schedule delivers artemether in a daily dosage of approximately 4 mg/kg/day for 3 days.

The Committee noted while the application identifies a need for a paediatric formulation suitable for children <10 kg, the current WHO Guidelines for the Treatment of Malaria 2006 suggest tablets can be used for children $\geq$ 5 kg. The Committee also expressed some concerns about the recommended doses. For children 5 - 10 kg, the population most likely to be prescribed the suspension, the recommended doses of suspension were substantially lower than the currently recommended doses of the tablet formulation. There are limited clinical trial data presented in the application to demonstrate the efficacy and safety of the suspension at this dose, and these are short-term studies in small numbers of children. None are rigorous randomized controlled trials comparing the combination suspension with the drugs administered in tablet form in the same populations of patients. While the application states registration has been achieved in 19 countries and pending in a further 8, none of these are stringent regulatory authorities. The Committee noted the comments from the Global Malaria Programme (WHO), which concluded it could not support the application as the doses per age groups, the dosage regimen (single daily dose), and dosage ratio recommended in the submitted dossier are at variance with the current recommended WHO schedules (WHO Guidelines for the Treatment of Malaria, 2006). There is no evidence provided to the GMP Department, nor is there evidence available on the safety and efficacy of the dosages and regimen recommended in this submission.

**Check list for application for addition: artemether /lumefantrine suspension**

1. Have all important studies that you are aware of been included?  
   Yes ☑

2. Is there adequate evidence of efficacy for the proposed use?  
   No ☑

3. Is there evidence of efficacy in diverse settings and/or populations?  
   No ☑

4. Are there adverse effects of concern?  
   Yes ☑ Underdosing

5. Are there special requirements or training needed for safe/effective use?  
   No ☑

6. Is this product needed to meet the majority health needs of the population?  
   No ☑ The currently available tablet form is easy to store, dose, and administer.

7. Is the proposed dosage form registered by a stringent regulatory authority?  
   No ☑

8. What action do you propose for the Committee to take?  
   Do not accept addition of at this time.

9. Additional comments, if any.

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References:


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