Document 1.3 Product Information

1.3.1 Summary of product characteristics

The proposed Summary of Product Characteristics (SPC) is present on the following pages.

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Artesunate 100 mg suppositories

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.

White to off white colored, elongated, soft gelatin capsules containing white to off white paste.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Severe malaria is a medical emergency. Artesunate suppositories 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 suppositories are not to be used for patients who can take oral medications
- Artesunate suppositories should not be used to prevent malaria

4.2 Posology and method of administration

Posology

Paediatric population

This medicine is recommended for antimalarial treatment as a 10mg/kg bodyweight single dose; while the patient is being transferred to the nearest health clinic or hospital.

The table below indicates 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.

Kilogram bodyweight	Age	No of 100mg suppositories
5 to ≤14	6 months to ≤3 years	1
>14 to 20	>3 to 6 years	2

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.

Method of administration

Artesunate suppositories are used by rectal route.

Artesunate suppositories 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 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 artesunate suppositories 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.

4.3 Contraindications

A 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

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

Prophylaxis

Artesunate suppositories should not be used to prevent malaria.

Plasmodium vivax Infection

P. vivax infections are not an important cause of severe malaria, but artesunate suppositories 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 Fertility, pregnancy and lactation

Not applicable.

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 suppositories 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 suppository or identical

placebo. The following tables present adverse reactions data from clinical trials of artesunate suppositories.

Hospital based clinical trials

Adverse experience data are reported from a total of 239 patients in open-labeled hospital based clinical trials. In these trials patients with moderately severe malaria or uncomplicated hyper-parasitaemia received a single dose of artesunate suppositories 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 pediatric 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 1 and 2 show the most frequently reported adverse reaction rates observed in children and adults respectively 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. In adults the most frequently reported adverse reactions were abdominal pain, vomiting, dizziness, and tinnitus.

Table 1: Adverse Reactions Occurring in 3% or More of Pediatric Patients Treated in Clinical Trials with the 10mg/kg regimen of Artesunate Suppositories

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

Table 2: Adverse Reactions Occurring in 3% or More of Adult Patients Treated in Clinical Trials with the 10mg/kg regimen of Artesunate Suppositories		
System Organ Class	**Preferred term**	**Rectal Artesunate 10mg/kg (n=108)**
Gastrointestinal disorders	Abdominal pain Vomiting	10 (9.3) 5 (4.6)
Nervous system disorders	Vertigo/Dizziness	4 (3.7)
Ear and labyrinth disorders	Tinnitus/hearing decreased	4 (3.7)
Infections and infestations	Rhinitis Upper/Lower respiratory infection	4 (3.7) 4 (3.7)

* Adult patients defined as >16 years of age.

One death occurred in an adult patient with severe malaria treated with rectal artesunate followed by IV quinine. This death was attributed to the underlying malarial disease.

Clinically significant adverse reactions reported in adults and/or children treated with the 10mg/kg regimen of artesunate suppositories 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, i.e. in remote malaria endemic communities (see section 5.1) 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 suppository 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 suppository or matching s 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 randomised to 400mg rectal artesunate suppository 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)				
Patients with malaria or parasitology unknown				
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	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				
System Organ Class	**Artesunate**	**N=1839**	**Placebo**	**N=1889**
Nervous system disorders				0.05%
Altered behaviour			1	
Brain syndrome acute	1	0.05%		
Cerebral palsy	1	0.05%		
Delirium	1	0.05%		
Gait abnormal	1	0.05%		0.21%
Hemiparesis	8	0.44%	4	0.11%
Hemiplegia			2	0.11%
Lower extremity weakness	2	0.11%	2	0.05%
Monoparesis			1	0.05%

Paraparesis Regression in development	 1	 0.05%	1	
Total	15		11	
Special senses Speech disorder Tinnitus/Hearing decreased Vision abnormal	 1 1 3	 0.05% 0.05% 0.16%	 2	 0.11%
Total	5	0.27%	2	0.11%
Non-malaria total	20		13	
Younger children total (Malaria + Non-malaria)	41		39	
Older patients (>72 months)				
Patients with malaria				
System Organ Class	**Artesunate N=2009**		**Placebo N=2009**	
Nervous system disorders Headache Gait abnormal Hemiparesis Vertigo/Dizziness	 1 1 1 1	 0.05% 0.05% 0.05% 0.05%		
Total	4	0.00%		
Special senses Tinnitus/hearing decreased Vision abnormal	 4	 0.20%	 1 1	 0.05% 0.05%
Total	4	0.20%	2	0.10%
Malaria total	8		2	
Patients without malaria				
System Organ Class	**Artesunate N=1043**		**Placebo N=987**	
Nervous system disorders Gait abnormal Hemiparesis Lower extremity weakness Vertigo/Dizziness	 2 1 1	 0.19% 0.10% 0.10%	 1 1	 0.00% 0.00% 0.10% 0.10%
Total	4	0.38%	2	0.20%
Special senses Diplopia Vision abnormal	 1	 0.10%	 1 1	 0.10% 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 suppositories, 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 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. The calculated intravenous LD_{50} and LD_{95} 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 4.22 mg/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 qinghao derivatives with demonstrated clinical antimalarial activity (artesunate, arteether, 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.

Clinical efficacy and safety

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 moderately severe malaria. Control arms were treated with oral 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 or a combination of oral artesunate with mefloquine.

Table 4 shows the percentage of patients in each study who required no additional 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 4. Proportion of Patients who Received a Single Dose of Artesunate and who did not Receive Additional Antimalarial Therapy and Achieved <10% 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%)
Adult (16 - 58 years)		
South Africa (Rectal Artesunate vs Parenteral Quinine)	22/26 (84.6%)	2/8 (25.0%)

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 6, 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 5. Cumulative Recrudescence Rates of Malaria in the Malawi Clinical Trial

		7 days post-treatment	**14 days post-treatment**	**28 days post-treatment**
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.

Patients in the clinical studies were hospitalized, the diagnosis of malaria was confirmed, ancillary therapy was provided as needed and patients with complications of malaria were excluded.

Community based studies

In a single 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. Primary endpoints were mortality, assessed 7-30 days later; permanent disability was reassessed periodically.

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 6. Mortality was 154/6072 artesunate versus 177/5996 placebo. 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%. 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), prereferral artesunate had no significant effect on death after 6 hours or permanent disability (70 vs 82).

Among those still not in clinic after >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.

Within Asia a favourable effect was observed in young children (7 vs 19) but an adverse effect in older patients (21 vs 9). Thus in children above 6 years and adults, the current evidence suggests

more deaths with treatment and treatment is therefore not recommended until results of further studies are available.

Table 6: 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 and Navrongo. For those who did not die in Handeni and Chittagong 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 36 healthy male adult volunteers, the following mean (%CV) artesunate and dihydroartemisinin pharmacokinetic parameters were obtained with single-dose administration of 4x100 mg rectal suppositories and 1 x400 mg rectal suppository:

Table 7: Mean (%CV) PK parameters of AS and DHA in Healthy Male Volunteers

Dose	Artesunate			Dihydroartemisinin		
	C_{max} (ng/mL)	T_{max} (hours)	$AUC_{(o-t)}$ (ng.hr/mL)	C_{max} (ng/mL)	T_{max} (hours)	$AUC_{(o-t)}$ (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).

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). The time of maximum plasma concentration (T_{max}) 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 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

Paediatric 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 paediatric 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

Hard fat (Softisan 378),
Medium chain triglyceride (Miglyol 812N),
Gelatin (Bloom strength 160)
Glycerol,
Titanium dioxide.

6.2 Incompatibilities

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

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 30^0C.

6.5 Nature and contents of container

Carton having one Alu - alu blister containing 6 suppositories and Carton having one Alu – alu blister containing 2 suppositories

6.6 Special precaution for disposal

No special requirements for disposal.

7. SUPPLIER

Cipla Limited.
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8. WHO REFERENCE NUMBER (PREQUALIFICATION PROGRAMME)

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9. DATE OF FIRST PREQUALIFICATION/ LAST RENEWAL

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10. DATE OF REVISION OF THE TEXT

12/2015