Essential Medicines

Regulatory action needed to stop the sale of oral artemisinin-based monotherapy

Continued use of oral artemisinin-based monotherapy is widely considered as one of the main contributing factors to the development and spread of resistance to artemisinin and its derivatives. Few patients take the full seven–day course of monotherapy required to achieve high cure rates — most patients tend to discontinue treatment after two or three days due to the rapid resolution of symptoms provided by artemisinin. This results in persistent parasitaemia exposed to sub-therapeutic drug levels. In 2007, the World Health Assembly adopted a resolution to progressively remove oral artemisinin-based monotherapy from the market and instead deploy artemisinin-based combination therapies (ACTs) for the treatment of uncomplicated falciparum malaria. While 34 countries have withdrawn marketing authorization for oral artemisinin-based monotherapy, 29 countries have not yet taken regulatory action. Out of 73 companies involved in the production and marketing of these medicines, a total of 36 companies have de-listed oral artemisinin-based monotherapy from their product catalogues but 37 companies — mainly those targeting the private sector markets of malaria-endemic countries — are still actively providing monotherapy in this sector. Progress made by regulatory authorities at country level shows that phasing out oral artemisinin-based monotherapy from the market is possible through a range of interventions as long as government commitment and strong stewardship of the national regulatory authorities is maintained.

Artemisinin-based monotherapy and risk of Plasmodium falciparum drug resistance

Malaria causes an estimated 243 million clinical attacks every year with 863 000 deaths, mostly in children under 5 years of age, due to Plasmodium falciparum (1). WHO recommends artemisinin-based combination therapies (ACTs) as the mainstay of treatment of uncomplicated P. falciparum malaria (2). The rationale of combining a rapidly acting artemisinin derivative with a second longer acting antimalarial partner — killing the parasite using two different modes of action — is to delay the development of resistance. Prevention of artemisinin resistance is particularly important as there are no alternative antimalarial medicines under development with equivalent levels of efficacy expected to become available over the next 7–8 years (3).

Artemisinin and its derivatives are highly efficacious. They rapidly eliminate asexual parasite stages and early sexual forms of falciparum malaria, producing a rapid clinical and parasitological response (4). When used as monotherapy, artemisinin derivatives need to be given for seven days to achieve high cure rates, while three-day monotherapy treatment

results in unacceptably high (48–54%) recrudescence rates (5). Consequently, there are two main product presentations which promote artemisinin resistance:

- Medicinal products with 5–7 day administration of artemisinin-based monotherapy.
- ACTs which are co-blistered rather than co-formulated.

Full seven-day treatment is impractical and most patients tend to discontinue treatment early due to the rapid clinical resolution provided by artemisinin. With co-blistered ACTs many patients tend to take the three-day treatment of the artemisinin derivative and discard the partner medicine (e.g. amodiaquine or mefloquine) due to the poor tolerability of the latter medicines. Both products, which lead to inadequately dosed artemisinin monotherapy, leave the parasite exposed to sub-therapeutic blood levels of the medicine which promotes the development of parasite resistance by eliminating the most sensitive parasite strains and leaving the more resistant ones to multiply unrestrained.

**Emergence and selection of drug resistant parasites**

The emergence of resistance to antimalarial medicines is initiated by rare spontaneous mutations which provide survival advantages to the parasite while exposed to a specific antimalarial compound. When exposed to the medicine in question (drug pressure), the mutant parasite strains which have a survival advantage get selected in favour of the sensitive ones. Mutations can originate in the population of parasites from the same geographical area or in parasites from different areas. Migrating populations contribute to the development and spread of resistance by importing mutated parasites from other geographical areas which then recombine with the local parasites to give rise to a pool of mutated and recombined parasites. Antimalarial immunity in patients, which increases in proportion to the intensity of malaria transmission, might conceal the effects of drug resistance and delay the detection of drug resistant infections (6).

*Plasmodium falciparum* has thus far developed resistance to all classes of antimalarial medicines used in its treatment (6). While quinine remained effective for decades after its large-scale introduction in the early 20th century, the development of resistance to the other antimalarial compounds emerged relatively faster, varying from 12 years for chloroquine to five years for mefloquine, to approximately one year for proguanil, sulfadoxine-pyrimethamine and atovaquone. In the 1950s and 1960s, *P. falciparum* resistance to chloroquine and sulfadoxine-pyrimethamine was first detected in the Pailin province, Western Cambodia (4), from where it subsequently spread to the Indian subcontinent in the 1970s and then to East African countries in the 1980s.

More recently in 2009, scientists confirmed the first cases of falciparum resistance to artemisinin derivatives in the same province of Pailin (8). In this area artemisinins have been extensively used as monotherapy over the past decade, and this may have contributed to the development of resistance together with other unidentified factors (4, 8). There is major concern that artemisinin resistance in *P. falciparum* malaria parasites may increase and spread to other areas of the world.

The loss of artemisinin derivatives will have devastating consequences on people’s health in malaria-endemic countries and threaten recent malaria control progress achieved in many countries.
Drug pressure and its impact on antimalarial drug resistance
Past experience shows that once resistance has arisen the removal of drug pressure can prolong the useful therapeutic life of the corresponding medicine (9). Mutations associated with drug resistance in *P. falciparum* generally affect the parasite’s fitness. Studies undertaken with chloroquine and mefloquine showed that parasite susceptibility to the corresponding active pharmaceutical ingredient was restored after discontinuing use of the medicines.

In China, in vivo resistance to chloroquine decreased over a 5–8 year period from more than 84% to 40%. In certain regions of Malawi — the first African country to discontinue chloroquine use in 1993 in favour of sulfadoxine-pyrimethamine — molecular markers of chloroquine resistant parasites decreased in prevalence over time (9). For other antimalarial medicines, such as sulfadoxine-pyrimethamine, drug resistant mutations may persist after drug pressure is removed if they do not affect the parasite’s fitness or if secondary mutations occur, providing compensatory mechanisms to strengthen parasite fitness.

Phasing out oral artemisinin-based monotherapy
Based on the biological mechanisms of resistance observed with the other antimalarial compounds, it is expected that with removal of oral artemisinin-based monotherapy the resistance of *P. falciparum* to artemisinins will either reduce or stabilize at prevailing levels rather than get worse. Both mechanisms will result in extending the useful therapeutic life of artemisinin derivatives. WHO therefore urges Member States to cease the marketing and use of oral artemisinin-based monotherapy in both the public and private sectors and to promote the use of artemisinin-based combination therapies. As part of World Health Assembly Resolution WHA60.18 (10), these recommendations were endorsed by all WHO Member States in May 2007. Since 2006, the WHO Global Malaria Programme has contacted the major procurement and funding agencies in relation to these recommendations and, as a result, all major agencies have progressively discontinued funding or procurement of these medicines.

Monitoring the phasing out of artemisinin-based monotherapy
Until all ACTs become available as fixed-dose combinations, oral artemisinin-based monotherapies will need to be manufactured for co-blistering with partner medicines; the call is against the sale and use of oral artemisinin-based monotherapy. To track compliance with Resolution WHA60.18 by pharmaceutical companies marketing these medicines and progress in implementation of regulatory action by national drug regulatory authorities, WHO has established a web-based monitoring system. Regularly updated information can be accessed through the following links: http://www.who.int/malaria/monotherapy_manufacturers.pdf (pharmaceutical companies) and http://www.who.int/malaria/monotherapy_NDRAs.pdf (national drug regulatory authorities).

Since 2005, WHO has identified a total of 73 pharmaceutical companies involved in the production and marketing of oral artemisinin-based monotherapy medicines. On a regular basis, WHO contacts these companies in order to update their positions with regard to WHO recommendations. All but one of the 36 companies which have ceased marketing so far have been identified in the period from 2005–2007; action was taken following repeated requests from WHO. Companies identified more recently are less prone to withdraw their products from the market. By April 2010, an additional six companies had declared their intentions to comply, but have not taken action so far and a total of 30 companies have not
disclosed their position (Figure 1). Nearly all companies which have a consistent market share in public sector procurement funded by international agencies have de-listed oral artemisinin-based monotherapy medicines from their product catalogues. However, smaller companies mainly targeting private sector markets are more prone to ignore the WHO appeal. When responsible companies comply with WHO recommendations and withdraw their monotherapy products, they leave ‘niche markets’ which are rapidly exploited by opportunistic companies manufacturing monotherapy and substandard products. Most of the companies still involved in the marketing of oral artemisinin-based monotherapy medicines are located in India (21), followed by Nigeria (5), Kenya (2) and Viet Nam (2), as well as the Democratic Republic of Congo, Dubai (United Arab Emirates), Ghana, Greece, Netherlands, Pakistan and Switzerland (1 company each).

One of the main reasons for the limited success in phasing out oral artemisinin-based monotherapy is the poor regulation of pharmaceutical markets in malaria-endemic countries. In February 2010, out of the 78 national regulatory authorities (NRAs) of falciparum-endemic countries, 49 have either never registered or have taken regulatory measures to withdraw marketing authorizations of oral artemisinin-based monotherapy and 29 still do not yet comply with WHO recommendations. Most of the countries which have not yet taken regulatory steps are located in the WHO African Region (16 NRAs) followed by the South-East Asia Region (6 NRAs) and the Western Pacific Region (3 NRAs).

The regulation of pharmaceutical markets in malaria-endemic countries is a complex process. A number of successful examples show that phasing out oral artemisinin-based monotherapy can succeed. Countries are adopting WHO recommendations to progressively phase out artemisinin-based monotherapies and adapt them to their national context. In some countries, like Cameroon and Côte d’Ivoire, the new regulations aim to align

![Figure 1. Companies marketing oral artemisinin-based monotherapies by year of identification by WHO updated on a regular basis (last update 13 April 2010)](image-url)
the availability of products for sale in the private sector with those listed in the national treatment guidelines and available in the public sector. Other countries like Benin have used this opportunity not only to remove oral artemisinin-based monotherapy but also all formulations of chloroquine, which is no longer effective due to high levels of *P. falciparum* resistance. The critical step in Benin was to ensure large-scale availability of ACTs. For some countries, e.g. China and Vietnam, the main target of decisions of the national health authorities has been the removal of oral artemisinin-based monotherapy from the public sector, following change of the national treatment guidelines. The examples of India and Pakistan show the importance of national regulatory authorities in coordinating this initiative and support provided by the national Malaria Control Programme and WHO in both countries to accelerate the process. The active recall of existing stocks of chloroquine and sulfadoxine-pyrimethamine in Burundi has proven to be highly effective.

The way forward: targets and timelines for action

The active withdrawal of a medicine from the market in the interest of public health through a regulatory approach — in this particular case to limit the risk of development of resistance — is unprecedented. Many steps are involved in the manufacture of artemisinin-based medicines, from the planting of the seeds to extraction of the active pharmaceutical ingredient (API) and subsequent manufacture of the finished pharmaceutical products (FPPs). Thereafter the sale of oral artemisinin-based monotherapy takes place in the context of domestic and international market dynamics. A variety of interventions can and have successfully been applied at these various steps in order to interrupt both the manufacture and sale of these monotherapies. Thus, measures affecting both international and domestic markets, and targeting both APIs and FPPs can be applied to phase out oral artemisinin-based monotherapy medicines from the markets.

Export markets can be influenced by regulatory actions targeting those countries which are the major exporters of these medicines. In particular, withdrawing manufacturing and export licenses for FPPs can prevent pharmaceutical companies from exporting their monotherapy products to malaria-endemic countries. To protect domestic markets, the most effective strategy is to stop import licences and not to grant marketing authorizations for such products. Domestic manufacturers should be regulated more stringently with regard to import licenses for APIs, e.g., not granting API import licenses to companies exclusively manufacturing oral artemisinin-based monotherapies. In addition, to regulate domestic companies involved in the re-packaging or re-branding of artemisinin-based FPPs produced in other countries, FPP import licenses should be suspended for companies exclusively marketing oral artemisinin-based monotherapies.

It is crucial to ensure large-scale availability of ACTs in both the public and private sectors, before oral artemisinin-based monotherapies can effectively be removed from the market. Based on the initial experiences of successful countries, Table 1 overleaf offers generic timelines for progressively removing these medicines from the market which can be adapted to specific situations.

Conclusion

Progress made by several pharmaceutical companies and regulatory authorities at country level show that phasing out oral artemisinin-based monotherapy medicines from the markets is possible through a range of interventions. However, the problem is still rife and is cur-
Currently one of the major threats for development of drug resistance. The response of pharmaceutical companies to stop marketing oral artemisinin-based monotherapies has been successful in those with a consistent market share in accessing international funds for public sector procurement. Smaller companies which mainly target the pharmaceutical private sector in developing countries have largely compromised the success of this approach. Thus, ultimate success in

<table>
<thead>
<tr>
<th>Action</th>
<th>Task</th>
<th>Timeline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1</td>
<td>Agreement on timeframe of phasing out oral artemisinin-based monotherapies in synchrony with large-scale implementation of artemisinin-based combination therapies (ACTs)</td>
<td>Immediate</td>
</tr>
<tr>
<td>Step 2</td>
<td>Suspension of new approvals of marketing authorizations for oral artemisinin-based monotherapies</td>
<td>Immediate</td>
</tr>
<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>
</tr>
<tr>
<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 X*</td>
</tr>
<tr>
<td>Step 5</td>
<td>Widespread availability and affordability of ACTs in the private sector</td>
<td>Time Z**</td>
</tr>
<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>
</tr>
<tr>
<td>Step 7</td>
<td>Suspension of export licence for oral artemisinin-based monotherapies as FPPs</td>
<td>6 months after time X</td>
</tr>
<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>
</tr>
<tr>
<td>Step 9</td>
<td>Active recall of oral artemisinin-monotherapies from the market</td>
<td>3 months after time Z</td>
</tr>
</tbody>
</table>

* 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 conditioned on this.

** Z requires distribution of quality ACTs at subsidized prices in the private sector, as expected in countries participating in the Affordable Medicines Facility – malaria (Global Fund to Fight AIDS, Tuberculosis and Malaria [GFATM]).
phasing out oral artemisinin-based monotherapy depends on effective drug regulation at country level. Only the removal of marketing authorizations for oral artemisinin-based monotherapies will make them unavailable in the public and formal private sectors. A flourishing informal private sector, which is common in many malaria-endemic countries, will still continue to provide oral monotherapy to potential users and can be overcome by the provision of good access to quality medicines through a national drug supply management system.

Experience shows that a number of critical steps should be taken in the process of phasing out oral artemisinin-based monotherapy from the market. It is essential to synchronize these with the large-scale deployment of ACTs in the public sector and the provision of reasonable timelines allowing the progressive adaptation and response of the private sector to new health directives.

Enhanced action to phase out oral artemisinin-based monotherapy medicines in the remaining malaria-endemic countries is urgently required. Government commitment and strong stewardship of national regulatory authorities is required to achieve this. Artemisinin resistance — which is being accelerated by the use of oral artemisinin-based monotherapy — is too grave a public health risk to continue deployment of these medicines.

References


10. World Health Organization. World Health Assembly Resolution 60.18 (WHA60.18) http://apps.who.int/gb/ebwha/pdf_files/WHA60/A60_R18-en.pdf