

ARTESUNATE FORMULATIONS

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Introductory comments

There is no doubt that artesunate is a very valuable drug against malaria. These comments relate to the proposal for rectal use. Data on efficacy and safety are encouraging but limited in patient numbers and relate to moderately severe malaria.

Addition of artesunate suppositories to the Essential Medicines List for initial treatment of **severe** malaria should be deferred pending results of apparently in-progress trials in severe malaria.

If added to the list, product information must ensure that adequate follow-on treatment is always given.

If added to the list, the addition should be accompanied by a strategy to ensure that multi-source products adequately reproduce the bioavailability characteristics of the innovator product.

Specific comments

1. How many subjects have been studied concerning rectal use in the initial treatment of moderately severe or severe malaria?

The information provided by the applicant concerning rectal use (section 9.2) is an *en bloc* extract of Appendix A9.8 of the WHO 2006 Guidelines for the treatment of malaria.

The information states that studies included two randomized, open-label Phase II and three randomised open label Phase III trials conducted in people with moderately severe malaria. However, only two references are given. (Krishna et al 2001; Barnes et al 2004).

The reference to two Phase II and three Phase III trials appears to include comparisons of intravenous artesunate as well as rectal artesunate with quinine treatments (IV or IM). It can be noted also that the Table 1 attached to Reviewer 2's comments (page 6) conveys that there have been no comparisons of artesunate suppositories vs quinine.

Krishna et al reported a crossover study comparing intravenous and rectal artesunate in 34 Ghanaian children with moderate falciparum malaria. Their preliminary clinical efficacy assessment was that parasitic clearance kinetics were comparable in all treatment groups and that intrarectal administered artesunate may be a useful alternative to parenterally administered artesunate in the management of moderate childhood malaria and “should be studied further.”

Barnes et al titled their paper in part “a randomised study”. The paper in effect describes two studies under a single protocol- a study in 109 children in Malawi and a study in 35 adults in South Africa, small proportions(about 1 in 5) of whom were given quinine and not rectal artesunate. The information provided in section 9.2 of the application “Artesunate had a superior effect.....and in 84/87 of the children.” is a summary of the results reported by Barnes et al. This appears to be the only direct evidence of a comparison of the clinical efficacy of rectal artesunate with parenteral quinine.

Barnes et al make a number of points that require consideration:

- A faster decrease in peripheral parasitaemia does not necessarily ensure improved clinical outcome. In their study, the clinical success rate was similar to that for parenteral quinine.
- Fever clearance times are shorter in artemisinin-treated patients than in quinine treated patients. By implication, the same may be true of artesunate. This is a important clinical benefit but carries the risk that it might give a false sense of security resulting in failure to give the necessary further curative treatment
- In the children in Malawi, the reappearance of parasites occurred significantly earlier with artesunate than with quinine –probably because the single dose of sulfadoxine-pyrimethamine given at 24 hours did not eradicate the infection. This underlines the need for effective follow-up treatment after the use of rectal artesunate.
- The study was confined to patients with moderately severe malaria, presenting to well equipped units. “Although several small studies confirm the therapeutic efficacy of repeated administration of rectal artesunate (followed by mefloquine, doxycycline or sulphadoxine-pyrimethamine) in severe malaria in adults (references are cited), further investigations are needed to confirm this benefit in children, and the therapeutic benefit of initial management with a single dose of rectal artesunate in severe malaria. Studies are being done to investigate the early administration of rectal artesunate in the planned context of remote rural communities in Africa and Asia.”

2. Formulation

The applicant (section 5.2) has given only limited details of the formulation of suppositories. It is stated that the rectal capsules contain 100mg or 400mg sodium artesunate.

The studies undertaken by Krishna et al and Barnes et al utilised 50mg and 200mg Plasmotrim Rectocaps, Mepha AB, Basel, Switzerland. The product is described

as thermostable suppositories of artesunate manufactured by MEPHA Ltd., (Aesch-Basel, Switzerland). Each of them contains 50 mg (Krishna study) of artesunate encapsulated as an oily solution into a torpedo-shaped, gelatin capsule shell (volume 50.592 cm³). (see Halpaap B et al, Am J Trop Med Hyg 1998;58:365-368).

Apart from the discrepancies in nominated strengths between the application and the clinical study reports, the Plasmotrim Rectocaps are in effect an innovator product. Addition to the Essential Medicines list of "artesunate suppositories" will open the way for the advent of multi-source products, sometimes on a national basis. No studies have been undertaken to demonstrate that alternative products adequately replicate the performance of the innovator product.