National Agency for Food & Drug Administration & Control (NAFDAC)

Registration & Regulatory Affairs (R & R) Directorate

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) TEMPLATE

1. NAME OF THE MEDICINAL PRODUCT

AGABA
ARTEMISININ 62.5 mg And PIPERAQUINE 375 mg TABLET

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Tablet Contains:
Artemisinin 62.5 mg
Piperaquine 375 mg
Excipients Q.S
Colour: TCT Green, Titanium Dioxide BP

3. PHARMACEUTICAL FORM

The product is an oval shaped, green coloured film coated tablet. Embossed “AGABA” on one side of tablet and other side plain.

4. Clinical particulars

4.1 Therapeutic indications

AGABA is indicated for the treatment of uncomplicated Plasmodium falciparum malaria in adults, adolescents, children and infants 6 months and over and weighing 5 kg or more.

Consideration should be given to official guidance on the appropriate use of antimalarial medicinal products.

4.2 Posology and method ofadministration

Posology

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

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

Age	'0' hr	'24' hrs
≥ 16 years	2 tablets	2 tablets
11 to 15 years	1½ tablets	1½ tablets
7 to 10 years	1 tablet	1 tablet

If a patient vomits within 30 minutes of taking AGABA, 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

AGABA 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 realized 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 AGABA may be given within a 12 month period (see sections 4.4 and 5.3).

A second course of AGABA should not be given within 2 months after the first course due to the long

elimination half-life of piperaquine (see sections 4.4 and 5.2).

Special populations

Elderly

Clinical studies of AGABA 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 (see sections 4.3 and 4.4), caution should be exercised when administering the product to the elderly.

Hepatic and renal impairment

AGABA has not been evaluated in subjects with moderate or severe renal or hepatic insufficiency.

Therefore, caution is advised when administering AGABA to these patients (see section 4.4).

Paediatric population

The safety and efficacy of AGABA in infants aged less than 6 months and in children weighing less than 5 kg

has not been established. No data are available for these pediatric subsets.

Method of administration

Tablets for oral use.

AGABA 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.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

- 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 medicinal products.

• Certain antimicrobial medicinal products, including medicinal products of the following classes:

- macrolides (e.g. erythromycin, clarithromycin),

- fluoroquinolones (e.g. moxifloxacin, sparfloxacin),

- imidazole and triazole antifungalmedicinal products,

- 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 AGABA is commenced (e.g. mefloquine, halofantrine, lumefantrine, chloroquine, quinine and other antimalarial medicinal products) taking into account their elimination half-life.

4.4 Special warnings and precautions for use

AGABA should not be used to treat severe falciparum malaria (see section 4.3) 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 (see below and sections 4.3 and 4.5).

Piperaquine is a mild inhibitor of CYP3A4. Caution is recommended when co-administering AGABA 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.

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 (see section 4.5).

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 AGABA 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 AGABA (see sections 4.5 and 5.2).

AGABA should not be used during pregnancy in situations where other suitable and effective antimalarials are available (see section 4.6).

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 AGABA should be given in a 12-month period (see sections 4.2 and 5.3).

Effects on cardiac repolarization

In clinical trials with AGABA limited ECGs were obtained during treatment. These showed that QTc prolongation occurred more frequently and to a larger extent in association with AGABA therapy than with the comparators (see section 5.1 for details of the comparators). Analysis of cardiac adverse events in clinical trials showed that these were reported more frequently in AGABA treated patients than in those treated with comparator antimalarial (see section 4.8). Before the third dose of AGABA, 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.

The potential for AGABA to prolong the QTc interval was investigated in parallel groups of healthy volunteers who took each dose with high (~1000 Kcal) or low (~400 Kcal) fat/calorie meals or in fasting conditions. Compared to placebo, the maximum mean increases in QTcF on Day 3 of dosing with AGABA were 45.2, 35.5 and 21.0 msec under respective dosing conditions. The QTcF prolongation observed under fasting conditions lasted between 4 and 11 hours after the last dose was administered on Day 3. The mean QTcF prolongation compared to placebo decreased

to 11.8 msec at 24 hours and to 7.5 msec at 48 hours. No healthy subject dosed in fasting conditions showed a QTcF greater than 480 msec or an increase over baseline greater than 60 msec. The number of subjects with QTcF greater than 480 msec after dosing with low fat meals was 3/64, while 10/64 had QTcF values over this threshold after dosing with high fat meals. No subject had a QTcF value greater than 500 msec in any of the dosing conditions.

An ECG should be obtained as early as possible during treatment with AGABA and ECG monitoring should be applied in patients who may have a higher risk of developing arrhythmia in association with QTc prolongation (see below).

When clinically appropriate, consideration should be given to obtaining an ECG from all patients before the last of the three daily doses is taken and approximately 4-6 hours after the last dose, since the risk of QTc interval prolongation may be greatest during this period (see section 5.2). QTc intervals of more than 500 ms are associated with a pronounced risk for potentially life-threatening ventricular tachyarrhythmias. Therefore, ECG monitoring during the following 24-48 hours should be applied for patients found to have a prolongation to this extent. These patients should not receive another dose of AGABA and alternative antimalarial therapy should be instituted.

Compared to adult males, female patients and elderly patients have longer QTc intervals. Therefore, they may be more sensitive to the effects of QTc-prolonging medications such as AGABA so that special caution is required.

Paediatric population

Special precaution is advised in young children when vomiting, as they are likely to develop electrolyte disturbances. These may increase the QTc-prolonging effect of AGABA (see section 4.3).

Hepatic and renal impairment

AGABA has not been evaluated in patients with moderate or severe renal or hepatic insufficiency (see section 4.2). Due to the potential for higher plasma concentrations of piperaquine to occur, caution is advised if AGABA is administered to patients with jaundice and/or with moderate or severe renal or hepatic insufficiency, and ECG and blood potassium monitoring are advised.

4.5 Pregnancy and Lactation

AGABA 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 (see sections 4.3 and 4.4).

A limited number of drug-drug pharmacokinetic interaction studies with AGABA 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 AGABA on co-administered medicinal products

Piperaquine is metabolised by, and is an inhibitor of CYP3A4. The concurrent administration of oral AGABA 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 AGABA. 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 AGABA.

From *in vitro* data, piperaquine undergoes a low level of metabolism by CYP2C19, and is also an inhibitor of this enzyme. There is the potential for reducing the rate of metabolism of other substrates of this enzyme, such as omeprazole, with consequent increase of their plasma concentration, and therefore, of their toxicity.

Piperaquine has the potential to increase the rate of metabolism for CYP2E1 substrates resulting in a decrease in the plasma concentrations of substrates such as paracetamol or theophylline, and the anaesthetic gases enflurane, halothane and isoflurane. The main consequence of this interaction could be a reduction of efficacy of the co-administered medicinal products.

AGABA administration may result in a slight decrease in CYP1A2 activity. Caution is therefore, advised when AGABA is administered concomitantly with medicinal products metabolised by this enzyme that have a narrow therapeutic index, such as theophylline. Any effects are unlikely to persist beyond 24 hours after the last intake of AGABA.

Effect of co-administered medicinal products on AGABA

Piperaquine is metabolised by CYP3A4 *in vitro.* The concurrent administration of a single dose of oral clarithromycin, (a strong CYP3A4 inhibitor probe) with a single dose of oral AGABA led to a modest increase (≤2-fold) in piperaquine exposure in healthy adult subjects. This increase in exposure to the antimalarial combination may result in an exacerbation of the effect on QTc (see section 4.4). Therefore, particular caution is required if AGABA is administered to patients taking potent CYP3A4 inhibitors (e.g. some protease inhibitors [amprenavir, atazanavir, indinavir, nelfinavir, ritonavir], nefazodone or verapamil), and ECG monitoring should be considered due to the risk of higher plasma concentrations of piperaquine (see section 4.4).

Enzyme inducing medicinal products such as rifampicin, carbamazepine, phenytoin, phenobarbital, St. John's wort (Hypericum perforatum) are likely to lead to reduced piperaquine plasma concentrations. The concentration of AGABA may also be reduced. Concomitant treatment with such medicinal products is not recommended.

Paediatric population

Drug-drug interaction studies have only been performed in adults. The extent of interactions in the paediatric population is not known. The above mentioned interactions for adults and the warnings in section 4.4 should be taken into account for the paediatric population.

Oral contraceptives

When co-administered to healthy women, AGABA exerted only a minimum effect on an estrogen/progestinic combination oral contraceptive treatment increasing the ethynilestradiol rate of absorption (expressed by geometric mean C_{max}) of about 28% but not significantly changing the exposure to ethynilestradiol and levonorgestrel and not influencing contraception activity as demonstrated by the similar plasma concentrations of follicle stimulating hormone (FSH), luteinizing hormone (LH) and progesterone observed after oral contraceptive treatment with or without concomitant AGABA administration.

Food interaction

Absorption of piperaquine is increased in the presence of fatty food (see sections 4.4 and 5.2) which may increase its effect on QTc interval. Therefore, AGABA should be taken with water only as described in section 4.2. AGABA should not be taken with grapefruit juice as it is likely to lead to increased piperaquine plasma concentrations.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are insufficient data on the use of AGABA and piperaquine in pregnant women. Based on animal data, AGABA is suspected to cause serious birth defects when administered during the first trimester of pregnancy (see sections 4.4 and 5.3). Reproductive studies with artemisinin derivatives have demonstrated teratogenic potential with an increased risk during early gestation (see section 5.3). 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.

AGABA should not be used during pregnancy in situations where other suitable and effective anti-malarials are available (see section 4.4).

Breast-feeding

Animal data suggest excretion of piperaquine into breast milk but no data are available in humans.

Women taking AGABA 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 AGABA in both females and males.

4.7 Effects on ability to drive and use machines

Adverse event data collected in clinical trials suggest that AGABA 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 AGABA 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 AGABA.
In a randomized trial in which 767 adults and children with uncomplicated *P*. *falciparum* malaria were exposed to AGABA, 25% of subjects were judged to have experienced an adverse drug reaction (ADR). No single type of ADR occurred at an incidence of ≥5%. The most frequent ADRs observed at an incidence ≥1.0% were: Headache (3.9%), Electrocardiogram QTc Prolonged (3.4%), *P*. *falciparum* infection (3.0%), Anaemia (2.8%), Eosinophilia (1.7%), Haemoglobin decreased (1.7%), Sinus tachycardia (1.7%), Asthenia (1.6%), Haematocrit [decreased] (1.6%), Pyrexia (1.5%), Red Blood Cell Count decreased (1.4%). A total of 6 (0.8%) subjects had serious ADRs in the study.
In a second randomized trial, 1,038 children, aged between 6 months and 5 years, were exposed to AGABA and 71% were judged to have experienced an ADR. The following ADRs were observed at an incidence of ≥5.0%: Cough (32%), Pyrexia (22.4%), Influenza (16.0%), *P. falciparum* infection (14.1%), Diarrhoea (9.4%), Vomiting (5.5%) and Anorexia (5.2%). A total of 15 (1.5%) subjects had serious ADRs in the study.
Tabulated list of adverse reactions
In the tables below, ADRs are listed under system organ class (SOC), and ranked by headings of frequency. Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness, using the following 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 the available data). The table in this section is for adult patients only. A corresponding table for paediatric patients is presented in the specific section below.
Frequency of ADRs in adult patients participating in clinical studies with AGABA:

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

SOC	Very Common	Common	Uncommon
Infections and infestations	Influenza P. falciparum infection	Respiratory tract infection Ear infection	
Blood and lymphatic system disorders		Thrombocytopenia Leukopenias/neutropenia Leuckocytoses NEC Anaemia	Thrombocythaemia Splenomegaly Lymphadenopathy Hypochromasia
Metabolism and nutrition disorders		Anorexia	
Nervous system disorders			Convulsion Headache
Eye disorders		Conjunctivitis	
Cardiac disorders		QT/QTc prolonged Heart rate irregular	Cardiac conduction disorders Cardiac murmur
Respiratory, thoracic and mediastinal disorders	Cough		Rhinorrhoea Epistaxis
Gastrointestinal disorders		Vomiting Diarrhoea Abdominal pain	Stomatitis Nausea
Hepatobiliary disorders			Hepatitis Hepatomegaly Abnormal liver function tests Jaundice
Skin and subcutaneous Tissue disorders		Dermatitis Rash	Acanthosis Pruritis
Musculoskeletal and connective tissue disorders			Arthralgia
General disorders and administration site conditions	Pyrexia	Asthenia	

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the the Yellow Card Scheme at the website: www.mhra.gov.uk/yellowcard.

4.9 Overdose

In clinical trials, nine patients received double the cumulative intended dose of AGABA. 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 (see section 4.4).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiprotozoals, antimalarials, artemisinin and derivatives, combinations, ATC code: P01BF05.

Pharmacodynamic effects

AGABA 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 piperaquine 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. Piperaquine 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.

Resistance to piperaquine (when used as monotherapy) has been reported.

The efficacy and safety of AGABA have been assessed in two large randomised, open-label clinical trials:

Study DM040010 was conducted in Asian adult and paediatric patients with uncomplicated *P. falciparum* malaria. AGABA treatment was compared with Artesunate + Mefloquine (AS + MQ). The primary end-point was the PCR-corrected cure rate at Day 63.

Study DM040011 was conducted in African paediatric patients with uncomplicated *P. falciparum* malaria. AGABA treatment was compared with Artemether + Lumefantrine (A + L). The primary end-point was PCR-corrected cure rate at Day 28.

The results for the primary endpoint in the modified intent to treat (m-ITT) populations (defined as all randomised patients who received at least one dose of the study treatment, with the exclusion of those patients lost to follow up for unknown reasons) were as follows:

Study	**PCR-corrected cure rate (m-ITT)**			
	AGABA	**AS + MQ**	**A + L**	**95 % two-sided CI on the treatment difference (AGABA - Comparator); p-value**
DM040010 (n=1087)	97.0%	95.3%	-	(-0.84, 4.19)%; p=0.161
DM040011 (n=1524)	92.7%	-	94.8%	(-4.59, 0.45)%; p=0.128

In each case the results confirmed that AGABA was not inferior to the comparator medicinal product. In both studies, the true treatment failure rate was below the 5% efficacy threshold set by WHO.

The age-specific PCR-corrected cure rates in the m-ITT populations are tabulated below for the Asian and African studies, respectively:

Study	PCR-corrected cure rate (m-ITT)			
	AGABA	**AS + MQ**	**A + L**	**95% two-sided CI on the treatment difference (AGABA - Comparator); p-value**
DM04010 (n=1087) ≤5years >5 to ≤12years >12 to ≤18 years >18 to ≤64 years	100.0% 98.2% 97.3% 96.6%	100.0% 96.5% 100.0% 94.4%	- - - -	- (-3.67, 7.09)%; 0.605 (-6.40, 0.99)%; 1.000 (-0.98, 5.30)%; 0.146
DM04011 (n=1524) ≤1 year >1 to ≤ 2 years >2 to ≤5 years	91.5% 92.6% 93.0%	- - -	98.5% 94.6% 94.0%	(-12.66, -1.32)%(1); 0.064 (-6.76, 2.63)%; 0.413 (-4.41, 2.47)%; 0.590

(1) This CI is asymptotic because the exact CI could not be computed

5.2 Pharmacokinetic properties

Pharmacokinetic profiles of AGABA and piperaquine have been investigated in animal models and in different human populations (healthy volunteers, adult patients and paediatric patients).

Absorption

AGABA 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 AGABA (observed after the first dose of AGABA) were 752 (47%) ng/ml and 2,002 (45 %) ng/ml*h, respectively.

AGABA bioavailability appears to be higher in malaria patients than in healthy volunteers, possibly because malaria *per se* has an effect on AGABA disposition. This may reflect malaria-associated impairment of hepatic function, causing an increase in AGABA 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 AGABA ranged between 180-252 ng/ml and 516-684 ng/ml*h, respectively.

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

In healthy volunteers, AGABA exposure was increased by 43% when administered with a high fat/high calorie meal.

Piperaquine, a highly lipophilic compound, is slowly absorbed. In humans, piperaquine has a T_{max} of approximately 5 hours following a single and repeated dose. In patients mean (CV%) C_{max} and AUC_{0-24} (observed after the first dose of AGABA) were 179 (62%) ng/ml and 1,679 (47%) ng/ml*h, respectively. Due to its slow elimination, piperaquine accumulates in plasma after multiple doses with an accumulation factor of approximately 3. Piperaquine pharmacokinetic parameters were found to be similar in healthy volunteers of Asian and Caucasian origin. On the other hand, on the last day of Eurtartesim treatment, the piperaquine maximum plasma concentration was higher in female than in male healthy volunteers, the difference being in the order of 30 to 50%.

In healthy volunteers, piperaquine 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, AGABA 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 (see section 4.2).

Distribution

Both piperaquine and AGABA are highly bound to human plasma proteins: the protein binding observed in *in vitro* studies was 44-93% for AGABA and >99% for piperaquine. Moreover, from *in vitro* and *in vivo* data in animals, piperaquine and AGABA tend to accumulate in RBC.

AGABA was observed to have a small volume of distribution in humans (0.8 l/kg; CV 35.5%). Pharmacokinetic parameters observed for piperaquine in humans indicate that this active substance has a large volume of distribution (730 l/kg; CV 37.5%).

Biotransformation

AGABA is principally converted to α- AGABA-β-glucuronide (α- AGABA-G). Studies in human liver microsomes showed that AGABA was metabolised by the UDP-glucuronosyltransferase (UGT1A9 and UGT2B7) to α- AGABA-G with no cytochrome P450-mediated metabolism.

In vitro drug-drug interaction studies revealed that AGABA is an inhibitor of CYP1A2; therefore, there is the potential for AGABA to increase plasma concentrations of CYP1A2 substrates (see section 4.5).

In vitro metabolism studies demonstrated that piperaquine is metabolised by human hepatocytes (approximately 85% of piperaquine remained after 2 hours incubation at 37°C). Piperaquine was mainly metabolised by CYP3A4 and to a lesser extent by CYP2C9 and CYP2C19. Piperaquine 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 piperaquine in human hepatocytes was observed when piperaquine was co-incubated withAGABA. The piperaquine major metabolites were a carboxyl acid cleavage product, and a mono-N-oxidated product.

In human studies, piperaquine was found to be a mild inhibitor of CYP3A4 enzyme while potent inhibitors of CYP3A4 activity caused mild inhibition of piperaquine metabolism (see section 4.5).

Elimination

The elimination half-life of AGABA 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%). AGABA is eliminated by metabolism (mainly glucuroconjugation). Its clearance was found to be slightly lower in female than in male healthy volunteers. Data regarding AGABA 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 piperaquine 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, piperaquine accumulates after multiple dosing.

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

Pharmacokinetics in special patient populations

No specific pharmacokinetic studies have been performed in patients with hepatic or renal insufficiency, or in elderly people.

In a paediatric pharmacokinetic study, and based on very limited sampling, minor differences were observed for AGABA pharmacokinetics between the paediatric and adult populations. The mean clearance (1.45 l/h/kg) was slightly faster in the paediatric patients than in the adult patients (1.34 l/h/kg), while the mean volume of distribution in the paediatric patients (0.705 l/kg) was lower than in the adults (0.801 l/kg).

The same comparison showed that piperaquine absorption rate constant and terminal half-life in children were predominantly similar to those seen in adults. However, the apparent clearance was faster (1.30 versus 1.14 l/h/kg) and the apparent total volume of distribution was lower in the paediatric population (623 versus 730 l/kg).

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.

AGABA and piperaquine were not genotoxic/clastogenic based on *in vitro* and *in vivo* testing.

No carcinogenicity studies have been performed.

AGABA causes embryolethality and teratogenicity in rats and rabbits.

Piperaquine did not induce malformation in rats and rabbits. In a perinatal and postnatal development study (segment III) in female rats treated with 80 mg/kg, some animals had a delay of delivery inducing mortality of the neonates. In females delivering normally the development, behaviour and growth of the surviving progeny was normal following exposure *in utero* or via milk. No reproduction toxicity studies have been performed with the combination of AGABA and piperaquine.

Central nervous system (CNS) toxicity

There is potential for neurotoxicity of artemisinin derivatives in man and animals, which is strongly related to the dose, route and formulations of the different AGABA pro-drugs. In humans, the potential neurotoxicity of orally administered AGABA can be considered highly unlikely, given the rapid clearance ofAGABA, and its short exposure (3 days of treatment for malaria patients). There was no evidence of AGABA-induced lesions in the specific nuclei in rats or dogs, even at lethal dose.

Cardiovascular toxicity

Effects on blood pressure and on PR and QRS duration were observed at high piperaquine doses. The most important potential cardiac effect was related to cardiac conduction.

In the hERG test, the IC_{50} was 0.15 µmol for piperaquine and 7.7 µmol forAGABA. The association of AGABA and piperaquine does not produce hERG inhibition greater than that of the single compounds.

Phototoxicity

There are no phototoxicity concerns withAGABA, as it does not absorb in the range of 290-700 nm.

Piperaquine has an absorption maximum at 352 nm. Since piperaquine is present in the skin (about 9% in the non-pigmented rat and only 3% in the pigmented rat), slight phototoxic reactions (swelling and erythema) were observed 24 hours after oral treatment in mice exposed to UV radiation.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Pre-gelatinised starch

Dextrin

Hypromellose

Croscarmellose sodium

Magnesium stearate

Film coating

Hypromellose

TCT GREEN

Titanium dioxide

Macrogol 400

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

36 months from the date of manufacturing

6.4 Special precautions for storage

Store below 30° C.
Store in the original package to protect from moisture.

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

AGABA tablets are packaged in PVC/PVDC/aluminum blisters containing 4 tablets

6.6 Special precautions for disposal <and other handling>

No special requirements.

7 <APPLICANT/MANUFACTURER>

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