

## **An evaluation of rectal artesunate for the pre-hospital management of severe malaria.**

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### **Abstract**

**Introduction:** Severe falciparum malaria stills accounts for around half a million childhood deaths per year in sub-Saharan Africa. Prompt treatment of sick children close to home starting with artesunate given rectally by appropriately trained people can be lifesaving.

**Areas covered:** Rectal artesunate (RAS) has been developed for use in the WHO approved strategy of pre-referral intervention. This review covers the formulation, pharmacokinetics, safety, efficacy and implementation of this drug. There is little RCT evidence and the only RCT has been controversial. It is unlikely that there will be further randomised studies in the field. There is a concern that administration of a single dose of artesunate without adequate follow up therapy may encourage the emergence of artemisinin resistance.

**Expert opinion:** Artesunate is an essential drug and RAS is a very useful, potentially lifesaving formulation designed to be quickly administered in remote areas to severely unwell children by non-medical personnel. However, its use needs to be monitored and onward referral for definitive antimalarial treatment ensured.

### **Keywords**

artesunate  
Dihydroartemisinin, Succinyl  
Dihydroartemisinin 12 alpha succinate  
Malacef  
Malartin  
SM 804  
sodium artesunate  
succinyl dihydroartemisinin

### **1. Introduction**

Malaria is caused by plasmodia transmitted by the bite of a female Anopheline mosquito. Five species infect humans but *Plasmodium falciparum* is the most dangerous leading to severe organ failure and death.

According to the World Health Organisation (WHO) in their 2018 report there were an estimated 219 million cases of falciparum malaria in 2017 worldwide. 90% of these occurred in Africa specifically Nigeria (25%), the Democratic Republic of the Congo (12%), Uganda (5%), and Côte d'Ivoire, Mozambique and Niger (4%). This resulted in an estimated 435,000 deaths. Nearly 80% of deaths in 2017 were in 17 countries from the WHO African Region and India. [1]

Children under 5 years old in high transmission areas are the most vulnerable to severe malaria infection due to a lack of immunity. They accounted for 61% of all malaria deaths. The number of childhood malaria deaths has in fact reduced from 440,000 in 2010 to

285,000 in 2016 probably due to insecticide impregnated bed-net use however, malaria is still one of the major killers of children under five years of age. [1] Part of this problem is because of delayed access to care in rural areas. [2]

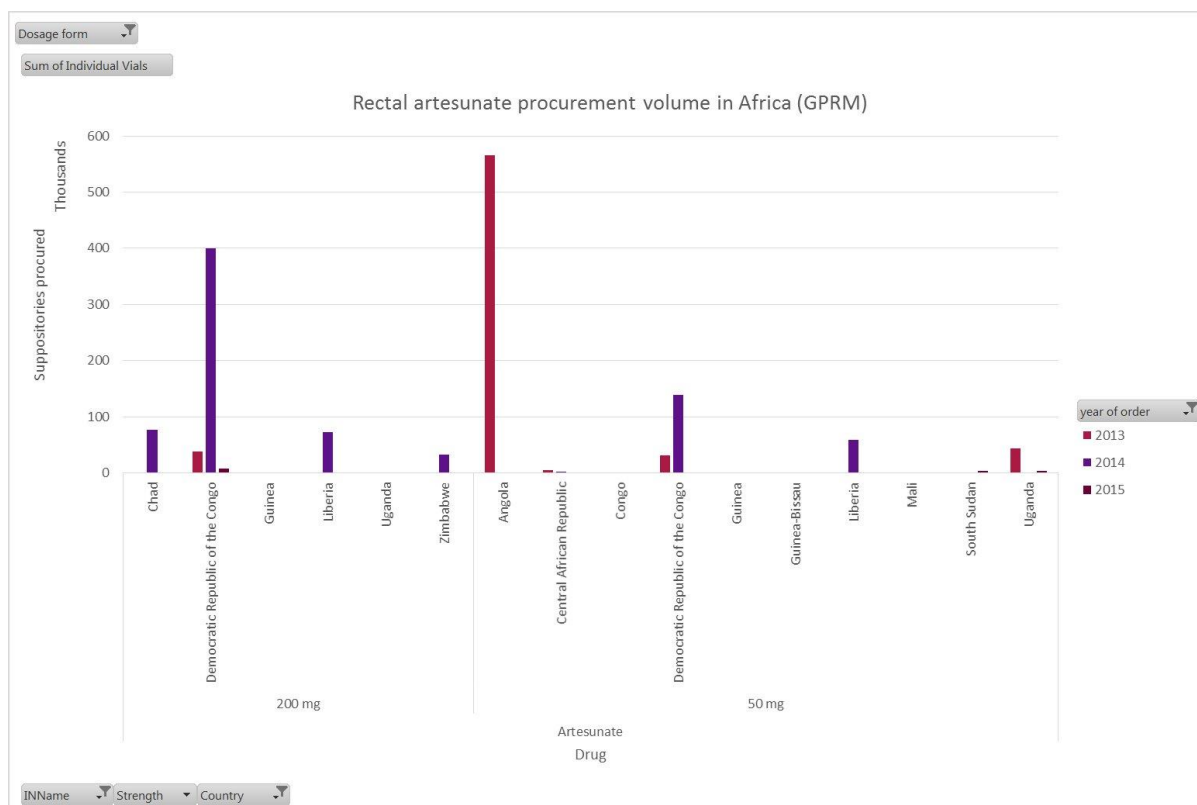
To address this WHO has recommended the concept of “pre-referral intervention” in order to rapidly administer antimalarials to children with suspected severe malaria in remote areas. The WHO recommended drug for children below the age of 6 years is rectal artesunate (RAS) in areas where intra-muscular injection is not available. The plan is not to replace parenteral artemisinin derivative use however the recommended intervention options are in descending order: intra-muscular artesunate > rectal artesunate > intra-muscular artemether > intra-muscular quinine. RAS can be delivered as a single rectal dose of artesunate at 10 mg/kg body weight. The child should then be referred immediately to an appropriate healthcare facility for further management. As summarised in the FDA briefing documentation “Artesunate Rectal Capsules are indicated for the initial management of acute severe malaria in children who cannot take medication by mouth and where parenteral treatment is not available.” [3]

WHO Guidelines for the Treatment of Malaria [4] have recommended the use of RAS for over 10 years but hampered by a lack of a quality-assured product on the market so restricting its availability and use. This forced countries to choose products that did not meet international manufacturing standards.

The “not-for-profit public-private partnership Medicines for Malaria Venture (MMV)”, was established in Switzerland in 1999 “to reduce the burden of malaria in disease-endemic countries by discovering, developing and facilitating delivery of new, effective and affordable antimalarial drugs”. MMV collaborated with Strides Pharma and Cipla to develop RAS and gain WHO prequalification as part of the Unitaid-funded project 'Improving Severe Malaria Outcomes' (ISMO).

## **1.1 Overview of the market**

In June 2017, the 100mg formulation of RAS from Cipla was added to the WHO Model List of Essential Medicines (EML) and the Model List of Essential Medicines for Children (EMLc). In 2018, both the Cipla and Strides Pharma RAS products secured WHO prequalification. Over 80% of procured RAS worldwide is now WHO prequalified. RAS is now fully registered in 16 countries. In 2018 there were 1.5 million orders of 100mg suppositories from international donor organisations for use in malaria-endemic countries. The MMV figures for procurement by African countries in 2017 is shown in figure 1. (WHO Global Price Referencing Mechanism, accessed 02/03/2017.)



**Figure 1:** Rectal artesunate procurement volume per country per dosage form (GPRM) [5]

## 2. Introduction to the compound

Artesunate (AS) is a semisynthetic derivative of artemisinin and is a prodrug [6]. It is rapidly converted to dihydroartemisinin (DHA) by hydrolysis. DHA is active against all of the intra-erythrocytic stages of the plasmodia and has some action on gametocytes.

The molecular antimalarial mechanism of action of artesunate is still controversial and theoretical mechanisms have not been validated experimentally. [7]

DHA activity is thought to involve cleavage of the  $\text{Fe}^{2+}$  within the endoperoxide bridge due to interaction with intracellular free haem producing free radicals and so damaging parasite proteins and there is interest in the anticancer properties of the compound. [8] Malaria parasites metabolise haemoglobin and in doing so release free haem. This means DHA is mainly activated in parasitized cells conferring selective toxicity. DHA may also inhibit calcium adenosine triphosphatase (cATP) in the sarcoplasmic endoplasmic reticulum and impair parasite protein folding. [9]

## 3. Chemistry

The chemical name for artesunate is succinyl dihydroartemisinin with a structure of 4-oxo-4-[[[(4S,5R,8S,9R,10R,12R,13R)-1,5,9-trimethyl-11,14,15,16-tetraoxatetracyclo[10.3.1.0<sup>4</sup>.13.0<sup>8</sup>.13]hexadecan-10-yl]oxy]butanoic acid and a molecular formula of  $\text{C}_{19}\text{H}_{28}\text{O}_8$  weighing 384.425 g/mol. Artesunate is an example of an antimalarial sesquiterpene lactone.

## 4. Pharmacodynamics

Artemisinin derivatives are extremely effective with fever and parasite clearance times below 24 hours. Worryingly “resistance” has developed recently resulting in longer parasite clearance times and failure of the longer acting partner drug in ACTs. [10]

## 5. Pharmacokinetics and metabolism

The pharmacokinetics of artesunate have been reviewed recently but with little discussion of the rectal route. [11]

### 5.1. Metabolism:

Artesunate is a prodrug and is rapidly hydrolyzed by plasma esterases to the active metabolite, DHA. DHA undergoes rapid hepatic metabolism via CYP2B6, CYP2C19, and CYP3A4 to inactive metabolites. [12] Consequently pharmacokinetic parameters are usually expressed separately for AS and DHA. Since RAS avoids first-pass metabolism, the differences in AS and DHA AUC values are not as striking as compared with the oral route.

In adults infected with severe malaria the following overall parameters were calculated for intravenous artesunate;

**Volume of Distribution at steady state: ( $V_{dss}$ ):** Artesunate: 15.2 L/kg (range: 2.2 to 39 L/kg); DHA: 1.9 L/kg (range: 0.8 to 11.5 L/kg) [13]

**Protein binding:** DHA: 93% [4]

**Half-life elimination:** Artesunate: 0.22 hours (range: 0.08 to 0.61 hours); DHA: 0.34 hours (range: 0.14 to 0.87 hours) [13]

**Time to peak ( $T_{max}$ ):** DHA: <15 minutes [13]

**Excretion:** Urine (as DHA-glucuronide) (WHO 2015)

The non-population pharmacokinetics of RAS have been reviewed and are summarised in the tables below.

Table 1: Summary of AS PK results following RAS (adapted from [14] with permission)						
Reference		Dose of RAS	Mean $C_{max}$ ng/mL	Mean $T_{max}$ hours	Mean $T_{1/2}$ hours	Mean AUC ng*hr/mL
[15]	16 paediatric patients with uncomplicated malaria	10mg/kg n=7 20mg/kg n=9	507 Median 561	0.8 Median 1.0	0.9 Median 0.9	692 Median 1076
[16]	12 paediatric patients with uncomplicated malaria	50mg 0.86 – 2.55 mg/kg	90	0.58		
[17]	12 healthy Malaysian adults	200 mg	448.5	1.43	0.95	796

Summary of DHA PK following rectal AS						
[15]	16 paediatric patients with uncomplicated malaria	10mg/kg n=7 20mg/kg n=9	898 Median 1535	1.5 Median 2.0	1.3 Median 1.8	2403 Median 5633
[16]	12 paediatric patients with uncomplicated malaria	50mg 0.86 – 2.55 mg/kg	180	1.13		
[18]	12 healthy Sudanese adults	200mg AS	219.1	1.95	1.21	1185.17
[17]	12 healthy Malaysian adults	200 mg AS	385.6	1.80		965
[19]	34 Ghanaian children with moderately severe malaria	Group 1 10mg/kg rectal AS	682	1.7	0.79	2787
[19]		Group 2 20mg/kg rectal AS	881	1.8	0.85	2753
[20]	12 Vietnamese adults with uncomplicated malaria	IV ARTS (120 mg) PR DHA (160 mg)	750	4.0		3.4 ( $\mu$ mol l <sup>-1</sup> h)

## 5.2. Rectal administration: bioavailability

The bioavailability of rectal AS can be best assessed by measuring levels of DHA and comparing with intravenous, intra-muscular or oral administration. Rectal blood flow can be restricted in severe malaria [21]. In children with moderately severe malaria given a dose of 20 mg/kg or 10 mg/kg bioavailability was estimated to be 23% and 58% respectively. [19]. In healthy adults, the ratio of mean bioavailability of rectal to oral AS, was estimated at 54.9% [18]. However, in another study there was no statistically significant difference. [17]. In an open crossover design 12 Vietnamese adult patients with uncomplicated malaria were randomised to receive 120 mg of either intra-muscular or intravenous AS with the crossover preparation given 8 h later. 12 patients were given 120 mg of intravenous AS at 0 h and 160 mg of rectal DHA 8 h later. [20] The relative bioavailability of intra-muscular DHA was 88% and for rectal DHA 16%. It was concluded that rectal DHA should be given at around four-

fold higher doses to achieve equivalent plasma DHA concentrations as the parenteral administration of AS. [20]

### 5.3. Rectal administration: population pharmacokinetic analyses

<b>Table 2: DHA Population pharmacokinetics (adapted from [22] with permission)</b>		
Parameter		Estimate (standard error)
$k_a$ (/h) - fixed		0.2
CL/F (l/kg/h)		2.64
V/F (l/kg)		2.75
Lag time (h) - fixed		0.14
Inter-individual variability for CL/F (% CV)		66
Inter-individual variability for V/F (% CV)		96
Intra-individual variability (% CV)		93

<b>Table 3: DHA Population pharmacokinetics (adapted from [23] with permission).</b>	
Parameter	Value (mean $\pm$ standard deviation)
V/F (L)	42.9 $\pm$ 8.1
$K_{30}$ (/h)	1.06 $\pm$ 0.28
$T_{1/2}$ elimination (h)	0.71 $\pm$ 0.22
CL/F elimination (L/h)	44.9 $\pm$ 13.0

#### Table footnotes

$C_{max}$	maximum (or peak) serum concentration
$T_{max}$	time at which the $C_{max}$ is observed
$T_{1/2}$	elimination rate half-life
AUC	Area under the curve
$k_a$	The rate at which drug is removed from the body.
CL/F	The population mean volume of plasma cleared of the drug per unit time.
V/F	The population mean apparent volume in which a drug is distributed
% CV	% coefficient of variation
$K_{30}$	The rate at which DHA is removed from the body in three compartment model

There are two population pharmacokinetic studies of RAS. Simpson et al [22] studied adults and children with moderately severe falciparum malaria. Patients were given a single dose of RAS 10 mg/kg with oral follow-on. 424 DHA levels from 164 patients fitted a one-compartment model with a fixed, lagged, first-order input. The most important covariates in the model were sex and body weight. Larger V/Fs were observed for patients requiring early rescue intervention compared with others independent of any confounders. No associations were found between the parasitological responses and the posterior individual estimates of

V/F, CL/F, and AUC<sub>0-6h</sub>. However, a number of modelling assumptions were required due to the large intra- and inter-individual variability of the DHA concentrations.

Karunajeewa studied 47 children with uncomplicated falciparum or vivax in Papua New Guinea who received 10 - 15 mg/kg RAS given as 2 doses, 12 hours apart. [23] The data for AS and DHA fitted a one-compartment model and first-order AS absorption was also modelled. The volume of distribution for AS and DHA was set as equal at 41.8 L. Weight was the most important covariate for V. Calculated bioavailability for the second dose relative to the first dose was 72% which the authors suggested might be due to high fever when the first dose was administered causing increased rectal blood flow with subsequent increased absorption.

## **6. Clinical efficacy**

In Southern Africa 109 children and 35 adults with moderately severe malaria were randomly assigned to a single dose of 10 mg/kg of RAS or parenteral quinine intervention (10 mg/kg at 0, 4, and 12 h) followed by sulfadoxine-pyrimethamine when able to take oral medication. Parasitological responses were faster with RAS but clinical recovery was equivalent. [24]

A large pragmatic placebo-controlled RCT involved 17,826 patients with severe malaria in rural Ghana, Tanzania and Bangladesh. Villagers were trained to make the diagnosis, administer RAS or placebo and then refer patients to secondary care for definitive treatment. Younger children aged 6 to 72 months were enrolled in Africa while older children and adults were enrolled in Bangladesh. There was significantly lower mortality in the 8050 African children studied following RAS (RR 0.74; 95% CI 0.59 to 0.93). Surprisingly there was significantly higher mortality (RR 2.21; 95% CI 1.18 to 4.15) in the 4018 older children and adults mainly in Asia. Only 56% of African children ever reached secondary healthcare within six hours with over 90% in Asia. There were no differences in the proportions reaching healthcare within six hours (RR 0.99; 95% CI 0.98 to 1.01; 12,068 participants), those with parasitaemia (RR 1.00; 95% CI 0.98 to 1.02; 17,826 participants), or comatose or seizing on arrival (RR 1.01; 95% CI 0.90 to 1.14; 12,068 participants). [25] Explanation of these findings has been controversial, and the trial has been criticised on the ethics of the use of placebo, conduct and analysis. [26, 27]

A recent Cochrane review included only this trial but concluded that “In rural settings without access to injectable antimalarials, RAS probably reduces mortality in young children (6 to 72 months old) being transported to hospital for further care. However, the unexpected finding of possible higher mortality in older children and adults should be taken into account when forming national and local policies about pre-referral intervention.” [28]

## **7. Post-marketing surveillance**

National malaria guidelines in Nigeria, DRC and Uganda recommend the approach but note that “operational barriers have prevented the implementation of this activity.” However not all countries have included pre-referral RAS in their guidelines for example the National Guidelines for the Treatment of Malaria, South Africa 2018 still recommends the intramuscular route. Community Access to Rectal Artesunate for Malaria (CARAMAL) is an ongoing study looking at pilot implementation of RAS for example in selected rural areas of the Democratic Republic of the Congo, Nigeria and Uganda. A study [29] in Malawi assessed the feasibility, acceptability and impact of integrating the two WHO recommendations of using Rapid Diagnostic Tests (RDT) for diagnosis and pre-referral RAS pathway for initial



treatment of severe malaria into the integrated Community Case Management programme in Malawi. They found that acceptability at community level was relatively high. However, it depended greatly on the established CHWs' skills and availability in remote rural areas. A review of the case records of 179 children enrolled in a large study in Burkina Faso, Nigeria and Uganda managed with pre-referral RAS showed that there was a very high level of compliance (90%) to guidelines among patients managed with pre-referral RAS [30] However, in a qualitative survey in Uganda it was found that caregivers often confused the use of emergency RAS with the general use of Artemisinin-based Combination Therapy (ACT). This led to the misconception that RAS was a complete treatment for severe malaria and reduced the likelihood of appropriate referral for definitive treatment. [31] In another study in Uganda CHW's referral rates were very low, with only 9.3% (263/2815) and 9.9% (112/1135) following advice to refer even when randomised to use RDTs for diagnosis.[32] Empowering mothers may be an effective strategy for managing children directly in a study of pre-referral RAS intervention which was provided in rural Ghana, Guinea-Bissau, Tanzania, and Uganda. Care was randomised to be delivered by CHWs, trained mothers (MUMs), or trained traditional healers (TH) over 19 months in 54 013 children. A third had neurological symptoms such as altered consciousness, coma, or convulsions. Compliance with referral guidelines overall was good at 81% but slightly higher for CHWs than mothers (87% vs 82% (risk ratio [RR], 1.1 [95% CI, 1.0-1.1];  $P < .0001$ ). Unfortunately there was higher mortality in the TH villages. (RR, 2.7 [95% CI, 1.4-5.6];  $P = .0040$ ) suggesting this is not the optimal group to deliver therapy. [33]

#### **8. Safety and tolerability**

In a review of individual data from 1167 patients in 15 clinical trials of rectal artemisinin derivative intervention (artesunate, artemisinin and artemether) RAS was deemed to be safe and effective. [34] Adverse events were estimated at between 2.7% and 9.0% in all rectal artemisinin-treated patients, compared with 22% of quinine-treated patients. The majority were mild gastrointestinal or non-specific. None were severe.

RAS was adopted into the PDR Laos national malaria policy however it was abandoned due to low acceptability in this population. [35]

#### **9. Regulatory affairs/Cost effectiveness**

A cost-effectiveness model of RAS suggested that at low intervention uptake and referral compliance (25%) to avert 19 disability-adjusted life-years (DALYs; 95% CI 16-21) and to cost I\$1173 (95% CI 1050-1297) per DALY averted. However at 100% uptake and compliance the intervention could avert 967 DALYs (884-1050) at a cost of I\$77 (73-81) per DALY averted. [36]

A study in Burkina Faso looked at the costs of RAS-managed children against non-RAS managed children. These were similar (\$5.83 vs. \$4.65;  $p = 0.52$ ), despite the higher transport costs (\$2.74 vs. \$0.91;  $p < 0.0001$ ) for children with evidence of neurological disease. Children with neurological problems reached CHWs 5 hours quicker for treatment (9.0 h vs. 16.1 h) [difference 7.1 h (95% CI - 1.8 to 16.1),  $p = 0.11$ ]. For other patients the average time to CHW-delivered RAS intervention was 12.2 h vs. 20.1 h [difference 7.9 h (95% CI 0.2-15.6),  $p = 0.04$ ]. More non-RAS managed children developed CNS symptoms while travelling to secondary healthcare (6% vs. 4%;  $p = 0.58$ ). In this population they concluded that CHW-delivered RAS did not affect the total out-of-pocket cost for families when used in children with CNS symptoms, but was associated with a higher total out-of-pocket cost when used in children with less severe symptoms. [37]



## 10. Conclusion

Implementation of the strategy has been recommended by WHO. However as seen even in the trial by Gomes et al [25] many children in Africa do not go onto secondary care even under trial conditions. To a certain extent it is the efficacy of the overall strategy that has to be assessed rather than the efficacy of the drug. Successful pre-referral intervention with RAS for suspected severe malaria requires complex operational linkages between community health workers and appropriate referral facilities.

## 11. Expert opinion

There is extensive evidence that parenteral artesunate is lifesaving and superior to quinine in severe malaria in children [38] [39]. The rectal route has obvious advantages. It is easy to administer by minimally trained nonmedical staff in rural areas and the pharmacokinetics of the rectal formulation are acceptable although the dose possibly needs to be higher. Production of a rectal formulation has been successfully developed by the Public Private Partnership Medicines for Malaria Venture. RAS therefore has a critical role in the pre-referral malaria intervention strategy of WHO.

However, there is a tension. WHO recommends that only artemisinin combination therapy should be used to successfully treat malaria worldwide in order to reduce the risk of the development of artemisinin resistance. A single dose of rectal artesunate is not in itself curative even if given intravenously and must be followed up with definitive ACT therapy in a medical facility. Underdosing especially if not weight adjusted in children is considered a risk for resistance development. [40] [41] There are case reports of slow parasite clearance in severe malaria in Africa associated with the typical kelch-13 mutations of artemisinin resistance. [42] The strategy depends not on the drug itself but on the training of the people who administer it, their compliance with the strategy and the ability of the health system to support it. On their website MMV make it clear that “RAS is not intended to substitute for WHO-recommended parenteral treatments, preferably injectable artesunate” as should be seen as part of pre-referral management [43]. However, there is already some confusion in the field about the use of RAS which does not exist with the use of parenteral artesunate in hospital settings as measured in the AQAMAT trials. Close monitoring of administration of RAS, compliance with referral patterns, confirmation of the diagnosis and the completion of treatment with an ACT will need to be monitored. Health systems will need to be developed to ensure adequate follow up is provided when RAS is administered. Conditional Cash Transfer (CCT) has been suggested as worthy of investigation. [32] Markers of artemisinin resistance will also need to be measured such as parasite and fever clearance times as well as genetic markers. Increasing the availability in order to enhance rapid administration means that there is less control of the single agent and so increases the vulnerability of artesunate to poor use and resistance. By the nature of its intended use in remote difficult to reach areas this monitoring is itself difficult.

The finding in the only RCT conducted that RAS reduced the risk of death in young children but increased the risk of death in older children and adults is difficult to explain biologically and probably due to chance. However, it may reflect poor compliance with guidance and further research is needed to clarify this question. There is of course a general need for improved health systems research and a wider cost-effectiveness analysis of how this

intervention fits in with the wider concept of managing the severely sick child in remote areas.

In summary RAS is a very useful, potentially lifesaving formulation of an effective antimalarial drug to be administered in remote areas in severely ill children. However, its use needs to be strictly monitored.

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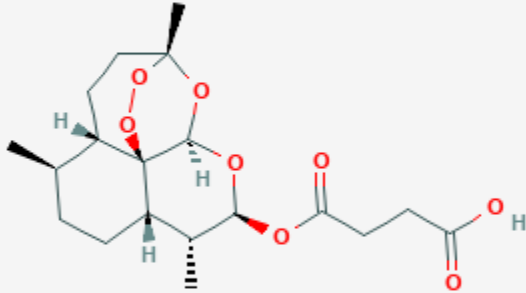
**Declaration of Interest:**

B Angus has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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### Drug summary box

Drug name	Artesunate (Artecap)
Phase	Launched
Indication	Severe falciparum malaria
Pharmacology description	Artemisinin derivative
Route of administration	Rectally
Chemical structure	
Pivotal trial	Gomes et al [25]

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