APPLICATION FOR REVISION AND INCLUSION OF MALARIA MEDICINES IN WHO MODEL LIST OF ESSENTIAL MEDICINES

The objective of this application is to assure compatibility between the WHO Model list of essential drugs with the revised WHO Guidelines for the Treatment of Malaria (WHO/HTM/MAL/2006.1108). This is an update of the severe malaria section already presented and discussed at the last meeting of the committee in March. This update became necessary at the request of the committee to review the section on rectal artesunate. Modification to the dosage strengths is highlighted below.

ARTESUNATE FOR THE TREATMENT OF SEVERE MALARIA

1. Summary statement of the proposed changes

Severe malaria is a medical emergency that requires prompt diagnosis and treatment**.** The mortality of untreated severe malaria is thought to be 100%. The worsening problems of drug resistance, and the limited number of drugs available mean that only the parenteral formulations of quinine and the artemisinin derivatives meet the requirements of rapid action and high efficacy required for the treatment of severe malaria.

As a consequence to this situation, WHO recommendations for the treatment of severe malaria have been recently reviewed and revised based on formal systematic reviews, comparative clinical trials, observational studies and expert opinion. *(WHO (2006) Guidelines for the treatment of malaria. pp251. WHO/HTM/MAL/2006.1108).*

The risk of death for severe malaria is greatest in the first 24 h, yet in most malaria endemic countries, the transit time between referral and arrival at appropriate health facilities is usually prolonged thus delaying the commencement of appropriate antimalarial treatment. During this time the patient may deteriorate or die. It is recommended that patients are treated with the first dose of one of the recommended parenteral treatments before referral (unless the referral time is very short). This could be intramuscular artemether, artesunate or quinine, or a rectal formulation of artemisinin or artesunate.

In light of these recommendations, it is proposed that the rectal formulation of artesunate is now included in the WHO Model List of Essential Medicines. Intravenous quinine, intravenous artesunate, and intramuscular artemether are currently included in the 15th Edition of the WHO Model list of Essential Drugs (revised March 2007).

2. WHO Focal Point for this application.

Dr P. Olumese
Global Malaria Programme

3. Organization supporting the application

Global Malaria Programme
World Health Organization
Geneva
Switzerland

4. International Nonproprietary Names (INNs) of medicines included in application.

Artesunate

5. Formulations proposed for inclusion

5.1. Artesunate Suppositoires

Currently available as rectal capsules containing 50mg or 200mg sodium artesunate

6. Public Health Relevance

6.1. Malaria as a disease burden

Malaria is an important cause of death and illness in children and adults living in tropical countries. It is estimated that 300-500 million people suffer from malaria related illness and over one million people die as a result of malaria disease. Malaria mortality has risen in recent years, probably due to increasing resistance to antimalarial drugs. If ineffective drugs are given or treatment delayed in falciparum malaria, the parasite burden increases and severe malaria ensues. A patient may progress from having minor symptoms to having severe disease within a few hours.

In areas of high and stable transmission, such as in most of Africa south of the Sahara and Oceania, young children and pregnant women are at greatest risk. In contrast, in areas of unstable malaria with low or moderate transmission such as Asia and Latin America, people of all ages are at risk.

Malaria in humans is caused by four species of *Plasmodium, P.falciparum, P. vivax, P.ovale* and *P.malariae*. *P.falciparum* is responsible for the majority of deaths and illness. *P. vivax* accounts globally for around 40% of malaria cases and is the dominant species outside tropical Africa. In most areas where *P. vivax* is prevalent, transmission rates are low and consequently people of all ages are at risk. *P.ovale* and *P.malariae* are less prevalent but are distributed world-wide

6.2. Definition of severe malaria

Severe malaria is a medical emergency that is not easily distinguished from other severe diseases such as severe pneumonia, meningitis and bacteraemia which require different therapies. It is defined in a patient with *P. falciparum* asexual parasitaemia and no other obvious cause of their symptoms. The presence of one or more of the following clinical or laboratory features classifies the patient as suffering from severe malaria:

- *Clinical manifestations*: prostration, impaired consciousness, respiratory distress (acidotic breathing), Multiple convulsions, circulatory collapse, pulmonary oedema (radiological), abnormal bleeding, jaundice, or haemoglobinuria.
- *Laboratory Tests*: severe anaemia, hypoglycaemia, acidosis, renal impairment, hyperlactataemia or hyperparasitaemia.

At the periphery, the priority requirement is the rapid recognition of the signs and symptoms of severe malaria that should lead to emergency care or referral to a higher level of care. These are a history of fever plus at least one of the following: prostration, altered consciousness, lethargy or coma; respiratory distress; severe anaemia; convulsions; inability to swallow; persistent vomiting, dark or limited urine (adults only).

6.3. Objectives of treating severe malaria

The main objective is to prevent the patient from dying, secondary objectives are prevention of recrudescence, transmission or emergence of resistance and prevention of disabilities.

The mortality of untreated severe malaria is thought to approach 100%. With antimalarial treatment the mortality falls to 15–20% overall, although within the broad definition are syndromes associated with mortality rates that are lower (e.g. severe anaemia) and higher (metabolic acidosis). Death from severe malaria often occurs within hours of admission to hospital or clinic, and so it is essential that therapeutic concentrations of antimalarial are achieved as soon as possible.

Management of severe malaria comprises four main areas: clinical assessment of the patient, specific antimalarial treatment, adjunctive therapy, and supportive care.

Optimal care for severe malaria, therefore, requires well developed diagnostic facilities and intensive care.

6.4. Specific antimalarial treatment

It is essential that antimalarial treatment in full doses is given as soon as possible in severe malaria. Two classes of drugs are currently available for the parenteral treatment of severe malaria: the cinchona alkaloids (quinine) and the artemisinin derivatives (artesunate, artemether and artemotil).

Intravenous quinine, intravenous artesunate, and intramuscular artemether are currently included in the 15th Edition of the WHO Model list of Essential Drugs (revised March 2007).

7. Deployment and Treatment Details

7.1. Deployment

Pre-referral Treatment at the periphery- Emergency treatment

The risk of death for severe malaria is greatest in the first 24 h, yet in most malaria endemic countries, the transit time between referral and arrival at appropriate health facilities is usually prolonged thus delaying the commencement of appropriate antimalarial treatment. During this time the patient may deteriorate or die. It is recommended that patients are treated with the first dose of one of the recommended parenteral treatments before referral (unless the referral time is very short). This could be intramuscular artemether, artesunate or quinine, or a rectal formulation of artemisinin or artesunate.

The administration of artemisinins by the rectal route as pre-referral treatment is feasible even at the community level.

There is insufficient evidence to show whether rectal artesunate is as good as intravenous or intramuscular options in the complete management of severe malaria. Pending research from current trials, the recommendation is to use artesunate or artemisinin suppositories as pre-referral treatment and to refer the patient to a facility where complete parenteral treatment with either artesunate, quinine or artemether can be instituted. If referral is impossible, rectal treatment should be continued until the patient can tolerate oral medication, at which point a full course of the recommended ACT for uncomplicated malaria in the locality can be administered.

7.2. Recommended Treatment Schedules

Rectal Artesunate

This is indicated only as an Initial (pre-referral) treatment of severe malaria.

The recommended dose for rectal artesunate is 10mg/kg body weight, given as a single dose followed by referral of the patient to a facility where appropriate continued treatment can be instituted. The appropriate single dose of artesunate given by suppository should be administered rectally as soon as the presumptive diagnosis of severe malaria is made. In the event that an artesunate suppository is expelled from the rectum within 30 min of insertion, a second suppository should be inserted and, especially in young children, the buttocks should be held together, for 10 min to ensure retention of the rectal dose of artesunate.

Artesunate administered through the rectal route has been registered for use in several countries[†], and can be is available through the WHO

Dosage for initial (pre-referral) treatment

Weight (kg)	Artesunate dose
<40	10 mg/kg body weight
40–59	400 mg
60–80	800 mg
>80	1200 mg

8. Comparative effectiveness

8.1. Comparison of rectal artesunate with intravenous quinine as pre-referral treatment of severe malaria.

Summary of Randomized clinical trials

The objective of the trials that have been conducted was to establish the safety and efficacy of rectal artesunate as pre-referral treatment where there is no access to parenteral treatment.

Comparisons between rectal artesunate and intravenous artesunate or intravenous and intramuscular quinine have been carried out to assess response in the 12 or 24 hours immediately after treatment (Krishna *et al*., 2001; Barnes *et al*., 2004). These studies included two randomized, open-label Phase II and three randomised open label Phase III trials conducted in people with moderately severe malaria, i.e. patients who could not take drugs by mouth but did not have features of severe malaria and its complications. Patients in the artesunate group in the Phase III studies were rescued if their parasitaemia did not decline to below 60% of baseline parasitaemia or if they deteriorated clinically and developed features of severe malaria, convulsions or coma within 24 hours of treatment.

Artesunate had a superior effect on all efficacy criteria measured immediately after treatment. In children treated with artesunate, 80/87 (92%) had a parasite density lower than 60% of baseline, compared with 3/22 (14%) of those who received quinine

[†] *Benin, Brazil, Burkina Faso, Cambodia, Cameroon, Chad, China, Colombia, Congo (Brazzaville), Ecuador, El Salvador, Gabon, Ghana, Guatemala, Guinea (Conakry), Honduras, Ivory Coast, Kenya, Mali, Myanmar, Nicaragua, Niger, Nigeria, Panama, Senegal, Sierra Leone, Sudan, Tanzania, Togo, Trinidad and Tobago, Uganda, Vietnam, Yemen, Zanzibar*

(RR 0.09, 95% CI 0.04–0.19, *P* <0.0001). In adults, parasitaemia at 12 hours was lower than 60% of baseline in 26/27 (96%) in the artesunate group, compared with 3/8 (38%) in the quinine group. (RR 0.06, 95% CI 0.01–0.44, *P* <0.001). The differences were more significant at 24 h. Artesunate and/or dihydroartemisinin were detected in plasma within 12 h in all adults and in 84/87 of the children.

9.1. Adverse reactions to artemisinin derivatives

Artemisinin derivatives

Artemether and artesunate are safe and remarkably well-tolerated (Ribeiro and Olliaro, 1998; Price *et al*, 1999). There have been reports of mild gastrointestinal disturbances, dizziness, tinnitus, reticulocytopaenia, elevated liver enzymes values, and ECG abnormalities, including bradycardia and prolongation of QT values. Most of the studies have not found any ECG abnormalities. The only potentially serious adverse effect reported is Type 1 hypersensitivity reactions in approximately 1 in 3000 (Leonardi *et al*., 2001)

The neurotoxicity observed in animals treated with artemisinin derivatives has prompted large prospective assessments in humans but no evidence of neurotoxicity has been found (Kissinger *et al*., 2000; van Vugt *et al*., 2000; Hien *et al*., 2003).

Evidence of deaths of embryo and morphological abnormalities in early pregnancy has been demonstrated also in animals but not in humans treated during the second and third trimesters. Artemisinin derivatives have not been evaluated in the first trimester of pregnancy in humans and therefore their use in patients with uncomplicated malaria during this period should be avoided until more information is available (WHO, 2006).

9.2 Comparison of rectal artemisinin formulations with intravenous quinine.

A single administration of artesunate suppositories at a dose of 10 mg/kg was well tolerated in both children and adults. There was no significant difference in frequency of adverse events (defined as any new symptom, worsening of any existing symptom, sign or abnormal laboratory value) between treatment groups. Other than local reactions at the site of the intramuscular quinine injection in three adult patients, the few adverse events that occurred could have been attributable to falciparum malaria or to pre-existing disease.

One randomized clinical trial in children found that artemisinin significantly reduced the risk of hypoglycaemia compared with quinine (3/30 (10%) with artemisinin, 19/30 (63%) with quinine, RR 0.16, 95% CI 0.05–0.48) (Birku *et al.*, 1999*).*

10. Pharmacopoeial Standards

Standards for artemether and artesunate are included in the 5th Edition of the International Pharmacopoeia.

12. Proposed text for WHO Model Formulary.

For curative treatment of severe *P.falciparum* and *P.vivax* infections.

Artesunate	• Injection: ampoules containing 60mg anhydrous artesunic acid with a separate ampoule containing 5%sodium bicarbonate solution[‡] • Rectal capsules containing 50mg and 200mg sodium artesunate[§]

[‡] Already in the 15th Edition

[§] For use only as pre-referral treatment of severe malaria

REFERENCES

Barnes KI *et al.* (2004). Efficacy of rectal artesunate compared with parenteral quinine in initial treatment of moderately severe malaria in African children and adults: a randomised study. *Lancet,* 363:1598–1605.

Birku Y, *et al.*, (1999). Comparison of rectal artemisinin with intravenous quinine in the treatment of severe malaria in Ethiopia. *East African Medical Journal*, 76:154–159.

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