SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) FOR DRUG PRODUCTS IN NIGERIA

AQUART

(Dihydroartemisinin and Piperaquine Tablets**)**

Summary of Product Characteristics (SPC)

1. Invented Name of the Medicinal Product

Brand Name: AQUART

Generic Name: Dihydroartemisinin and Piperaquine Tablets

Strength

Dihydroartemisinin 40 mg

Piperaquine Phosphate 320 mg

Dosage Form

Solid Oral Dosage Form

Rout of administration: Oral

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Film Coated Tablet Contains:

Dihydroartemisinin..... 40 mg

Piperaquine Phosphate ..... 320 mg

Excipients..... Q.S.

Colour: Permitted Colour

3. PHARMACEUTICAL FORM

Film Coated Tablet

4.1 CLINICAL PARTICULARS

Therapeutic indications

AQUART 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 OF ADMINISTRATION

Posology

AQUART 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.

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

If a patient vomits within 30 minutes of taking AQUART, 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 AQUART 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 Aquart may be given within a 12 month period. A second course of Aquart should not be given within 2 months after the first course due to the long elimination half-life of piperaquine.

Method of administration

AQUART 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, AQUART may be crushed and mixed with water. The mixture should be used immediately after preparation.

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 Ole inteival that may still be circulating at the time that Aquart is commenced (e.g. mefloquine, halofantrine, lumefantrine, chloroquine, quinine and other antimalarial medicinal products) tak ng into account their elimination half-life.

4.4 WARNING AND PRECAUTION

AQUART 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 AQUART 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.

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 AQUART 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 AQUART.

AQUART 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 AQUART should be given in a 12-month period.

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 AQUART.

Hepatic and renal impairment

AQUART has not been evaluated in patients with moderate or severe renal or hepatic insufficiency. Due to the potential for higher plasma concentrations of piperaquine to occur, caution is advised if AQUART 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 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

AQUART 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 AQUART 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 AQUART on co-administered medicinal products

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

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.
Artenimol administration may result in a slight decrease in CYP1A2 activity. Caution is therefore, advised when AQUART 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 artenimol.

Effect of co-administered medicinal products on AQUART
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 AQUART 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 AQUART 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 artenimol 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, AQUART 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 AQUART 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, AQUART should be taken with water only as described in section 4.2. AQUART should not be taken with grapefruit juice as it is likely to lead to increased piperaquine plasma concentrations.

4.6 PREGNANCY AND LACTATION

Pregnancy

There are insufficient data on the use of artenimol and piperaquine in pregnant women. Based on animal data, AQUART 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.

AQUART 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 AQUART 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 artenimol in both females and males.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 UNDESIRABLE EFFECTS

Nausea or vomiting may occur occasionally with incidence of less than 6% No noticeable side effect of Dihydroartemisinin is reported. The Dihydroartemisinin would for certain individuals, bring effects of greater or lesser severity for example reversible reduction in reticulocyte counts. Possible side effects of Piperaquine Phosphate includes mild dizziness, vertigo, headache, nausea, vomiting and abdominal discomfort. Reversible leucopenia was frequently reported. Dyspnea and palpitations were also reported but not further specified.

4.9 OVERDOSE

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties:

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

P01 05. BF Dihydroartemisinin mainly interferes with the membrane structures of trophozoites (erythrocytic asexual forms) i.e. whorled food vacuole membrane, distended mitochondria, swollen nuclear membranes, dissociation of ribosomes from endoplasmic reticulum leading to cytoplasmic vacuolization and autophagocytosis. In addition, biochemical depression of protein synthesis and nucleic acid synthesis are exhibited. Piperaquine Phosphate interferes with physiological function of the food vacuole membrane of the trophozoites leading to autophagocytosis of the parasites. It has no marked effect on the ring worms, immature or mature schizonts and the male or female gametocytes. The two active ingredients of Dihydroartemisinin+Piperaquine Phosphate have synergistic effect

5.2 Pharmacokinetic properties

Upon oral administration, Dihydroartemisinin is rapidly absorbed and maximum blood concentration is attained 1 hour afterwards, with a half life of about 4 hours. It is widely distributed in the body but with more concentration in liver, bile 3/767 patients (0.4%) were reported to have a QTcF value of >500 ms versus none in the comparator group.

The potential for Aquart to prolong the c interval was investigated in parallel groups of healthy volunteers who took QT 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 cF on Day 3 of dosing with Aquart were 45.2, 35.5 and 21.0 msec under respective QT dosing conditions. The cF prolongation observed under fasting conditions lasted between 4 and 11 hours after the QT

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

An should be obtained as early as possible during treatment with Aquart and monitoring should be applied in ECG ECG patients who may have a higher risk of developing arrhythmia in association with c prolongation.

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

Compared to adult males, female patients and elderly patients have longer c intervals. Therefore, they may be QT more sensitive to the effects of c-prolonging medications such as Aquart 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 c-prolonging effect of Aquart.

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

5.3 Preclinical safety data

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.

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 artenimol and piperaquine.

6. PHARMACEUTICAL PARTICULARS

List of Excipients

Excipient
Insta Coat Simply enteric IHS
Dichloromethane BP
Calcium Carbonate BP
Polyvinyl pyrrolidone BP
Purified Talc BP
Magnesium Stearate BP
Cross Povidone BP
Colloidal Anhydrous Silica BP
Colour Coat FC4W-H5180912 Blue IHS
Isopropyl Alcohol BP

6.1 Incompatibilities

Not applicable.

6.2 Shelf life

36 Months

6.3 Special precautions for storage

Store below 30°C. Protected from light.

6.4 Nature and contents of container

Available as blister of 9 Tablets in each inner carton and such 10 inner carton in one outer carton.

6.7 Special precautions for disposal and other Special handling

Not Applicable

7. **Manufacture by:**

   M/s. McW Healthcare Pvt. Ltd.

   286, 287-A, 287-B, Sector-E,

   Industrial Area, Sanwer Road,

   Indore (M.P.) India

8. **Marketed by:**

   AQUATIX PHARMACEUTICALS LIMITED

   No.7, Sapara Williams Street, Industrial

   Estate, lkeja, Lagos, Nigeria.

9. **NAFDAC REGISTRATION NUMBER(S):** C4-1135