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Artesunate-Mefloquine (ASMQ) Fixed-Dose Combination (FDC) Registration approval in Malaysia

Artesunate-Mefloquine (ASMQ) Fixed Dose Combination (FDC) tablets were approved on 29th March 2012 by the Malaysian Ministry of Health's National Pharmaceutical Control Bureau for the treatment of acute uncomplicated malaria resulting from *Plasmodium falciparum* mono infections or from mixed *P. falciparum* and *P. vivax* infections.

Because Malaysia is a PIC/S (Pharmaceutical Inspection Convention Scheme) member, this approval is a major step towards further registration of ASMQ FDC in the region, within the ASEAN Pharmaceutical Harmonization Scheme.

Malaysia is the second Asian country after India to approve ASMQ FDC.

Background and international product status of ASMQ FDC

Both artesunate (AS) and mefloquine (MQ) are well-established drugs for the treatment of *P. falciparum* malaria, and their combination has proven its efficacy after 20 years of clinical use. It is aligned with WHO recommendations and national malaria policies. The majority of studies reporting clinical data on AS+MQ were carried out in Asia, two-thirds of them concerning patients in South East Asia and the Western Pacific.

2002-2008: within the multi-partner Fixed-Dose, Artesunate-Based Combination Therapies (FACT) Consortium created by DND*i* and the WHO Special Programme for Research and Training in Tropical Diseases (TDR), Farmanguinhos/Fiocruz and DND*i* developed the artesunate-mefloquine (ASMQ) fixed-dose combination (FDC).

2008: ASMQ FDC was granted Brazilian registration approval on 3rd March, ensuring the supply of treatments to patients in Brazil.

2008-2010: The ASMQ FDC technology transfer between the Brazilian government-owned pharmaceutical company Farmanguinhos/Fiocruz and India's generic pharmaceutical company, Cipla, was completed in 2010 through DND*i* support and facilitation. Cipla is in charge of manufacturing ASMQ FDC to make it available in Southeast Asia and in other parts of the world at pre-agreed, affordable prices for the public sector.

2010: The ASMQ FDC registration dossier was submitted for WHO pre-qualification and is currently under final assessment.

2010: The ASMQ FDC regulatory file, prepared by DND*i* within the FACT partnership, was reviewed by an Expert panel of ASEAN Regulators in a meeting in Kuala Lumpur, in the autumn of 2010. The existing file was complemented with the quality section related to the manufacture of ASMQ by Cipla at its manufacturing site in India.

2011: ASMQ FDC was granted Indian registration approval on 30th November, ensuring that an Asian manufacturer will be able to supply endemic countries in the region.

29th March 2012: Registration approval was granted by the Malaysian National Pharmaceutical Control Bureau (NPCB).

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The relevance of ASMQ FDC use in Asia

Asia was instrumental in the adoption of ACTs (artemisinin-based combination therapies) in general, and in the use of artesunate and mefloquine combination in particular.

In displaced persons camps along the Thai-Myanmar border, mefloquine and artesunate therapy has been evaluated since 1991 and the combination of 25 mg/kg of mefloquine and 12 mg/kg of artesunate given over 3 days, MAS3, deployed as first-line treatment.

Since 1991, clinical data on the use of AS+MQ from almost 8,000 patients in South East Asia and over 2,000 in the Western Pacific has been published.

The strategy of artemisinin-based combination therapies containing mefloquine was adopted in Thailand in 1994, where treatment of uncomplicated malaria was modified several times in the past 30 years to counter the rapid emergence and spread of drug resistance. The deployment of the combination therapy led to a reduction in incidence of *P. falciparum* malaria and has been associated with a halt of mefloquine resistance.[1]

Based on very large studies that confirmed its safety and efficacy[2] and through continuous parasitological efficacy monitoring,[3] MAS3 has remained the treatment of choice in this area[4] and over the 13 years of continuous MAS3 deployment, assessed cure rates at day-42 remain well above 90%.[5]

Resistance of *P. falciparum* to artemisinins was confirmed at the Cambodia-Thailand border in 2009, but the clinical and parasitological efficacy of ACTs has not yet been compromised, despite the observed changes in parasite sensitivity. Since 2008, containment activities to limit the spread of artemisinin-resistant parasites are ongoing.[6]

One of the most urgent and challenging priorities of the Global Plan for Artemisinin Resistance Containment (GPARC) at the Cambodia-Thailand border is to replace the use of artemisinin monotherapy with an FDC, such as ASMQ or DHA-PQ (Dihydroartemisinin – Piperaquine).[7]

ASMQ FDC is a user-friendly, co-formulated drug regime that facilitates patient compliance and improves dosing accuracy, eliminating the possibility of patients taking only one component of the combination. By avoiding the risks associated with monotherapy and improving drug acceptability, FDCs provide better efficacy, greatly contributing to controlling ACT resistance development.

With specific presentations for children aged between 6 months and 11 years, ASMQ FDC also addresses the needs of children, the primary victims of malaria worldwide.

The fact that Malaysia is a PIC/S member has the potential to provide an active and constructive co-operation for a rapid ASMQ FDC registration in countries within the ASEAN Pharmaceutical Harmonization Scheme. Indeed, PIC/S membership facilitates networking between participating authorities and maintenance of mutual confidence, exchange of information and experience in the field of GMP and related areas, and mutual training of GMP inspectors.

The deployment of ASMQ FDC in countries that have already adopted ACTs can be of immediate benefit to patients suffering from uncomplicated malaria and is of great public health relevance.

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[2] Price RN, Nosten F, Luxemburger C, van Vugt M, Phaipun L, et al. (1997) . Artesunate/mefloquine treatment of multi-drug resistant falciparum malaria. Thai-Burmese border. Trans R Soc Trop Med Hyg 91: 574–577.

[3] Ashley EA, McGready R, Hutagalung R, Phaiphun L, Slight T, et al. (2005) A Randomized, Controlled Study of a Simple, Once-Daily Regimen of Dihydroartemisinin-Piperaquine for the Treatment of Uncomplicated, Multidrug-Resistant Falciparum Malaria. Thailand.Clin Infect Dis 41: 425–432.

[4] Carrara VI, Sirilak S, Thonglairuam J, Rojanawatsirivet C, Proux S, et al. 2006 Deployment of Early Diagnosis and Mefloquine- Artesunate Treatment of Falciparum Malaria in Thailand: The Tak Malaria Initiative. PLoS Med 3(6): e183.

[5] Carrara VI, Zwang J, Ashley EA, Price RN, Stepniewska K, et al. (2009) Changes in the Treatment Responses to Artesunate-Mefloquine on the Northwestern Border of Thailand during 13 Years of Continuous Deployment. PLoS ONE 4 (2): e4551.

[6] WMR 2011

[7] Yeung S, Socheat D, Moorthy VS, Mills AJ. Artemisinin resistance on the Thai–Cambodian border. Lancet. 2009 Oct 24;374(9699):1418-9.