

An Update on

Quality Assurance and Procurement through WHO for
Improving Access to Artemisinin-Based Combination Treatments
(ACTs) for Malaria



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Background

Consistent with WHO recommendations, malaria-endemic countries which are experiencing high levels of resistance to currently used antimalarial drugs such as chloroquine and sulfadoxine/pyrimethamine (SP) are changing treatment policies from monotherapies to artemisinin-based combination treatments (ACTs).^{1,2}

ACTs combine an artemisinin compound with a partner antimalarial drug to which there is little or no resistance in the country or situation in which the ACT is to be deployed. The advantages of ACTs relate to the properties of artemisinin compounds, which include rapid reduction of the parasite biomass with fast resolution of clinical symptoms, effectiveness against multidrug-resistant *falciparum* malaria, resistance not being documented yet, and a good safety profile. They also reduce gametocyte carriage, which in some settings may lower malaria transmission.²

The cost of ACTs is, however, significantly greater than previously used antimalarial monotherapies. At current market prices ACTs cost 10 to 20 times more than chloroquine and SP. The prices are expected to come down as the demand for these drugs increase.^{3,4}

At present, only one ACT (artemether-lumefantrine) is available as a fixed dose drug in which both compounds are co-formulated into a single tablet (Courted®) and as a prequalified product (see below). Other ACTs are available as individual products that need to be co-administered. Co-packaging of the combination partner drugs in a blister is highly recommended in order to make them user-friendly and to increase adherence to the complete therapy. Artemisinin compounds are sensitive to moisture. The shelf-life of most products is around two years and this is contingent on high standards of blister-packaging and good storage. Attention must therefore be paid to their manufacturing and storage conditions. Furthermore, there is limited experience with these products by drug regulatory authorities and health care professionals. It is therefore necessary to adhere to stringent raw material standards, drug-manufacturing practices, norms and standards (Good Manufacturing Practices, GMP).

What is being done by WHO to assist countries to access ACTs?

WHO has, in collaboration with other UN agencies, taken several steps to assist member countries to purchase quality assured ACTs:

1) Quality Assurance: Prequalification and Sourcing Project

This is an initiative through which WHO, in collaboration with other UN agencies, will pre-qualify manufacturers of artemisinin compounds and ACTs on the basis of compliance with internationally recommended standards of manufacturing and quality.^{3,4}

WHO has requested an expression of interest to participate in this initiative from pharmaceutical manufacturers of the following products⁵:

- Artesunate (oral preparations)
- Dihydroartemisinin (tablets, capsules, pediatric granules, suppositories)
- Artemether (oral preparations)

- Artemether (intramuscular preparations)
- Artemether + lumefantrine (oral preparations)
- Artesunate (injection for IV and IM)
- Artemotil (injectable forms)
- Artesunate + mefloquine (oral preparations)
- Artesunate + amodiaquine (oral preparations)
- Artesunate + sulphadoxine/pyrimethamine (oral preparations)

Information submitted by manufacturers is assessed by a panel of external, independent reviewers for compliance with recommended standards, and their manufacturing sites are assessed for compliance with Good Manufacturing Practices (GMP). Products and manufacturers which meet the aforesaid standards will be included in a list considered acceptable for procurement by UN agencies. Manufacturers included in this list may be invited to bid for the supply of products, individually or collectively, directly by UN agencies. The list of pre-qualified manufacturers could also serve as a guide to Governments, NGOs and other partners purchasing ACTs on behalf of endemic countries.

2) Centralised Procurement: WHO-UNICEF Call for Tenders for the Supply of One ACT, (artesunate/AS and amodiaquine/AQ)

While the ‘prequalification and sourcing’ project is underway, some countries have found themselves in immediate need of procuring the ACT artesunate and amodiaquine. Although quality products for each of the two drugs are available, it has not been possible, until now, to source this combination drug as a co-blisterpacked product, which meets required standards. As an interim measure, and to meet the immediate requirement of some countries for the coming months, WHO and UNICEF have therefore called for a joint tender for the procurement of AS and AQ as separate blisterpacks which will then be packed and dispensed together.

A technical review of the bids for tender, and assessment of the GMP compliance of the manufacturers has been done. WHO, together with UNICEF will monitor the delivery of AS and AQ to malaria control programs and provide technical assistance for the deployment of these products in the malaria-endemic countries.

WHO’s efforts to procure AS and AQ *co-blisterpacked* to GMP standards continues in parallel with this effort.

3) Negotiated Prices and Centralized Procurement: Artemether-lumefantrine (Coartem®)

In a joint effort to provide essential medicines at affordable prices, the World Health Organization and the Swiss pharmaceutical company *Novartis*, which manufacture the ACT artemether-lumefantrine (Coartem®), have come to a special pricing agreement. Novartis will provide the drug at cost price (US \$2.40 per full adult treatment and considerably less for a child dose) for use in the public sector of malaria-endemic countries.

WHO, through its panel of experts, reviews requests for supplies of Coartem®, and procures and distributes the drug through the Governments of malaria-endemic countries and/or NGOs.⁶ WHO and Novartis have jointly developed specially designed packs for Coartem® to facilitate proper use of the drug, and continue to conduct joint research to improve treatment regimens. Full details are available on the RBM website (<http://rbm.who.int>).

Conclusion

The following must be taken into consideration in the procurement and use of ACTs:

- ACTs should be procured from pharmaceutical companies with an assured competence to manufacture the product(s) to GMP standards.
- The product(s) should be appropriately blister-packed to assure maximal stability and product integrity.
- Appropriate transportation and storage facility must be ensured to maintain product stability and integrity.
- Ministries of Health must ensure rational deployment of ACTs with regimen adherence for optimal treatment and to prolong the useful therapeutic life of these drugs
- Comprehensive monitoring and evaluation of product use, including therapeutic efficacy assessment and post-marketing surveillance for safety, is recommended.

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- 1 World Health Organization and UNICEF (2003) *The Africa Malaria Report 2003* (WHO/CDS/MAL/2003.1093). Geneva: World Health Organisation (WHO).
 - 2 WHO (2001) *Antimalarial Drug Combination Therapy. Report of a WHO Technical Consultation, 4-5 April, 2001* (WHO/CDS/RBM/2001.35). Geneva: WHO.
 - 3 WHO (2003) *Access to Antimalarial Medicines: Improving the Affordability and Financing of Artemisinin-Based Combination Therapies* (WHO/CDS/MAL/2003.1095 (ed. H Haak). Geneva: WHO.
 - 4 WHO (2003) *Improving Access to Antimalarial Medicines - Roll Back Malaria Partnership Meeting* (in press). Geneva: WHO.
 - 5 Expression of Interest for Pre-Qualification of Artemisinin Products (at WHO Essential Drugs and Medicines website at <http://www.who.int/medicines/organization/qsm/activities/pilotproc/malaria/pilotprocmal.shtml>).
 - 6 *Procurement of Artemether-Lumefantrine (COARTEM®) through WHO*: Full Details on the WHO website at http://mosquito.who.int/cmc_upload/0/000/015/789/CoA_website5.pdf.