

MODULE-1	ADMINISTRATIVE INFORMATION AND PRODUCT INFORMATION
BRAND NAME:	AGABA
GENERIC NAME:	ARTEMISININ AND PIPERAQUINE TABLETS

1.3 PRODUCT INFORMATION

1.3.1 Summary of Product Characteristics (SmPC)

Enclosed

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1.3 PRODUCT INFORMATION

1.3.1 Summary of Product Characteristics (SmPC)

1. Name of the medicinal product: AGABA (ARTEMISININ AND PIPERAQUINE TABLETS)

2. Qualitative and Quantitative composition:

Sr. No.	Ingredient	Specification	Qty/Tablets (mg)	Over ages	Qty/batch (Kg)	Function
1.	Artemisinin	IH	62.5	-	6.25	Active ingredient
2.	Piperaquine	IH	375.00	-	37.50	Active ingredient
3.	Lactose	BP	145.00	-	14.50	Diluent
4.	Maize Starch	BP	145.00	-	14.50	Diluent
5.	Povidone	BP	11.25	-	1.125	Binder
6.	Purified Talc	BP	16.00	-	1.600	Glidant
7.	Magnesium Stearate	BP	16.00	-	1.600	Lubricant
8.	Colloidal Anhydrous Silica	BP	8.00	-	0.800	Lubricant
9.	Croscarmellose Sodium	BP	16.00	-	1.600	Disintegrant
10.	Polacrillin Potassium	USP	8.00	-	0.800	Taste-masking agent
11.	Brilliant Blue FCF & Tartrazine	IH	25.00	-	2.500	Colouring agent
12.	Dichloromethane	BP	Q.S.	-	Q.S.	Solvent
13.	Isopropyl Alcohol	BP	Q.S.	-	Q.S.	Solvent
Total weight of coated tablets			827.75 mg		82.775 Kg	

where, IH=In house,
BP=British Pharmacopoeia,
USP= United States Pharmacopoeia

3. Pharmaceutical Form: Tablet.

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4. Clinical Particulars:

4.1 Therapeutic indications

Artemisinin and Piperaquine Tablets are indicated for the treatment of uncomplicated Plasmodium falciparum malaria in adults, children and infants 6 months and over and weighing 7 kg or more.

4.2 Posology and method of administration

Posology

Artemisinin and Piperaquine Tablets should be administered over three consecutive days for a total of three doses taken at the same time each day.

Dosage

Dosing should be based on body weight as shown in the table below.

Body weight (kg)	Daily dose (mg)		Tablet strength and number of tablets per dose
	PQP	DHA	
5 to <7	80	10	½ x 160mg / 20mg tablet
7 to <13	160	20	1 x 160mg / 20mg tablet
13 to <24	320	40	1 x 320mg / 40mg tablet
24 to <36	640	80	2 x 320mg / 40mg tablets
36 to <75	960	120	3 x 320mg / 40mg tablets
75 to 100	1,280	160	4 x 320mg / 40mg tablets
>100	There are no data on which to base a dose recommendation in patients weighing >100kg.		

If a patient vomits within 30 minutes of taking Artemisinin and Piperaquine Tablets, the whole dose should be re-administered; if a patient vomits within 30-60 minutes, half the dose should be re-administered. Re-dosing with Artemisinin and Piperaquine Tablets should not be attempted more than once. If the second dose is vomited, alternative antimalarial therapy should be instituted. If a dose is missed, it should be taken as soon as realised and then the recommended regimen continued until the full course of treatment has been completed. There is no data on a second course of treatment. No more than two courses of Artemisinin and Piperaquine Tablets may be given within a 12 month period. A second course of Artemisinin and Piperaquine Tablets should not be given within 2 months after the first course due to the long elimination half-life of piperaquine.

Hepatic and renal impairment

Artemisinin and Piperaquine Tablets has not been evaluated in subjects with moderate or severe renal or hepatic insufficiency. Therefore, caution is advised when administering Artemisinin and Piperaquine Tablets to these patients. Older people Clinical studies of Eurartesim tablets did not include patients aged 65 years and over, therefore no dosing recommendation can be made. Considering the possibility of age-associated decrease in hepatic and renal function, as well as a potential for heart disorders, caution should be exercised when administering the product to the elderly.

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The safety and efficacy of Artemisinin and Piperaquine Tablets in children aged less than 6 months and in children weighing less than 5 kg has not been established. No data are available for these paediatric subsets.

Method of administration

Artemisinin and Piperaquine Tablets should be taken orally with water and without food. Each dose should be taken no less than 3 hours after the last food intake. No food should be taken within 3 hours after each dose. For patients unable to swallow the tablets, such as infants and young children, Artemisinin and Piperaquine Tablets may be crushed and mixed with water. The mixture should be used immediately after preparation.

4.3 Contraindications

Hypersensitivity to any of the active substances or to any of the excipients.

Severe malaria according to WHO definition.

Family history of sudden death or of congenital prolongation of the QTc interval.

Known congenital prolongation of the QTc-interval or any clinical condition known to prolong the QTc interval.

History of symptomatic cardiac arrhythmias or with clinically relevant bradycardia.

Any predisposing cardiac conditions for arrhythmia such as severe hypertension, left ventricular hypertrophy (including hypertrophic cardiomyopathy) or congestive cardiac failure accompanied by reduced left ventricle ejection fraction.

Electrolyte disturbances, particularly hypokalaemia, hypocalcaemia or hypomagnesaemia.

Taking medicinal products that are known to prolong the QTc interval. These include (but are not limited to):

Antiarrhythmics (e.g. amiodarone, disopyramide, dofetilide, ibutilide, procainamide, quinidine, hydroquinidine, sotalol).

Neuroleptics (e.g. phenothiazines, sertindole, sultopride, chlorpromazine, haloperidol, mesoridazine, pimozide, or thioridazine), antidepressive agents.

Certain antimicrobial agents, including agents of the following classes:

- macrolides (e.g. erythromycin, clarithromycin),
- fluoroquinolones (e.g. moxifloxacin, sparfloxacin),
- imidazole and triazole antifungal agents,
- and also pentamidine and saquinavir.

Certain non-sedating antihistamines (e.g. terfenadine, astemizole, mizolastine).

Cisapride, droperidol, domperidone, bepridil, diphemanil, probucol, levomethadyl, methadone, vinca alkaloids, arsenic trioxide.

Recent treatment with medicinal products known to prolong the QTc interval that may still be circulating at the time that Eurartesim is commenced (e.g. mefloquine, halofantrine, lumefantrine, chloroquine, quinine and other antimalarial agents) taking into account their elimination half-life.

4.4 Special warnings and precautions for use

Artemisinin and Piperaquine Tablets should not be used to treat severe falciparum malaria and, due to insufficient data, should not be used to treat malaria due to *Plasmodium vivax*, *Plasmodium malariae* or *Plasmodium ovale*.

The long half-life of piperaquine (about 22 days) should be kept in mind in the event that another anti-malarial agent is started due to treatment failure or a new malaria infection.

Piperaquine is a mild inhibitor of CYP3A4. Caution is recommended when co-administering Artemisinin and Piperaquine Tablets with medicinal products exhibiting variable patterns of inhibition, induction or competition for CYP3A4 as the therapeutic and/or toxic effects of some co-administered medicinal products could be altered.

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Piperaquine is also a substrate of CYP3A4. A moderate increase of piperaquine plasma concentrations (< 2 -fold) was observed when co-administered with strong CYP3A4 inhibitors, resulting in a potential exacerbation of the effect on QTc prolongation. Exposure to piperaquine may also be increased when co-administered with mild or moderate CYP3A4-inhibitors (e.g. oral contraceptives). Therefore, caution should be applied when co-administering Eurartesim with any CYP3A4-inhibitor and ECG monitoring should be considered. Due to the lack of multiple dose PK data for piperaquine, administration of any strong CYP3A4- inhibitors should be discouraged after initiation (i.e. the first dose) of Artemisinin and Piperaquine Tablets.

Artemisinin and Piperaquine Tablets should not be used during pregnancy in situations where other suitable and effective antimalarials are available. In the absence of carcinogenicity study data, and due to lack of clinical experience with repeated courses of treatment in humans, no more than two courses of Artemisinin and Piperaquine Tablets should be given in a 12- month period.

Effects on cardiac repolarization In clinical trials with Artemisinin and Piperaquine Tablets limited ECGs were obtained during treatment. These showed that QTc prolongation occurred more frequently and to a larger extent in association with Artemisinin and Piperaquine Tablets therapy than with the comparators. Analysis of cardiac adverse events in clinical trials showed that these were reported more frequently in Artemisinin and Piperaquine Tablets treated patients than in those treated with comparator antimalarial. Before the third dose of Artemisinin and Piperaquine Tablets, in one of the two Phase III studies 3/767 patients (0.4%) were reported to have a QTcF value of > 500 ms versus none in the comparator group.

4.5 Interaction with other medicinal products and other forms of interaction

Artemisinin and Piperaquine Tablets is contraindicated in patients already taking other medicinal products that are known to prolong the QTc interval due to the risk of a pharmacodynamic interaction leading to an additive effect on the QTc interval.

A limited number of drug-drug pharmacokinetic interaction studies with Artemisinin and Piperaquine Tablets have been performed in healthy adult subjects. Therefore the assessment of the potential for drug-drug interactions to occur is based on either in vivo or in vitro studies.

Effect of Artemisinin and Piperaquine Tablets on co-administered medicinal products
Piperaquine is metabolised by, and is an inhibitor of CYP3A4. The concurrent administration of oral Artemisinin and Piperaquine Tablets with 7.5 mg oral midazolam, a CYP3A4 probe substrate, led to a modest increase (≤ 2 -fold) in midazolam and its metabolites exposures in healthy adult subjects. This inhibitory effect was no longer evident one week after last administration of Artemisinin and Piperaquine Tablets. Therefore, particular attention should be paid when medicinal products that have a narrow therapeutic index (e.g. antiretroviral medicinal products and cyclosporine) are co-administered with Artemisinin and Piperaquine Tablets.

4.6 Pregnancy and Lactation:

Pregnancy

There are insufficient data on the use of DHA and piperaquine in pregnant women. Based on animal data, Artemisinin and Piperaquine Tablets is suspected to cause serious birth defects when administered during the first trimester of pregnancy. Reproductive studies with artemisinin derivatives have demonstrated teratogenic potential with an increased risk during early gestation. Piperaquine was not teratogenic in the rat or rabbit. In perinatal and postnatal studies in rats, piperaquine was associated with delivery complications. However, there was no delay in neonatal development following exposure in utero or via milk.

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Artemisinin and Piperaquine Tablets should not be used during pregnancy in situations where other suitable and effective anti- malarials are available.

Breast-feeding

Animal data suggest excretion of piperaquine into breast milk but no data are available in humans. Women taking Artemisinin and Piperaquine Tablets should not breast-feed during their treatment.

Fertility

There are no specific data relating to the effects of piperaquine on fertility, however, to date no adverse events have been reported during clinical use. Moreover, data obtained in animal studies show that fertility is unaffected by DHA in both females and males.

4.7 Effects on ability to drive and use machines:

Adverse event data collected in clinical trials suggest that Artemisinin and Piperaquine Tablets has no influence on the ability to drive and operate machines once the patient has recovered from the acute infection.

4.8 Undesirable effects:

Summary of the safety profile The safety of Artemisinin and Piperaquine Tablets has been evaluated in two phase III open-label studies involving 1,239 paediatric patients up to 18 years and 566 adult patients >18 years treated with Artemisinin and Piperaquine Tablets. In a randomized trial in which 767 adults and children with uncomplicated *P. falciparum* malaria were exposed to Artemisinin and Piperaquine Tablets, 25 % of subjects were judged to have experienced an adverse drug reaction

Frequency of ADRs in adult patients participating in clinical studies with Artemisinin and Piperaquine Tablets :

SOC	Very Common	Common	Uncommon
Infections and infestations		<i>P. falciparum</i> infection	Influenza Respiratory tract infection
Blood and lymphatic system disorders		Anaemia	
Metabolism and nutrition disorders			Anorexia
Nervous system disorders		Headache	Dizziness Convulsion
Cardiac disorders		QTc prolonged Tachycardia	Cardiac conduction disorders Sinus arrhythmias Bradycardia
Respiratory, thoracic and mediastinal disorders			Cough
Gastrointestinal disorders			Vomiting Abdominal pain Diarrhoea Nausea

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SOC	Very Common	Common	Uncommon
Hepatobiliary disorders			Hepatitis Hepatomegaly Abnormal liver function tests
Skin and subcutaneous Tissue disorders			Pruritis
Musculoskeletal and connective tissue disorders			Arthralgia Myalgia
General disorders and administration site conditions		Asthenia Pyrexia	

Description of selected adverse reactions

The ADRs noted for Artemisinin and Piperaquine Tablets were generally mild in severity, and the majority were non-serious. Reactions such as cough, pyrexia, headache, *P. falciparum* infection, anaemia, asthenia, anorexia and the observed changes in blood cell parameters are consistent with those expected in patients with acute malaria. The effect on prolongation of the QTc interval was observed on Day 2, and had resolved by Day 7 (the next time point at which ECGs were performed).

Paediatric population

A tabular overview of the frequency of the ADRs in paediatric patients is given below. The majority of paediatric experience is derived from African children aged 6 months to 5 years.

Frequency of ADRs in paediatric patients participating in clinical studies with Artemisinin and Piperaquine Tablets:

SOC	Very Common	Common	Uncommon
Infections and infestations	Influenza <i>P. falciparum</i> infection	Respiratory tract infection Ear infection	
Blood and lymphatic system disorders		Anaemia Leucocytoses NEC Leukopenias/neutropenia Thrombocytopenia	Hypochromasia Lymphadenopathy Splenomegaly Thrombocythaemia
Metabolism and nutrition disorders		Anorexia	
Nervous system disorders			Convulsion Headache
Eye disorders		Conjunctivitis	
Cardiac disorders		Heart rate irregular QT/QTc prolonged	Cardiac murmur Cardiac conduction disorders

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SOC	Very Common	Common	Uncommon
Hepatobiliary disorders			Hepatitis Hepatomegaly Jaundice Abnormal liver function tests
Skin and subcutaneous Tissue disorders		Dermatitis Rash	Pruritis Acanthosis
Musculoskeletal and connective tissue disorders			Arthralgia
General disorders and administration site conditions	Pyrexia	Asthenia	

4.9 Overdose:

In clinical trials, nine patients received double the cumulative intended dose of Artemisinin and Piperaquine Tablets. The safety profile of these patients did not differ from that of patients receiving the recommended dose, with no patient reporting SAEs. In cases of suspected overdose, symptomatic and supportive therapy should be given as appropriate, including ECG monitoring because of the possibility of QTc interval prolongation.

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5. PHARMACOLOGICAL PROPERTY

5.1 Pharmacodynamic properties: -

Pharmacotherapeutic group: Antiprotozoals, antimalarials, Artemisinin and derivatives, combinations

ATC code: P01BF05

Pharmacodynamic effects DHA is able to reach high concentrations within the parasitized erythrocytes. Its endoperoxide bridge is thought to be essential for its antimalarial activity, causing free-radical damage to parasite membrane systems including:

Inhibition of falciparum sarcoplasmic-endoplasmic reticulum calcium ATPase,

Interference with mitochondrial electron transport

Interference with parasite transport proteins

Disruption of parasite mitochondrial function

The exact mechanism of action of piperazine is unknown, but it likely mirrors that of chloroquine, a close structural analogue. Chloroquine binds to toxic haeme (derived from the patient's haemoglobin) within the malaria parasite, preventing its detoxification via a polymerisation step.

Piperazine is a bisquinoline, and this class has shown good antimalarial activity against chloroquine-resistant Plasmodium strains in vitro. The bulky bisquinolone structure may be important for activity against chloroquine-resistant strains, and may act through the following mechanisms:

Inhibition of the transporters that efflux chloroquine from the parasite food vacuole

Inhibition of haem-digestion pathway in the parasite food vacuole.

5.2 Pharmacokinetic properties: -

Pharmacokinetic profiles of DHA and piperazine have been investigated in animal models and in different human populations (healthy volunteers, adult patients and paediatric patients). Absorption DHA is very rapidly absorbed, T_{max} being approximately 1-2 hrs after single and multiple dosing. In patients, mean C_{max} (CV %) and AUC_{INF} of DHA (observed after the first dose of Eurartesim) were 752 (47 %) ng/ml and 2,002 (45 %) ng/ml*h, respectively.

DHA bioavailability appears to be higher in malaria patients than in healthy volunteers, possibly because malaria per se has an effect on DHA disposition. This may reflect malaria-associated impairment of hepatic function, causing an increase in DHA bioavailability (reduction of first hepatic effect) without affecting its apparent elimination half-life, which is absorption rate limited. In healthy male volunteers under fasting conditions, mean C_{max} and AUC_{INF} of DHA ranged between 180-252 ng/ml and 516-684 ng/ml*h, respectively.

The systemic exposure to DHA was slightly lower following the last dose of Artemisinin and Piperazine Tablets (lower than after the first dose by up to 15 %). DHA pharmacokinetic parameters were found to be similar in healthy volunteers of Asian and Caucasian origin. DHA systemic exposure on the last day of treatment was higher in females than in males, the difference being within 30 %.

In healthy volunteers, DHA exposure was increased by 43 % when administered with a high fat/high calorie meal. Piperazine, a highly lipophilic compound, is slowly absorbed. In humans, piperazine has a T_{max} of approximately 5 hours following a single and repeated dose. In patients mean (CV %) C_{max} and AUC₀₋₂₄ (observed after the first dose of Artemisinin and Piperazine Tablets) were 179 (62 %) ng/ml and 1,679 (47 %) ng/ml*h, respectively. Due to its slow elimination, piperazine accumulates in plasma after multiple doses with an accumulation factor of approximately 3.

Piperazine pharmacokinetic parameters were found to be similar in healthy volunteers of Asian and Caucasian origin. On the other hand, on the last day of Artemisinin and Piperazine Tablets treatment, the piperazine maximum plasma concentration was higher in female than in male healthy volunteers, the difference being in the order of 30 to 50 %.

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In healthy volunteers, piperazine exposure is increased approximately 3-fold when administered with a high fat/high calorie meal. This pharmacokinetic effect is accompanied by an increased effect on prolongation of the QT interval. Accordingly, Eurartesim should be administered with water no less than 3 hours after the last food intake, and no food should be taken within 3 hours after each dose.

Distribution

Both piperazine and DHA are highly bound to human plasma proteins: the protein binding observed in in vitro studies was 44-93 % for DHA and >99 % for piperazine. Moreover, from in vitro and in vivo data in animals, piperazine and DHA tend to accumulate in RBC. DHA was observed to have a small volume of distribution in humans (0.8 l/kg; CV 35.5 %). Pharmacokinetic parameters observed for piperazine in humans indicate that this active substance has a large volume of distribution (730 l/kg; CV % 37.5 %).

Biotransformation

DHA is principally converted to α -DHA- β -glucuronide (α -DHA-G). Studies in human liver microsomes showed that DHA was metabolised by the UDP-glucuronosyltransferase (UGT1A9 and UGT2B7) to α -DHA-G with no cytochrome P450-mediated metabolism. In vitro drug-drug interaction studies revealed that DHA is an inhibitor of CYP1A2; therefore, there is the potential for DHA to increase plasma concentrations of CYP1A2 substrates.

In vitro metabolism studies demonstrated that piperazine is metabolised by human hepatocytes (approximately 85 % of piperazine remained after 2 hours incubation at 37°C). Piperazine was mainly metabolised by CYP3A4 and to a lesser extent by CYP2C9 and CYP2C19. Piperazine was found to be an inhibitor of CYP3A4 (also in a time-dependent way) and to a lesser extent of CYP2C19, while it stimulated the activity of CYP2E1. No effect on the metabolite profile of piperazine in human hepatocytes was observed when piperazine was co-incubated with DHA. The piperazine major metabolites were a carboxyl acid cleavage product, and a mono-N-oxidated product. In human studies, piperazine was found to be a mild inhibitor of CYP3A4 enzyme while potent inhibitors of CYP3A4 activity caused mild inhibition of piperazine metabolism.

Elimination

The elimination half-life of DHA is approximately 1 hour. The mean oral clearance for adult patients with malaria was 1.34 l/h/kg. The mean oral clearance was slightly higher for paediatric patients, however the differences were minor in magnitude (<20 %). DHA is eliminated by metabolism (mainly glucuroconjugation). Its clearance was found to be slightly lower in female than in male healthy volunteers. Data regarding DHA excretion in humans are scarce. However, it is reported in the literature that the excretion of unchanged active substance in human urine and faeces is negligible for artemisinin derivatives.

The elimination half-life of piperazine is around 22 days for adult patients and around 20 days for paediatric patients. The mean oral clearance for adult patients with malaria was 2.09 l/h/kg, while in paediatric patients was 2.43 l/h/kg. Due to its long elimination half-life, piperazine accumulates after multiple dosing.

Animal studies showed that radiolabelled piperazine is excreted by the biliary route, while urinary excretion is negligible.

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5.3 Preclinical safety data

General toxicity

Literature data concerning chronic toxicity of piperaquine in dogs and monkeys indicate some hepatotoxicity and mild reversible depression of total white cell and neutrophil counts. The most important nonclinical safety findings after repeated dosing were the infiltration of macrophages with intracytoplasmic basophilic granular material consistent with phospholipidosis and degenerative lesions in numerous organs and tissues. These adverse reactions were seen in animals at exposure levels similar to clinical exposure levels, and with possible relevance to clinical use. It is not known whether these toxic effects are reversible. DHA and piperaquine were not genotoxic/clastogenic based on in vitro and in vivo testing

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6. Pharmaceutical Particulars:

List of Excipients:

Not applicable

6.2 Incompatibilities: Nil

6.3 Shelf Life: 36 months.

6.4 Special Precautions for storage:

Store below 30°C. Protect from light and moisture.

6.5 Nature and contents of container:

1 X 4 Tablets in Alu-PVC blister pack.

6.6 Special precautions for disposal and other handling:

No special requirements.

7. Marketing Authorization Holder:

MEDICROWN NIGERIA LTD.
7,JIARO ROAD,OFF AIRPORT ROAD,
SABON GARI, KANO, KANO STATE, NIGERIA

8. Marketing Authorization Number: ---

B4-5408

9. Date of first Authorization /renewal of the authorization: ---

10. Date of revision of text: -----