



**Artesunate  
+Mefloquine**

*Fixed-Dose Combination*

**ARTESUNATE-  
MEFLOQUINE  
FIXED-DOSE  
COMBINATION  
THERAPY  
(ASMQ FDC)**



**AN EASY TO USE,  
HIGHLY EFFICACIOUS  
AND AFFORDABLE  
THERAPY  
TO FIGHT MALARIA**

DNDi

**DNDi**

*Drugs for Neglected Diseases initiative*



TO FIGHT MALARIA

## IN BRIEF

- **Artemisinin-based combination therapies (ACTs)** are recommended for the treatment of uncomplicated *Plasmodium falciparum* malaria. ACTs are crucial for global malaria control strategy and to reduce transmission and the number of new malaria cases.
- **The WHO recommends** that fixed-dose combinations (FDCs) are adopted whenever possible because, in addition to their ease-of-use, they ensure simultaneous administration of the artemisinin derivative and its partner drug, thus facilitating compliance and delaying occurrence of resistance<sup>1</sup>. 24 million new malaria cases and 40,000 deaths occur each year in Asia – nearly 5% of the global malaria-related mortality – and one million in Latin America (32% of which are *P. falciparum* cases, mostly in Brazil)<sup>2</sup>.
- **One of the best documented treatments** for malaria, the combination of artesunate (AS) and mefloquine (MQ), has been widely used in Southeast Asia over the past 18 years, and has been shown effective and safe in the treatment of uncomplicated *P. falciparum* malaria<sup>3</sup>. To address the treatment needs of people affected by malaria, the FACT (Fixed-dose ACT) Consortium, created by DNDi and the WHO Special Programme for Research and Training in Tropical Diseases (WHO/TDR), developed the **artesunate-mefloquine fixed-dose combination (ASMQ FDC)**, in a partnership with Farmanguinhos, a Brazilian government-owned pharmaceutical company, and, following a South-South technology transfer, with Cipla Ltd, an Indian pharmaceutical company.
- **Safe, well known, convenient and highly effective**, the combination of AS and MQ is today one of the five ACTs recommended by WHO as effective first-line treatments for uncomplicated *P. falciparum* malaria. The combination of AS and MQ is especially important in Southeast Asia and Latin America, where a number of countries have adopted the combination as first-line treatment<sup>4</sup>.

1. Chan M (World Health Organization Director General). Opening Speech to the 120th Session of Executive Board. January 22, 2007; Geneva, Switzerland. <http://www.who.int/mediacentre/events/2007/eb120/en/index.html>. Accessed March 2, 2010.

2. PAHO and world malaria report 2009.

3. Nosten F et al. Lancet. 2000;356:297-302.

4. Myanmar, Thailand, Cambodia, Malaysia, Bolivia, Peru, Columbia, Venezuela and Brazil for the state of Accre.

# ASMQ FDC

is easy to use

as **1** **2** **3**!

**1** dose      **2** products      **3** days

One single daily dose of 1 or 2 tablets of two highly effective combined products for three days of affordable medicine

- **ASMQ FDC demonstrated high cure rate and good efficacy** in various studies in Asia and Latin America, including a large intervention study in Brazil with over 30,000 patients. This study led the Brazilian Ministry of Health to include ASMQ FDC in the national malaria treatment policy and in the National Control Programme.
- **ASMQ FDC is well tolerated.** The 2010 WHO malaria guidelines<sup>5</sup> acknowledge that “side effects, where this [ASMQ] ACT has been deployed, were seldom debilitating and it has been well tolerated”.
- **ASMQ FDC is designed to ensure treatment adherence** and decrease the risk of emergence of resistance. In addition to a better compliance, its major benefits are an optimised short-term gastro-intestinal tolerance, the gametocytocidal effects of the artemisinin derivative and the prophylactic effect of mefloquine. These effects, combined with the long half-life of mefloquine, may lead to a significant impact on transmission.

5. WHO guidelines, 2010, 2nd edition.

# AN EASY-TO-USE AND SHORT-COURSE (3-DAY) TREATMENT

■ **Easy-to-use** ASMQ FDC offers a quality, convenient, safe, and highly effective drug.

■ **Easy-to-use** for children & adults as 1-2-3! with :

- One single daily dose of 1 or 2 tablets of
- Two highly effective combined products for
- Three days of affordable medicine



















■ **Dosage adapted to age and weight.**

ASMQ FDC tablets of AS + MQ (25/55 mg and 100/220 mg) are offered in 4 dosage forms based on a weight-for-age reference.

With age-based dosing, patients are more likely to receive the dose they need.

## RECOMMENDED DOSAGE FOR ASMQ FDC TABLETS

The simple administration of ASMQ FDC for each age/weight category facilitates compliance, providing a better chance of cure and less risk of emergence of parasitic resistance to treatment. The disintegration of the tablet with water in a spoon allows easy administration to infants and small children.

Weight (Kg)	Age	Recommended Dose	Day 1	Day 2	Day 3
 5 – 8	2 – 11 months	One Tablet 25/55 mg <sup>1</sup> daily for 3 days			
 9 – 17	1 – 6 years	Two Tablets 25/55 mg <sup>1</sup> daily for 3 days			
 18 – 29	7 – 12 years	One Tablet 100/220 mg <sup>2</sup> daily for 3 days			
 ≥ 30	≥ 13 years	Two Tablets 100/220 mg <sup>2</sup> daily for 3 days			

1. Mefloquine HCl 55 mg are equivalent to 50 mg of mefloquine  
2. Mefloquine HCl 220 mg are equivalent to 200 mg of mefloquine

■ **An Affordable treatment with a 3-year shelf life.** ASMQ FDC is available “at cost” to the public/NGO sector of endemic countries. US\$2.50 is currently the price per adult treatment of ASMQ FDC (at cost price) and compares favorably with the loose AS+MQ combination. DNDi and partners are working to reduce the cost and price in the coming years. Moreover, the 3-year shelf-life of ASMQ FDC facilitates deployment and availability in rural health centers.

# HIGH EFFICACY AND EXTENSIVE CLINICAL EVIDENCE

■ **The loose combination of AS and MQ** was demonstrated safe and efficacious in at least 74 trials involving over 11,000 patients in 20 countries, including Bangladesh, Cambodia, Laos, Myanmar, India, and Thailand. Systematic deployment of AS+MQ was shown effective to stop resistance and reduce malaria incidence along the border between northwestern Thailand and Myanmar.

■ **Large studies confirmed its safety and efficacy<sup>6</sup>** and through continuous parasitological efficacy monitoring, MQ and AS given over 3 days (MAS3) has remained the treatment of choice since 1992 in Thailand. Over the subsequent 13 years of continuous MAS3 deployment, the cure rates assessed at day 42 remained well above 90%. The good efficacy of the FDC was demonstrated in Brazil, Myanmar, India, and Thailand, showing 100% cure rates in Myanmar and in India, and 91.9% in one study in Thailand.

■ **In 2009 in Myanmar, the effectiveness** of all four WHO-recommended fixed-dose ACTs – artesunate-amodiaquine, dihydroartemisinin-piperaquine, artemether-lumefantrine and AS-MQ, including ASMQ FDC and loose AS+MQ – was compared in over 800 Burmese adults and children<sup>7</sup>. All regimens were well tolerated and all but artesunate-amodiaquine are highly effective with cure rates >90%. ASMQ FDC had the highest cure rate and the lowest rate of gametocytes carriage, providing the greatest post-treatment suppression of recurrent *P. falciparum* malaria and the most effective suppression of blood-stage *P. vivax* malaria.

■ **In Latin America**, ASMQ FDC was evaluated for programmatic use by the National Programme of Control of Malaria and Health Authorities of Brazil in the State of Acre (Amazon Basin) between 2006 and 2008. In this study, one year after the introduction of ASMQ FDC, *P. falciparum* malaria cases were reduced by 80% and malaria-related hospitalisations dropped by over 60%. The ratio of *P. falciparum* to *P. vivax* infections decreased from 70% to 20%; decreases in the proportion of patients with recurrent *P. falciparum* infections and in the proportion of slides with gametocytes were also observed.

■ **In Africa**, the use of AS+MQ has also been documented in 10 countries that provided data for over 1,800 patients treated with various dose regimens of AS+MQ loose combination since 1994 with overall very good efficacy results.

6. Price RN, Nosten F, Luxemburger C, van Vugt M, Phaipun L, et al. Artesunate/mefloquine treatment of multi-drug resistant *falciparum* malaria. Thai-Burmese border. Trans R Soc Trop Med Hyg 1997, 91: 574–77.  
7. Smithuis F, Moe Kyaw Kyaw, Ohn Phe, Thein Win, Pyay Phy Oo, Aung Pyay Phy Oo, Arkar Linn Naing, Mya Yee Nyo, Naing Zaw Htun Myint, Mallika Imwong, Ashley E, Lee SJ, White N. Effectiveness of five artemisinin combination regimens with or without primaquine in uncomplicated *falciparum* malaria: an open-label randomised trial. Myanmar. The Lancet Infectious Diseases Published online September 9, 2010 DOI:S1473-3099(10)70187-0



## A WELL-TOLERATED TREATMENT



- **Good overall tolerance** of ASMQ has been indicated by several studies, in particular in the large Brazil intervention study during which no serious adverse events were notified. The observed reduced early vomiting compared to other AS plus MQ dosage schedules has been described as the main advantage of ASMQ FDC.

An individual-patient meta-analysis of 16 published clinical studies with a total of 5,487 patients randomly assigned to receive one of 10 different dosing and timing schedules of AS 4 mg/kg once daily for 3 days combined with MQ 15 or 25 mg/kg over 1 to 3 days<sup>8</sup> showed excellent results.

Concerns have been raised about potential central nervous system (CNS) adverse effects of ASMQ FDC due to the known effects of MQ. According to the 2010 WHO Malaria Guidelines<sup>9</sup>, the repeated use of MQ-containing ACT within 60 days of first treatment is associated with an increased risk of neuropsychiatric reactions. In the event of a new *P. falciparum* malaria infection during this period, it is recommended to take a medication without MQ if the initial treatment was AS+MQ.

More data are still needed regarding this aspect of the tolerability of ASMQ FDC since CNS events have been mostly related to the use of MQ in monotherapy and in prevention rather than treatment.

- **Reduced vomiting.** According to the 2010 WHO Malaria Guidelines<sup>9</sup>, the main reason for previously restricting the use of AS+MQ in African children was excessive vomiting associated with MQ at the recommended dose of 25 mg/kg. Based on some recent publications<sup>10</sup>, the WHO recommends reconsidering the use of AS+MQ in Africa, stating that adverse events “are seldom debilitating, where this ACT has been deployed it has been well tolerated. To reduce acute vomiting and optimise absorption, the 25 mg/kg dose is usually split”. The FDC split the total dose over three days. A DNDi-supported study is undergoing in Tanzania, Kenya, and Burkina Faso to specifically assess the potential use of ASMQ FDC in African children, comparing its efficacy and safety to that of artemether-lumefantrine.

8. Prof. Nosten F., Personal communication.

9. WHO Guidelines for the treatment of malaria. 2nd Edition. 2010

10. Faye B, Ndiaye JL, Tine R, Sylla K, Gueye A, Lô AC, Gaye O. A randomized trial of artesunate mefloquine versus artemether lumefantrine for the treatment of uncomplicated *Plasmodium falciparum* malaria in Senegalese children. Am J Trop Med Hyg 2010;82: 140-44

## OTHER EVIDENCE FOR ASMQ

- **First-line treatment in some countries in Southeast Asia and Latin America.** WHO regards both AS and MQ as “essential medicines” for the treatment of *P. falciparum* malaria<sup>11</sup> and since 2001, the combination of AS and MQ has been one of the WHO-recommended ACTs for first-line antimalarial treatment. ASMQ is first-line malaria treatment policy in Myanmar, Thailand, Cambodia, Malaysia and Bolivia, Peru, Columbia, Venezuela and Brazil (State of Acre). In India<sup>12</sup>, ASMQ FDC – when registered – could be used as an alternative treatment to the recommended AS+SP(sulfadoxine-pyrimethamine). ASMQ FDC is planned for first deployment in all countries where AS+MQ is the policy and in others depending upon their resistance profile.

- **ASMQ FDC may have an effect on malaria transmission and is active against mixed infections.** ACTs reduce gametocyte carriage, which was significantly lower in patients treated with ASMQ compared to other ACTs<sup>13</sup> in a study performed in Myanmar. Reducing gametocyte carriage might affect the transmissibility of malaria.

*P. vivax* infections following *P. falciparum* infections are of considerable public health importance and, in co-endemic regions, a unified ACT-based strategy for *P. vivax* and *P. falciparum* malaria may be needed. In the study performed in Myanmar, the ASMQ FDC regimen provided the most effective suppression of blood-stage *P. vivax*.

- **ASMQ FDC has been developed through an innovative partnership.** Not patented, ASMQ has been developed by the international FACT Consortium of Institutes and Experts as a “public good”, with financial support from not-for-profit organisations (NGOs), public institutions, and governments. The Brazilian manufacturer, Farmanguinhos, has been involved in the development and production of ASMQ, and in its implementation that followed a large-scale intervention study in Brazil, supported by the Brazilian Malaria Programme. ASMQ FDC, registered in Brazil since 2008, is distributed free to patients by the Ministry of Health.

- **A South-South technology transfer between Brazil and Cipla Ltd in India** was signed in 2008 with DNDi support and facilitation. This is the first between a company in Brazil and one in India for malaria, and the first involving a public entity, Farmanguinhos, and a private one, Cipla Ltd. Cipla Ltd, in charge of production and distribution outside Latin America, filed for WHO pre-qualification in 2010 and is planning to register ASMQ FDC in India and the ASEAN countries throughout 2011.

11. [http://www.who.int/selection\\_medicines/committees/expert/17/sixteenth\\_adult\\_list\\_en.pdf](http://www.who.int/selection_medicines/committees/expert/17/sixteenth_adult_list_en.pdf) and [http://www.who.int/selection\\_medicines/committees/expert/17/second\\_children\\_list\\_en.pdf](http://www.who.int/selection_medicines/committees/expert/17/second_children_list_en.pdf).

12. [http://www.mrcindia.org/Guidelines\\_for\\_Diagnosis2010.pdf](http://www.mrcindia.org/Guidelines_for_Diagnosis2010.pdf), accessed December 14, 2010.

13. Smithuis F, et al. Effectiveness of five artemisinin combination regimens with or without primaquine in uncomplicated *falciparum* malaria: an open-label randomised trial. Myanmar. The Lancet Infectious Diseases Published online September 9, 2010 DOI:S1473-3099(10)70187-0.

# MORE ABOUT...

## The FACT Project Consortium: A Worldwide Collaboration to Develop and Deliver ASMQ

In 2002, in order to address the treatment needs of people most threatened by malaria, the FACT Consortium developed ASMQ as a FDC. Key partners include the Instituto de Tecnologia em Fármacos of Farmanguinhos/Fiocruz, Mahidol University, Université Victor Segalen Bordeaux 2 (TROPICAL), University of Oxford, University Sains Malaysia, the Shoklo Malaria Research Unit, the Mae Sot Clinic, MSF, DNDi, and Cipla Ltd. DNDi plays an active role to facilitate FACT development and implementation by engaging partners such as pharmaceutical companies, national malaria programmes, research institutes, contract research organisations, and NGOs, as well as the WHO and TDR. DNDi convened an independent panel of experts, the FACT Implementation Advisory Group, who meets on an annual basis to provide external advice and critical guidance on development and facilitation of rational use and equitable access.

## Farmanguinhos

Farmanguinhos, part of the Oswaldo Cruz Foundation (Fiocruz) of the Government of Brazil, is one of the largest pharmaceutical laboratories in Brazil. Located in the state of Rio de Janeiro, Farmanguinhos produces more than two billion pharmaceutical components each year for HIV/AIDS and for the treatment of endemic diseases such as malaria (ASMQ, primaquine and chloroquine), leprosy, tuberculosis, and filariasis. Today, Farmanguinhos is one of the most important national laboratories, ensuring the Brazilian population's access to essential medicines; it aims to be a centre of reference for research, technology and production of medicines.

## To learn more...

- ASMQ: [www.actwithasmq.org](http://www.actwithasmq.org)
- Cipla: [www.cipla.com](http://www.cipla.com)
- Drugs for Neglected Diseases initiative: [www.dndi.org](http://www.dndi.org)
- Farmanguinhos/Fiocruz: [www.far.fiocruz.br](http://www.far.fiocruz.br)
- Impact Malaria: [www.impact-malaria.com](http://www.impact-malaria.com)
- Medicines for Malaria Venture: [www.mmv.org](http://www.mmv.org)
- Roll Back Malaria: [www.rbm.who.int](http://www.rbm.who.int)
- Shoklo Malaria Research Unit: [www.shoklo-unit.com](http://www.shoklo-unit.com)
- TDR: [www.who.int/tdr/diseases/malaria/default.htm](http://www.who.int/tdr/diseases/malaria/default.htm)
- WHO Global Malaria Program: [www.who.int/malaria/](http://www.who.int/malaria/)

## Cipla Ltd

Cipla Ltd is a prominent Indian pharmaceutical company, actively engaged in manufacturing and exporting bulk drugs and finished products, and best-known for manufacturing low-cost anti-AIDS drugs for HIV-positive patients in developing countries. Founded by Khwaja Abdul Hamied as The Chemical, Industrial & Pharmaceutical Laboratories in 1935, Cipla has a wide portfolio with over 1,200 drugs ranging from cardiovascular to cancer, AIDS, malaria, asthma, diabetes, arthritis, diabetes and many other health conditions. Manufacturing facilities – 40 in India – have approvals from various regulatory agencies, including FDA (USA), WHO (Geneva), the MHRA (UK), MCC (South Africa), TGA (Australia) and PIC (Germany). Products are regularly sold to around 170 markets across the globe besides catering to the domestic market.

## DNDi

Founded in 2003, DNDi (Drugs for Neglected Diseases *initiative*) is a needs-driven, not-for-profit product development partnership (PDP) working to research and develop new treatments for neglected diseases such as sleeping sickness (human African trypanosomiasis), leishmaniasis, Chagas disease and malaria. DNDi drew founding partners primarily from the public sector in neglected disease-endemic countries: the Oswaldo Cruz Foundation in Brazil, the Indian Council for Medical Research (ICMR), the Kenya Medical Research Institute (KEMRI) and the Ministry of Health in Malaysia, along with Médecins Sans Frontières (MSF), the Institut Pasteur, and the WHO/TDR as permanent observer. DNDi has built regional networks of scientists and clinicians actively involved in the research of new drugs for neglected diseases in Asia, Africa, and Latin America, as well as in the conduct of clinical trials in endemic countries. DNDi has developed 3 treatments: two fixed-dose ACTs (artesunate + amodiaquine and ASMQ) have been developed and registered by DNDi and its partners. Over 70 million treatments of ASAQ, the FDC of artesunate and amodiaquine, have been distributed by industrial partner, sanofi-aventis, and the treatment is now registered in 29 African countries and in India. To learn more about DNDi's activities, please visit [www.dndi.org](http://www.dndi.org) or contact [info@dndi.org](mailto:info@dndi.org).

# DNDi

Drugs for Neglected Diseases *initiative*