National Essential Medicine List Medication Review Process
Primary Healthcare
Component: Malaria

Medication: Parenteral Artesunate **Date:** 20 January 2014

Executive summary

Currently intravenous quinine is the only treatment registered for the treatment of patients with severe malaria in South Africa. However, the current World Health Organisation Guidelines for the treatment of malaria (WHO 2010) recommend that: Intravenous artesunate should be used in preference to quinine in the treatment of severe *P. falciparum* malaria in adults and in children. A Cochrane review (Sinclair *et al*, 2012) comparing parenteral artesunate and quinine in severe malaria showed a relative reduction in mortality of 39% in adults (RR 0.61, 95% CI 0.50 to 0.75; 1664 participants, five trials) and 24% in children (RR 0.76, 95% CI 0.65 to 0.90; 5765 participants, four trials).

Parenteral artesunate is easier to administer than intravenous quinine. Complications associated with the administration of intravenous quinine have contributed to malaria related deaths in South Africa (Mehta *et al*, 2007).

The Medicines Control Council approved the fast tracking of the Equity Pharmaceuticals /Guilin Pharmaceutical Factory application for the registration of parenteral artesunate.

South African Parenteral Artesunate Access Programme

In response to the evidence of survival benefit, the South African Parenteral Artesunate Access Programme provided parenteral artesunate on a named patient basis from 2010 to 2013, following Medicines Control Council approval in 2009 under Section 21 of the Medicines and Related Substances Act. Quality assurance of parenteral artesunate batches imported through this access programme were performed by the Mahidol Oxford Research Unit in Bangkok, Thailand where the pivotal SEAQUAMAT and AQUAMAT study batches were quality assured, and by Potchefstroom University (accredited by the Medicines Control Council). Updated programme results and enrolled patients' Progress Reports (case management records on outcome and drug safety) are submitted to the MCC's Section 21 unit on a six monthly basis. The Parenteral Artesunate Access Programme is subject to MCC review on an annual basis in view of the unregistered status of the drug. In February 2011 the MCC approved the continuation programme on a named-patient basis and expanded the programme to include treatment of severe malaria in children under the age of 12 years with artesunate. By the time of the last 6-monthly report to the MCC, 462 patients in 31 participating hospitals[i] in seven provinces had received IV artesunate with a low in-hospital severe malaria case fatality rate of 7.5%. To date, two Serious Adverse Events (SAE's) were reported since the start of the programme, one renal failure (in Jan 2012) and one haemolysis (in April 2012).

[i]Enrolment of a hospital in the Parenteral Artesunate Access Programme was usually based on the Malaria Control Programme identifying the hospital as a site where severe malaria cases are regularly treated and required a local hospital doctor and pharmacist to formally take responsibility for the programme at that site. The hospital was then provided with training, drug supplies and required documentation (informed consent and case record forms). Individual named-patient authorisation is applied for as each patient requires this unregistered product.

Guilin Pharmaceutical Factory (Guangxi, People's Republic of China) is the main source of parenteral artesunate internationally. This product has been extensively evaluated clinically, and was the product used in all the studies that demonstrated a significant survival advantage with artesunate over quinine. Guilin Pharmaceutical Factory received WHO pre-accreditation of its parenteral artesunate in November 2010, with over 12 million vials delivered since then. It has been licensed for use in at least 30 countries to date. Priority has understandably been given to countries with the highest malaria burden, which has resulted in slower progress being made with the South African MCC submission. Equity Pharmaceuticals (the local applicant) and Guilin Pharmaceuticals with the support of the Medicines for Malaria Venture (www.mmv.org) have submitted the application for registration to the MCC. The MCC approved fast tracking of this application on 07 August 2013, their satisfaction with the screening dossier on 13 September 2013 and the full submission was made on 04 October 2013.

Search strategy

The Cochrane Collaboration (Sinclair et al, 2012) searched the Infectious Diseases Group Specialized Register, CENTRAL (The Cochrane Library),MEDLINE, EMBASE, LILACS, ISI Web of Science, the metaRegister of Controlled trials (mRCT), conference proceedings, and reference lists of articles to November 2010 for Randomized controlled trials comparing intravenous, intramuscular, or rectal artesunate with intravenous or intramuscular quinine for treating adults and children with severe malaria who are unable to take medication by mouth. Two authors independently assessed the eligibility and risk of bias of trials, and extracted and analysed data.

In addition a PUBMED search using the search terms artesunate, quinine and severe malaria was conducted to identify additional relevant evidence since November 2010. No subsequent randomized controlled trials were identified.

Selection of studies:

Sixteen trials detected by the search specifications were excluded from the Cochrane Review (Sinclair et al, 2012), with the reasons for exclusion listed below:

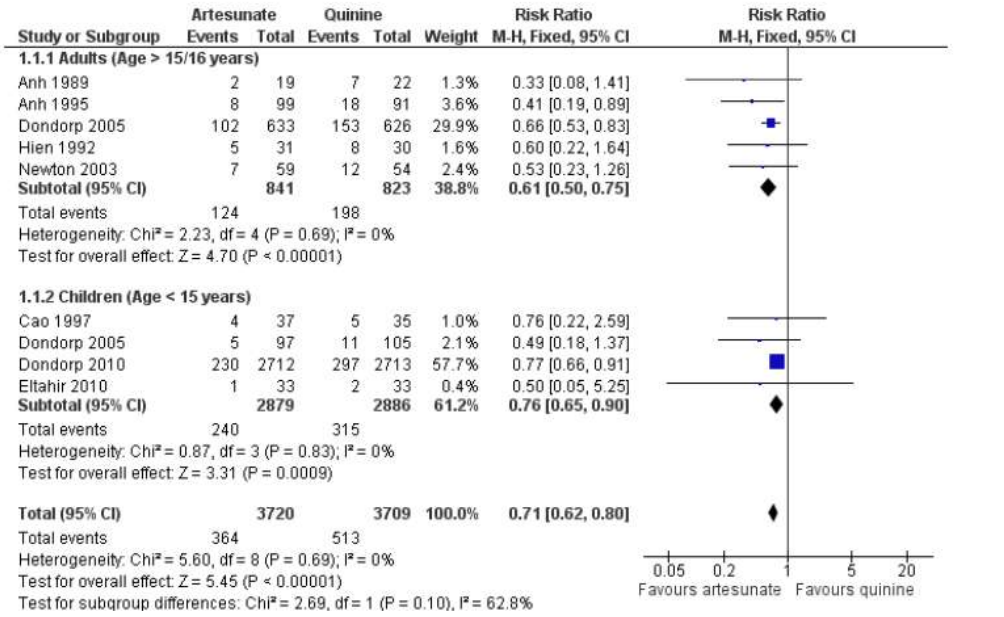
- Not severe malaria (Barnes 2004; Bounyasong 2001; Li 1990; Pukrittayakamee 2004; Zhao 2001)
- Quasi-randomized controlled trial (Haroon 2005; Mohanty 2004)
- Not aRCT (Awad 2003; Krudsood 2003; McGready 2001a; McGready 2001b; Win 1992)
- Treatment comparison is artesunate versus artesunate and quinine (Newton 2001)
- Artemether versus quinine (Aguwa 2010; Osanuga 2009)
- Artesunate versus artemether (Phu 2010)

Evidence synthesis

The 2012 Cochrane Review (Sinclair *et al*, 2012) included eight trials that enrolled a total of 7429 participants (1664 adults and 5765 children). Of the two African studies; Eltahir 2010 was conducted at a single study site in Sudan, and Dondorp 2010 had 11 centres in nine African countries (Mozambique, The Gambia, Ghana, Kenya, Tanzania, Nigeria, Uganda, Rwanda, and the Democratic Republic of the Congo).Six trials were conducted in Asia; four took place in single centres in Vietnam (Anh 1989; Anh 1995; Cao 1997; Hien 1992), Newton 2003 had two centres in Thailand; and Dondorp 2005 had 11 centres throughout Bangladesh, Myanmar, India, and Indonesia.

The Cochrane Review concluded that treatment with artesunate significantly reduced the risk of death both in adults (RR 0.61, 95% CI 0.50 to 0.75; 1664 participants, five trials) and children (RR 0.76, 95% CI 0.65 to 0.90; 5765 participants, four trials). This reduction was consistent across all trials regardless of participant age or geographic region (I^2 test for statistical heterogeneity= 0%). Artesunate appears superior to quinine at reducing the parasite clearance time PCT (MD -9.77h 95%CI -18.11 to -1.44, 419 patients; four trials). The two large multicentre trials (Dondorp 2005; Dondorp 2010) conducted multiple subgroup analyses according to the presence or absence of coma, anaemia, shock, acidosis, respiratory distress, or hyperparasitaemia at the time of admission. Mortality was consistently lower with artesunate in all of these subgroups but some were underpowered to show statistically significant differences.
Artesunate appears superior to quinine irrespective of intramuscular or intravenous administration. In adults neurological sequelae following treatment for severe malaria appears to be very low (< 1 %) and no difference has been shown between artesunate and quinine.
In children, treatment with artesunate increased the incidence of neurological sequelae at the time of hospital discharge. The majority of these sequelae were transient and no significant difference between treatments was seen at later follow up. No trial reported discontinuation of medication. With the exception of hypoglycaemia and tinnitus, all adverse effects reported could be attributable to malaria. Artesunate was associated with a statistically significant reduction in episodes of hypoglycaemia (RR 0.55, 95% CI 0.41 to 0.74; 7137 participants, 4 trials).

Figure 2. Forest plot of comparison: 1 Artesunate vs quinine, outcome: 1.1 Death: participant age [Relative effect].



NNT was reported in two large studies. In the multi-centre SEAQUAMAT study conducted predominantly in Asian adults, the NNT (with parenteral artesunate rather than quinine) to avert one death ranged from 11.1 to 20.2 depending on the treatment

site (Dondorp *et al,* 2005). In the multi-centre AQUAMAT study conducted in African children, NNT was 41 (95% CI 25 to 112), with no heterogeneity between study sites (p=0·99) (Dondorp *et al*, 2010).

When compared with quinine in Asian adults with severe malaria, the cost per death averted was US$ 135.60, while in African children the incremental cost per death averted was US$ 123.The mean costs of treating severe malaria were similar between treatment groups (Quinine US$ 63.50 vs Artesunate US$ 66.50 in African children and Quinine US$ 32.40 vs Artesunate US$ 43.00 in Asian adults). Thus, artesunate is considered a highly cost effective and affordable alternative to quinine (Lubell *et al* 2009; Lubell *et al* 2011).

Parenteral artesunate is easier to administer than intravenous quinine. Complications associated with intravenous quinine administration have contributed to malaria related deaths in South Africa. These included failure to administer the required quinine loading dose; life-threateningly rapid administration of quinine loading doses; and repeated administration of quinine loading doses following clinical deterioration in patients receiving quinine maintenance therapy (Mehta *et al,* 2007).

In response to the evidence of survival benefit, the South African Parenteral Artesunate Access Programme provided parenteral artesunate on a named patient basis from 2010 to 2013 (Visser-Kift *et al*, 2011), following Medicines Control Council approval in 2009 under Section 21 of the Medicines and Related Substances Act. In addition to providing the drug, training and technical support have been provided to the 31 participating hospitals identified by the malaria control programmes. By the time of the last 6-monthly report to the MCC, 462 patients (294 males) at 31 hospitals in 7 provinces had received IV artesunate. The mean (SD) age was 33.7 years (16.2). Complications included impaired consciousness (n=220), respiratory distress (n=81), hyperparasitaemia (n=238), raised bilirubin (n=148), renal impairment (n=115), acidosis (n=51), hyperlactataemia (n=43), macroscopic haematuria and abnormal bleeding. Of these - acidosis, renal impairment, hyperlactataemia, impaired consciousness, macroscopic haematuria (n=24) and abnormal bleeding (n=15) on admission were significantly associated with death (p = 0.02 to <0.0001). Of the 413 patients for whom we had received reports on treatment outcome, 321 (77%) were well on discharge, 59 (14%) were not yet fully recovered, 2 (0.5%) had an ongoing disability and there were 31 deaths (7.5%). This in hospital severe malaria case fatality rate is consistent with the survival advantage over parenteral quinine, which is associated with a higher case fatality rate (~15 to 40%). There have only been two SAE's reported since the start of the programme, one renal failure (in Jan 2012) and one haemolysis (in April 2012) (Parenteral Artesunate Access Programme, November 2013).

Similar programmes for the compassionate use of parenteral artesunate have been implemented in a number of countries awaiting registration of IV artesunate, including the USA, United Kingdom, European Union and Australia. In a retrospective evaluation in one UKcentre, Eder *et al* (2012) describe a series of 167 patients (24 IV artesunate and 143 IV quinine). There was one potential artesunate-associated adverse event, a case of late onset haemolysis. Median length of stay was significantly shorter for artesunate (3.5 vs 5 days, p = 0.017). In the artesunate group, there were no fatalities (vs five in quinine group, NS) and fewer intensive ICU admissions (NS). Median parasite clearance was significantly faster in artesunate (65 vs 85 hours in quinine, p = 0.0045) with no hypoglycaemic episodes (vs five in quinine).

HIV co-infection is an important consideration in southern Africa. Hendriksen *et al* (2012) studied the effect of HIV status on severe malaria diagnosis, clinical presentation and in-hospital mortality in Mozambican children and adults. HIV-1 seroprevalence was 11% (74/655) in children under 15 years and 72% (49/68) in adults with severe malaria. Children with HIV co-infection presented with more severe acidosis, anemia, and respiratory distress, and higher peripheral blood parasitemia and plasma *Plasmodium falciparum* histidine-rich protein-2 (PfHRP2). During hospitalization, deterioration in coma score, convulsions, respiratory distress, and pneumonia were more common in HIV-coinfected children, and mortality was 26% (19/74) versus 9% (53/581) in uninfected children ($p < 0.001$). Although this study was not powered to look at the treatment effect of artesunate vs quinine, the mortality in HIV-positive children treated with artesunate was 22.2% vs 31% with quinine (OR 0.63 (95% CI 0.22 to 1.85; $p = 0.40$) and in HIV-negative children 8.1% vs 10.1% (OR 0.78 95% CI 0.44 to 1.38; $p = 0.39$) for artesunate.

Pregnant women are at higher risk of severe malaria than non-pregnant women. While IV artesunate has been recommended by the WHO as the preferred treatment for severe malaria in the second and third trimester of pregnancy (WHO 2010), published evidence on the effects of malaria and antimalarial drug exposure during the first trimester was scarce. McGready *et al* (2012) recently published a population-based study on the adverse effects of falciparum and vivax malaria, and the safety of antimalarial treatment, in early pregnancy (n=945). The odds of miscarriage increased in women with asymptomatic malaria (adjusted OR 2.70, 95% CI 2.04 to 3.59) and symptomatic malaria (3.99, 95% CI 3.10 to 5.13), and were similar for *Plasmodium falciparum* and *Plasmodium vivax*. In women with malaria, additional risk factors for miscarriage included severe or hyper-parasitaemic malaria (adjusted OR 3.63, 95% CI 1.15 to 11.46) and parasitaemia (adjusted OR 1.49, 95% CI 1.25 to 1.78 for each ten-fold increase in parasitaemia). The risk of miscarriage was similar for women treated with chloroquine (26%; 92/354), quinine (27%; 95/355), or artesunate (31%; 20/64; p=0.71). Adverse effects related to antimalarial treatment were not observed.

A number of cases of delayed haemolyticanaemia have been identified following treatment of severe malaria with injectable artesunate in non-immune travellers (Zoller *et al* 2011 (n=6); Rolling *et al* 2013 (n=5); Kreeftmeijer-Vegter *et al* 2012 (n=7); Carmello *et al* 2012 (n=1); Kano 2010 (n=2)) and subsequently in young African children (Rolling *et al* 2014 (n=5)).For all patients, haemolysis and worsening anaemia were described after parasite clearance, 8 to 32 days after completion of artesunate therapy. The haemolysis resolved, and haemoglobin improved in all patients within 4 to 8 weeks after artesunate therapy.

In October 2013 the WHO published the following note in this regard: Delayed haemolyticanaemia following treatment with injectable artesunate has been observed in non-immune travellers presenting with severe falciparum malaria and particularly in patients presenting with hyperparasitaemia. Post-treatment haemolyticanaemia is not specific to a particular injectable artesunate formulations, and has been described following use of injectable artesunate, intra-muscular artemether and, also, oral artemether-lumefantrine. Available data are mainly from case reports and retrospective studies, conducted with different study designs, case definitions and study endpoints, with delayed anaemia defined differently across the various studies. Definitions of severe malaria have also varied across studies. As a result the incidence and predisposing

factors (other than hyperparasitaemia) remain uncertain. The mechanisms of delayed haemolyticanaemia following the treatment of severe malaria are multiple, and are not fully understood. Conditions such as blackwater fever (sudden massive haemolysis and haemoglobinuria associated with malaria), and severe haemolysis caused by malaria itself, may overlap with delayed haemolyticanaemia. Other mechanisms, such as delayed auto-immune haemolysis may contribute in some cases. Preliminary evidence suggests that the key pharmacodynamic advantage of artesunate over quinine, that it kills young circulating ring stage parasites before they sequester in the microcirculation, could explain the delayed haemolysis. This mechanism explains the rapid action of artesunate and its beneficial effect on mortality and other clinical outcomes. Most of the killed ring stage parasites are cleared rapidly by the spleen by 'pitting' of erythrocytes whereby the dead parasite is removed from within the erythrocyte. These 'once infected' erythrocytes are returned to the circulation but they have a reduced lifespan of about 7 to 15 days: the delayed destruction of 'once infected' erythrocytes corresponds with the time course of post-treatment delayed anaemia seen clinically. The patients saved by artesunate, who might have died had they received quinine, are particularly those with high parasitaemias. All reported cases of delayed haemolyticanaemia after injectable artesunate have been managed successfully. Some patients have required transfusions, but there have been no reports of fatal outcome.

The therapeutic benefits far outweigh the risk of artemisinin-related adverse events, including post-treatment delayed haemolyticanaemia (WHO 2013).

Evidence quality
A Cochrane review, two large multi-centred RCTs and WHO Guidelines were considered to guide the recommendations.

Alternative agents
Currently parenteral quinine is the only treatment registered for the treatment of patients with severe malaria in South Africa.

- Parenteral quinine is associated with a significantly higher severe malaria case fatality rate than parenteral artesunate in both adults and children (Sinclair *et al,* 2012).
- The complex administration of parenteral quinine requires the use of a rate-controlled infusion for the administration of a loading dose and the maintenance dose; inappropriate administration has been associated with severe malaria deaths in South Africa (Mehta *et al,* 2007).
- Parenteral quinine is associated with a 3-fold higher risk of hypoglycaemia (3%), compared to artesunate therapy (0.8%) (Sinclair *et al,* 2012)
- Parenteral quinine requires dosage adjustment in patients with impaired renal function, a relatively frequent complication of severe malaria in adults (WHO 2010).
- Quinine is contra-indicated in patients with myasthenia gravis. Dournon *et al* (2012) reported the safe and effective treatment with parenteral artesunate of a patient with underlying myasthenia gravis.

Malaria elimination
South Africa has committed to malaria elimination by 2018. While South Africa has successfully moved from the effective control to the pre-elimination phase on the malaria elimination continuum, the national malaria case fatality rate has remained essentially unchanged over the last decade and is currently 0.76%, well above the WHO target of 0.5%. This indicator reflects a range of factors including delays in treatment seeking,

prevalence of co-morbidities, and effectiveness of uncomplicated malaria treatment as well as the factors that influence the severe malaria case fatality rates – treatment efficacy and standard of supportive high / intensive care facilities. As malaria incidence decreases, malaria case fatality rates often increase - as the lower malaria risk is associated with lower malaria awareness, delayed treatment seeking, delayed diagnosis, and limited healthcare worker experience in the complex management of severe malaria.

As artesunate appears superior to quinine irrespective of intramuscular or intravenous administration (Sinclair *et al,* 2012), parenteral artesunate could also be used intramuscularly for pre-referral treatment in clinics in malaria endemic areas in South Africa.

Recommendation:
Parenteral artesunate be included in the Essential Medicines List, subject to MCC registration. Once parenteral artesunate is registered by the MCC, it should replace intravenous quinine on the essential medicines list.

Rationale:

- Artesunate IV demonstrated superiority in terms of efficacy and safety (reduction in mortality) compared to quinine IV.
- It was noted that many of the RCTs were done in several African malaria endemic countries; which makes the results generalisable to the South African setting.

Level of evidence: I Meta-analysis, RCTs

Further recommendations:

- Healthcare professionals should be made aware of the potential for delayed haemolyticanaemia for up to one month post treatment, usually among hyper-parasitaemic patients.

References:

Briggs M &Arguin PM. Published reports of delayed haemolyticanaemia after treatment with artesunate for severe malaria - Worldwide, 2010-2012. CDC MMWR 2013;62(01):5-8

Dondorp A, et al; AQUAMAT group. Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomised trial. Lancet. 2010;376:1647-57.

Dondorp A, et al; SEAQUAMAT group. Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial. Lancet. 2005;366:717-25.

Dournon N, et al. Case Report: Artesunate for severe acute P. falciparum infection in a patient with myaesthenia gravis. Am J Trop Med Hyg 2012; 87(3):435-6.

Eder M, et al. Intravenous artesunate versus intravenous quinine in the treatment of severe falciparum malaria: a retrospective evaluation from a UK centre. Pathog Glob Health. 2012;106(3):181-7.

Hendriksen IC, et al. Diagnosis, clinical presentation, and in-hospital mortality of severe malaria in HIV-coinfected children and adults in Mozambique. Clin Infect Dis. 2012;55(8):1144-53.

Lubell Y et al. Cost effectiveness of artesunate for the treatment of severe malaria. Trop Med IntHlth 2009;14(3):332-337.

Lubell Y et al. Cost-effectiveness of parenteral artesunate for treating children with severe malaria in sub-Saharan Africa. Bull WHO 2011;89:504-512.

McGready R, et al. Adverse effects of falciparum and vivax malaria and the safety of antimalarial treatment in early pregnancy: a population-based study. Lancet Infect Dis. 2012;12(5):388-96.

Mehta U et al. Malaria deaths as sentinel events to monitor healthcare delivery and antimalarial drug safety. Trop Med IntHlth 2007; 12(5): 617-28.

Parenteral Artesunate Access Programme. Six-monthly programme progress report. November 2013.

Rolling T et al. Delayed hemolysis after treatment with parenteral artesunate in African children with severe malaria – a double-center prospective study. JID (in press)

Sinclair D, et al. Artesunate versus quinine for treating severe malaria. Cochrane Database Syst Rev. 2012 Jun 13;6: CD005967.

South East Asian Quinine Artesunate Malaria Trial (SEAQUAMAT) group. Artesunate versus quinine for treatment of severe falciparum malaria: a randomized trial. Lancet 2005;366:717-725.

Visser-Kift et al. Parenteral artesunate access programme aims at reducing malaria fatality rates in South Africa. S Afr Med J 2011;101(4):240-241.

World Health Organisation (2010, updated 2011). Guidelines for the treatment of malaria 2nd Edition. Geneva.
WHO Global Malaria Programme. WHO Information note on Delayed HaemolyticAnaemia following treatment with artesunate. October 2013