SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Artesunate Rectal Capsules [100mg] [Soft Gelatin]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 General description

Artesunate Rectal Capsules [100mg] [Soft Gelatin] are Ivory/White coloured soft gelatin capsules.

2.2 Qualitative and quantitative composition

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

100mg artesunate, Ivory/White coloured elongated shaped, soft gelatin capsules

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Severe malaria is a medical emergency. Artesunate rectal capsules are to be used as pre-referral treatment for patients aged between 6 months and 6 years, with suspected moderate or severe malaria who are unable to take oral medication or obtain injectable antimalarial treatment. Diagnosis through microscopy or a rapid diagnostic test may not be available. A patient with suspected severe malaria no longer able to take oral medication should be treated and immediately referred to a facility where full diagnosis and complete treatment with effective antimalarials can be instituted.

Limitations of use:

- Artesunate rectal capsules are not to be used for patients who can take oral medications
- Artesunate rectal capsules should not be used to prevent malaria

4.2 Posology and method of administration

Administration Instructions

Artesunate rectal capsules should be inserted in the rectum with the rounded end first. It should be administered 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 some hours before the patient can be treated at a health facility. Treatment should be followed as soon as possible by transfer to a hospital.

Care should be taken to be sure that the capsule is retained after insertion. Especially in young children, the buttocks should be held together for about 10 minutes to prevent expulsion of the artesunate capsule. 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 artesunate rectal capsules 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 facility for confirmation of diagnosis and further management, including additional antimalarial therapy.

Dosage

- Artesunate rectal suppositories are for rectal administration only, as a 10mg/kg bodyweight single dose while the patient is being transferred to the nearest health clinic or hospital.
- The number of suppositories is determined by bodyweight. However, patients may not know their weight and may be treated by age according to age-weight data from WHO Integrated Management of Childhood Illnesses (IMCI) guidelines.

The recommended regimen is 10mg/kg in a single dose.

- A single capsule of 100mg should be given to paediatric patients with a bodyweight of 5kg to <14kg.
- Two capsules of 100mg should be given to paediatric patients with a bodyweight of >14 to 20kg.

Table 1: Rectal capsules by bodyweight or age to be given in a single dose

Age	Weight	Rectal artesunate (10mg/kg body weight dose)
6 months to <3 years	5kg to <14kg	1 x 100mg capsule
>3 to 6 years	>14kg to 20kg	2 x 100mg capsules

Dosage in Patients with Hepatic or Renal Impairment

Most patients with severe malaria present with some degree of related hepatic and/or renal impairment but this appears to be pronounced in adults with severe malaria, particularly in Asia, who usually die from complications such as pulmonary oedema and renal failure. No specific pharmacokinetic studies were carried out in patients with hepatic or renal impairment.

4.3 Contraindications

- Artesunate capsules are contraindicated in individuals with known hypersensitivity to artesunate or related artemisinin derivatives.

4.4 Special warnings and precautions for use

Referral of patient

Artesunate rectal capsules are 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 rectal capsules may be reduced in patients with diarrhoea. If used in patients with frequent occurrence of diarrhoea, the patient should be closely monitored. An additional dose of artesunate rectal capsules may need to be administered per rectum if the initial capsule is expelled whole within 30 minutes.

Prophylaxis

Artesunate rectal capsules should not be used to prevent malaria.

Plasmodium vivax Infection

P.vivax infections are not an important cause of severe malaria, but artesunate capsules have been studied in 707 older patients and 488 children in Asia. *P. vivax* infections require microscopic diagnosis to identify the species and specific antimalarial treatment to achieve radical cure (i.e. prevent later relapse).

4.5 Interaction with other medicinal products and other forms of interaction

Limited data are available from formal drug interaction studies.

4.6 Use in Specific Population

Paediatric Use

Safety and efficacy of artesunate rectal capsules in the initial treatment of malaria in paediatric patients younger than 6 months of age has not yet been established.

4.7 Effects on ability to drive and use machines

Not Relevant

4.8 Undesirable effects

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials cannot be directly compared to rates observed in clinical trials of another drug and may not reflect the rates observed in practice.

In severe malaria it is difficult to distinguish adverse experiences associated with the underlying disease from those attributable to the therapy. The data described below reflect exposure to a single dose of artesunate rectal capsules in hospital and community based studies. Hospital studies were carried out in Africa and Asia, among patients requiring parenteral antimalarial therapy for moderately severe malaria who were randomised to a single dose of rectal artesunate and compared to standard alternative therapy. These studies were followed by a large community based study in which children with clinically suspected malaria were treated with either a single 100mg artesunate capsule or identical placebo. The following tables present adverse reactions data from clinical trials of artesunate rectal capsules.

1.1. Adverse experiences in clinical trials

Hospital based clinical trials **-** Adverse experience data are reported from a total of 239 patients in open-labelled hospital based clinical trials. In these trials patients with moderately severe malaria or uncomplicated hyper-parasitaemia received a single dose of artesunate rectal capsules at 10 mg/kg as initial treatment of malaria (26 patients received

a single dose of 20 mg/kg). Concomitant treatment was provided as necessary. After 24 hours all patients were given definitive antimalarial therapy with sulfadoxine/pyrimethamine (in Africa) or a combination of oral artesunate with mefloquine (in Thailand).

Three studies treated 207 children aged up to 15 years with either moderately severe malaria or uncomplicated hyper-parasitaemia. A further three studies enrolled altogether 152 adults aged 16 through 60 years with moderately severe malaria, and 11 patients with severe malaria. Most paediatric malaria patients were enrolled in African hospitals, whereas most adult malaria patients were studied in hospitals in Thailand. Artesunate treatment alone was not intended to provide cure of malaria.

Tables 2 show the most frequently reported adverse reaction rates observed in children who received a 10mg/kg single dose regimen of artesunate rectal capsules 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 2: Adverse Reactions Occurring in 3% or More of Paediatric Patients Treated in Clinical Trials with the 10mg/kg regimen of Artesunate Rectal Capsules

System Organ Class	Preferred term	Rectal Artesunate 10mg/kg (n=143)
Gastrointestinal disorders	Vomiting	3.6 (6)
Nervous system disorders	Headache	3.0 (5)
	Convulsions	1.8 (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).

Clinically significant adverse reactions reported in children treated with the 10mg/kg regimen of Artesunate rectal capsules which occurred in the hospital studies at <3% regardless of causality are listed below:

Cardiovascular disorders: ejection systolic murmur
Eye disorders: conjunctivitis
Nervous system disorders: Convulsions, impaired consciousness, dysdiadochokinesis

Community based clinical trials **-** A placebo-controlled trial was conducted in the conditions in which the drug is most likely to be used, ie in remote malaria endemic communities. [*see 13.2 Clinical studies*] Patients with a history of fever, unable to take oral drugs and without immediate access to hospital were treated close to their homes with a single capsule of artesunate or placebo and referred to hospital. The data in Table 3 reflect the outcome of exposure to treatment in 17826 patients, 8954 allocated artesunate and 8872 allocated placebo. 11778 of these patients were aged below 6 years (52% male) treated with a single 100mg rectal artesunate capsule or matching placebo in Bangladesh (22.8%), Ghana (24.4%) and Tanzania (52.9%). 7028 were malaria positive without prior treatment, 1022 had an unknown malaria status, 2618 were parasite negative and 1110 had an antimalarial injection immediately before treatment. 6048 older patients (> 6 years) were treated with a single 400mg rectal artesunate capsule or matching placebo, all in Bangladesh (57% male, 4018 malaria positive, 2030 malaria negative).

All patients were followed up to assess one of two outcomes: death or functional changes requiring a clinical neurological assessment. Patients with clinically confirmed neurological damage were reassessed periodically until symptoms resolved, the patient died, or the study ended; classification of persistent damage was made without knowledge of treatment allocation.

Frequency of adverse events defined as functional deficits in patients alive at 7-30days after treatment were <0.005%: 99/17826, excluding 12 cases of sciatic nerve injury associated with delivery of intramuscular treatment. The majority of sequelae were in children under 72 months, 80/99 in children (78 in African children) 19 in older patients.

Table 3: Treatment-observed sequelae and malaria (placebo) associated sequelae, in patients with and without malaria, in young children and older patients.					
YOUNG CHILDREN (≤72months)					
SYSTEM ORGAN CLASS					
PATIENTS WITH MALARIA OR PARASITOLOGY UNKNOWN					
		ARTESUNATE	**N=4063**	**PLACEBO**	**N=3987**
Nervous	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	1	0.02%	3	0.08%
	Vision abnormal	1	0.02%	1	0.03%
	Total	2		4	
MALARIA TOTAL		21		26	
PATIENTS WITHOUT MALARIA OR PRIOR INJECTION					
		ARTESUNATE	**N=1839**	**PLACEBO**	**N=1889**
Nervous system	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%		
	Vision abnormal	3	0.16%	2	0.11%
	Total	5	0.27%	2	0.11%

Table 3: Treatment-observed sequelae and malaria (placebo) associated sequelae, in patients with and without malaria, in young children and older patients.					
YOUNG CHILDREN (≤72months)					
NON-MALARIA TOTAL		20		13	
YOUNGER CHILDREN TOTAL (Malaria + Non-Malaria)		41		39	
OLDER PATIENTS (>72 months)					
PATIENTS WITH MALARIA					
		ARTESUNATE	**N=2009**	**PLACEBO**	**N=2009**
Nervous system	Headache	1	0.05%		
	Gait abnormal	1	0.05%		
	Hemiparesis	1	0.05%		
	Vertigo/Dizziness	1	0.05%		
	Total	4			
Special senses	Tinnitus/hearing decreased		0.00%	1	0.05%
	Vision abnormal	4	0.20%	1	0.05%
	Total	4	0.20%	2	0.10%
MALARIA TOTAL		8		2	
PATIENTS WITHOUT MALARIA					
		ARTESUNATE	**N=1043**	**PLACEBO**	**N=987**
Nervous system	Gait abnormal	2	0.19%		0.00%
	Hemiparesis	1	0.10%		0.00%
	Lower extremity weakness			1	0.10%
	Vertigo/Dizziness	1	0.10%	1	0.10%
	Total	4	0.38%	2	0.20%
Special senses	Diplopia			1	0.10%
	Vision abnormal	1	0.10%	1	0.10%
	Total	1	0.10%	2	0.20%
NON-MALARIA TOTAL		5	0.48%	4	0.41%
OLDER PATIENTS TOTAL (Malaria+Non-Malaria)		13		6	
ALL PATIENTS (CHILDREN + OLDER PATIENTS) TOTAL		54		45	

In children with malaria, artesunate was associated with a lower number of fatal (1/7) and persistent sequelae (1/9) and a higher number of sequelae that were resolving (5/6) or resolved (14/26) than placebo; early antimalarial treatment in severe malaria is important to prevent neurological sequelae and death. In young children without malaria, there was no difference between artesunate and placebo in the frequency and resolution of sequelae.

In older patients the frequency of any sequelae was <0.003% (11/4018) in patients with

malaria, and <0.009% (19/2030) in patients without malaria.

In addition to the data accumulated on artesunate rectal capsules, information is available on the safety of artesunate and other artemisinin derivatives from the literature. Relatively few side effects have been noted overall, and these were mainly mild and transient. Thus far, there have been no reports of an increased incidence of neurotoxic events associated with artemisinin derivatives.

4.9 Overdose

A fatal case report of a child, negative for Plasmodium on rapid tests and bone marrow examination, treated with rectal artesunate capsules at a dose of 200mg bid for 4 days (total dose 1600mg, weight of child 18kg, 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 Warnings and Precautions]

There is no known antidote for artesunate, and it is currently unknown if artesunate is dialyzable. The calculated intravenous LD50 and LD95 in rats were 553.1 and 884.1 mg/kg, respectively. Total treatment doses of rectal artesunate up to 1600 mg have been administered and intravenous and intramuscular doses of artesunate up to doses of 4.22mg/kg have been administered without serious adverse effect.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of Action: Artesunate (AS) is rapidly converted in the animals studied into the metabolite, dihydroartemisinin (DHA), a mixture of stereoisomers at the C-10 anomeric center. Such transformation in vivo occurs either chemically or enzymatically by hydrolysis of the ester linkage of the drug in position 10.

Chemically, Artesunate and DHA contain a 1,2,4-trioxane ring with an endoperoxide bridge. The presence of the endoperoxide bridge appears to be essential for antimalarial activity. Incubation of erythrocytes with Artesunate leads to an increase in hydrogen peroxide, superoxide anions and lipid peroxidation. The precise mechanism by which Artesunate exhibits anti-plasmodial activity is not known.

Human erythrocytes infected *in vitro* with the ring or the trophozoite forms of *Plasmodium*

falciparum accumulate 171- and 300-fold higher concentrations of DHA, respectively, compared to the culture medium. The clinical significance of this finding is not known.

Activity *In Vitro and In Vivo*: Among the 5 artemisinin derivatives with demonstrated clinical antimalarial activity (Artesunate, Artemether, dihydroartemisinin and artemisinin), artesunate has been shown to be the most potent *in vitro*. Artesunate and its metabolite, DHA, are active against erythrocytic stages of *P. falciparum*. Activity against the exo-erythrocytic stages of *P. falciparum* has not been well documented.

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 36 healthy male adult volunteers, the following mean (%CV) artesunate and dihydroartemisinin pharmacokinetic parameters were obtained with single-dose administration of 4x100 mg rectal capsules and 1 x400mg rectal capsule:

Table 4: Mean (%CV) PK parameters of AS and DHA in Healthy Male Volunteers

	Artesunate			Dihydroartemisinin		
Dose	Cmax (ng/mL)	Tmax (hours)	AUC (0-t) (nghour/mL)	Cmax (ng/mL)	Tmax (hours)	AUC(0-t) (nghour/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(0-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).

The disposition of artesunate in patients with malaria has not been fully characterised. 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). The time of maximum plasma concentration (Tmax) of AS and DHA occurs approximately 2 and 3 hours after dosing, respectively.

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 paediatric 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.

Metabolism: Artesunate is rapidly hydrolysed 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 capsule appears to be absorption-rate limited.

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

5.3 Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Artesunate Rectal Capsules [100mg] [Soft Gelatin] contains the following excipients:

- Gelatin
- Glycerol
- Titanium Dioxide
- Medium chain Triglyceride
- Hard Fat

6.2 Incompatibilites

None known.

6.3 Shelf life

The product has a shelf life of 24 Months.

6.4 Special precautions for storage

Artesunate rectal capsules, containing 100 mg artesunate, are Ivory/White coloured elongated shaped soft gelatin capsules packaged in aluminum foil blister packs.

Store at 25° C (77° F); excursions permitted to 15° to 30° C (59° to 86°F). Keep out of reach of children.

The appropriate single dose of artesunate rectal capsules should be administered rectally as soon as the presumptive diagnosis of malaria is made. In the event that an artesunate rectal capsule is expelled from the rectum within 30 minutes of insertion, a second capsule should be inserted and, especially in young children, the buttocks should be held together for 10 minutes to ensure retention of the rectal dose of artesunate.

6.5 Nature and contents of container

Description (including materials of construction)	Strength	Unit count or fill size	Container size
Primary Packaging Material Printed blister foil-[228/0.025mm][Artecap][Artesunate rectal Capsules 100mg] Plain aluminium foil-[245mm/0.13mm][25micron OPA/45micron aluminium/60micron PVC] [238 GSM]	Artesunate 100mg	2 capsules in a blister	Not Applicable
Printed blister foil-[191/0.025mm][ARTECAP][Artesunate rectal Capsules 100mg] Plain aluminium foil-[210mm][Cold Form Blister Laminate][25micron OPA/45micron aluminium/60micron PVC] [240GSM] [140microns]		6 capsules in a blister	
Secondary Packaging Material Printed carton [94x20x80mm] [1x2] [92x20x192mm] [1x6]	Artesunate 100mg	1 blister in a mono carton.	Not Applicable

6.6 Special precautions for disposal

No special requirements

Any unused product or waste material should be disposed of in accordance of with local requirement

7. MARKETING AUTHORISATION HOLDER

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8. **WHO REFERENCE NUMBER (PREQUALIFICATION PROGRAMME)**

Not Applicable

9. DATE OF FIRST <PREQUALIFICATION / RENEWAL OF THE AUTHORISATION

Not Applicable

10. DATE OF REVISION OF THE TEXT

Not Applicable