1. NAME OF THE MEDICINAL PRODUCT

{(SARTEM® 20/120 TABLET (Artemether/Lumefantrine)}

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each caplet contains:

Artemether	20mg
Lumefantrine	120mg
Excipients	Q.S.

3. PHARMACEUTICAL FORM

Light yellow coloured oval shaped, uncoated tablet with plain on one side and break line on the other side

4. Clinical particulars

4.1 Therapeutic indications

Indicated for the treatment of acute uncomplicated *Plasmodium falciparum* malaria in adults.

4.2 Posology and method of administration

Posology

Adults and children weighing 35 kg and above

For patients 12 years of age and above and 35 kg body weight and above, a course of treatment comprises six doses of four tablets i.e. total of 24 tablets, given over a period of 60 hours as follows: the first dose of four tablets, given at the time of initial diagnosis, should be followed by five further doses of four tablets given at 8, 24, 36, 48 and 60 hours thereafter.

Children and infants weighing 5 kg to less than 35 kg

A six-dose regimen is recommended with 1 to 3 tablets per dose, depending on bodyweight:

5 to less than 15 kg bodyweight: the first dose of one tablet, given at the time of initial diagnosis, should be followed by five further doses of one tablet given at 8, 24, 36, 48 and 60 hours thereafter.

15 to less than 25 kg bodyweight: the first dose of two tablets, given at the time of initial diagnosis, should be followed by five further doses of two tablets given at 8, 24, 36, 48 and 60 hours thereafter.

25 to less than 35 kg bodyweight: the first dose of three tablets, given at the time of initial diagnosis, should be followed by five further doses of three tablets given at 8, 24, 36, 48 and 60 hours thereafter.

Infants weighing less than 5 kg

The safety and efficacy of tablets have not been established in infants weighing less than 5 kg and no dosing recommendations can be made.

Older people

There is no information suggesting that the dosage in patients over 65 years of age should be different than in younger adults.

Method of administration

Tablets for oral administration.

Take with food or milky drink to increase absorption. For administration to small children and infants, the tablet/s may be crushed.

4.3 Contraindications

It is contraindicated in patients with:

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- patients with severe malaria according to WHO definition*.
- patients who are taking any drug which is metabolised by the cytochrome enzyme CYP2D6 (e.g. metoprolol, imipramine, amitryptyline, clomipramine).
- patients with a family history of sudden death or of congenital prolongation of the QTc interval on electrocardiograms, or with any other clinical condition known to prolong the QTc interval.
- patients taking drugs that are known to prolong the QTc interval (proarrythmic). These drugs include:
- antiarrhythmics of classes IA and III, neuroleptics, antidepressive agents, certain antibiotics including some agents of the following classes: macrolides, fluoroquinolones, imidazole and triazole antifungal agents, certain non-sedating antihistamines (terfenadine, astemizole), cisapride. Flecainide
- patients with a history of symptomatic cardiac arrythmias or with clinically relevant bradycardia or with congestive cardiac failure accompanied by reduced left ventricle ejection fraction.
- patients with disturbances of electrolyte balance e.g. hypokalemia or hypomagnesemia
- patients taking drugs that are strong inducers of CYP3A4 such as rifampin, carbamazepine, phenytoin, St. John's wort (Hypericum perforatum).
- (*Presence of one or more of the following clinical or laboratory features:
- Clinical manifestation: Prostration; impaired consciousness or unarousable coma; failure to feed; deep breathing, respiratory distress (acidotic breathing); multiple convulsions; circulatory collapse or shock; pulmonary edema (radiological); abnormal bleeding; clinical jaundice; hemoglobinuria
- Laboratory test: Severe normocytic anemia; hemoglobuniuria; hypoglycemia; metabolic acidosis; renal impairment; hyperlactatemia; hyperparasitemia)

4.4 Special warnings and precautions for use

It is not recommended during the first trimester of pregnancy in situations where other suitable and effective antimalarials are available (see section 4.6).

It has not been evaluated for the treatment of severe malaria, including cases of cerebral malaria or other severe manifestations such as pulmonary oedema or renal failure.

Due to limited data on safety and efficacy, it should not be given concurrently with any other antimalarial agent (see section 4.5) unless there is no other treatment option.

If a patient deteriorates whilst taking drug, alternative treatment for malaria should be started without delay. In such cases, monitoring of the ECG is recommended and steps should be taken to correct any electrolyte disturbances.

If it is given after mefloquine, close monitoring of food intake is advised.

In patients previously treated with halofantrine, it should not be administered earlier than one month after the last halofantrine dose.

It is not indicated and has not been evaluated for prophylaxis of malaria. It should be used cautiously in patients on anti-retroviral drugs (ARTs) since decreased artemether, DHA, and/or lumefantrine concentrations may result in a decrease of antimalarial efficacy of drug. Like other antimalarials (e.g. halofantrine, quinine and quinidine) it has the potential to cause QT prolongation.

Caution is recommended when combining with drugs exhibiting variable patterns of inhibition, moderate induction or competition for CYP3A4 as the therapeutic effects of some drugs could be altered. Drugs that have a mixed inhibitory/induction effect on CYP3A4, especially anti-retroviral drugs such as HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors should be used with caution in patients taking drug.

Caution is recommended when combining with hormonal contraceptives. It may reduce the effectiveness of hormonal contraceptives. Therefore, patients using oral, transdermal patch, or other systemic hormonal contraceptives should be advised to use an additional non-hormonal method of birth control for about one month. Patients who remain averse to food during treatment should be closely monitored as the risk of recrudescence may be greater.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction with drugs that are known to prolong the QTc interval

It is contraindicated with concomitant use of drugs (they may cause prolonged QTc interval and Torsade de Pointes) such as: antiarrhythmics of classes IA and III, neuroleptics and antidepressant agents, certain antibiotics including some agents of the following classes: macrolides, fluoroquinolones, imidazole, and triazole antifungal agents, certain non-sedating antihistamines (terfenadine, astemizole), cisapride, flecainide.

Interaction with drugs metabolized by CYP2D6

Lumefantrine was found to inhibit CYP2D6 in vitro. This may be of particular clinical relevance for compounds with a low therapeutic index. Co-administration with drugs that are metabolised by this iso-enzyme is contraindicated (e.g. neuroleptics, metoprolol, and tricyclic antidepressants such as imipramine, amitriptyline, clomipramine) is contraindicated.

Interaction with strong inducers of CYP3A4 such as rifampin

Oral administration of rifampin (600 mg daily), a strong CYP3A4 inducer, with drug (6-dose regimen over 3 days) in six HIV-1 and tuberculosis coinfected adults without malaria resulted in significant decreases in exposure to artemether (89%), DHA (85%) and lumefantrine (68%) when compared to exposure values after drug alone. Concomitant use of strong inducers of CYP3A4 such as rifampin, carbamazepine, phenytoin, St. John's Wort is contraindicated.

4.6 Pregnancy and Lactation

Women of childbearing potential

Women using oral, transdermal patch, or other systemic hormonal contraceptives should be advised to use an additional non-hormonal method of birth control for about one month.

Pregnancy

A meta-analysis of observational studies including over 500 artemether-lumefantrine exposed women in their first trimester of pregnancy assessed adverse pregnancy outcomes. The data showed that compared to quinine, artemisinin treatment, including artemether-lumefantrine, was not associated with an increased risk of miscarriage, stillbirth or congenital anomalies. However, due to the limitations of these studies, the risk of adverse pregnancy outcomes for artemether-lumefantrine exposed women in early pregnancy cannot be excluded.

Safety data from pregnancy studies including over 1200 pregnant women who were exposed to artemether-lumefantrine during the second or third trimester did not show an increase in adverse pregnancy outcomes or teratogenic effects over background rates.

Studies in animals have shown reproductive toxicity.

This treatment is not recommended during the first trimester of pregnancy in situations where other suitable and effective antimalarials are available. However, it should not be withheld in life-threatening situations, where no other effective antimalarials are available. During the second and third trimester, treatment should be considered if the expected benefit to the mother outweighs the risk to the foetus.

Breast-feeding

Animal data suggest excretion into breast milk but no data are available in humans. Women taking drug should not breast-feed during their treatment. Due to the long elimination half-life of lumefantrine (2 to 6 days), it is recommended that breast-feeding should not resume until at least one week after the last dose unless potential benefits to the mother and child outweigh the risks of treatment.

Fertility

There is no information on the effects on human fertility.

4.7 Effects on ability to drive and use machines

Patients may experience drowsiness, dizziness, hypotension or headache as side-effects. It is advisable to avoid driving or operating heavy machinery.

4.8 Undesirable effects

The safety has been evaluated in 20 clinical trials with more than 3500 patients. A total of 1810 adults and adolescents above 12 years of age as well as 1788 infants and children of 12 years of age and below has received drug in clinical trials.

Adverse reactions reported from clinical studies and post-marketing experience are listed below according to system organ class.

Adverse reactions are ranked under headings of frequency using the MedDRA frequency convention:

Very common (≥ 1/10)

Common (≥ 1/100 to <1/10)

Uncommon (≥ 1/1,000 to <1/100)

Rare (≥ 1/10,000 to <1/1,000)

Very rare (<1/10,000)

Not known (cannot be estimated from available data).

Table 1 Frequency of Undesirable effects.

Adults and adolescents above 12 years of age	Infants and children of 12 years of age and below (incidence estimates)	
Blood and lymphatic system disorders		
Delayed haemolytic anaemia#	Not Known	Not Known
Immune system disorders		
Hypersensitivity	Not known	Rare
Metabolism and nutrition disorders		
Decreased appetite	Very common	Very common (16.8 %)
Psychiatric disorders		
Sleep disorders	Very common	Common (6.4 %)
Insomnia	Common	ncommon
Nervous system disorders		
Headache	Very common	Very common (17.1 %)
Dizziness	Very common	Common (5.5 %)
Paraesthesia	Common	--
Ataxia, hypoaesthesia	Uncommon	--
Somnolence	Uncommon	Uncommon
Clonus	Common	Uncommon
Cardiac disorders		
Palpitations	Very common	Common (1.8 %)
Electrocardiogram QT prolonged	Common	Common (5.3 %)
Respiratory, thoracic and mediastinal disorders		
Cough	Common	Very common (22.7 %)
Gastrointestinal disorders		
Vomiting	Very common	Very common (20.2 %)
Abdominal pain	Very common	Very common (12.1 %)
Nausea	Very common	Common (6.5 %)
Diarrhoea	Common	Common (8.4 %)
Hepatobiliary disorders		
Liver function tests increased	Uncommon	Common (4.1 %)
Skin and subcutaneous tissue disorders		
Rash	Common	Common (2.7 %)
Pruritus	Common	Uncommon
Urticaria	Uncommon	Uncommon
Angioedema*	Not known	Not known
Musculoskeletal and connective tissue disorders		
Arthralgia	Very common	Common (2.1 %)
Myalgia	Very common	Common (2.2 %)
General disorders and administration site conditions		
Asthenia	Very common	Common (5.2 %)
Fatigue	Very common	Common (9.2 %)
Gait disturbance	Common	

4.9 Overdose

In cases of suspected overdosage symptomatic and supportive therapy should be given as appropriate, which should include ECG and blood potassium monitoring.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties:

Pharmacotherapeutic group: antimalarials, blood schizontocide, ATC code: P01 BF01.

It comprises a fixed ratio of 1:6 parts of artemether and lumefantrine, respectively. The site of antiparasitic action of both components is the food vacuole of the malarial parasite, where they are thought to interfere with the conversion of haem, a toxic intermediate produced during haemoglobin breakdown, to the nontoxic haemozoin, malaria pigment. Lumefantrine is thought to interfere with the polymerisation process, while artemether generates reactive metabolites as a result of the interaction between its peroxide bridge and haem iron. Both artemether and lumefantrine have a secondary action involving inhibition of nucleic acid- and protein synthesis within the malarial parasite. Drug has been reported to have potent activity in terms of clearing gametocytes.

5.2 Pharmacokinetic properties

Artemether is absorbed fairly rapidly and dihydroartemisinin, the active metabolite of artemether, appears rapidly in the systemic circulation with peak plasma concentrations of both compounds reached about 2 hours after dosing. Mean Cmax and AUC values of artemether ranged between 60.0– 104 ng/ml and 146– 338 ng· h/ml, respectively, in fed healthy adults after a single dose, 80 mg artemether/480 mg lumefantrine. Mean Cmax and AUC values of dihydroartemisinin ranged between 49.7– 104 ng/mL and 169-308 ng· h/ml, respectively. Absorption of lumefantrine, a highly lipophilic compound, starts after a lag-time of up to 2 hours, with peak plasma concentration (mean between 5.10– 9.80 µ g/ml) about 6– 8 hours after dosing. Mean AUC values of lumefantrine ranged between 108 and 243 µ g· h/ml. Food enhances the absorption of both artemether and lumefantrine: in healthy volunteers the relative bioavailability of artemether was increased more than two-fold, and that of lumefantrine sixteen-fold compared with fasted conditions when drug was taken after a high-fat meal.

Food has also been shown to increase the absorption of lumefantrine in patients with malaria, although to a lesser extent (approximately two-fold), most probably due to the lower fat content of the food ingested by acutely ill patients. The food interaction data indicate that absorption of lumefantrine under fasted conditions is very poor (assuming 100% absorption after a high-fat meal, the amount absorbed under fasted conditions would be <10% of the dose). Patients should therefore be encouraged to take the medication with a normal diet as soon as food can be tolerated.

Distribution

Artemether and lumefantrine are both highly bound to human serum proteins in vitro (95.4% and 99.7%, respectively). Dihydroartemisinin is also bound to human serum proteins (47– 76%).

Biotransformation

Artemether is rapidly and extensively metabolised (substantial first-pass metabolism) both in vitro and in humans. Human liver microsomes metabolise artemether to the biologically active main metabolite dihydroartemisinin (demethylation), predominantly through the isoenzyme CYP3A4/5. This metabolite has also been detected in humans in vivo.

Glucuronidation of dihydroartemisinin is predominately catalysed by UGT1A9 and UGT2B7.

Dihydroartemisinin is further converted to inactive metabolites.

The pharmacokinetics of artemether in adults is time-dependent. During repeated administration, plasma artemether levels decreased significantly, while levels of the active metabolite (dihydroartemisinin) increased, although not to a statistically significant degree. The ratio of day 3/day 1 AUC for artemether was between 0.19 and 0.44, and was between 1.06 and 2.50 for dihydroartemisinin. This suggests that there was induction of the enzyme responsible for the metabolism of artemether. Artemether and dihydroartemisinin were reported to have a mild inducing effect on CYP3A4 activity. The clinical evidence of induction is consistent with the in vitro data described in section 4.5

Lumefantrine is N-debutylated, mainly by CYP3A4, in human liver microsomes. In vivo in animals (dogs and rats), glucuronidation of lumefantrine takes place directly and after oxidative biotransformation. In humans, the exposure to lumefantrine increases with repeated administration over the 3-day treatment period, consistent with the slow elimination of the compound (see section 5.2 Elimination). Systemic exposure to the metabolite desbutyl-lumefantrine, for which the in vitro antiparasitic effect is 5 to 8 fold higher than that for lumefantrine, was less than 1% of the exposure to the parent drug. Desbutyl-lumefantrine data is not available specifically for an African population. In vitro, lumefantrine significantly inhibits the activity of CYP2D6 at therapeutic plasma concentrations.

Elimination

Artemether and dihydroartemisinin are rapidly cleared from plasma with a terminal half-life of about 2 hours. Lumefantrine is eliminated very slowly with an elimination half-life of 2 to 6 days. Demographic characteristics such as sex and weight appear to have no clinically relevant effects on the pharmacokinetics.

Limited urinary excretion data are available for humans. In 16 healthy volunteers, neither lumefantrine nor artemether was found in urine after administration, and only traces of dihydroartemisinin were detected (urinary excretion of dihydroartemisinin amounted to less than 0.01% of the artemether dose).

In animals (rats and dogs), no unchanged artemether was detected in faeces and urine due to its rapid and extensive first-pass metabolism, but numerous metabolites (partly identified) have been detected in faeces, bile and urine. Lumefantrine was excreted unchanged in faeces and with traces only in urine. Metabolites of lumefantrine were eliminated in bile/faeces.

Dose proportionality

No specific dose proportionality studies were performed. Limited data suggest a dose-proportional increase of systemic exposure to lumefantrine when doubling the dose. No conclusive data is available for artemether.

Bioavailability/bioequivalence studies

Systemic exposure to lumefantrine, artemether and dihydroartemisinin was similar following administration as dispersible tablets and crushed tablets in healthy adults.

Systemic exposure to lumefantrine was similar following administration of dispersible tablets and intact tablets in healthy adults. However, exposure to artemether and dihydroartemisinin was significantly lower (by 20-35%) for the dispersible than for the intact tablet. These findings are not considered to be clinically relevant for the use of the dispersible tablets in the paediatric population since adequate efficacy of dispersible tablets was demonstrated in this population. The dispersible tablet is not recommended for use in adults.

Older people

No specific pharmacokinetic studies have been performed in elderly patients. However, there is no information suggesting that the dosage in patients over 65 years of age should be different than in younger adults.

Paediatric population: In paediatric malaria patients, mean Cmax (CV%) of artemether (observed after first

dose) were 223 (139%), 198 (90%) and 174 ng/ml (83%) for body weight groups 5-<15, 15-<25 and 25-<35 kg, respectively, compared to 186 ng/ml (67%) in adult malaria patients. The associated mean Cmax of DHA were 54.7 (108%), 79.8 (101%) and 65.3 ng/mL (36%), respectively compared to 101 ng/ml (57%) in adult malaria patients. AUC of lumefantrine (population mean, covering the six doses) were 577, 699 and 1150 µ g• h/ml for paediatric malaria patients in body weight groups 5-<15, 15-<25 and 25-<35 kg, respectively, compared to a mean AUC of 758 µ g• h/ml (87%) in adult malaria patients. The elimination half-lives of artemether and lumefantrine in children are unknown.

Infants weighing <5 kg

Study B2306 showed that the Cmax of artemether and DHA in infants with uncomplicated P. falciparum malaria weighing <5 kg and older than 28 days of age who were treated with artemether/lumefantrine dispersible tablets, was on average 2- to 3-fold higher than that in pediatric patients with a body weight ≥ 5 kg and children up to 12 years of age treated with the same dose of tablets. The mean Cmax of lumefantrine was similar to that observed in pediatric patients with a body weight ≥ 5 kg.

Race/Ethnicity: Pharmacokinetics of artemether, DHA and lumefantrine in the Japanese population was found to be consistent with other populations.

Hepatic and Renal impairment

No specific pharmacokinetic studies have been performed either in patients with hepatic or renal insufficiency or elderly patients. The primary clearance mechanism of both artemether and lumefantrine may be affected in patients with hepatic impairment. In patients with severe hepatic impairment, a clinically significant increase of exposure to artemether and lumefantrine and/or their metabolites cannot be ruled out. Therefore, caution should be exercised in dosing patients with severe hepatic impairment. Based on the pharmacokinetic data in 16 healthy subjects showing no or insignificant renal excretion of lumefantrine, artemether and dihydroartemisinin, no dose adjustment for the use in patients with renal impairment is advised.

5.3 Preclinical safety data

General toxicity: The main changes observed in repeat-dose toxicity studies were associated with the expected pharmacological action on erythrocytes, accompanied by responsive secondary haematopoiesis.

Neurotoxicity: Studies in dogs and rats have shown that intramuscular injections of artemether resulted in brain lesions. Changes observed mainly in brainstem nuclei included chromatolysis, eosinophilic cytoplasmic granulation, spheroids, apoptosis and dark neurons. Lesions were observed in rats dosed for at least 7 days and dogs for at least 8 days, but lesions were not observed after shorter intramuscular treatment courses or after oral dosing. The estimated artemether 24 h AUC after 7 days of dosing at the no observed effect level is approximately 7-fold greater or more than the estimated artemether 24 h AUC in adult humans. The hearing threshold was affected at 20 dB by oral artemether administration to dogs at a dose of about 29 times the highest artemether clinical dose (160 mg/day) based on body surface area comparisons. Most nervous system disorder adverse events in the studies of the 6-dose regimen were mild in intensity and resolved by the end of the study.

Mutagenicity: Artemether and lumefantrine were not genotoxic/clastogenic based on in vitro and in vivo testing.

Carcinogenicity: Carcinogenicity studies were not conducted.

Reproductive toxicity studies: Embryotoxicity was observed in rat and rabbit reproductive toxicity studies conducted with artemether, a derivative of artemisinin. Artemisinins are known to be embryotoxic. Lumefantrine alone caused no sign of reproductive or development toxicity at doses up to 1,000 mg/kg/day in rats and rabbits, doses which are at least 10 times higher than the daily human dose based on body surface area comparisons.

Reproductive toxicity studies performed with the artemether-lumefantrine combination caused maternal toxicity and increased post-implantation loss in rats and rabbits.

Artemether caused increases in post-implantation loss and teratogenicity (characterised as a low incidence of cardiovascular and skeletal malformations) in rats and rabbits. The embryotoxic artemether dose in the rat yields artemether and dihydroartemisinin exposures similar to those achieved in humans based on AUC.

Fertility: Artemether-lumefantrine administration yielded altered sperm motility, abnormal sperm, reduced epididymal sperm count, increased testes weight, and embryotoxicity; other reproductive effects (decreased implants and viable embryos, increased preimplantation loss) were also observed. The no adverse effect level for fertility was 300 mg/kg/day. The relevance to this finding in humans is unknown.

Juvenile toxicity studies: A study investigated the neurotoxicity of oral artemether in juvenile rats. Mortality, clinical signs and reductions in body weight parameters occurred most notably in younger rats. Despite the systemic toxicity noted, there were no effects of artemether on any of the functional tests performed and there was no evidence of a direct neurotoxic effect in juvenile rats. Very young animals are more sensitive to the toxic effect of artemether than adult animals. There is no difference in sensitivity in slightly older animals compared to adult animals. Clinical studies have established the safety of artemether and lumefantrine administration in patients weighing 5 kg and above.

Cardiovascular Safety Pharmacology: In toxicity studies in dogs at doses >600 mg/kg/day, there was some evidence of prolongation of the QTc interval (safety margin of 1.3-fold to 2.2-fold for artemether using calculated free Cmax), at higher doses than intended for use in man. In vitro hERG assays showed a safety margin of >100 for artemether and dihydroartemisinin. The hERG IC50 was 8.1 μ M for lumefantrine and 5.5 μ M for its desbutyl metabolite.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

hypromellose, microcrystalline cellulose, colloidal anhydrous silica, croscarmellose sodium and magnesium stearate, talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store in a cool dry place. Below 30°C.

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

Pack size: 1 x 24 tablets.

6.6 Special precautions for disposal <and other handling>

No special requirements.

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

7. APPLICANT

Savannah Pharmaceutical Limited,

22 I.T Igbani, Jabi, Abuja

Nigeria.

8. Manufacturer
Savatem Pharmaceutical
Limited, Abuja Nigeria.