




		EMLc	ATC codes: <a href="#">P01BE03</a>
Indication	Malaria due to Plasmodium falciparum	ICD11 code: <a href="#">1F40</a>	
INN	Artesunate		
Medicine type	Chemical agent		
List type	Core (EML) (EMLc)		
Additional notes	For use in the management of severe malaria		
Formulations	Parenteral > General injections > IV: 60 mg in ampoule containing anhydrous artesunic acid with a separate ampoule of 5% sodium bicarbonate solution Oral > Solid: 50 mg tablet Local > Rectal > Other: 50 mg capsules (EMLc) ; 200 mg capsules (EMLc) ; 100 mg capsules (EMLc)		
EML status history	First added in 1999 ( <a href="#">TRS 895</a> ) Changed in 2002 ( <a href="#">TRS 914</a> ) Changed in 2007 ( <a href="#">TRS 946</a> ) Changed in 2007 ( <a href="#">TRS 950</a> ) Changed in 2017 ( <a href="#">TRS 1006</a> )		
Sex	All		
Age	Also recommended for children		
Therapeutic alternatives	The recommendation is for this specific medicine		
Patent information	Patents have expired in most jurisdictions Read more <a href="#">about patents</a> . 		
Wikipedia	<a href="#">Artesunate</a> 		
DrugBank	<a href="#">Artesunate</a> 		

### Expert Committee recommendation

The Expert Committee recommended addition of the new strength formulation of rectal artesunate to the EMLc for pre-referral treatment of severe malaria. The Committee accepted that the 100-mg formulation can offer an age-appropriate and suitable treatment option for children weighing 5–14 kg.

### Background

Artesunate rectal dosage form in 50-mg and 200-mg strengths has been included on the EMLc since 2007. Listing includes the same restriction on use for pre-referral treatment of severe malaria only as is requested in the current application. This additional strength of 100 mg rectal artesunate can offer better compliance in children weighing 5 to < 14 kg.

### Public health relevance

In 2015, there were an estimated 214 million new cases of malaria globally, with 438 000 deaths due to the disease, including an estimated 306 000 malaria deaths in children under 5 years of age. The vast majority of cases occurred in the African and south-east Asian regions (1). Mortality approaches 100% in untreated severe malaria but falls to 10–20% with prompt treatment and supportive care. The risk for death from severe malaria is greatest in the first 24 hours: in most endemic countries, transit times

between referral and presentation at health facilities are usually long and initiation of treatment is delayed. Pre-referral treatment is recommended, particularly in young children (unless the referral time is less than 6 hours) (2).

### Benefits

Evidence for the clinical effectiveness of rectal artesunate was evaluated at the time of listing. The application presented the results of two randomized clinical trials in support of the benefits of rectally administered artesunate. In one trial, 12 068 patients with suspected malaria who could not be treated orally were randomized to receive a single artesunate or placebo suppository. All patients were then referred to facilities where injections could be administered. For the primary end-points of mortality (assessed 7–30 days later) and permanent disability, pre-referral rectal artesunate was associated with a significantly reduced risk of death or permanent disability compared with placebo (1.9% versus 3.8%; risk ratio (RR) 0.49; 95% confidence interval (CI) 0.32–0.77;  $P = 0.0013$ ) in the group of patients who did not reach treatment facilities in less than 6 hours. In patients who did reach facilities within 6 hours, there was no significant reduction in mortality (3). A second trial compared the efficacy of artesunate suppositories and IM artemether in paediatric malaria patients aged 1–10 years. Seventy-nine children were randomized to receive a combination of one or two 50-mg and/or 200-mg thermostable artesunate suppositories to a total dose of 8–17 mg/kg or IM artemether at a dose of 3.2 mg/kg. Compared with the artemether-treated children, those receiving artesunate suppositories had a significantly shorter mean time to 50% parasite clearance (PCT50) (9.1 versus 13.8 hours;  $P = 0.008$ ) and mean time to 90% parasite clearance (PCT90) (15.6 vs 20.4 hours;  $P = 0.011$ ) (4). The application also presented the results of a study of the use, efficacy and parental perception of rectal suppositories in the management of childhood malaria. Rectal artesunate at a dose of 5–10 mg/kg was given to 264 children. After 24 hours, no parasite cells were observed in blood samples of 74% of study participants. Acceptability among parents was high (5).

### Harms

Evidence for the safety of rectal artesunate was evaluated at the time of listing. The application presented results of hospital- and community-based studies involving single-dose artesunate suppositories in relation to harms (6, 7). Refer to the application for a summary of adverse events and treatment-observed sequelae associated with rectal artesunate.

### Additional evidence

N/A

### Cost / cost effectiveness

The unit price for artesunate suppositories 100 mg averages US\$ 0.33.

### WHO guidelines

WHO's 2015 Guidelines for the treatment of malaria (2) makes the following recommendations in relation to rectal artesunate as a pre-referral treatment option: "Where intramuscular injection of artesunate is not available, treat children <6 years with a single rectal dose (10 mg/kg body weight) of artesunate, and refer immediately to an appropriate facility for further care. Do not use rectal artesunate in older children and adults. (Strong recommendation, moderate-quality evidence)."

### Availability

Artesunate 100 mg rectal dose form has been submitted for WHO prequalification. The formulation is manufactured by Cipla Ltd, India.

### Other considerations

N/A

### Implementation considerations

N/A

1. World malaria report 2015. Geneva: World Health Organization; 2015 ([http://apps.who.int/iris/bitstream/10665/200018/1/9789241565158\\_eng.pdf?ua=1](http://apps.who.int/iris/bitstream/10665/200018/1/9789241565158_eng.pdf?ua=1), accessed 26 January 2017).
2. Guidelines for the treatment of malaria, third edition. Geneva: World Health Organization; 2015 ([http://apps.who.int/iris/bitstream/10665/162441/1/9789241549127\\_eng.pdf?ua=1&ua=1](http://apps.who.int/iris/bitstream/10665/162441/1/9789241549127_eng.pdf?ua=1&ua=1), accessed 26 January 2017).
3. Gomes MF, Faiz MA, Gyapong JO, Warsame M, Agbenyega T, Babiker A et al. Pre-referral rectal artesunate to prevent death and disability in severe malaria: a placebo-controlled trial. *Lancet*. 2009;373(9663):557–66.
4. Karunajeewa HA, Reeder J, Lorry K, Dabod E, Hamzah J, Page-Sharp M et al. Artesunate suppositories versus intramuscular artemether for treatment of severe malaria in children in Papua New Guinea. *Antimicrob Agents Chemother*. 2006;50(3):968–74.
5. Sam-Wobo SO, Agbeyangi OA, Ekpo UF, Akinloye OA, Mafiana CF, Adeleke MA. Rectal artesunates, their utilization, and parental perception in the management of malaria in children from Abeokuta, southwestern Nigeria. *Vector Borne Zoonotic Dis*. 2012;12(2):151–5.
6. Krishna S, Planche T, Agbenyega T, Woodrow C, Agranoff D, Bedu-Addo G et al. Bioavailability and preliminary clinical efficacy of intrarectal artesunate in Ghanaian children with moderate malaria. *Antimicrob Agents Chemother*. 2001;45(2):509–16.
7. Gomes M, Ribeiro I, Warsame M, Karunajeewa H, Petzold M. Rectal artemisinins for malaria: a review of efficacy and safety from individual patient data in clinical studies. *BMC Infect Dis*. 2008;8:39.

