WHO-PQ RECOMMENDED
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ARTECAP[1]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each rectal suppository contains: Artesunate Ph.Int.100mg.

Approved colours used in capsule shell.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suppositories.

Ivory coloured, elongated shaped soft gelatin capsules, containing white to off white coloured oily mass

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ARTECAPisto be used as pre-referral treatment for suspected or proven severe malaria in children aged between 2 months and 6 years, who are unable to take oral medication or obtain injectable antimalarial treatment. The patient should be immediately referred to a facility where accurate diagnosis and complete treatment with effective antimalarials can be instituted.

4.2 Posology and method of administration

Limitations of use:

- ARTECAP should not be used for patients age 7 and over
- ARTECAP should not be used to prevent malaria
- ARTECAP are for severe malaria only, and should not be used for uncomplicated malaria

Paediatric population up to age 6

This medicine is recommended for antimalarial treatment as a 10mg/kg bodyweight single dose. It should be given rectally as soon as a presumptive diagnosis of severe malaria has been made; while the patient is being transferred to the nearest health clinic or hospital.

[1]Trade names are not prequalified by WHO. This is the national medicines regulatory authority's (NMRA) responsibility. Throughout this WHOPAR the proprietary name is given as an example only.

The table below indicates the number of suppositories determined by body weight.

Body Weight (kg)	**Number of 100 mg suppositories**
≤ 10 kg	1
≤ 20 kg	2

For community health workers and in places with limited diagnostic capacity for severe malaria, the WHO algorithm for giving rectal artesunate for pre-referral treatment of severe febrile illness in children under 6 years described below should be followed.

▪ **if fever AND** ▪ Convulsions or ▪ Unusually sleepy or unconscious or ▪ Not able to drink or feed anything or ▪ Vomits everything	**Give rectal artesunate suppository (100 mg)** ▪ Age 2 months up to 3 years - 1 suppository ▪ Age 3 years up to 6 years – 2 suppositories

Hepatic or Renal impairment
No specific pharmacokinetic studies were carried out in patients with hepatic or renal impairment.

Method of administration

ARTECAP is to be used by rectal route only.

ARTECAP should be inserted in the rectum with the rounded end first. Administration should be started as soon as a presumptive diagnosis of severe malaria is made, the patient is judged unable to take oral medication and it is likely to be several hours before the patient can be treated at a health care facility. Treatment should be followed as soon as possible by transfer to a hospital.

Care should be taken to be sure that the suppository is retained after insertion. Especially in young children, the buttocks should be held together for about 10 minutes to prevent expulsion of the artesunate suppository. In the event that the dose is expelled from the rectum within 30 minutes of insertion, a repeat dose should be inserted.

Patients and their guardians should be informed that ARTECAP do not cure malaria and that urgent further management of the patient will be necessary; immediate steps should be taken by the guardians of the patient to transport the patient to the nearest health care facility for confirmation of diagnosis and further management, including curative antimalarial therapy.

4.3 Contraindications

Known hypersensitivity to the artesunate or related artemisinin derivatives or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Referral of patient

ARTECAP is intended for use as stand-by emergency treatment for malaria to enable the patient to reach a facility without complications for complete diagnosis and treatment. Consequently there should be strong emphasis on proceeding to the nearest facility; referral is important both to complete the treatment of malaria and to diagnose any other underlying life-threatening infection.

Absorption

Absorption of artesunate suppositories may be reduced in patients with diarrhoea. If used in patients with diarrhoea, the patient should be closely monitored. An additional dose of ARTECAP should be administered per rectum if the initial suppository is expelled within 30 minutes.

4.5 Interaction with other medicinal products and other forms of interaction

Insufficient information is available from formal drug interaction studies

4.6 Fertility, pregnancy and breast-feeding

Not applicable.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

Note: This product is intended only for children up to age 6 years. Some of the data on undesirable effects were obtained in studies which included older children and adults.

Hospital-based clinical trials

Table 1 shows the most frequently reported adverse reactions observed in children who received a 10mg/kg single dose regimen of artesunate rectal suppositories in hospital studies. Adverse reactions identified in clinical trials included treatment emergent adverse events, defined as events that appeared or worsened after the start of treatment. In children the most frequently reported adverse reactions were headache, convulsions and vomiting.

Table 1: Common Adverse Reactions in Paediatric Patients Treated in Hospital in Clinical Trials with the 10mg/kg regimen of Artesunate Suppositories

System Organ Class	Preferred term	Rectal Artesunate 10 mg/kg (n=143)
Gastrointestinal disorders	Vomiting	4.2% (n=6)
Nervous system disorders	Headache Convulsions	3.5% (n=5) 2.1% (n=3)

One death occurred in a 3-year-old patient with moderately severe malaria treated with artesunate rectal dose of 11.5 mg/kg. Death was attributed to iatrogenic fluid overload, but it was also noted that the patient's serum dihydroartemisinin levels were higher (2002 ng/mL at 2 hours; 977 ng/ml at 4 hours) than the mean levels from similar age paediatric patients (653 ± 353 at 2 hours; 397 ± 545 at 4 hours).

Community-based clinical trials

Study 13 was a large trial in Bangladesh, Ghana and Tanzania (2 sites) conducted in conditions in which rectal artesunate is most likely to be used, i.e. resource-limited community settings (see section 5.1). 11778 of the children studied were 6 years old or younger. 5902 of these received a single 100 mg dose of rectal artesunate, and 5876 received placebo. Collection of safety data was limited, and consisted mostly of mortality and neurological serious adverse events, thus overlapping with the study's primary efficacy endpoints. Data concerning other AEs were not collected systematically.

No clear safety signal was evident in Study 13 in children aged 6 years and younger.

Of 7709 young children in the modified intent-to-treat population who survived the index malaria episode (3940 artesunate, 3824 placebo), 47 children had neurological sequelae not involving sciatic nerve damage, including 21 children treated with artesunate and 26 placebo treated with placebo.

Assessment of safety was bolstered by examination of the sub-population with negative malaria smears, including 1839 patients who received artesunate suppositories, and 1889 patients who received placebo.

Table 2: Treatment-observed sequelae and malaria (placebo) associated sequelae, in patients with and without malaria

Children ≤ 72months

Patients with malaria (n=7028) or parasitology unknown (n=1022)

System Organ Class	**Artesunate N=4063**		**Placebo N=3987**	
Nervous system disorders				
Altered behaviour	4	0.10%	4	0.10%
Ataxia			1	0.03%
Convulsions	1	0.02%	2	0.05%
Decortication	1	0.02%		
Delirium			1	0.03%
Gait abnormal	4	0.10%	2	0.05%
Hemiparesis	7	0.17%	8	0.20%
Hemiplegia			1	0.03%
Inability to sit unsupported	1	0.02%		
Lower extremity weakness	1	0.02%		
Monoparesis			1	0.03%
Strasbismus			1	0.03%
Tremor			1	0.03%
Total	19		22	
Special senses				
Tinnitus/Hearing decreased Vision abnormal	1	0.02%	3	0.08%
	1	0.02%	1	0.03%
Total	2		4	

Malaria + unknown parasitology total	21		26	
Patients without malaria (n=2618) or with prior antimalarial injection(n=1110)				
System Organ Class	**Artesunate N=1839**		**Placebo N=1889**	
Nervous system disorders				
Altered behaviour			1	0.05%
Brain syndrome acute	1	0.05%		
Cerebral palsy	1	0.05%		
Delirium	1	0.05%		
Gait abnormal	1	0.05%		
Hemiparesis	8	0.44%	4	0.21%
Hemiplegia			2	0.11%
Lower extremity weakness	2	0.11%	2	0.11%
Monoparesis			1	0.05%
Paraparesis			1	0.05%
Regression in development	1	0.05%		
Total	15		11	
Special senses				
Speech disorder	1	0.05%		
Tinnitus/Hearing decreased	1	0.05%	2	0.11%
Vision abnormal	3	0.16%		
Total	5	0.27%	2	0.11%
Non-malaria +prior injection total	20		13	
Total	41		39	

There is no clear evidence of neurotoxicity in humans for single-dose rectal artesunate. Intravenous/intramuscular formulations of artesunate have shown adverse events of dizziness, light-headedness, headache, insomnia, and tinnitus.

4.9 Overdose

A fatal case report of a child, negative for *Plasmodium* on rapid tests and bone marrow examination, treated with rectal artesunate suppositories at a dose of 200 mg bid for 4 days (total dose 1600 mg, weight of child 18 kg, 88 mg/kg/day) leading to severe cardiovascular collapse, liver failure, coagulopathy, renal insufficiency and death 13 days after the first dose of artesunate has been documented (see section 4.4).

There is no known antidote for artesunate, and it is currently unknown if artesunate is dialyzable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimalarial, ATC code: P01BE03

Mechanism of action

Artesunate is a hemisuccinate derivative of dihydroartemisinin, which is itself formed by the reduction of artemisinin. Artemisinin is a sesquiterpene lactone endoperoxide extracted from qinghao (sweet wormwood, Artemisia annua L.), a plant which has been used for centuries in traditional Chinese medicine.

The mechanism of action of the artemisinins likely involves cleavage of the internal endoperoxide bridge through reaction with haeme within the infected erythrocyte, thereby generating free radicals which alkylate vital parasite proteins. However, artemisinins have also been reported to inhibit an essential parasite calcium adenosine triphosphatase.

The artemisinins are distinguished from other antimalarials by their ability to kill all erythrocytic stages of the malaria parasite, including the relatively inactive ring stage and late schizonts, as well as the gametocytes responsible for malaria transmission. Artesunate and the other artemisinins are the most rapid acting of the antimalarials, and they have also been shown to enhance splenic clearance of infected erythrocytes by reducing cytoadherence.

In vitro, dihydroartemisinin (DHA), the active metabolite of artesunate, exhibits similar potency against chloroquine-resistant and chloroquine-sensitive clones of P. falciparum.

Artesunate and the other artemisinins are essentially inactive against extra-erythrocytic forms, sporozoites, liver schizontes or merozoites.

Clinical efficacy and safety

Note: This product is intended only for children up to age 6 years. Some of the data below was obtained in studies which included older children and adults.

Hospital-based studies

Three controlled, open-label, clinical studies in Thailand, Malawi and South Africa evaluated artesunate suppositories given as a single 10 mg/kg dose for the first 24 hours of treatment, to hospitalized children and adults with confirmed moderately severe malaria. Control arms were treated with oral or IV artesunate in the study in Thailand, and quinine in the two studies in Malawi and South Africa. After 24 hours all patients were given definitive antimalarial therapy using either sulfadoxine/pyrimethamine (Africa) or a combination of oral artesunate with mefloquine (Asia).

Table 3 shows the percentage of patients in each study who required no additional rescue therapy during the first twenty-four hours, and whose parasite counts at 24 hours fell to less than 10% of the baseline parasite count. The proportions of patients successfully meeting this endpoint were greater for those receiving artesunate rectal suppositories than those receiving parenteral quinine and similar for rectal, oral or IV artesunate-treated patients.

Table 3. Proportion of patients who received a single dose of rectal artesunate and who did not receive additional rescue antimalarial therapy and achieved >90% reduction of their baseline parasite count at 24 hours

Study Site (Regimen)	**Artesunate suppositories**	**Comparator**
Pediatric (1 - 15 years)		
Thailand (Rectal Artesunate vs Oral Artesunate)	31/41 (75.6%)	10/14 (71.4%)

Malawi (Rectal Artesunate vs Parenteral Quinine)	74/84 (88.1%)	3/22 (13.6%)

Recrudescence rates during the first 28 days were highest in the Malawian study, where sulfadoxine/pyrimethamine was used as definitive therapy. Recrudescence was infrequent in the South African study where sulfadoxine/pyrimethamine was used as definitive therapy and was not observed in the study in Thailand, where a combination of mefloquine and oral artesunate was used for definitive therapy. As shown in Table 4, during the Malawian study, recrudescence was observed earlier and more often in patients initially treated with artesunate suppositories than those initially treated with quinine. By 28 days post-enrolment, 45.3% of subjects receiving artesunate suppositories had recrudesced while 22.7% of the parenteral quinine-treated patients recrudesced by this time point, a finding noted only in the Malawi study.

Table 4. Cumulative Recrudescence Rates of Malaria in the Malawi Clinical Trial

		7 days posttreatment	**14 days posttreatment**	**28 days posttreatment**
Artesunate Suppositories N=84	Positive smear	14 (16.3%)	25 (29.1%)	39 (45.3%)
	Missing data*	15 (17.4%)	20 (23.3%)	28 (32.6%)
Parenteral Quinine N=22	Positive smear	0 (0.0%)	2 (9.1%)	5 (22.7%)
	Missing data*	2 (9.1%)	5 (22.7%)	10 (45.5 %)

* Missing observations were considered negative for malaria since patients who did not return to the only locally available medical site were assumed to be clinically well.

Community-based studies

In a large multi-country study in Bangladesh, Ghana and Tanzania, 17826 patients with suspected severe malaria who could not be treated orally were allocated randomly to an artesunate or placebo suppository, then referred to clinics where injections could be given. (11778 patients were age 6 or under.) The primary efficacy endpoint was the number of deaths at day 7-30, based on the modified intent-to-treatanalysis set, for patients receiving artesunate suppositories, compared to those receiving placebo. Permanent (i.e. persisting) neurological disability was considered a co-primary efficacy endpoint.

After excluding those with pre-randomisation antimalarial injections or negative blood smears 12,068 patients remained; half were in Africa (where all were aged 6-72 months) and half in Bangladesh (where older patients were also recruited, hospitalisation was rapid and mortality rates were low). The effects on mortality are summarized in Table 5. Mortality was 154/6072 in the artesunate versus 177/5996 in the placebo group. Another 2 artesunate vs 13 placebo were permanently disabled; total dead or disabled 156 artesunate vs 190 placebo.

Rectal artesunate takes 6-12 hours to reduce parasitaemia by 50%. In a post-hoc analysis, there was no reduction in early mortality (57 vs 51 deaths within 6 hours; median 2 hours). Among patients reaching clinic within 6 hours (median 3 hours), pre-referral artesunate had no significant effect on death after 6 hours or permanent disability (70 vs 82).

Among patients whose arrival in clinic was delayed by more than 6 hours, pre-referral rectal artesunate significantly reduced death or permanent disability (29 vs 57). All patients in this group were children under 6 years of age.

In Asia a favourable outcome was observed in young children given rectal artesunate (7 vs 19), but an adverse outcome was seen in older patients (22 vs 9). Thus in children above 6 years and adults, the current evidence suggests more deaths with treatment. Rectal artesunate suppositories should not be given over age 6.

Table 5: Effects of treatment on death or permanent disability, subdivided by study site and time taken to reach clinic.

	(a) Risk of death in 0-6 hours (at a median of 2 hours)		**(b) Risk of later death/disability (if survived >6 hours)† REACHED CLINIC IN 0-6 HOURS?**			
	ALL PATIENTS		**YES (at ~3 hours*)**		**NO (~15 hours**)**	
	Artesunate	**Placebo**	**Artesunate**	**Placebo**	**Artesunate**	**Placebo**
Africa: Age 6-72 months						
Handeni, Tanzania	22/726	21/737	15/286	17/292	17/418	33/424
Kilosa, Tanzania	11/1170	6/1169	8/542	11/539	8/617	14/624
Navrongo, Ghana	9/1145	12/1093	19/816	26/798	2/320	5/283
All in Africa	42/3041	39/2999	42/1644	54/1629	27/1355	52/1331
	1.4%	1.3%	2.6%	3.3%	2.0%	3.9%
Chittagong, Asia (by age)						
6-72 months	5/1022	7/988	7/947	19/918	2/70	5/63
School age/adult	9/2009	5/2009	22/1858	9/1879	0/141	0/125
All in Asia	15/3031	12/2997	29/2805	28/2797	2/211	5/188
	0.5%	0.4%	1.0%	1.0%	0.9%	2.7%
TOTAL, Africa & Asia	**56/6072**	**51/5996**	**71/4449**	**82/4426**	**29/1566**	**57/1519**
	0.94%	**0.85%**	**1.6%**	**1.9%**	**1.9%**	**3.8%**
	RR 1.10 (CI 0.75-1.61)		**RR 0.86 (CI 0.63-1.18)**		**RR 0.49 (CI 0.32-0.77)**	
	P=0.61		**P=0.35**		**P=0.0013**	

† Denominators = numbers alive >6h after entry, subdivided by whether patient reached clinic in 0-6 hours. Time to clinic was recorded in all who died or had neurological damage; otherwise, it was recorded routinely only in Kilosa(Tanzania) and Navrongo (Ghana). For those who did not die in Handeni (Tanzania) and Chittagong (Bangladesh) it was recorded whether they reached a clinic. For this table it is assumed that, if they did, the proportions doing so in 0-6 hours were 50% in Handeni and 95% in Chittagong.

* For those who reached clinic in 0-6 hours and then died after hour 6, median time to arrival was 2 hours in Chittagong and 4 hours in Africa.

** For those still not in clinic after >6 hours who died, the median time to reach clinic (or to death without reaching clinic) was 15 hours

5.2 Pharmacokinetic properties

There is considerable inter-individual variability in the plasma pharmacokinetics of artesunate (AS) and its principal active metabolite dihydroartemisinin (DHA) in healthy volunteers and patients with malaria.

In a study with 36 healthy male adult volunteers, the following mean (%CV) artesunate and dihydroartemisinin pharmacokinetic parameters were obtained with a single-dose administration of 4 x100 mg rectal suppositories and 1 x 400 mg rectal suppository:

Table 6: Mean (%CV) PK parameters of AS and DHA in healthy male volunteers

Dose	Artesunate			Dihydroartemisinin		
	Cmax (ng/mL)	Tmax (hours)	AUC (0-t) (ng.hr/mL)	Cmax (ng/mL)	Tmax (hours)	AUC (0-t) (ng.hr/mL)
4 x 100 mg	293 (76.5)	1.7 (80)	733 (75.8)	442 (52.5)	2.4 (55)	1692 (79.8)
1 x 400 mg	261 (65.4)	3.8 (150)	1053 (130)	399 (60.2)	3.4 (41)	1374 (70.4)

$AUC_{(o-t)}$ represents the area under the plasma concentration versus time curve from time zero (dosing) until the end of the sampling period (24 hours post-dose).

A bioequivalence study was performed with 72 participants; data generated from a total of 69 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

The arithmetic mean and geometric mean values of the pharmacokinetic variables for artesunate as well as statistical results are summarised in the following table:

Table 7: Mean (± s.d.) PK parameters of AS in Healthy Male Volunteers

Dose	Artesunate		
	Cmax (ng/mL)	Tmax (hours)	AUC (0-t) (ng.hr/mL)
1 x 100 mg	100 ± 63	0.92 ± 0.57	142 ± 90

$AUC_{(o-t)}$ represents the area under the plasma concentration versus time curve from time zero (dosing) until the end of the sampling period (10 hours post-dose).

The disposition of artesunate in patients with malaria has not been fully characterized. Dihydroartemisinin (DHA), the principal active metabolite of artesunate, accumulates selectively in parasitized red blood cells via binding to unidentified receptor(s).

Absorption

Following rectal administration, AS and DHA concentrations are detectable in plasma beginning 0.25 to 0.5 hours after administration in most adult and paediatric subjects. Concentrations of AS remain detectable for up to 4 - 6 hours, while DHA can be observed for a longer period of time (i.e., up to 12 hours in some subjects).

Distribution

DHA is largely confined to body water and is 43% bound to plasma proteins, primarily albumin. DHA binds to P. falciparum-parasitized red blood cells. The volume of distribution of DHA was estimated to be

1.93 L/kg in pediatric patients aged 2-15 years. In these patients volume of distribution of DHA was found to be linearly related to patient age. As patient age increased, the volume of distribution increased. The volume of distribution of DHA was estimated to be 1.22 L/kg in adult patients. While female gender is predictive of a lower volume of distribution, it does not have obvious therapeutic implications.

Biotransformation
Artesunate is rapidly hydrolyzed to its principal active metabolite, dihydroartemisinin (DHA), presumably through the action of plasma and/or tissue esterases. DHA is believed to be at least partially converted to inactive metabolites and eliminated renally. In vitro data indicate that dihydroartemisinin (DHA) is mainly metabolized by glucuronidation.

Elimination
Artesunate and DHA are almost completely cleared from the plasma by 12 hours. The elimination half-life for both compounds is less than 3 hours. The elimination of DHA following the soft gelatin suppository appears to be absorption-rate limited.

Pediatric population
After adjustment for total body weight, systemic clearance of DHA was greater in pediatric patients than in adults, and volume of distribution was larger in pediatric patients than in adult patients. In addition, absorption from a suppository formulation appeared to be faster in pediatric patients compared with adult patients. The pharmacokinetics of artesunate in pediatric patients (0-24 months) is not known.

5.3 Preclinical safety data

Carcinogenicity studies were not conducted.

Artesunate was not genotoxic in the in vitro bacterial reverse mutation assay, the Chinese hamster ovary cell chromosomal aberration assay, or the in vivo mouse micronucleus assay. There was no effect on fertility in male rats following the administration of artesunate at doses up to 13 mg/kg (approximately 0.2 times the clinical dose adjusted for body surface area). In female rats, there was no significant difference in fertility rates compared to controls at a dose of up to 30 mg/kg (approximately 0.5 times the clinical doses adjusted for body surface area).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule shell: Gelatin, glycerol, titanium dioxide

Fill blend: hard fat, medium chain triglycerides

6.2 Incompatibilities

Artesunate suppositories should not be given concomitantly with other rectal medications.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at 25°C (77°F); excursions permitted between 15° to 30°C (59° to 86°F). Avoid excursions over 30°C. Do not freeze.

6.5 Nature and contents of container

Carton with one Alu – Alu blister card containing 2 soft rectal capsules.

6.6 Special precaution for disposal

No special requirements for disposal.
Any unused product or waste material should be disposed of in accordance with local requirements

7. SUPPLIER

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8. WHO REFERENCE NUMBER (PREQUALIFICATION PROGRAMME)

MA123

9. DATE OF FIRST PREQUALIFICATION/ LAST RENEWAL

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Detailed information on this medicine is available on the World Health Organization (WHO) web site: https://extranet.who.int/prequal

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