GLOBAL MALARIA PROGRAMME:

The World Health Organization (WHO) urges regulatory measures to stop marketing of oral artemisinin-based monotherapies and to promote access to artemisinin-based combination therapies (ACTs)

Key facts

• Falciparum malaria has become increasingly resistant to all previous first-line drug therapies, but new combination medicines containing artemisinin derivatives show an over 95 percent cure rate after a standard short three-day regimen.

• It is critical that the parasite remains sensitive to artemisinin derivatives. In order for this situation to continue, artemisinin derivatives need to be used in combination with other effective antimalarial medicines for the treatment of uncomplicated falciparum malaria.

• Yet, the widespread practice of using oral artemisinin-based monotherapies, which are easier and cheaper to produce and buy, places an enormous risk of losing artemisinin (and its derivative) to parasite resistance.

• Artemisinins, if used as monotherapy, require to be taken as a full seven-day treatment course in order to completely eliminate the parasite. However, due to the rapid resolution of clinical signs and symptoms, most patients do not complete the required full seven-day treatment, leaving the parasite exposed to sub-therapeutic blood levels, which promote the development of resistance.

• Artemisinin-based combination therapies remain the only medicines for effective treatment of uncomplicated falciparum malaria for several years to come, because alternative treatments are unlikely to enter the market at least until 2015.
Milestones

JANUARY 2006

In line with new WHO Guidelines for the Treatment of Malaria, pharmaceutical companies were asked to stop the production and marketing of oral artemisinin-based monotherapies. Major procurement and funding agencies as well as international suppliers have since accepted WHO recommendations and agreed not to fund or procure oral artemisinin-based monotherapies.

APRIL 2006

WHO hosted the first technical briefing in Geneva for 25 pharmaceutical companies producing and marketing artemisinin-based medicines. Several among the participating companies make formal commitment to stop marketing oral artemisinin monotherapies over a limited time period.

MAY 2007

The World Health Assembly approved Resolution 60.18 on malaria. As part of multiple recommendations to strengthen malaria control and elimination, the Resolution urges all WHO Member States to deploy artemisinin-based combination therapies and to progressively withdraw oral artemisinin-based monotherapies from the market.

AUGUST 2007

WHO hosted a 2nd briefing in Geneva for 24 pharmaceutical companies to present its Code for Artemisinin Marketing Practice (CAMP). The Code was accepted by all participating companies, requiring them to:
- i) manufacture and market medicines in line with the WHO Guidelines for the Treatment of Malaria;
- ii) observe Good Manufacturing Practices certified after inspection by WHO or stringent drug regulatory authorities;
- iii) not misuse WHO name/logo for commercial purposes;
- iv) report to WHO, under confidential cover, evidence of companies marketing oral artemisinin-based monotherapies, or selling substandard or counterfeit products.*

OCTOBER 2008

WHO hosted a meeting in India with the Drugs Controller General, the Malaria Control Programme, the Antimalarial Drug Committee, representatives of pharmaceutical companies and key national partners to discuss strategies and opportunities for expanding access to malaria treatment and progressively phase out artemisinin monotherapies from the market in line with the most recent WHO recommended policies and strategies.

* More information on WHO CAMP and how to report can be found at: http://www.who.int/malaria/docs/diagnosisandtreatment/MtgManufacturersArtemisininDerivatives.pdf
Country examples: progress to date

**BENIN**

- Malaria is a major public health problem in Benin, representing 41 percent of reported diseases. It is the main cause for outpatient visits and hospital admissions.
- A consensus meeting was held in March 2006 to agree on the withdrawal of oral artemisinin-based monotherapies. Challenges were identified in relation to the availability, use and affordability of artemisinin-based combination therapy.
- A transitional period was agreed upon to give all parties time to adapt to the new regulation, provide training to drug sellers, and information/communication to the general public.
- The critical step in Benin is to ensure large scale availability of artemisinin-based combination therapies before withdrawing the monotherapies from the market. With the implementation of ACT treatment policy and inclusion of Benin in the AMFm initiative, this requirement will be met in the near future.

**CHINA**

- In October 2006, WHO met Chinese health authorities and manufacturers in Beijing to discuss phasing out of monotherapies and promoting quality artemisinin-based combination therapies in both domestic and international markets.
- The Ministry of Health (MoH) of China proposed to WHO four areas of collaboration for the future that include: i) monitoring drug resistance; ii) technical assistance to Chinese manufacturers to enable the pre-qualification of new, affordable and quality artemisinin-based combination therapies; iii) research on new combinations in order to expand the list of antimalarial medicines recommended by WHO, and iv) involvement of Chinese scientists in WHO expert consultations to share Chinese scientific data as well as operational experience in malaria chemotherapy.
- WHO proposed that China considers artemisinin-based combination therapies instead of oral artemisinin-based monotherapies in the drug donation programmes that are part of China’s Bilateral Aid programmes with African countries. The government of China implemented this policy in 2007. In 2008 oral artemisinin-based monotherapies were de-listed from the national antimalarial treatment policy of China.

**INDIA**

- Indian pharmaceutical companies play a major role in exporting artemisinin-based antimalarial medicines to African countries. Up to 70 Indian companies marketing these medicines have been identified so far.
- Two meetings (April 2006 and October 2008), were convened with Indian manufacturers to inform them of WHO recommendations regarding oral artemisinin-based monotherapies and to understand the wide range of stakeholders involved in the production and marketing of artemisinin-based monotherapies.
- At the meeting in October 2008, the rationale for the WHO Code for Artemisinin Marketing Practice was presented and feasible mechanisms and timelines for the progressive withdrawal of oral artemisinin-based monotherapies from the Indian market were defined. The meeting was chaired by the Drug Controller General of India.
- It was agreed that regulatory measures to phase out oral artemisinin-based monotherapies will be implemented. The Drugs Controller General of India informed in December 2008 the State Licensing Authorities to withdraw the permission for marketing these products, over a 6 months period, potentially affecting both their domestic and export markets.
PAKISTAN

- Malaria, after acute respiratory infections, represents the second priority disease in Pakistan.
- In May 2007, a meeting with 14 manufacturers of oral artemisinin-based monotherapies was convened by the National Drug Controller of the Ministry of Health, in collaboration with the Directorate of Malaria Control and WHO.
- Following the agreement of the manufacturers to phase out monotherapies, an agreement was reached with the Directorate of Malaria Control for the fast track registration of artemisinin-based combination therapies.
- A deadline was agreed to stop the production of oral artemisinin-based monotherapies by November 2007, with these medicines being no longer available for sale by March 2008. The pharmaceutical companies followed the timeline of phasing out these products as notified by the Drug Controller Office of the MoH.

VIET NAM

- Due to the successful implementation of malaria control since 1991, malaria cases have significantly decreased in Viet Nam.
- In December 2007, WHO and the national health authorities met with manufacturers of artemisinin-based pharmaceutical products in Viet Nam.
- The Ministry of Health of Viet Nam requested WHO to host a training workshop in Good Manufacturing Practices for companies producing artemisinin/artesunate as an active pharmaceutical ingredient. This meeting has not been scheduled yet.
- WHO reiterated the need to have an on-going dialogue with companies exporting artemisinin-based medicines to invest in the production and marketing of artemisinin-based combination therapies instead of monotherapies.
- In 2008 oral artemisinin-based monotherapies were de-listed from the national antimalarial treatment policy of Viet Nam.

Main challenges

Since pharmaceutical markets of malaria endemic countries are largely unregulated, pharmaceutical companies are prone to ignore the WHO appeal.

There is an urgent need for more stringent regulations and enforcement mechanisms in countries to regulate the private sector.

Responsible companies complying with WHO recommendations, by withdrawing monotherapies leave ‘niche markets’ which are exploited by opportunistic companies manufacturing substandard products.

Closer monitoring of marketing practices by WHO is vital to ensure the complete elimination of oral artemisinin-based monotherapies.
Continuous monitoring

The position of manufacturing companies and of national drug regulatory authorities in relation to WHO’s appeal to withdraw the marketing authorization of oral artemisinin-based monotherapies is monitored on a regular basis.

Information on manufacturing companies is available here:
http://www.who.int/malaria/publications/monotherapy_manufacturers.pdf

Information on countries is available here:
http://www.who.int/malaria/monotherapy_NDRAs.pdf
The way forward

The recent Report of the Affordable Medicines Facility – Malaria Ad-Hoc Committee from the Global Fund to fight AIDS, Tuberculosis and Malaria recommended that manufacturers who market oral artemisinin-based monotherapy would not be eligible to participate in the Affordable Medicines Facility. This new global initiative will be implemented initially in 9 malaria endemic countries, to prove the feasibility and effectiveness of supplying quality ACTs at highly subsidized prices to both public and private sector markets. The objectives are to save lives ensuring widespread access to affordable ACTs and to contain artemisinin resistance by displacing oral artemisinin-based monotherapies from the market with quality ACTs.

National governments have an important part to play. Empowerment of national drug regulatory authorities of malaria endemic countries is essential to stop marketing authorizations of oral artemisinin-based monotherapies.

The following time-table, based on the initial experience of some successful countries, is a generic guide that countries can adapt to phase out oral artemisinin-based monotherapies from the market.

<table>
<thead>
<tr>
<th>ACTION</th>
<th>TASK</th>
<th>TIMELINE</th>
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<tbody>
<tr>
<td>Step 1</td>
<td>Agreement on time frame of phasing out oral artemisinin-based monotherapies in synchrony with large-scale implementation of artemisinin-based combination therapies (ACTs)</td>
<td>Immediate</td>
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<tr>
<td>Step 2</td>
<td>Suspension of new approvals of marketing authorizations for oral artemisinin-based monotherapies</td>
<td>Immediate</td>
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<tr>
<td>Step 3</td>
<td>Suspension of import licences for artemisinin or its derivatives (as API or FPP) to domestic companies exclusively marketing oral artemisinin-based monotherapies</td>
<td>3 – 4 months</td>
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<td>Step 4</td>
<td>Large-scale deployment of ACTs in the public sector and communication to prescribers and consumers to move away from monotherapies</td>
<td>Time X1</td>
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<td>Step 5</td>
<td>Widespread availability and affordability of ACTs in the private sector</td>
<td>Time Z2</td>
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<tr>
<td>Step 6</td>
<td>Withdrawal of marketing authorization and of manufacturing licences for oral artemisinin-based monotherapies as FPPs</td>
<td>6 months after time X</td>
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<tr>
<td>Step 7</td>
<td>Suspension of export license for oral artemisinin-based monotherapies as FPPs</td>
<td>6 months after time X</td>
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<tr>
<td>Step 8</td>
<td>Complete elimination of oral artemisinin-based monotherapy medicines as FPPs from the market</td>
<td>10 – 12 months after time X</td>
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<tr>
<td>Step 9</td>
<td>Active recall of oral artemisinin-monotherapies from the market</td>
<td>3 months after time Z</td>
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Progress in selected countries and positive responses by several manufacturers show that phasing out artemisinin-based monotherapies is possible; however, more remains to be done. The Road Map is known, but the journey is arduous, and will only succeed under the strong stewardship of the national health authorities of malaria endemic countries.

We have witnessed that the irrational use of antibiotics has generated a widespread resistance. With the artemisinin-based antimalarial medicines, we now have the opportunity not to go down a similar road. It is a chance that must not be missed.

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1 X refers to the time at which a country will deploy on a large-scale artemisinin-based combination therapies in the public sector, generally associated with external funding for procurement (e.g. from GFATM or other sources). All subsequent timelines are conditional to this.

2 Z requires distribution of quality ACTs at subsidized prices in the private sector, as expected in countries participating to the Affordable Medicine Facility.