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# Malaria

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|  | **Artemisinin-Based Suppositories** |
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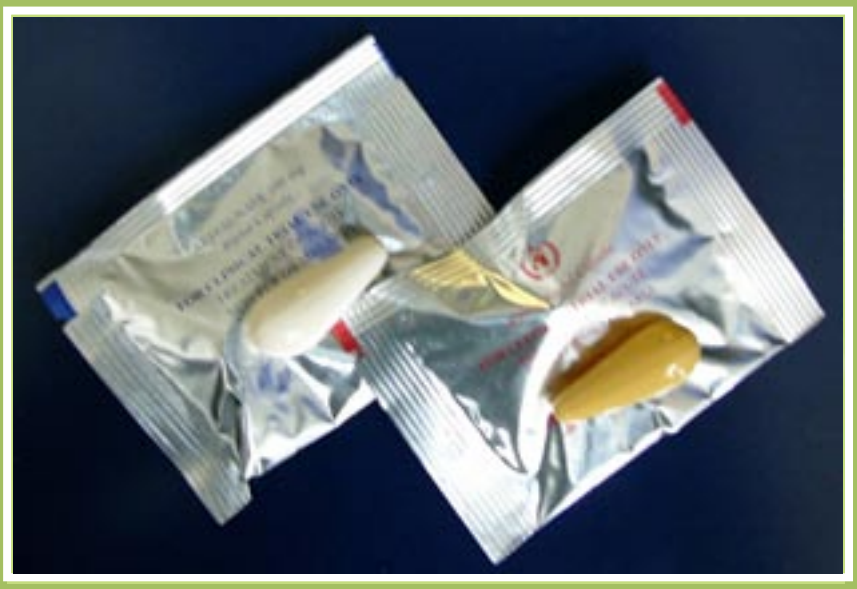
Global Malaria Programme

# Artemisinin-based suppositories

## Use of rectal artemisinin-based suppositories in the management of severe malaria



Report of a WHO Informal Consultation

World Health Organization

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Global Malaria Programme

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Report of a WHO Informal Consultation, 27–28 March 2006

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# 1. Background

Intrarectal administration represents a promising administration route of antimalarial medicines in the field, and is especially convenient for patients unable to swallow and when parenteral formulations are unavailable or cannot be administered. *Plasmodium falciparum* malaria is associated with severe morbidity and, in the absence of early diagnosis and effective treatment, it may be fatal. The cumulative probability of death increases with each hour's delay in treating the disease (*1*).

The immediate objective of therapy in severe malaria is to save life and to reduce the risk of serious complications. This can be achieved by rapidly reducing the total parasite biomass, and the artemisinin derivatives are of special value as they achieve a faster reduction in parasitaemia by acting principally on young parasites, preventing their development into the more mature pathological stages which adhere to the vascular endothelium and in this way are sequestered in the microvasculature of vital organs (*2*).

The correct use of effective antimalarial medicines should not only shorten the duration of malaria illness and reduce the incidence of complications and the risk of death, but should also safeguard the medicine against development of resistance. The rectal administration of antimalarial medicines is simple and can easily be done by non- medical persons, especially in rural peripheral settings at different levels of health care (community or health facility). In addition, even when medicine can be given intravenously, patient discomfort and inconvenience, staff time, and risks such as overhydration and thrombophlebitis, may make parenteral administration less attractive than rectal administration.

In malaria-endemic countries, patients frequently present with severe malaria and require urgent therapy. However, at health institutions, particularly at the peripheral level, and even in some instances at the district level, facilities may not exist for parenteral administration, and yet oral dosing is precluded by the patient's altered level of consciousness or protracted vomiting. In these circumstances, emergency treatment with artemisinin-based suppositories can be instituted as pre-referral therapy while patients await transfer to a hospital, a process that may take many hours or even days (*3*). If referral to a higher level of care is not possible, this therapy may be the only alternative for severely ill malaria patients.

Results from a variety of clinical studies have indicated that artemisinin- based suppositories can be used for initial emergency and curative treatment in uncomplicated (*4–6*), moderate (*7, 22*), severe (*9–17*), and cerebral malaria (*18–20*). The compounds of therapeutic interest are artesunate, artemisinin and artemether, and their common metabolite, dihydroartemisinin. All reduce parasitaemia significantly faster than quinine or any other drug used for malaria in parenteral, oral and suppository formulations. Given the high level of malaria mortality, particularly in children in Africa, these compounds in suppository formulation may constitute a major advance when given as pre-referral therapy by preventing the evolution of the disease to its severe form and complications, thus saving the patient's life and making it possible for curative therapy to be instituted.

However, the World Health Organization (WHO) does not recommend the sole use of an artemisinin derivative except for the treatment of patients with severe falciparum malaria. The treatment guidelines drawn up by WHO emphasize the need for follow-up treatment of severe malaria with a complete course of an effective artemisinin-based combination therapy (ACT) in order to protect the therapeutic lifespan of the artemisinin derivatives. Measures should be taken to ensure follow-up treatment with an ACT in order to reduce the risk of shortening the lifespan of the artemisinin derivative if used as a monotherapy.

In the light of these considerations, WHO convened an informal consultation on the use of rectal suppositories of artemisinin derivatives in the management of severe malaria. The consultation was held at WHO headquarters in Geneva from 27 to 28 March 2006. The participants reflected a wide range of expertise and the meeting brought together experts in clinical pharmacology, including clinicians, pharmacists and field researchers. Its purpose was to enable a group of scientific and clinical experts to review all the evidence on the efficacy and safety of artemisinin-based suppositories, given in single and multiple doses, and to make recommendations on their clinical use for the treatment of severe malaria, bearing in mind concerns regarding the development of *P. falciparum* resistance to artemisinin when such medicines are used as a monotherapy. A list of the participants in the consultation appears in the Annex.

# 2. Review of the evidence

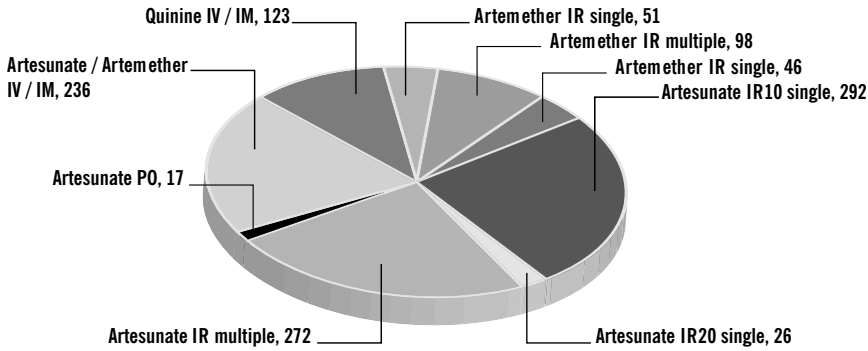
## 2.1 General findings

2.1.1 Artemisinin derivatives are effective against multidrug-resistant *P. falciparum* malaria, and, in the treatment of severe malaria, they have been shown to be either equivalent or superior to quinine when administered parenterally. It has also been shown that artemisinins administered by the rectal route are absorbed rapidly, and, despite considerable inter-individual pharmacokinetic variability, are effective in malaria (*5, 15, 17, 21–24*). Rectal artesunate has been used mostly in South-East Asia, especially China, Thailand and Viet Nam, but in recent years its use has been rapidly expanding in other regions, particularly in Africa (*7, 15, 20, 22, 23, 28*).

2.1.2 Rectal dihydroartemisinin, in combination with other antimalarials, has also been used to treat cases of severe malaria (*25, 26*). Rectal artemisinin and artemether have been proven to be safe and efficacious compared with parenteral quinine in the treatment of severe malaria in both children and adults (*10, 11, 18–20, 26–28*).

2.1.3 There are inherent difficulties in the clinical diagnosis of malaria, but information from the large-scale use of artemisinin-based suppositories in Africa, where practical clinical definitions of nil per os status – repeated vomiting, inability to eat/drink/suck, recurrent convulsions, obtunded response to painful stimuli, and coma or absent motor response – have been used in large-scale community-based trials, has shown that there is a high correlation (>75%) between *P. falciparum* malaria and these clinical signs.

2.1.4 Early treatment in high parasite biomass infections is likely to result in a survival benefit. Intervening rapidly in severe malaria changes the prognosis and the subsequent outcome. Artemisinin-based suppositories have been widely used in South-East Asia, notably in Viet Nam, for the reduction of malaria mortality, and a number of studies using artemisinin suppositories have been conducted over the years in most malaria-endemic regions. Published and unpublished individual patient data have been reviewed and analysed to provide scientific evidence for the clinical use of artemisinin-based suppositories (Figure 1).




IR = intrarectal; IV = intravenous; PO = oral; IV/IM = intravenous/intramuscular.

**Figure 1. Individual patient data provided for analysis, by treatment group**

## 2.2 Efficacy

2.2.1 The experts reviewed a large body of efficacy and safety data from clinical trials carried out in Asia and Africa (Figure 2). The integrated analysis demonstrated that artemisinin-based suppositories achieved a parasite response that was equivalent to parenterally administered artemisinins at 12 hours following

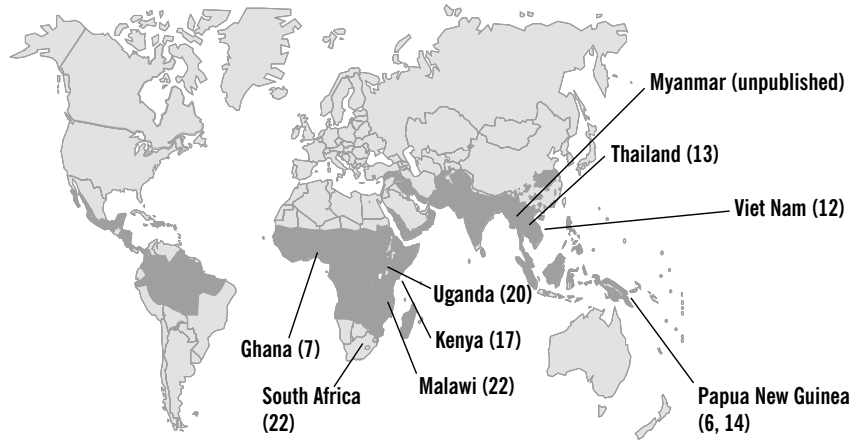



**Figure 2. Studies included in the integrated analyses**

initiation of treatment. The reduction in parasitaemia at 12 and 24 hours was consistently superior to that achieved by quinine, regardless of the route of administration or the number of doses of artemisinin derivative given.

2.2.2. The largest body of efficacy and safety evidence is related to artesunate suppositories (591 patients) and artemisinin suppositories (144 patients). The data analysed showed that multiple-dose schedules over a 24-hour period provided no added benefit over a single-dose treatment over the same period for either artesunate or artemisinin-based suppositories (Figure 3).

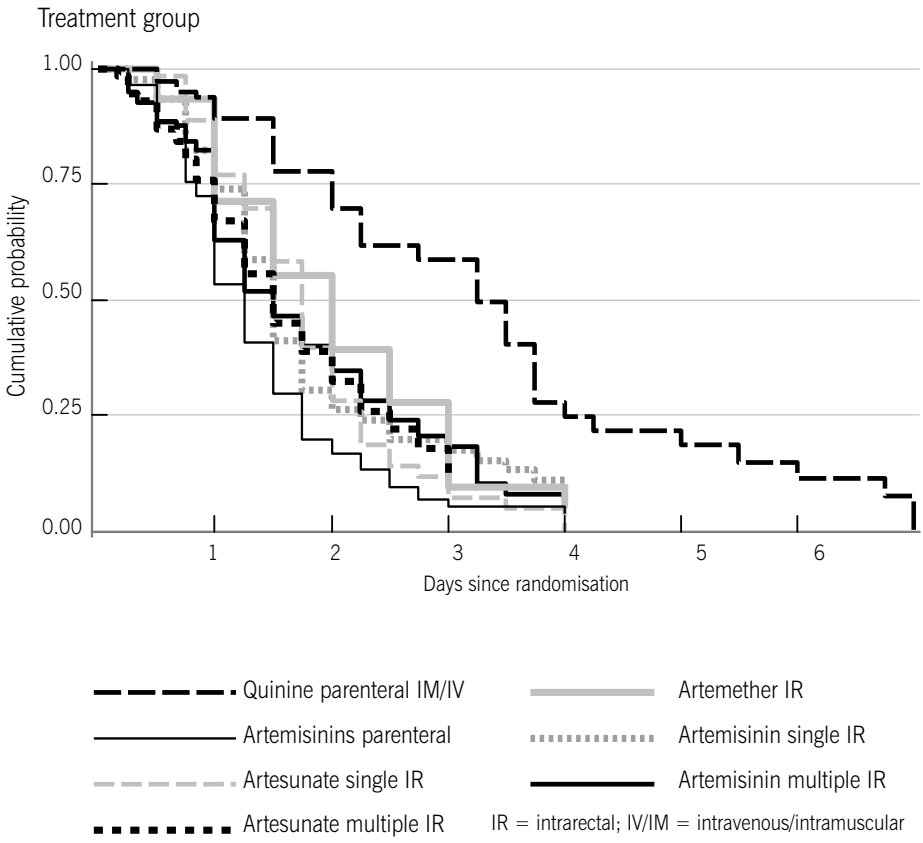



**Figure 3. Cumulative probability of having parasitaemia Quinine vs. Artemisinins**

2.2.3 In all multiple-dose studies conducted with artesunate suppositories, a mean total dose of 7.9 mg/kg over 12 hours was given, which is lower than the dose in the studies using a single dose of artesunate, where the mean dose was 8.5 mg/kg. The parasite reduction ratio over 12 hours was 32.7% with multiple dosing and 57.7% with a single, higher mean dose. An adjusted logistic regression model identified the total dose over 24 hours as a variable independently influencing the odds of achieving a 90% reduction in parasitaemia at 24 hours (odds ratio [OR] 1.14, $p = 0.000$) in a patient with moderately severe or severe falciparum malaria.

2.2.4 A single dose of rectal artesunate was superior in parasite response over 24 hours to parenteral quinine (hazard ratio [HR] 2.98, $p < 0.0001$; 95% confidence interval [CI] 1.79 – 4.95). These results were consistent irrespective of age, severity of disease, baseline parasitaemia and region of use. Equally, a single dose of rectal artemisinin was superior in parasite response over 24 hours to parenteral quinine (HR 2.96, $p = 0.005$; 95% CI 1.37 – 6.27).

2.2.5 There was no difference in clinical outcomes – time to regaining consciousness, time to return to per os status or to sit unaided – or in fever clearance time between treatment with an artemisinin-based suppository and parenteral treatment with quinine.

## 2.3 Safety

2.3.1 In the experts' review, the data provided on safety in relation to individual patients were primarily clinical. Where laboratory information was available, the schedules of evaluation were not consistent between the studies, making comparisons difficult. Because the methodology of trials included in the pooled analysis had not been prospectively standardized, there existed substantial inter-trial differences in defining, assessing, reporting and classifying adverse events. In addition, reliably distinguishing drug side-effects from manifestations of malarial infection (especially severe malaria) is often difficult and largely dependent on a subjective clinical assessment performed at the time of the event. These difficulties were partially addressed by contact with the principal investigators and reassessments of the individual patient data from the case record forms, where archived data were accessible. Each reported event was thus reclassified by the clinical investigator as being unlikely, possibly, probably or definitely due to the treatment. Those events considered possibly, probably or definitely drug-related were then all reclassified as "potentially drug-related" for the purposes of the pooled analysis.

2.3.2 A total of 306 adverse events were reported in 194 patients (16.7%) out of 1162 adults, adolescents and children exposed to the different drugs in the pooled analyses. Excluding the 5 patients who received rectal artesunate and quinine simultaneously and the 253 patients who received parenteral or oral artemisinins, there were 196 adverse events in 140 out of 786 patients exposed to the rectal artemisinin suppositories and 67 adverse events in 30 out of 123 patients treated with parenteral quinine.

2.3.3 Of the 196 adverse events reported in patients treated with artemisinin-based suppositories, 37 events in 21 patients were considered to be potentially drug-related, 105 events in 69 patients were not considered drug-related, and 54 events in 50 patients could not be assigned cause or were not assigned causality. Therefore, 2.7% (21/786) of all rectally artemisinin-treated patients were thought to have had a potentially drug-related adverse event, 8.8% (69/786) had a non-drug-related adverse event and an additional 6.4% (50/786) of rectally artemisinin-treated patients had an adverse event of uncertain causality. By comparison, 27 adverse events occurring in 11 patients of the 123 quinine-treated patients were considered drug-related, which means that 8.9% (11/123) of quinine-treated patients experienced an adverse event that was considered potentially drug-related.

2..3.4 For the rectally administered artemisinins, approximately 29.7% (11/37) of adverse events considered drug-related were defined as affecting the body as a whole (including fever, headache and unspecified pain), 2.7% (1/37) were related to the nervous system (dizziness), 8.1% (3/37) were related to the special senses (hearing impairment) and 48.6% (18/37) related to the gastrointestinal system (vomiting, nausea, diarrhoea, constipation, abdominal pain). For quinine, 25.9% (7/27) of adverse events were considered to be related to the nervous system, 29.6% related to the digestive system, 18.5% (5/27) were defined as affecting the special senses/hearing, and 14.8% (4/27) related to the haemopoietic system.

2.3.5 A meaningful comparison of safety profiles between the different artemisinin products was beyond the scope of this analysis. It should be noted that most of the safety data presented were derived from patients treated with either rectal artesunate (591) or artemisinin suppositories (144) and extrapolation from these safety data should be made with caution.

2.3.6 Despite the methodological limitations of this analysis, overall, the safety profile of artemisinin-based suppositories in the studies analysed appeared to be benign. The total incidence of adverse events considered by clinicians to be possibly drug-related was estimated at between 2.7% and 9.0% of

all rectal artemisinin-treated patients, compared with 8.9% of quinine-treated patients. The majority of possibly drug-related adverse events in rectal artemisinin-treated patients either involved the gastrointestinal system or were generalized and non-specific in nature and were not severe. In general, the safety profile of the artemisinin drugs (when given by other routes of administration) appears to be excellent (*30, 31*). The data from this analysis therefore do not suggest that there are any additional concerns related specifically to the rectal route of administration (Table 1)

**Table 1. Adverse events noted in patients treated with suppositories and parenterally, by treatment group**

| | Rectal artemisinin | Non-rectal artemisinin comparator | Non-artemisinin comparator (quinine) | **TOTAL** |
|---|---|---|---|---|
| Total no. of patients included in analysis | 786 | 253 | 123 | **1162** |
| Total no. (%) of patients in whom one or more adverse event reported | 140 (18) | 24 (9) | 30 (24) | **194** |
| Total no. of adverse events | 196 | 43 | 67 | **306** |
| **Classification (aetiology)** | | | | |
| Possibly drug-related | 37 | 14 | 27 | **78** |
| Not likely to be drug-related | 105 | 28 | 40 | **173** |
| Unable to be classified | 54 | 1 | 0 | **55** |
| **Classification of possibly drug-related events according to body system** | | | | |
| Generalized | 11 | 1 | 0 | **12** |
| Neurological | 1 | 1 | 7 | **9** |
| Digestive | 18 | 10 | 8 | **36** |
| Urogenital | 1 | 1 | 0 | **2** |
| Haemopoietic | 3 | 1 | 4 | **8** |
| Special senses (hearing) | 3 | 0 | 5 | **8** |
| Other | 0 | 0 | 3 | **3** |

# 3. Conclusions

3.1 Artemisinin-based suppositories, particularly artesunate and artemisinin suppositories, are safe and efficacious for pre-referral treatment of severe malaria. The clinical evidence provided by the data analysed is overwhelmingly in favour of their use because they rapidly eliminate parasites and are safe, although there is not yet proof that such an intervention reduces mortality. Most of the clinical data are derived from studies conducted using artemisinin and artesunate suppositories. This safety and efficacy information cannot, therefore, yet be extrapolated to suppositories containing other artemisinin derivatives and those of different formulations.

3.2 Substantially less information exists on artemisinin suppository bioavailability than on artesunate suppository bioavailability; more information on artemether and dihydroartemisinin suppositories is required before any conclusions can be drawn about these or any other formulation of artemisinin suppositories. Moreover, no study has been carried out that provides a direct assessment of bioavailability between the different rectal artemisinin-based derivatives.

An assessment of the pharmacokinetic information (for all the routes of administration) needs to be undertaken in order to identify the minimum inhibitory drug concentrations that should be achieved in order to allow the comparison of different artemisinin suppository formulations. The assessment will require guidance on the minimum standards for all the other artemisinin derivative and artesunate-based suppositories.

3.3 The clinical indications for the use of rectal artemisinin-based suppositories as pre-referral treatment should be limited to acute, suspected life-threatening malaria, where patients cannot take medicines by mouth and where patients cannot access injectable treatment. There is, at present, insufficient evidence to demonstrate that rectal artesunate/artemisinin is as good as intravenous or intramuscular options in the complete treatment of severe malaria.

3.4 An analysis of the integrated data indicates that multiple dosing schedules show no superiority over a single-dose treatment for either artesunate or other artemisinin-based suppositories. A single dose of treatment should, therefore, be sufficient, prior to the patient's immediate referral to a hospital or health facility as soon as possible for definitive therapy. If the patient responds and referral is not possible, rectal treatment should be continued once daily until the

patient can tolerate oral medication, at which point a full course of the nationally recommended artemisinin-based combination therapy for uncomplicated malaria should be administered.

3.5 Data available from Viet Nam, Bangladesh, Tanzania and Ghana show that deployment of rectal suppositories is feasible at the community level. In Viet Nam, the drugs were provided following a rapid diagnostic test; in different resource-poor settings in Africa, they have been provided on the basis of clinical diagnosis of the danger signs (see paragraph 2.1.3 above), which correlates highly with laboratory diagnosis of *P. falciparum* malaria in children. It has therefore been recognized that deployment of rectal suppositories as pre-referral treatment in the community is feasible and can be successful. It is not dependent upon the literacy of the population.

However, the experiences of Viet Nam, Cambodia, Tanzania and Bangladesh in deploying suppositories at the community level have shown that the implementation of artemisinin-based suppository treatment should be accompanied by a minimum package of activities that should include:

- engaging communities and raising the awareness not only of community-based health providers and medical personnel but also of communities;
- training community-based health providers in the clinical recognition, diagnosis and treatment of malaria;
- establishing a system of continuous supervision and monitoring of community-based health providers;
- providing supportive job aides; and
- establishing a clear link between communities and health facilities.

3.6 WHO should engage with the national regulatory authorities that have registered artemisinin-based suppositories and with pharmaceutical manufacturers to ensure that artemisinin-based suppository treatment is used and marketed specifically as pre-referral treatment, followed by a course of ACT, and that the use and registration of such suppositories as stand-alone monotherapy is discouraged and disallowed. Such use could contribute to the development of artemisinin resistance, and it is therefore essential that artemisinin-based suppositories are used in conjunction with an artemisinin-based combination treatment designed to maximize cure rates and minimize the selection of artemisinin-resistant parasites (*32*).

# 4. Policy recommendations

4.1 Artesunate or artemisinin-based suppositories are recommended for use as pre-referral treatment for severe malaria combined with either (i) referral of the patient to a facility where parenteral treatment with artesunate, quinine or artemether can be instituted; or (ii) follow-up treatment with a full course of ACT.

4.2 Artesunate or artemisinin-based suppositories should be both packaged for marketing and used for pre-referral treatment of severe malaria as a single dose (or, in the event that referral is not possible, as a single daily dose) until parenteral treatment or oral ACT treatment is instituted.

4.3 Artesunate or artemisinin-based suppositories used as pre-referral treatment for severe malaria should be deployed where parenteral pre-referral treatment is difficult or not possible at peripheral health institutions, and at the community level in the context of home management of malaria.

# 5. Identified research gaps

A number of research gaps were identified during the informal consultation, and the lack of sufficient data in several key areas prevented conclusions from being drawn for the deployment of artemisinin-based suppositories. Some of these areas are:

5.1 The impact of deploying artemisinin-based suppositories for pre-referral treatment of severe malaria on the overall strategy of home management of malaria.

5.2 The comparative efficacy, safety and bioavailability of different artemisinin-based suppositories.

5.3 Basic community-level research into such aspects as acceptability, the best dispensers, and community health education to ensure effective deployment of artemisinin-based suppositories within communities.

5.4 Development of a combination suppository.

5.5 Demonstration of the efficacy and safety of an artemisinin-based suppository in the full treatment of severe malaria at the health facility as an alternative to parenteral treatment.

5.6 Establishing the dosing regimen where referral is not possible.

5.7 Post-marketing surveillance – includes monitoring of efficacy, safety and resistance.

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# Annex – List of participants

**WHO Informal Consultation on the Use of Rectal Artemisinin-based Suppositories in the Management of Severe Malaria**

**WHO headquarters, Geneva, Switzerland, 27–28 March 2006**

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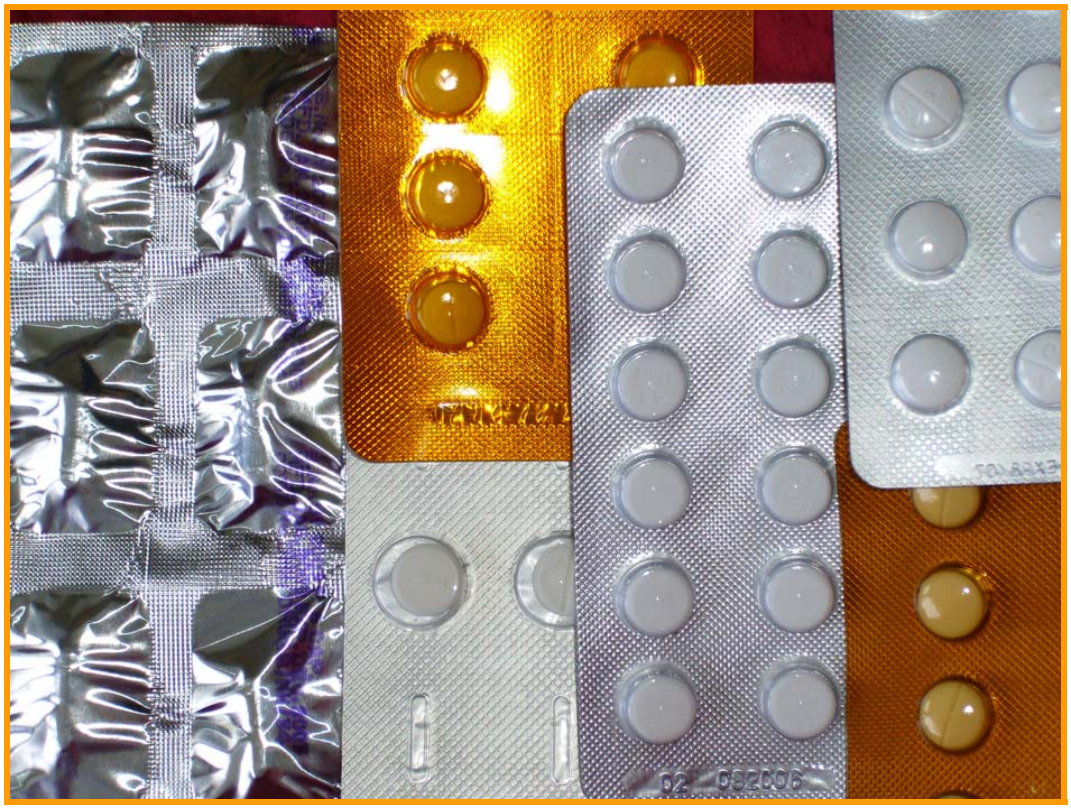
World Health Organization

# WHO briefing on *Malaria Treatment Guidelines* and artemisinin monotherapies



**Geneva, 19 April 2006**

# EXECUTIVE SUMMARY

WHO recommends the use of artemisinin-based combination therapies (ACTs) in order to ensure high cure rates of *Plasmodium falciparum* malaria and to reduce the spread of drug resistance. The majority of falciparum endemic countries have adopted ACTs as first-line treatment and deployment of ACTs in the public sector has increased exponentially during the past 3 years. In the private sectors, however, the artemisinin derivatives are mainly marketed as monotherapies, and their consumption, if unabated, will promote development and spread of resistance and compromise the effectiveness of ACTs. In order to stimulate the pharmaceutical sector to invest on WHO recommended products and to move away from the marketing of oral artemisinin derivatives, 41 manufacturers active in this sector were invited to a meeting in Geneva.

Twenty-six pharmaceutical companies involved in production and marketing of artemisinin monotherapies for oral treatment of uncomplicated falciparum malaria attended the "WHO Briefing on Malaria Treatment Guidelines and Artemisinin Monotherapies", held on 19 April 2006 in Executive Board Room, WHO Geneva. With the exception of Sanofi-Aventis, all invited companies were generic manufacturers from Africa (Cameroon, Ghana and United Republic of Tanzania), Asia (China, Malaysia, India and Viet Nam) and Europe (Belgium, Denmark, Germany and Switzerland). The remaining 15 invited companies did not attend for various reasons.

The WHO position was presented and openly discussed with the manufacturers, with specific reference to: *i*) active promotion of ACTs as the best standard of care for malaria treatment, with a rapidly expanding market size; *ii*) ongoing efforts to ensure long-term effectiveness of ACTs, reducing deployment of artemisinin monotherapies especially in the private sector to prevent the development of resistance; *iii*) promoting ACTs of high quality, efficacy and safety and the intention to collaborate with pharmaceutical companies to ensure that they meet quality standards; *iv*) promoting competition between high quality multi-source products as a sustainable mechanism to ensure low pricing and affordability.

A total of 15 companies declared their willingness to support the WHO position and will stop marketing artemisinin monotherapies over a short period of time. These companies will also increase production and marketing of ACTs in both public and private sector markets. They include: CIPLA, Guilin, IPCA, MEPHA and Sanofi-Aventis, the main producers of ACT in compliance with Good Manufacturing Practices, and currently the sources of ACT procurement for both WHO and UNICEF. Two additional companies expressed their willingness to collaborate with WHO in this endeavour, but the remaining did not disclose their marketing plans for the future.

Most companies requested technical support from WHO to meet the standards of the WHO prequalification programme. In addition, companies demanded clear communication to national drug regulatory authorities of malaria endemic countries to withdraw the marketing authorization for all oral artemisinin monotherapies. This will ensure compliance by all manufacturers and avoid that some companies exploit market opportunities created by the withdrawal of products by manufacturers complying with WHO recommendations.

WHO will work with international funding agencies, multilateral and bilateral agencies, international suppliers to discontinue funding and procurement of oral artemisinin monotherapies and to exclusively procure WHO recommended antimalarial medicines. Multiple fora at international, regional and national levels will be used over the next months to communicate WHO recommendations to National Drug Regulatory Authorities of malaria endemic countries. WHO will work with health professionals to promote rational drug use and abandon the use of oral artemisinin monotherapies.

# 1. Introduction

Since April 2001, WHO has recommended the use of artemisinin-based combination therapies (ACTs) in countries where *Plasmodium falciparum* malaria is resistant to chloroquine, sulfadoxine-pyrimethamine and amodiaquine. ACTs ensure the highest cure rates and have the potential to reduce the spread of drug resistance. At present, 60 countries have adopted ACTs as recommended by WHO, and 33 are deploying ACTs in the general health services. With increased mobilization of international funds, mainly from the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM), the procurement of ACTs for the public health sector has increased exponentially during the past three years, with more than 30 million ACT treatment courses procured and delivered in 2005. However, in the private sector markets of endemic countries, artemisinin derivatives are used more widely, mainly as monotherapies at lower prices compared to ACTs. Only 11 countries with falciparum-resistant malaria do not currently allow marketing of artemisinin monotherapies (Afghanistan, Brazil, Eritrea, Iran, Mexico, Malaysia, Philippines, Saudi Arabia, Sudan, South Africa and Thailand).

The increasing consumption of artemisinin monotherapies in the private sector, if unabated, will promote resistance to artemisinins and compromise the effectiveness of ACTs. This has happened with the large-scale deployment of all other antimalarial medicines as monotherapies, and for the artemisinin derivatives in particular, the risk is confirmed by the progressive reduction of *in vitro* susceptibility to artemisinin of *P. falciparum* in China and Viet Nam, countries where artemisinins were deployed as monotherapies for many years. If falciparum malaria develops resistance to the artemisinin derivatives, there will be no alternative effective compounds to treat malaria over the next ten years.

# 2. Background and objectives of the meeting

In January 2006, on the occasion of the release of the *WHO Guidelines for the Treatment of Malaria*, WHO issued a press release urging 17 known companies to stop marketing artemisinin monotherapies, and to re-direct their production efforts towards artemisinin-based combination therapies. The press release received major attention in the international media (newspapers, radio and television) and in the national press in endemic countries. Before the press release was issued, all concerned companies were invited to a technical briefing in Washington, but only two were able to attend. In order to share more information with 41 companies active in this sector, a second meeting was scheduled in Geneva in April 2006, with the following objectives:

- To present and discuss with manufacturers of oral artemisinin derivatives the evidence of potential risks of development of resistance to artemisinins, the WHO recommended product profile for antimalarial medicines, the quality requirements for UN procurement agencies and the ACT forecast for the public sector based on country plans and availability of international funds.

- To receive commitments and realistic implementation plans from manufacturers for re-orienting production and marketing efforts away from oral artemisinin monotherapies and towards quality ACTs, in line with the WHO recommendations and regulatory measures from the national drug regulatory authorities of endemic countries.

The topics presented by WHO and list of participants are provided in Annexes I and II.

# 3. Discussion points

WHO has made clear communications to pharmaceutical companies on the need to re-orient production and marketing towards the recommended ACTs and away from oral monotherapies. In addition to this, it must be made clear to national drug regulatory authorities of malaria endemic countries that artemisinin suppositories and injectable formulations as monotherapy are recommended only for the management of severe malaria and should not be used for the treatment of uncomplicated malaria.

A total of 9 countries (Afghanistan, Brazil, Eritrea, Ethiopia, Iran, Malaysia, Philippines, Saudi Arabia, and South Africa) with resistant *P.falciparum* malaria, have never registered oral artemisinin monotherapies. Thailand has registered oral artesunate in 1994 with a restriction in distribution regulated by the Ministry of Health, which resulted in very limited use, i.e. as third-line treatment for quinine + tetracycline treatment failures. One country, Sudan, has withdrawn the marketing authorization for these products after it adopted and started implementing the new treatment policy based on ACTs. After the WHO press call in January 2006, national health authorities of Benin, Comoros and Gabon have taken formal steps to withdraw marketing authorizations for artemisinin monotherapies in their respective countries.

WHO/GMP has recommended through its Representatives in malaria endemic countries, that national health authorities of all countries with falciparum malaria to comply with newly published *WHO Guidelines for the Treatment of Malaria* and withdraw the marketing of oral artemisinin monotherapies for the treatment of uncomplicated falciparum malaria. Recently, countries such as India, Kenya, and eleven others in Southern Africa belonging to the Southern African Development Community (Angola, Botswana, Democratic Republic of Congo, Madagascar, Malawi, Mozambique, Namibia, Swaziland, United Republic of Tanzania, Zambia, Zimbabwe) are considering withdrawing marketing authorization for these products.

Apart from the important role of national drug regulatory authorities, pharmaceutical companies also have a shared responsibility in the health of people who consume their products. Companies can contribute to rational drug use by developing antimalarial medicines with therapeutic indications in compliance with WHO treatment guidelines and by influencing prescription practices, especially in the private sector, through their presence and marketing efforts in the countries. In addition, by producing more ACTs of high efficacy, quality and safety, manufacturers will meet the increasing

demand for these medicines and will contribute, through open competition, to reduce the price for end-users.

New ACTs in fixed-dose combination are under development and will enter the market by late 2006 and 2007, including artesunate-amodiaquine, artesunate-mefloquine, artesunate-pyronaridine, dihydroartemisinin-piperaquine and chlorproguanil-dapsone-artesunate. Several manufacturers are working on the fixed-dose combination of artesunate-amodiaquine, including Sanofi-Aventis in partnership with Drugs for Neglected Disease Initiative (DNDi). It was highly appreciated by all that Sanofi-Aventis will not apply intellectual property rights/patents to this medicine and that it will submit the dossier for review to the UN prequalification programme as an innovator product. Several manufacturers are currently developing generic versions of artemether-lumefantrine, with improved dosage forms and formulations that could reduce the number of tablets/dose. These efforts are likely to contribute to an increase in production of this ACT and could lead to price reductions through market competition. An acceleration of the procedure for prequalification of a generic artemether-lumefantrine was requested by several company representatives at the meeting.

There is a need to provide technical and financial resources to support manufacturers in developing countries to meet the requirements of the prequalification programme. WHO encourages companies to apply to this process and will broker financial support from Development Banks, and technical assistance from Development Agencies to support this process. In the interim period, and until more ACT products are prequalified WHO will inform Member States of products and manufacturers meeting Good Manufacturing Practices (GMP) and meeting standards acceptable for procurement by WHO/UNICEF.

The WHO appeal to reduce the use of oral artemisinin monotherapies has had wide resonance and received support from public health specialists, international initiatives such as the Drugs for Neglected Disease Initiative (DNDi), the Médecins Sans Frontières (MSF) Access Campaign and Medicine for Malaria Venture (MMV), as well as from consumer associations in countries. This public health issue and the response to it by pharmaceutical companies has received wide media attention, and the pressure is on WHO to provide regular updates and reports on the alignment by companies, and the results thereof. The issue will be in the media eye in the months to follow.

# 4. Position statement of participating pharmaceutical companies

The short statements below represent the position expressed by representatives of the companies participating to the meeting.

Activa Pharmaceuticals (FCZ)

- This newly established company is a joint venture of Holley-IPCA and is exclusively committed to the marketing of ACTs, which has given the name to this company.

Ajanta Pharma Limited

- The company decided to stop production and marketing of monotherapies and is investing exclusively in ACT fixed-dose combinations.

Arenco Pharmaceutica

- The company decided in January not to launch its oral paediatric formulation of artemisinin monotherapy following WHO appeal to manufacturers, despite considerable R&D investment in this product. The company is investing in the development of a fixed-dose combination as they do not believe coblistering to be a good solution in an African setting.

Chongqing Holley Holding Co., Ltd. (representing also Holley-Cotec Pharmaceuticals and Holleypharm France)

- The company is fully committed to ACT as one of the major pharmaceutical products to launch the image of company at international level. The company will progressively stop producing its dihydroartemisinin monotherapy and will invest in marketing of a new fixed-dose combination therapy, dihydroartemisinin+piperaquine. This medicine is entering Phase III clinical trials as part of a collaborative project with MMV. In addition, the company is willing to submit its product dossier to the UN prequalification programme, once this ACT is added to the list of medicines to be prequalified.

Cipla Limited

- The company is committed to work with WHO on the progressive reduction of marketing of artemisinin monotherapies, and requested WHO support to increase reliability of forecasting of requirements for public sector use, promote sustained financial mechanisms for ACT procurement and support development of generic artemether-lumefantrine.

Dafra Pharma NV

- The company agrees fully to phase out its oral single tablet artesunate and artemether suspension monotherapies for uncomplicated malaria in favour of introducing ACTs. The company points out that it has already shifted its entire R&D budget to ACTs since the first recommendation of the WHO in this regard in 2001. The company has developed several ACTs, initially in co-blisters and some already in fixed-dose combinations: artesunate+sulfadoxine-pyrimethamine; arthemether+lumefantrine; artesunate+amodiaquine; artesunate+sulphamethoxypyrazine-pyrimethamine. All these ACTs are already present in the market or are at the phase of being registered. The company will proceed in its marketing strategy to actively promote ACTs and to help convince local health authorities to withdraw the marketing authorization for all oral artemisinin monotherapies for uncomplicated malaria. According to the company this phasing out can only be successful if all partners involved

(manufacturers, national health authorities & customs services in Africa, hospitals & pharmacies, NGOs, primary health care services and health professionals) work closely together under WHO's guidance. Control systems to ascertain that all oral monotherapies are eliminated from the registration lists in each country should be set up.

Danpong-Adams Pharmaceutical Industry Ltd.

- The company is investing in amodiaquine+artesunate as co-blister product for registration in Ghana and requested technical support to WHO to achieve GMP. The company did not express its position on marketing of artemisinin monotherapies.

Denk Pharma GmbH & Co. KG

- The company decided to stop production and marketing of oral artemisinin monotherapies following WHO press release in January and will now stop marketing its artemether oral suspension. It will invest in the development of a rectal artemether formulation for use as a pre-referral treatment option, and concentrate marketing and sales activities on its combination of artesunate+ sulphamethoxypyazine-pyrimethamine.

Guilin Pharmaceutical Co., Ltd.

- The company will comply with WHO's request and has stopped new production of artesunate monotherapies; it expects stocks to be progressively extinguished over the next few months. It will invest its marketing efforts on the artesunate+amodiaquine co-blisters for which its manufacturing sites have been inspected and certified as GMP compliant by the WHO inspection team.

Hovid Bhd

- The company has registered an artemisinin monotherapy in Malaysia after a long regulatory process, but following the WHO recommendations will proceed to the phasing out of this product. The company requested technical support from WHO on selection and investment of alternative ACTs.

IPCA Laboratories Ltd.

- The company is committed to research and development for fixed-dose ACT products, and to invest in sustained-release products and paediatric formulations. IPCA is committed to collaborate with WHO and will stop marketing of artemisinin monotherapy once the national drug regulatory authority of India withdraws its marketing authorization.

Kakwa Biofarm, Ltd.

- The company has developed amodiaquine+artesunate co-blister, which has been submitted for registration in Cameroon and will be mainly marketed for the domestic use. The company had stopped the manufacture of artesunate monotherapy and is working towards formulating a fixed-dose combination of amodiaquine+artesunate and requested technical support to WHO to comply with GMP.

Kinapharma Ltd.

- The company did not express its position on marketing of artemisinin monotherapies.

Kunming Pharmaceuticals

- KPC will cooperate with WHO for implementing the policy of stopping oral artemisinin monotherapy, on general concerns on risk of development of resistance to artemisinin monotherapy. KPC will stop marketing of artemisinin monotherapy over a certain timeframe taking into consideration the availability of effective antimalarials by the patients. KPC has made progress in the development of a new fixed-dose combination (artemisinin+ naphthoquine phosphate tablets) and will invest in the development of this new ACT as the company's major product in the future.

Mediplantex National Pharmaceutical Joint Stock Co.

- The company has developed both amodiaquine+artesunate and dihydroarte-misinin-piperaquine as co-blisters, which have been submitted for registration in Viet Nam. The company has a major role as supplier of artemisinin raw materials, 70% of which are for export. The company is prepared to halt the production and marketing of oral artemisinin monotherapies according to WHO's recommendation.

Mepha Ltd.

- The company provided clear commitment to stop marketing its oral artesunate monotherapy, and expects that sales for this product will progressively decline over the remaining part of the year. It will focus its production and marketing efforts on its artesunate rectocaps (suppositories) for pre-referral treatment of severe malaria and on artesunate+mefloquine co-blister for treatment of uncomplicated malaria. The company is developing a fixed-dose paediatric formulation of artesunate+mefloquine, and would appreciate WHO support to meet the requirements of the UN prequalification programme.

Phyto-Riker Pharmaceuticals Ltd.

- The company did not express its position on marketing of artemisinin monotherapies.

Sanofi-Aventis

- The company markets artesunate from Guilin Pharmaceutical Co. Ltd., as a stand-alone drug, and within a co-blister presentation of artesunate and amodiaquine. The company is committed to the development of a fixed-dose combination of artesunate-amodiaquine and has stopped marketing activities for artesunate monotherapy. It expects that sales for the latter product will be progressively reduced over the remaining duration of 2006, and will stop distribution with the launch of the new fixed-dose combination. As a results of the revised marketing strategy recent figures showed that artesunate-amodiaquine already represented 70% of sales as compared to 30% for artesunate monotherapy, a trend that is expected to further increase over the coming months.

Saokim Pharma

- The company has a major role as supplier of artemisinin raw materials, both for domestic use and for export, and is establishing new facilities for the production of finished pharmaceutical products. The company did not express its position on the marketing of artemisinin monotherapies. Saokim is developing fixed-dose combination of atesunate-amodiaquine and would appreciate technical support from WHO to improve manufacturing process and the preparation of the drug regulatory dossier.

Scanpharm A/S

- The company fully supports WHO's call to ban artemisinin monotherapy and will invest on production and marketing of a co-blister of artesunate+ amodiaquine and artesunate rectal capsules.

Shelys Pharmaceuticals Ltd.

- The company has developed an amodiaquine+artesunate as co-blister and needs GMP certification and technical support to conduct bioequivalence studies. The company did not express its position on marketing of artemisinin monotherapies.

Standard Pharma Ltd.

- The company has a major role as supplier of artemisinin raw materials, which are both for domestic and for export markets, and is not involved in the production of pharmaceutical finished products.

Themis Medicare Ltd

- The company is involved in the production of different artemisinin derivatives, including artemether and artemotil for treatment of severe malaria. The company will stop marketing oral artemisinin monotherapies and will continue investing in production and marketing of parenteral artemisinin formulations.

# 5. Next steps of WHO Global Malaria Programme

1. WHO will continue to work with manufacturers of artemisinin derivatives to promote the production and marketing of quality ACTs in line with *WHO Guidelines for Treatment of Malaria*, and to stop the marketing of oral artemisinin monotherapies for the treatment of uncomplicated malaria.

2. WHO will promote technical support to companies manufacturing ACTs to internationally agreed standards of efficacy, safety and quality. Information on companies producing quality products and found acceptable for procurement by WHO/UNICEF will be shared with all WHO Member States, funding agencies and NGOs.

3. WHO will also work with international funding agencies, multilateral and bilateral agencies, and international medicine suppliers to discontinue funding for, and procurement of oral artemisinin monotherapies and to exclusively procure WHO recommended antimalarial medicines.

4. WHO will share information on the progress made with the pharmaceutical manufacturers, using public forums such as the web and media communication to report positively on companies which act responsibly, complying with the WHO recommendations, and will expose companies which place life-saving ACTs at risk of resistance by continued monotherapy malpractice.

5. Multiple fora at international, regional and national levels will be used over the next months to communicate WHO recommendations to National Drug Regulatory Authorities of malaria endemic countries; 48 countries with falciparum-resistant malaria, including 16 high-burden countries in Africa, have yet to respond to the WHO appeal to withdraw oral artemisinin monotherapies from their markets.

6. WHO will work with health professionals to promote rational drug use and abandon the use of artemisinin monotherapies. The *WHO Treatment Guidelines* will be widely publicized and disseminated, through professional associations, teaching institutions and active distribution networks in the private sector, including the pharmaceutical sector. WHO will continue to work with Member States in adopting these recommendations, and adapting the malaria treatment guidelines to local situations.

# ANNEX I

## *WHO briefing sessions*

### 1. The threat of resistance to artemisinin derivatives

WHO has established a Global database on therapeutic efficacy of antimalarials (www.who.int/malaria/resistance.htm), which is regularly updated on the basis of published studies and validated reports from academic/research institutions and malaria control programmes in endemic countries. When used as monotherapy on a large-scale, *P. falciparum* has developed resistance to all antimalarial medicines over a period of time ranging from less than 1 year (sulfadoxine-pyrimethamine and atovaquone), to 1 year (proguanil), to 5 years (mefloquine), to up to 12 years (chloroquine).

The artemisinin derivatives are one of the most promising antimalarial medicines, offering the following pharmacological properties: *i*) rapid and sustained reduction of the parasite biomass; *ii*) effective against resistant parasites; *iii*) rapid resolution of clinical symptoms; *iv*) reduction of gametocyte carriage; *v*) broad stage specificity; vii) 7-day treatment in monotherapy. Resistance to artemisinin derivatives has been induced experimentally in rodent malaria; resistance to artemisinin and artemether has been obtained in *P. yoelii* and *P. berghei*, with reversal after drug pressure removal. Stable genetic resistance to artemisinin and artesunate has been induced in *P. chabaudi chabaudi*, growing the parasites in presence of increasing drug concentrations.

Although clinical resistance to artemisinin has not been yet confirmed, three types of evidence indicate that the risk for artemisinin resistance is emerging:

a) decreasing sensitivity of *P. falciparum* to artemisinin derivatives

In China, where artemisinin derivatives were deployed for more than a decade on a large scale as monotherapy, the *in vitro* sensitivity of *P. falciparum* to artesunate fell significantly between 1988 and 1999, i.e. the 50% inhibitory concentration ($IC_{50}$) tripled and the MIC doubled. In Viet Nam, where artemisinin monotherapy was also deployed on a large scale, the artemisinin $IC_{50}$ remained stable between 1998 and 2001, while the $IC_{90}$ and the $IC_{99}$ doubled and quadrupled, respectively. On the other hand, in countries such as Cambodia, Cameroon or Thailand, where the deployment of artemisinin monotherapy was more contained, there has not been *in vitro* evidence of an increased $IC_{50}$ value for artemisinin derivatives.

b) decreasing drug efficacy from therapeutic efficacy studies

In Viet Nam, the efficacy of artesunate at a dose of 12 mg/kg over 5 days was 71–87.5% but increased to 93.1% at a dose of 16 mg/kg over 7 days. As for initial resistance to all other antimalarial medicines, most of the failures were late treatment failures; however, it has been shown that failures after artesunate treatment result not only from decreased sensitivity of strains to artesunate but also from relatively high pretreatment parasitaemia.

c) decreasing drug efficacy from isolated case reports

Four cases, two in India and two in Thailand, are suspected treatment failures. The precise immunological status and the presence or absence of genetic disease were not established in all patients, and drug quality control was not evaluated. In India, an adult still had parasitaemia after 5-day parenteral treatment with artemether (total dose, 480 mg

administered by intramuscular injection), and another adult reported recrudescence on day 14 after 7-day treatment with artesunate at a dose of 13.3 mg/kg. In Thailand, two children aged 2 and 5 years had positive blood smears on day 7 after a dose of 12 mg/kg artesunate, and one had persistent parasitaemia throughout treatment.

Currently, the consumption of artemisinin monotherapies, often of heterogeneous quality, is unacceptably high and is increasing, mainly in the private sector. Artemisinin produces early remission of clinical symptoms of malaria and therefore, adherence to the full 7-day treatment regimen is generally poor. While increased drug pressure is probably the main determinant for spreading drug resistance to antimalarial drugs, high exposure of the parasite to incomplete treatment courses and to medicines of substandard quality may also play a significant role. If the high consumption of oral monotherapies is not reversed in favour of quality ACTs as recommended by WHO, the development and spread of resistance to artemisinin derivatives is very likely to occur, as has been the case with other antimalarial monotherapies.

## 2. Implications for industry of the *WHO Guidelines for treatment of malaria*

WHO has recently published *Guidelines*[*] *for the treatment of malaria* that provides comprehensive, global and evidence-based recommendations for the formulation of national policies and protocols for treatment of both uncomplicated and severe malaria. In addition, the *WHO Guidelines* include recommendations for treatment of special groups (young children, pregnant women, people living with HIV/AIDS), travellers (from non-endemic malaria regions) and treatment in epidemics and complex emergency situations.

The standards for drug efficacy have been raised*:* medicines must be discontinued before resistance reaches 10% treatment failure rates (assessed through monitoring of therapeutic efficacy at 28 days) and new antimalarial medicines must have therapeutic efficacy higher than 95%.

The *WHO Guidelines* recommend parasitological confirmation (microscopy or RDT) before treatment, with the only exceptions for children under 5 years of age in areas of high transmission, where treatment in this group should be based on clinical diagnosis, and for suspected severe malaria if parasitological confirmation is not immediately possible.

a) uncomplicated *P. falciparum* malaria

ACTs are recommended for all cases of uncomplicated falciparum malaria except in the first trimester of pregnancy, during which ACTs should be given only if no other effective alternative antimalarial medicine is available. The following ACTs are recommended as first-line treatment of malaria: *i*) artemether-lumefantrine; *ii*) artesunate+amodiaquine; *iii*) artesunate+mefloquine; *iv*) artesunate+sulfadoxine-pyrimethamine. None of the artemisinin derivatives (oral, rectal, or parenteral formulations) should be used as monotherapy for treatment of uncomplicated malaria. For second-line treatment, the following options are recommended: *i*) alternative ACT or *ii*) quinine in combination with either tetracycline or doxycycline or clindamycin.

[*] ***http://www.who.int/malaria/docs/TreatmentGuidelines2006.pdf,***

b) *P. vivax* malaria

The current options are recommended for treatment of vivax malaria: *i*) chloroquine+ primaquine; *ii*) amodiaquine+primaquine for treatment of chloroquine-resistant vivax malaria. Where ACT is the first-line treatment of *P. falciparum* malaria, this may also be used for *P. vivax* malaria in combination with primaquine, with the exception of artesunate+sulfadoxine-pyrimethamine, which is not effective against this species.

c) severe *P. falciparum* malaria

Quinine or an artemisinin derivative (artesunate, artemether or artemotil) by i.v. or i.m. route are recommended for treatment of severe malaria. This must be followed by a full treatment course of an effective ACT as soon as patients are able to tolerate oral medication. Artemisinin derivatives administered through the rectal route are recommended only for pre-referral treatment of severe malaria.

The implications for the pharmaceutical industry of the new WHO malaria treatment guidelines are to reorient production and marketing activities to ensure that:

- Artemisinin monotherapies are not used for treatment of uncomplicated malaria, whether in the form of tablets, oral suspensions, suppositories, recto-capsules or vials for parenteral administration.
- Artemisinin monotherapies in rectal formulations are used only for pre-referral treatment of severe malaria.
- Artemisinin monotherapies in parenteral formulations are only used for the management of severe malaria.

## 3. Antimalarial medicines of the future

The ideal product profile of antimalarial medicines for large-scale deployment in malaria endemic countries includes the following properties:

- Highly effective in providing both clinical and parasitological cure
- Very safe, including in infancy and pregnancy
- Guaranteed against resistance
- Potent anti-gametocyte (transmission blocking) activity
- Effective against all malaria species
- Have applications in intermittent preventive treatment
- Available in fixed-dose combinations
- Simple regimen – ideally as single dose
- Long shelf-life (at least 3 years)
- Available in paediatric formulations and course-of-therapy packaging

The current treatment strategy to delay emergence of resistance to antimalarial medicines is to use two medicines in combination. In the future, it should be possible to combine more than two active pharmaceutical ingredients, as in the case of medicines to treat other diseases, such as TB and leprosy. In addition, the spread of resistant genes could be reduced by including transmission-blocking components of the drugs. Research on molecular mechanisms of resistance would lead to more strategic combinations, in which the partner drugs have unrelated modes of action and different biochemical targets of the parasites.

Safety is a major requirement for antimalarial medicines, since consumption of antimalarial medicines is very high (estimated at around 315 million treatment courses per year in Africa and more than 0.5 billion in the world), over-the-counter use and self-treatment are common and pharmacovigilance systems in malaria-endemic countries are poor. Paradoxically, while safety in pregnancy and infancy is critical, as these are the groups most vulnerable to malaria, all new antimalarials have a restricted labelling for these groups. Therefore, safety of antimalarials in these vulnerable population groups should be addressed as part of the drug development plan.

## 4. Current status of ACT implementation

In 2000, before WHO delivered its policy recommendations on ACT, only a few countries in South-East Asia (Cambodia, Thailand and Viet Nam) deployed these medicines on a pilot basis in selected provinces/districts. To date, 60 countries, the majority countries with falciparum-resistant malaria, have adopted ACT in their national treatment policy, primarily as first-line treatment. The adoption of these medicines has occurred over a relatively short period of time – most countries adopted these medicines in 2004 and 2005, following GFATM's appeal for increased funding for ACTs. A total of 33 countries are deploying ACTs in general health services to variable extent, and implementation rates are higher in South America (71%) and Asia (65%) compared to Africa (44%), due to both the higher malaria burden and poverty in the latter.

Although more countries have adopted artemether-lumefantrine as first-line treatment (26) compared to artesunate+amodiaquine (16), in 2005 orders by UN procurement agencies for artesunate+amodiaquine exceeded those for artemether-lumefantrine. The selection of a new treatment policy at country level is a complex process, involving review of therapeutic efficacy studies and consensus building among many stakeholders. However, even after completion of this process, country choices of ACTs in 2005 have changed following global product shortage or failure to meet Good Manufacturing Practices by the respective manufacturers.

There is generally a lag time of 12–18 months between country adoption and implementation, due to multiple complex factors often occurring in combination, such as:

- late disbursements by external funding agencies,
- complex financial/procurement requirements of funding agencies,
- administrative/procedural conflicts between national procedures and those of international financial and procurement agencies,
- administrative delays in transferring funds to countries and back to international procurement agencies,
- lack of experience in drug supply management, with antimalarial medicines presenting with limited shelf-life (2 years) and multiple course-of-therapy blister packs,
- poor capacity for estimating drug requirements, poor stock management and drug supply and distribution,
- late re-ordering at peripheral and central levels, and sometimes even
- conflicting interests between manufacturers of competing ACTs, with attempts to revert treatment policy decisions or to influence international tenders.

WHO will work more closely with recipient Ministries of Health and with the main funding agencies such as the GFATM and the World Bank to resolve the major bottlenecks in financial disbursements and procurement.

## 5. Forecast of ACTs demand for the public sector

The procurement of ACTs for public sector use by WHO represents approximately 80% of orders placed through the UN Agencies, most of the remaining being procured by UNICEF. In 2005 the orders placed for ACTs through WHO showed a major increase compared to 2004, and the total annual reached 13.9 million treatment courses of artesunate+amodiaquine, 9.9 million treatment courses of artemether-lumefantrine and 5.6 million treatment courses of artesunate+sulfadoxine-pyrimethamine.

The procurement of ACTs for the public sector on a global level was relatively low in 2001 and 2002 (0.5–0.6 million treatment courses) and started to increase in 2003 (2.1 million treatment courses), 2004 (5 million treatment courses) and reached 31.3 million treatment courses ordered and delivered in 2005. The number of treatments delivered in the first part of 2006 have increased compared with the number of treatments delivered in the same period in 2005. From 1 January to 15 April, the number of treatments of artemether-lumefantrine has increased from 1.1 million in 2005 to 17 million in 2006.

Africa, south of the Sahara represents the major market for ACTs, due to its very high malaria burden; 36 African countries have adopted ACTs, 16 of them are deploying these medicines in the public sector, and a total of 25.5 million treatment courses have been procured and delivered in these countries in 2005.

Based on the trends of country adoption and implementations, and availability of international funds for ACT procurement, the global forecast for ACT for public sector use is 110 million treatment courses for 2006. The demand for the public sector is expected to increase to 155 million in 2007 and to 200 million in 2008, while the epidemiological needs for malaria treatments are estimated at more than 500 million treatment courses per year, considering both falciparum and vivax malaria.

The demand and market size for ACTs are in rapid expansion, and needs far exceed the current procurement figures. Among the multiple factors that influence the receptivity of the market and product penetration, the following deserve specific attention:

- availability of new fixed-dose combinations,
- price,
- paediatric formulations,
- penetration in the private sector,
- international funding initiatives
  (e.g. global ACT subsidy, round 6 of GFATM), and
- managerial, procurement, logistic capacity at country level.

## 6. WHO prequalification of antimalarial medicines

The WHO prequalification programme, a United Nations project managed by WHO, is an action plan for expanding access to HIV/AIDS, tuberculosis and malaria medicines of ensured quality, efficacy and safety, using international funds (for detailed information

see: http://mednet3.who.int/prequal/). The programme started with HIV/AIDS products in 2001; malaria and TB products were added later.

Substandard and counterfeit products are present in different countries, and systems for quality assurance of medicines supply chain are weak or absent. Although significant funds are invested in procurement, there are not yet harmonized quality assurance systems available for procurement organizations/initiatives and, as a consequence, products with very different quality are being sourced. The risks of sourcing poor quality products or even counterfeit medicines creates risk to patients, toxic reactions, treatment failure, and finally, resistance. In addition, bad quality products undermine public confidence.

The prequalification programme is voluntary for participating manufacturers, open to both innovators and multisource/generic manufacturers, and operates at no cost/fee for applicants (in future, fees are considered). It is based on general procedures and standards approved through WHO Expert Committee system involving all WHO Member States and WHO Governing bodies, and supported by the International Conference of Drug Regulatory Authorities (ICDRA) in 2002 and 2004, representing more than 100 national drug regulatory authorities; procedures will also be discussed in 12th ICDRA 2006.

The expected outcome of the prequalification programme is to generate public lists of products and manufacturing units meeting international norms and standards on quality, safety, and efficacy. It also contributes to capacity building and harmonization among National Drug Regulatory Authorities (DRAs), manufacturers, WHO technical programmes, NGOs and procurement agencies. In addition, it ensures continuous monitoring of prequalified products, based on prequalified quality control laboratories.

WHO is managing the prequalification programme on behalf of the United Nations. It provides technical and scientific support, and guarantees that international norms and standards are applied throughout the whole process, including product dossier assessment, inspection (GMP, GCP, GLP) and quality control. The partners include UNICEF, UNFPA, UNAIDS and the World Bank. The WHO technical programmes (Global Malaria Programme, Stop TB and HIV/AIDS Departments) define the list of products to be prequalified.

The assessment is carried out by qualified assessors and inspectors from National DRAs (also from National Quality Control Laboratories) of ICH and associated countries, and inspectorates belonging to Pharmaceutical Inspection Cooperation Scheme countries (PIC/S). The assessment of products' dossiers on quality specifications, pharmaceutical development, bioequivalence, etc. is done by teams of professionals from national drug regulatory authorities, which includes at present Brazil, China, Canada, Denmark, Estonia, Finland, France, Germany, Hungary, Indonesia, Malaysia, Philippines, Spain, South Africa, Sweden, Switzerland, Uganda, UK, UR Tanzania and Zimbabwe. The assessment is carried out by 8 to 16 assessors together during one week at least every two months at UNICEF in Copenhagen. Every dossier is assessed by at least two assessors, producing an assessment report. A letter is then sent to the applicant summarizing the findings and asking for clarification and additional data if necessary.

The assessment of product dossier has a specific procedure for innovator products: if approved by stringent authorities like EMEA and US FDA the procedure is abridged, trusting the expertise of well-established DRAs. The assessment in these cases is based on the report from the DRAs, WHO Certificate of Pharmaceutical Product (CPP), batch

certificate and update on changes. For multi-source products, the full dossier is requested with all data and information on quality (information on starting materials and finished product including API details, specifications, stability data, formulation, manufacturing method, packaging, labelling, etc.) and efficacy and safety (bioequivalence study or clinical study report). A confidentiality agreement has been signed between US FDA and WHO for mutual recognition of scientific assessment based on information exchange; the same approach will soon apply for EU Art. 58 and Canadian JCPA procedure. A commercial sample is requested, but not always analysed before prequalification (quality control analysis is increasingly part of proactive follow up after the product has been prequalified).

Prequalification requirements for generics are fully in line with major regulatory agencies. For instance, the US FDA requirements for generic drugs (www.fda.gov/cder/ogd) state that generic drugs must: *i*) contain the same active ingredients as the innovator drug; *ii*) be identical in strength, dosage form, and route of administration; *iii*) have the same use indications; *iv*) meet the same batch requirements for identity, strength, purity and quality; *v*) be manufactured under the same strict standards of GMP required for innovator products; *vi*) be bioequivalent. In practice for many products in the prequalification pipeline no innovator "reference" product may be available and, for this reason, they cannot be defined as generics. If the medicines are not generics, then the full data set needs to be submitted to prove safety (including preclinical toxicology) as well as efficacy.

The inspection procedure involves a WHO representative (qualified GMP inspector) and an inspector from well-established inspectorate (Pharmaceutical Inspection Cooperation Scheme countries – PIC/S). National inspector(s) is(are) invited to be part of the team but have no decision making power, because of possible different GMP standards and potential conflict of interest.

The inspection covers the following areas:

- manufacturing site (final product, packaging),
- active pharmaceutical ingredient (API),
- research laboratory or Contract Research Organization (CRO).

As part of the prequalification programme a series of training activities are being conducted. In 2005, three one-week comprehensive training courses on quality of TB drugs and ARVs were carried out in China, Malaysia, Ukraine. GMP training courses have been conducted in South Africa and China, and a new GMP training course will be conducted in United Republic of Tanzania. In addition, training has been organized for QC lab officials. Specific training courses for regulators and industries on antimalarial medicines have been conducted in Thailand (2004) and China (2006). An introduction course to the prequalification programme has been conducted in Viet Nam (2006), and two courses are planned on antimalarials and anti-TB medicines, in United Republic of Tanzania and China, respectively. All training course materials are posted on the web site to assist manufacturers to prepare quality dossiers and to be ready for inspections.

The current situation of prequalified products for the three diseases, with dossiers in the pipeline, is presented below:

| *Prequalified products (April 2006)* | | *"Active" dossiers in pipeline (2006)* | |
|---|---|---|---|
| 121 | HIV related medicines | 200 | (April 2006) |
| 8 | anti-tuberculosis medicines | 65 | |
| 5 | antimalarial medicines | 40 | |
| 134 | | 305 | |

*The antimalarials prequalified so far include:*

| | |
|---|---|
| Artesunate 50 mg tabs | Sanofi-Synthelabo – box of 25 blisters of 12 |
| Artemether 20 mg tabs<br>Lumefantrine 120 mg | Novartis Pharma – box of 30 blisters of 6, 12, 18 or 24 |
| Artemotil 50 mg/ml, sol. inj. | ARTECEF BV – 10 or 100 ampoules, each of 1 ml |
| Artemotil 150 mg/ml, sol. inj. | ARTECEF BV – 10 or 100 ampoules, each of 1 ml |
| Artesunate 50 mg tabs | Guilin Pharmaceutical Co Ltd PVC/AI – blisters of 12 |

The prequalification of artemisinin derivatives have encountered problems because very few are innovator products and most are not typical generics. Very few artemisinin derivatives are recommended by treatment guidelines approved in ICH and associated countries, and in general there are few DRAs and regulatory experts that have experience with these compounds. In addition the artemisinin derivatives often present quality related issues: manufacturers do not comply with GMP (even if located in the EU or EFTA countries – products not registered in the country of origin and produced for export only). Many dossiers have outstanding deficiencies in proving the quality of the product: e.g. non-compliance with established specifications or poorly defined manufacturers specifications; stability data either missing or not meeting requirements; no method validation, etc. Most manufacturers can overcome these problems if motivated, but this may take a lot of time.

For most of the artemisinin derivatives there is a lack of reference products for bio-equivalence studies. For generic drugs, safety and efficacy are proved by bio-equivalence studies assuming that the same blood concentrations of active ingredient give the same safety and efficacy profile. The only reference products are artesunate from Guilin Pharma and the artemether+lumefantrine FDC from Novartis. In relation to safety and efficacy, product dossier often have insufficient reports of the evidence about the clinical efficacy and safety, no fully documented trial reports, no full evaluation of published literature, and often no characterization of pharmacokinetic properties of the product. Often the product dossier contains incorrect general statements, such as "No interaction known", clearly not true; "No (or minimal) adverse events", available from literature survey. In addition the galenical development history is often not provided, making difficult to assess if results of earlier studies apply to current formulation. Many manufacturers applying for prequalification of artemisinin derivatives have very limited experience in these areas.

A series of measures have been taken to get more products prequalified, despite the limited resources. The prequalification programme started with only one professional; today it has three and by the end of 2006 it will have at least six. Internal SOPs and work

procedures to facilitate process have been created, specific "Note for Applicants" on antimalarials have been prepared and literature reviews for the various artemisinin derivatives will be made available to manufacturers. More direct discussions with manufacturers have started, including specific training workshops for manufacturers producing antimalarials.

In conclusion, a relatively large number of products and suppliers comply with the standards (mostly ARVs so far) and many potential suppliers appreciate feedback and are willing to improve. Unfortunately only a limited number of products have met the required standards (especially malaria products), and specific requirements (data to be generated, tests to be carried out, GMP upgrade, etc.) will demand time and funds. More technical support to manufacturers is needed especially to companies in developing countries.

## 7. WHO/UNICEF procurement of ACTs

In March 2003, two countries (Burundi and Zanzibar) adopted as first-line treatment artesunate+amodiaquine, for which there was no prequalified product available nor likely to be prequalified in the short term. At that time UNICEF and WHO established an interim procedure for issuing joint request for proposals for ACTs which lacked prequalified products.

A series of joint tenders were issued from 2003 to 2005, with evaluation based on a product quality questionnaire (which has now become the Interagency quality questionnaire), review of compliance to WHO-Good Manufacturing, registration information (countries), Active Pharmaceutical Ingredient, stability, resulting shelf-life and storage conditions. Quality assurance is based on a review of the documentation submitted, effected jointly by UNICEF Pharmaceutical Team and WHO (Procurement team with assistance from QSM when necessary).

The list of products selected considered as acceptable, based on the quality evaluation, is submitted to the WHO Contract Review Committee (CRC). The contract is awarded by the CRC to the bidder offering the lowest acceptable prices, shortest lead time, most suitable product conditioning in compliance with all instructions, contractual and technical provisions/ terms contained in the Request for Proposal. Once accepted, a letter of agreement is sent to the manufacturer, setting the price and other conditions for a period (usually 1 year). The product is then added to the Malaria catalogue of the electronic catalogue of WHO (WebBuy).

Following the first WHO/UNICEF joint tender in March 2003, no co-packaged product of artesunate+amodiaquine could be selected, due to lack of stability data. By June, only two products (artesunate and amodiaquine in separate blisters) satisfied the evaluation and allowed to place the first orders at a high cost (US$ 2.60 per adult treatment course). By December of the same year, it was possible to select three artesunate 50 mg tabs and two for amodiaquine 153 mg base tabs, lowering the price of artesunate+amodiaquine adult treatment to US$ 1.68.

At the second WHO/UNICEF joint tender, in 2004, a series of ACTs (in co-blister) were initially selected: five offers of artesunate+amodiaquine, one offer of

artesunate+mefloquine, one offer of artesunate+sulfadoxine-pyrimethamine and one offer of amodiaquine+ sulfadoxine-pyrimethamine. However, after the GMP inspection of the manufacturing site, only three offers of artesunate+amodiaquine were accepted for procurement.

To the third WHO/UNICEF joint tender, in 2005, manufacturers responded with better quality products and several artemisinin derivatives GMP compliant were selected. This includes artesunate+amodiaquine from CIPLA, IPCA and Sanofi/Aventis, artesunate+ mefloquine from MEPHA, artesunate+sulfadoxine-pyrimethamine from Guilin, artesunate suppositories from MEPHA and artesunate i.v./i.m. from Guilin. These products are being procured by UN procurement agencies and international drug suppliers. They are all included in the WHO e-procurement (WHO WebBuy) catalogue, which is in use across the Organization to allow standardization of items, rapid procurement and assistance in programme planning.

# ANNEX II

## *List of participating companies*

### Activa Pharmaceuticals (FCZ)
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Dr Wei LI, Technical Director

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*Representatives:*
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### Dafra Pharma NV

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Dr Herwig JANSEN, Director, Research and Development
Mr Paul LONGMOOR, Regional Director
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Mr Xiaohua YAN, Chairman of the Board and General Manager
Mr Xiaojie FENG, International Cooperation Majordomo & Representative of Guilin Pharma in Europe
Ms Bin JIANG, Director of Overseas Department
Ms Yahui WU, Drug International Registration Group Overseas Department

### Holley-Cotec Pharmaceuticals

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# WORLD HEALTH ORGANIZATION SECRETARIAT

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Dr Pascal RINGWALD, Medical Officer

### *Roll Back Malaria Partnership Secretariat (RPS)*

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### *Quality Assurance and Safety: Medicines (QSM)*

Dr Lembit RAGO, Coordinator

### *Contracting and Procurement Services (CPS)*

Mrs Françoise Blanche MAS, Procurement Officer (unable to attend)

Global Malaria Programme

# Indoor residual spraying

## Use of indoor residual spraying for scaling up global malaria control and elimination


World Health Organization

**Indoor residual spraying (IRS)** is one of the primary vector control interventions for reducing and interrupting malaria transmission. In recent years, however, it has received relatively little attention. Recent data re-confirms the efficacy and effectiveness of IRS in malaria control in countries where it was implemented well.

Effective implementation of IRS with DDT or other recommended insecticides should be a central part of national malaria control strategies where this intervention is appropriate. It is implemented with the objective of reducing malaria morbidity and mortality and accelerating progress towards global and national malaria targets. However, there are important considerations that must be taken into account when considering whether to introduce or scale up IRS. In particular, there must be sufficient capacity to deliver the intervention effectively, prevent unauthorized and un-recommended use of public health pesticides, and manage insecticide resistance. Intensified research efforts are needed, for example to develop new insecticides, long-acting formulations and improved application technologies.

Along with producing IRS manuals and guidelines, the World Health Organization (WHO) will support countries to collect and analyse data, towards determining potential effectiveness and feasibility of IRS in the national context, and with planning and implementing the intervention. WHO requests countries to report on coverage and impact as IRS is implemented or scaled up.

This position statement is intended for public health policy makers, malaria control programme managers, development agencies, development banks, academic and research institutions and private sector corporations involved in scaling up malaria control programmes.

WHO/HTM/MAL/2006.1112

Global Malaria Programme

# Indoor residual spraying

## Use of indoor residual spraying for scaling up global malaria control and elimination

WHO Position Statement

World Health Organization

# CONTENTS

# 1. Introduction

## 1.1 Global malaria control interventions

WHO's Global Malaria Programme recommends the following three primary interventions that must be scaled up in countries to effectively respond to malaria, towards achieving the Millennium Development Goals for malaria by 2015 and other health targets:

- diagnosis of malaria cases and treatment with effective medicines;
- distribution of insecticide-treated nets (ITNs) to achieve full coverage of populations at risk of malaria; and
- indoor residual spraying (IRS) as a major means of malaria vector control to reduce and eliminate malaria transmission including, where indicated, the use of DDT.

Scaling up access and achieving high coverage of these effective interventions, particularly to populations who are at the highest risk of malaria, and sustaining their implementation, remain major challenges for achieving current global malaria control goals.

## 1.2 Indoor residual spraying (IRS)

IRS is the application of long-acting chemical insecticides on the walls and roofs of all houses and domestic animal shelters in a given area, in order to kill the adult vector mosquitoes that land and rest on these surfaces. The primary effects of IRS towards curtailing malaria transmission are: *i)* to reduce the life span of vector mosquitoes so that they can no longer transmit malaria parasites from one person to another, and *ii)* to reduce the density of the vector mosquitoes. In some situations, IRS can lead to the elimination of locally important malaria vectors. Some insecticides also repel mosquitoes and by so doing reduce the number of mosquitoes entering the sprayed room, and thus human-vector contact.

# 2. IRS in context

## 2.1 Malaria control and elimination since 1950

The efforts of the Malaria Eradication Programme (1955–1969) contributed to significantly reducing the global malaria burden, particularly in Asia, Latin America and Southern Africa. The eradication programme was based on IRS against the vector mosquitoes, as endorsed by the WHO Kampala Conference of 1950. These efforts, combined with other measures, led to malaria eradication from Europe, the former USSR, and several countries in Asia and

the Caribbean. About 700 million people, or more than half of the previously exposed populations, were no longer at risk (*1*).

Most of the African continent, however, was not involved in this effort. Subsequent attempts to control malaria through primary health care strategies were largely unsuccessful. The burden of malaria that remains today, much of which is in sub-Saharan Africa and in remote rural areas of Asia and Latin America or among marginalized populations, is unacceptably high. Today malaria remains a major cause of poverty and underdevelopment, and it is estimated that 3.2 billion people live at continuous risk of this disease. Each year, there are more than 350 million cases of malaria and more than a million deaths from the disease. More than two-thirds of malaria cases occur in Africa, as well as approximately 90% of deaths, which are mainly in children under five years of age.

Initial optimism about the possibility for prompt global eradication of malaria, due to early successes obtained largely in temperate or subtropical areas, gave way to support for more long-term control strategies (*2*). In areas where the elimination of malaria is not feasible with existing tools and technologies, the objective should be to reduce malaria burden to a level that is socially and economically acceptable.

## 2.2 Decline in the use of IRS

Despite its initial widespread use and contribution to the success of malaria eradication and control efforts, in recent years, the use of IRS has declined. This is due in part to lack of government commitment and financing to sustain these efforts over the long term and to concerns about insecticide resistance and community acceptance. However, another important factor has been general disapproval of DDT use, due to fears of its harmful effects on the environment and on human health, fears which are unjustified when DDT is used appropriately for IRS. In the past, DDT was widely used in agriculture and domestic hygiene, leading to massive release of the compound into the environment.

## 2.3 Evidence of IRS efficacy and effectiveness

Scientific evidence of IRS efficacy in reducing or interrupting malaria transmission in different epidemiological settings has been available since the 1940s and 1950s (*3,4,5*). Numerous studies have shown that IRS has substantially reduced infant and child mortality. This evidence formed the rationale for introduction of IRS as a primary intervention for malaria control and eradication.

Evidence over several decades has confirmed the effectiveness of IRS in reducing levels of infection and incidence of malaria. For example, the malaria incidence was reduced by 90% or more in major areas of tropical Asia and Southern America during the eradication programme through a combination of IRS and other measures.

In Africa, malaria eradication pilot projects were initiated from the 1950s to the 1970s in Benin, Burkina Faso, Burundi, Cameroon, Kenya, Liberia, Madagascar, Nigeria, Rwanda, Senegal, Uganda and the United Republic of Tanzania. These projects demonstrated that malaria was highly responsive to control by IRS with significant reduction of anopheline vector mosquitoes and malaria, although in most cases, transmission could not be interrupted (*6,7,8,9,10*). However, with a few exceptions, IRS was not taken to scale in large parts of sub-Saharan Africa.

The application of IRS consistently over time in large areas has altered the vector distribution and subsequently the epidemiological pattern of malaria in Botswana, Namibia, South Africa, Swaziland and Zimbabwe. The major vector, *An. funestus*, has been eliminated or reduced to negligible levels. Where present, the other major vector, *An. gambiae* s.s., which rests and bites mostly indoors, was also well-controlled. Another vector, *An. arabiensis*, which does not rest indoors as much as *An. gambiae*, is less affected by IRS, even at high coverage levels, and is responsible for low levels of transmission and seasonal increases and outbreaks (*11,12,13*).

## 2.4 Choosing to implement or scale up IRS

Scientific evidence therefore indicates that IRS is effective to control malaria transmission and thus reduce the related burden of morbidity and mortality as long as most premises (houses, animal shelters) (e.g. $>$ 80%) within targeted communities are treated. Furthermore, studies confirm that IRS is cost-effective, although developments such as insecticide resistance could change the cost-effectiveness over time (*14*). There is no definitive conclusion on the comparative cost-effectiveness of IRS versus ITNs since it depends on the local context. Thus, countries should maintain IRS in their malaria control strategies, where indicated, until further information, including locally-generated data, is available and can be used to fine-tune national interventions and better guide resource allocation.

In a single country, several epidemiological patterns and situations are commonly found requiring different interventions or combinations of interventions. These must be taken into account when deciding whether to use IRS. IRS can be effective in almost all settings as long as certain conditions for implementation are met.

- In unstable, epidemic-prone malaria transmission areas, IRS will prevent seasonal increase in transmission, will prevent and control epidemics and can be used for the elimination of local transmission of malaria.
- In stable-endemic malaria areas with moderately intense but seasonal transmission, IRS can prevent seasonal increase in transmission and reduce levels of infection prevalence and highly seasonal morbidity and mortality.
- In stable-hyperendemic areas where very intense seasonal or perennial transmission occurs, IRS, with a higher frequency of application than in the above instances, can reduce the level of transmission and reduce levels of infection prevalence, morbidity and mortality.*

There are some situations in which IRS is not a suitable intervention, notably where there are no structures to spray. Therefore, IRS has almost no utility in the control of malaria in forested areas of South-East Asia and the Amazon region, where personal protection measures are the best option.

The choice of IRS, or any other vector control intervention, must be made by careful consideration of the factors mentioned above, and will depend on the local context and the strategic objectives, whether elimination of local transmission, transmission control, or personal protection. The role and limitations of existing malaria vector control interventions and personal protection measures have been reviewed by a WHO Study Group and a comprehensive report recently published (*15*).

# 3. Realizing the potential of IRS

## 3.1 Selection of insecticide

There are currently 12 insecticides recommended by WHO for IRS, belonging to four chemical groups (one organochlorine, six pyrethroids, three organophosphates and two carbamates). The choice of insecticide must be informed by the following considerations:

- insecticide susceptibility and vector behaviour;
- safety for humans and the environment;
- efficacy and cost-effectiveness.

### 3.1.1. Insecticide susceptibility

IRS will only be effective if the target vectors are susceptible to the insecticide in use. The development of resistance to insecticides constitutes a major threat to the chemical control of malaria vectors, as it compromises the insecticide's

** IRS has commonly been the intervention of choice in these settings in areas of a particular economic interest (e.g. tourism, mining, oil extraction, agricultural schemes) that requires a rapid and very effective prevention, where financial and logistic constraints do not prevail.*

efficacy. In the past, countries deploying IRS have often been forced to switch to alternative and more expensive insecticides on account of the development of vector resistance. Outside Africa, the prevalence and distribution of insecticide resistance in malaria vectors have not, so far, been a major impediment to insecticide-based interventions, except in some areas of India, the Middle East and Central America.

However, in Africa, the potential threat of resistance to public health insecticides appears to be significant. Resistance to DDT and pyrethroids in major malaria vectors has been found throughout West and Central Africa, in some areas at a high level, as well as in several parts of Eastern and Southern Africa. Resistance to carbamates has been found in countries of West Africa, with a mechanism that also induces cross resistance to organophosphates. The selection of resistance in most malaria vectors is thought to be largely the result of past and present use of insecticides in agriculture. The precise operational implications of insecticide resistance are not yet fully understood.

A comprehensive assessment of resistance at the local level must be carried out before planning any IRS programme, especially in West and Central Africa. The possibility of insecticide resistance calls for the careful monitoring of the susceptibility of malaria vectors to insecticides throughout the world, and the sound management of resistance.

There are specific interactions between insecticides and malaria vectors. Some insecticides tend to repel more than to kill vector mosquitoes. Changes in vector behaviour induced by insecticides may have important operational implications, and it is important to be aware of them when selecting insecticides for IRS.

DDT is the only insecticide which is used exclusively for public health, and, therefore, unlike with other insecticides, resistance development to it is no longer influenced by other uses such as in agriculture. In the context of resistance management, it is, therefore, advisable to maintain the use of DDT until a suitable alternative is available.

#### 3.1.2. Safety for humans and the environment

Another major consideration when selecting an insecticide is safety. Insecticides recommended by WHO are deemed safe for public health use under the recommended conditions of use. Concerns over the safety of DDT, a persistent organic pollutant, have also been comprehensively addressed in the framework of the Stockholm Convention on Persistent Organic Pollutants (POPs). The Convention bans the use of DDT, except for public health purposes. Therefore, DDT can be used for IRS where it is indicated, provided that stringent measures are taken to avoid its misuse and leakage outside public health.

#### 3.1.3. Efficacy and cost-effectiveness

The choice of insecticide has implications for the cost-effectiveness of the IRS intervention. Insecticides suitable for IRS have to be sufficiently stable to maintain biological efficacy on treated surfaces over time, so as to minimize the number of spray cycles needed to cover a malaria transmission season.

DDT has long been the cheapest insecticide and the one with the longest residual efficacy against malaria vectors (6–12 months depending on dosage and substrate). Other insecticides have relatively shorter residual effect (pyrethroids: 4–6 months; organophosphates and carbamates: 2–6 months). Thus, the use of DDT alternatives might require two to four spray cycles per year instead of one, depending on the length of the transmission season, with important operational and financial implications for spraying programmes.

Currently, the cost of using some of the pyrethroid insecticides is almost equivalent to that of using DDT, but other alternatives might be at least four times more expensive depending on the number of spray cycles required. The widescale use of organophosphates or carbamates in areas of year-round high-level transmission might be very difficult to sustain unless improvements in their formulations result in higher residual efficacy and lower cost.

### 3.2 Effective implementation

Malaria vector control operations have to be targeted, treating only where and when necessary. IRS is a method for community protection, and given its mode of action, the highest possible level of coverage is required to achieve the maximum impact on malaria transmission. Achieving this level of coverage and timing spraying correctly (in a short period of time before the onset of the transmission season) are crucial to realize the full potential of IRS. IRS is indicated only in those settings where it can be implemented effectively, which calls for a high and sustained level of political commitment. Transmission control operations based on IRS, or any other vector control intervention, have to be maintained at high coverage levels for extended periods of time, for as long as impact is needed.

IRS requires effective leadership and management for planning, organization and implementation. Operations must be managed by skilled professional staff, based on an analysis of local epidemiological data and a sound understanding of transmission patterns, vector behaviour and insecticide resistance status. Significant strengthening of human and technical resources, accompanied by sufficient financial resources, is needed to develop or reorganize existing IRS operations.

Finally, community acceptance of house spraying and cooperation, for example by allowing access and removing some household contents prior to spraying, are critical for the programme to be successful. Repeated spraying of houses commonly generates fatigue and refusal by householders. Reduced acceptability has been an impediment to effective IRS implementation in various parts of the world.

### 3.3 Preventing unauthorized and un-recommended use of public health pesticides

When implementing IRS, it is critical to ensure that adequate regulatory control is in place to prevent unauthorized and un-recommended use of public health pesticides in agriculture, and thus contamination of agricultural products. Pesticide contamination can have serious ramifications for trade and commerce for countries exporting agricultural products.

Maximum residual limits (MRLs) of pesticides in food products intended for human or animal consumption are established and strictly enforced by some countries. The standards vary across countries and according to the type of pesticide (see Annex), resulting in different requirements for exported agricultural products. For example, MRL levels for DDT for the European Union usually range from five to ten times lower than equivalent levels for other countries, such as Japan and the United States. Therefore, to export to the European Union, countries must ensure that their products meet much more stringent standards than they must meet for other countries.

DDT, as a persistent organic pollutant, is now banned for agricultural use. There is, however, no justification for preventing the use of DDT for IRS based solely on fear of contamination of agricultural products, provided a clear national policy and adequate safeguards for storage, transport and disposal are in place and there is adherence to WHO recommendations.

## 4. Research and development

Growing concerns over insecticide resistance in malaria vectors, and the particularly heavy reliance of ITN interventions on pyrethroid insecticides, call for research and development on new insecticides as alternatives to DDT and pyrethroids. Innovative approaches and alliances may be needed to increase financing and improve research efforts. In addition, studies must be carried out in the field, particularly in Africa, to assess the potential impact of resistance on efficacy and effectiveness of IRS for different resistance mechanisms, insecticides and vectors.

More effective, longer-acting and user-friendly formulations of existing insecticides are needed, as well as improved technologies for their application.

Research and development on refined tools, for example those based on improving malaria surveillance and use of remote sensing technologies, should be undertaken, as well as entomological and epidemiological field investigations to optimally select, combine and target vector and malaria control interventions at country level.

## 5. Conclusion and recommendations

WHO reaffirms the importance of IRS as one of the primary interventions for reducing or interrupting malaria transmission. WHO's Global Malaria Programme will work together with countries, development agencies, research institutions and the private sector to review, expand and improve IRS interventions, where they can be implemented properly, to complement or supplement other interventions as part of national malaria control policies and programmes.

WHO recommends that national governments should:

1. Introduce and/or scale up coverage of targeted IRS as a primary malaria control intervention in countries where available data indicates that it can be effective towards achieving malaria targets.
2. Take all necessary steps to ensure effective implementation of IRS interventions, including selecting the appropriate insecticide, spraying where and when necessary and sustaining a high level of coverage, and to prevent unauthorized or un-recommended use of public health insecticides.
3. Strengthen the managerial capacity of national malaria control programmes and improve human, technical and financial resources for the timely delivery and high coverage of effective interventions including IRS, with adequate monitoring and evaluation.

WHO will:

1. Support countries to strengthen field entomological and epidemiological services to carry out epidemiological stratification, map distribution of malaria vectors and document key features of their behaviour and insecticide resistance in relation to transmission of malaria.
2. Support countries with planning, implementation, monitoring and evaluation of the intervention, including fostering linkages between the public and private sectors for improving product support on malaria insecticides in the areas of quality control, public information and health worker education and training for IRS.
3. Promote heightened research and development efforts to improve the formulation of existing insecticides for longer duration of efficacy and support the development and deployment of new long acting insecticides and novel tools for malaria control.

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# ANNEX

## Food residue limits of selected pesticides that are recommended for indoor residual spraying (expressed as maximum residual limits (MRLs) or tolerance levels: ppm = parts per million in mg/kg)

| Pesticides recommended for IRS | | Examples of food types | US tolerance levels* (ppm) | Japan (MRLs ppm) | European Union (MRLs mg/kg) |
|---|---|---|---|---|---|
| Chemical groups | Name of pesticide | | | | |
| Organochlorine | DDT | Avocado | 0.2 | 0.5 | 0.05 |
| | | Corn | 0.1 | 0.2 | 0.05 |
| | | Cherries | 0.2 | 0.2 | 0.05 |
| | | Eggs | 0.5 | 0.1 | 0.05 |
| | | Mango | 0.2 | 0.5 | 0.05 |
| | | Onion | 0.2 | 0.5 | 0.05 |
| | | Papaya | 0.2 | 1.0 | 0.05 |
| | | Pineapples | 0.2 | 0.5 | 0.05 |
| | | Peanuts | 0.2 | 0.2 | 0.05 |
| | | Tomato | 0.05 | 0.2 | 0.05 |
| Organophosphates | Malathion | Apple | 8 | 0.5 | 0.5 |
| | | Carrots | 8 | 0.5 | 0.5 |
| | | Orange | 8 | 4 | 2 |
| | | Mango | 8 | 8 | 0.5 |
| | | Pepper | 8 | 0.5 | 3 |
| | | Pineapple | 8 | 8 | 0.5 |
| | | Potato | 8 | 0.5 | 0.5 |
| | | Onions | 8 | 8 | 3 |
| | | Tomato | 8 | 0.5 | 3 |
| | | Yams | 1 | 0.5 | 0.5 |
| Pyrethroids | Cyfluthrin | Apple | N-E | 1.0 | 0.2 |
| | | Carrot | 0.2 | 0.1 | 0.02 |
| | | Pepper | 0.5 | 5 | 0.3 |
| | | Potato | 0.01 | 0.1 | 0.02 |
| | | Pineapple | N-E | 0.02 | 0.02 |
| | | Mango | N-E | 0.2 | 0.02 |
| | | Milk (dairy) | 1 | 0.04 | 0.02 |
| | | Onion | N-E | 2 | 0.02 |
| | | Tomato | 0.2 | 2 | 0.05 |
| | | Yams | N-E | 0.1 | 0.02 |
| | Deltamethrin | Apple | 1.0 | 0.5 | 0.1 |
| | | Bananas | N-E | 0.5 | 0.05 |
| | | Beans | N-E | 0.1 | 1 |
| | | Corn (sweet) | 0.03 | 1.0 | 0.05 |
| | | Mangoes | N-E | 0.5 | 0.05 |
| | | Onion | 0.1 | 0.5 | 0.1 |
| | | Papaya | N-E | 0.5 | 0.05 |
| | | Pepper | 0.3 | 0.5 | 0.05 |
| | | Peanuts | N-E | 0.1 | 0.05 |
| | | Tomato | 0.2 | 0.5 | 0.2 |

* For DDT, figures presented are action levels. The FDA takes action to make the food item unavailable to the consumer when these action levels are exceeded. N-E = MRL or tolerance level not established

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