

APPLICATION FOR THE INCLUSION OF ARTESUNATE -AMODIAQUINE FIXED DOSE COMBINATION IN THE WHO ESSENTIAL DRUG LIST

Comments from GMP/CMR

The Global Malaria Programme WHO supports the availability of fixed dose formulations of antimalarial medicines, as this simplifies treatment regimens, and improves patients' adherence, thus facilitating implementation and effectiveness of treatment. Artesunate plus amodiaquine is one of the artemisinin combination therapies (ACTs) recommended by WHO for the treatment of malaria. Up until now, only blister packed co-packing of the individual medicines is available and thus included in the Guidelines for the Treatment of Malaria. The production of a fixed dose combination is a welcome development, however, the GMP Department cannot presently support this particular application for the following major reasons:

- The ratio of artesunate: amodiaquine in the formulation is not consistent with the recommendation of the WHO Guidelines for the Treatment of Malaria, thus delivering a lower dose of amodiaquine. This is justified in the submission by the profound parasitocidal effect of artesunate - *"the higher degree of under-dosing with 67.5 and 270mg tablets was considered less critical because of the profound parasitocidal effect of artesunate reduces substantially the parasite biomass leaving a small number of parasites to be killed by amodiaquine"* (pg 23). Thus only about 80% of patients are predicted to receive a therapeutic dose of amodiaquine.
- The clinical efficacy and safety is supported by 14 studies, however only one of these studies is based on the fixed dose combination. Thus, in only one study was this formulation used, the remaining 13 studies are based on the loose combination which uses a different artesunate:amodiaquine ratio.
- Three dosage strengths of artesunate-amodiaquine is being presented in this application, however the only clinical study on safety and efficacy presented in the submission is based on a study that utilized only one of these strengths (25mg artesunate/ 67.5mg amodiaquine). There is no evidence that the other strengths - 50mg artesunate /135mg amodiaquine or 100mg artesunate / 270mg amodiaquine ever being used in any clinical studies.
- There are a few inaccuracies in the information provided in the submission:
 - Artemether-lumefantrine listed in the WHO Guidelines for the Treatment of Malaria is recommended for children from 5kg body weight and not 10kg as indicated in this submission (*pages 5, 17*).
 - The current price of artemether-lumefantrine is 1.8 and 0.45 USD for the adult and paediatric doses respectively, so the target price of this product as indicated in the submission of 0.8 and 0.5 Euros respectively for the adult and paediatric treatment courses cannot be 50% cheaper as presented in the submission. (*pg 9*).
- Inclusion of this fixed dose combination in the WHO Treatment Guidelines for Malaria would await the WHO pre-qualification process, to which the dossier has already been submitted by the manufacturer.