1. NAME OF THE MEDICINAL PRODUCT:

1.1 Product Name: HCQS (Hydroxychloroquine Sulfate Tablets BP 200mg)

1.2 Strength: Each film coated tablet contains:
Hydroxychloroquine Sulfate BP ….200mg

1.3 Pharmaceutical dosage form: Film coated Tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

2.1 Qualitative Declaration:

Hydroxychloroquine is a 4-aminoquinoline derivative. Chemically it is 2-[[4-[(7-Chloro-4-quinolyl) amino] pentyl] ethylamino] ethanol sulphate.

2.2 Quantitative Declaration:

Each film coated tablet contains:
Hydroxychloroquine Sulfate BP ….200mg

3. Pharmaceutical Form:

HCQS (Hydroxychloroquine Tablets BP 200mg) are "White, circular, biconvex film coated Tablets"

4. CLINICAL PARTICULARS:

4.1 INDICATIONS

Hydroxychloroquine is indicated for:

Adults **-** Treatment of rheumatoid arthritis, discoid and systemic lupus erythematosus, and dermatological conditions caused or aggravated by sunlight.

It is also indicated as an adjunct to diet and exercise to improve glycemic control of patients on Metformin, sulfonylurea combination in Type II diabetes mellitus.

Paediatric population **-** Treatment of juvenile idiopathic arthritis (in combination with other therapies), discoid and systemic lupus erythematosus.

4.2 DOSAGE AND ADMINISTRATION:

The tablets are for oral administration. Each dose should be taken with a meal or glass of milk.

The minimum effective dose should be employed. This dose should not exceed 6.5mg/kg/day (calculated for oral administration from ideal body weight and not actual body weight).

Rheumatoid arthritis: The compound is cumulative in action and will require several weeks to exert its beneficial therapeutic effects, where as minor side effects may occur relatively early. Several months of therapy may be required before maximum effects can be obtained. If objective improvement (such as reduced joint swelling, increased mobility) does not occur within six months, the drug should be discontinued. Safe use of the drug in the treatment of juvenile rheumatoid arthritis has not been established.

Initial dosage – In adults, from 400 mg to 600 mg (=310mg to 465 mg base) daily in divided doses, each dose to be taken with a meal or a glass of milk. In a small percentage of patients, troublesome side effects may require temporary reduction of the initial dosage. Later (usually from five to ten days) the dose may gradually be increased to the optimal response level, often without return of side effects.

Maintenance dosage - When a good response is obtained (usually in 4 to 12 weeks), the dosage is reduced by 50% and continued at a usual maintenance level

of 200mg to 400mg (=155 mg to 310 mg base) daily, each dose to be taken with a meal or a glass of milk. The incidence of retinopathy has been reported to be higher when this maintenance dose is exceeded.

If relapse occur after medication is withdrawn, therapy may be resumed or continued on an intermittent schedule if there are no ocular contraindications.
Corticosteroids and salicylates may be used in conjunction with compound, and they can generally be decreased gradually in dosage or eliminated after the drug has been used for several weeks.

Lupus erythematosus: Initially the average adult dose is 400 mg (= 310mg base) once or twice daily. This may be continued for several weeks or months, depending upon the response of the patient. For prolonged maintenance therapy, a smaller dose, from 200mg to 400 mg (=155 to 310 mg base) daily will frequently suffice.

The incidence of retinopathy has been reported to be higher when this maintenance dose is exceeded.

Dermatological conditions caused and aggravated by sunlight: The minimum effective dose should be employed. This dose should not exceed 6.5mg/kg/day (calculated from ideal body weight and not actual body weight) and will be either 200mg or 400mg per day.
Treatment should only be given during periods of maximum exposure to light.

Type 2 diabetes mellitus: The usual recommended dose is 400mg (310mg base) once daily (not exceeding 6.5mg/kg/day of ideal body weight) as an adjunct to diet and exercise in Type 2 diabetes patients on Metformin and sulfonylurea combination.

Juvenile idiopathic arthritis: The minimum effective dose should be employed and should not exceed 6.5mg/kg/day based on ideal body weight. The 200mg tablet is therefore not suitable for use in children with an ideal body weight of less than 31kg.

4.3 CONTRAINDICATIONS:

Hydroxychloroquine is contraindicated:

i. In patients who are hypersensitive to 4-aminoquinoline compounds

ii. In patients with retinopathy and pre-existing maculopathy of the eye

iii. In patients with retinal or visual field changes attributable to any 4-aminoquinoline compound

iv. Pregnancy

4.4. WARNINGS:

Physicians should completely familiarize themselves with the complete contents of this leaflet before prescribing hydroxychloroquine sulfate tablets.

Retinal toxicity is largely dose-related. The risk of retinal damages is small with daily doses of up to 6.5 mg/kg body weight.

The occurrence of retinopathy is very uncommon if the recommended daily dose is not exceeded. The administration of doses in excess of the recommended maximum is likely to increase the risk of retinopathy, and accelerate its onset.

All patients should have an ophthalmological examination before initiating treatment with hydroxychloroquine. Thereafter, ophthalmological examinations must be repeated at least every 12 months.

The ophthalmology examination should include testing visual acuity, careful ophthalmoscopy, fundoscopy, central visual field testing with a red target, and colour vision.

This ophthalmology examination should be more frequent and adapted to the patient in the following situations:

- Daily dosage exceeds 6.5mg/kg ideal body weight. Absolute body weight used as a guide to dosage could result in an overdosage in the obese.
- Renal insufficiency or liver insufficiency
- Visual acuity below 6/8
- Age above 65 years
- Cumulative dose more than 200g.

Hydroxychloroquine should be discontinued immediately if there is any indication of abnormality in the visual acuity, visual field, color vision, or retinal macular areas (such as pigmentary changes, loss of foveal reflex), or any visual symptoms (such as light flashes and streaks) which are not fully explainable by difficulties of accommodation or corneal opacities. Patients should continue to be observed for possible progression of the changes.

Patients should be advised to stop taking the drug immediately and seek the advice of their prescribing doctor if any disturbances of vision are noted, including abnormal colour vision.

Hydroxychloroquine should be used with caution in patients taking medicines, which may cause adverse ocular or skin reactions. Caution is also advised in patients with a sensitivity to quinine.

Caution should also be applied when it is used in patients with hepatic or renal disease, in those taking drugs known to affect those organs, and in patients with severe gastrointestinal, neurological or blood disorders. Estimation of plasma hydroxychloroquine level should be under taken in patients with severely compromised renal or hepatic function and dosage adjusted accordingly.

Use of hydroxychloroquine in patients with psoriasis may precipitate a severe attack of psoriasis. When used in patients with porphyria, the condition may be exacerbated. Hydroxychloroquine should not be used in these conditions unless in the judgment of physician the benefit to the patient outweighs the possible hazard.

Although the risk of bone marrow depression is low, periodic blood counts are advisable as anaemia, aplastic anaemia, agranulocytosis, a decrease in white blood cells, and thrombocytopenia have been reported and hydroxychloroquine should be discontinued if abnormalities develop.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Patients receiving prolonged therapy with hydroxychloroquine should be questioned and examined periodically for the evidence of muscular weakness; knee and ankle reflexes should be tested. If muscular weakness occurs during therapy with hydroxychloroquine, the drug should be discontinued.

Hydroxychloroquine has been shown to cause severe hypoglycaemia including loss of consciousness that could be life threatening in patients treated with and without antidiabetic medications. Patients treated with hydroxychloroquine should be warned about the risk of hypoglycaemia and the associated clinical signs and symptoms. Patients presenting with clinical symptoms suggestive of hypoglycaemia during treatment with hydroxychloroquine should have their blood glucose level checked and treatment reviewed as necessary.

Life-threatening cutaneous reactions Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with the use of hydroxychloroquine. Patients should be advised of the signs and symptoms and monitored closely for skin reactions. The highest risk for occurrence of SJS or

TEN is within the first weeks of treatment. If symptoms or signs of SJS or TEN (e.g. progressive skin rash often with blisters or mucosal lesions) are present, hydroxychloroquine treatment should be discontinued. The best results in managing SJS and TEN come from early diagnosis and immediate discontinuation of any suspect drug. Early withdrawal is associated with a better prognosis. If the patient has developed SJS or TEN with the use of hydroxychloroquine, hydroxychloroquine must not be re-started in this patient at any time.

Cases of cardiomyopathy resulting in cardiac failure, in some cases with fatal outcome, have been reported in patients treated with hydroxychloroquine. Clinical monitoring for signs and symptoms of cardiomyopathy is advised and hydroxychloroquine should be discontinued if cardiomyopathy develops. Chronic toxicity should be considered when conduction disorders (bundle branch block / atrio-ventricular heart block) as well as biventricular hypertrophy are diagnosed.

PRECAUTIONS:

Because hydroxychloroquine may concentrate in liver, the drug should be used with caution in patients with hepatic disease or alcoholism or in conjunction with known hepatotoxic drugs.

Periodic blood cell counts should be made if patients are given prolonged therapy. Hydroxychloroquine should be discontinued if there is evidence of adverse hematologic effects that are severe and not attributable to the disease being treated. The drug should be administered with caution to patients having G-6-PD (glucose-6-phosphate dehydrogenase) deficiency.

Hydroxychloroquine has also shown to possess anti-platelet and anti-thrombotic activity. Hence, caution needs to be exercised in patients already receiving concomitant anti-platelet agents, anti-coagulants, or any other drugs affecting hemostasis.

Dermatologic reactions to hydroxychloroquine may occur and therefore, proper care should be exercised when it is administered to any patient receiving a drug with a significant tendency to produce dermatitis.

If serious toxic symptoms occur, administer ammonium chloride (8g daily in divided doses for adults) 3 or 4 days a week for several months after therapy has been stopped; acidification of the urine increases renal excretion by 20% to 90%. Exercise caution in patients with impaired renal function and/or metabolic acidosis.

Effects on ability to drive and use machines:
Impaired visual accommodation soon after the start of treatment has been reported and patients should be warned regarding driving or operating machinery. If the condition is not self-limiting, it will resolve on reducing the dose or stopping treatment.

Usage in pregnancy and lactation:
Hydroxychloroquine crosses the placenta. Data are limited regarding the use of hydroxychloroquine during pregnancy. It should be noted that 4-aminoquinolines in therapeutic doses have been associated with central nervous system damage, including ototoxicity (auditory and vestibular toxicity, congenital deafness), retinal hemorrhages and abnormal retinal pigmentation. Therefore hydroxychloroquine should not be used in pregnancy.

Careful consideration should be given to using hydroxychloroquine during lactation, since it has been shown to be excreted in small amounts in human breast milk, and it is known that infants are extremely sensitive to the toxic effects of 4-aminoquinolines.

Usage in paediatrics:

The minimum effective dose should be employed and should not exceed 6.5mg/kg/day based on ideal body weight.

Small children are particularly sensitive to the toxic effects of 4-aminoquinolines; therefore patients should be warned to keep the drug out of the reach of children.

Safety and effectiveness of hydroxychloroquine in pediatric patients with diabetes have not been established. Hydroxychloroquine is not recommended for use in pediatric patients with diabetes.

Usage in geriatrics:

No special precautions are necessary in elderly patients provided that renal function is normal.

4.5. DRUG INTERACTIONS:

Hydroxychloroquine sulphate has been reported to increase plasma digoxin levels. Serum digoxin levels should be closely monitored in-patients receiving combined therapy.

Hydroxychloroquine sulphate may also be subject to several of the known interactions of chloroquine even though specific reports have not appeared, which include: potentiation of its direct blocking action at the neuromuscular junction by aminoglycoside antibiotics; inhibition of its metabolism by cimetidine which may increase plasma concentration of hydroxychloroquine; antagonism effect of neostigmine and pyridostigmine; reduction of the antibody response to primary immunisation with intradermal human-diploid cell rabies vaccine.

Antacids may reduce absorption of hydroxychloroquine so it is advised that a 4 hour interval be observed between hydroxychloroquine and antacid dosing.

Concurrent use of penicillamine with hydroxychloroquine may increase penicillamine plasma concentrations, increasing the potential for serious hematologic and/or renal adverse reactions, as well as the possibility of severe skin reactions.

As hydroxychloroquine may enhance the effects of a hypoglycaemic treatment, a decrease in doses of insulin or antidiabetic drugs may be required.

Hydroxychloroquine has also shown to possess anti-platelet and anti-thrombotic activity. Inhibition of platelet aggregation was significantly increased when hydroxychloroquine was given concomitantly with aspirin. Hence, caution needs to be exercised in patients already receiving concomitant anti-platelet agents, anti-coagulants, or any other drugs affecting hemostasis.

Concomitant administration of hydroxychloroquine with halofantrine is not indicated due to increase in risk of QT prolongation and inducing potential cardiac arrhythmias. Also, there may be an increased risk of inducing ventricular arrhythmias if hydroxychloroquine is used concomitantly with other arrhythmogenic drugs, such as amiodarone and moxifloxacin.

An increased plasma ciclosporin level was reported when ciclosporin and hydroxychloroquine were co-administered.

Hydroxychloroquine can lower the convulsive threshold. Co-administration of hydroxychloroquine with other antimalarials known to lower the convulsion threshold (e.g. Mefloquine) may increase the risk of convulsions. Also, the

activity of antiepileptic drugs might be impaired if co-administered with hydroxychloroquine.

Chloroquine has been reported to reduce the bioavailability of praziquantel. It is not known if there is a similar effect when hydroxychloroquine and praziquantel are coadministered. Per extrapolation, due to the similarities in structure and pharmacokinetic parameters between hydroxychloroquine and chloroquine, a similar effect may be expected for hydroxychloroquine.

There is a theoretical risk of inhibition of intra-cellular α-galactosidase activity when hydroxychloroquine is co-administered with agalsidase.

4.6. PREGNANCY AND LACTATION:

Hydroxychloroquine crosses the placenta. Data are limited regarding the use of hydroxychloroquine during pregnancy. It should be noted that 4-aminoquinolines in therapeutic doses have been associated with central nervous system damage, including ototoxicity (auditory and vestibular toxicity, congenital deafness), retinal hemorrhages and abnormal retinal pigmentation. Therefore hydroxychloroquine should not be used in pregnancy.

Careful consideration should be given to using hydroxychloroquine during lactation, since it has been shown to be excreted in small amounts in human breast milk, and it is known that infants are extremely sensitive to the toxic effects of 4-aminoquinolines.

4.7 EFFECT ON ABILITY TO DRIVE AND USE MACHINE:

Impaired visual accommodation soon after the start of treatment has been reported and patients should be warned regarding driving or operating machinery. If the condition is not self-limiting, it will resolve on reducing the dose or stopping treatment.

4.8. ADVERSE DRUG REACTIONS:

The adverse events reported with hydroxychloroquine are as follows. The below frequency rating is used, when applicable:

Very common ≥ 10 %; Common ≥ 1 and <10 %; Uncommon ≥ 0.1 and < 1 %; Rare ≥ 0.01 and <0.1 %; Very rare < 0.01 %; Not known (frequency cannot be estimated from available data).

Blood and Lymphatic system disorders - *Not known:* Bone-marrow depression, anaemia, aplastic anaemia, agranulocytosis, anaemia, leucopenia and thrombocytopenia (hemolysis in individuals with glucose-6-phosphate dehydrogenase deficiency).

Cardiac disorders – *Uncommon:* Chest pain, acute pulmonary oedema; *Not known:* Cardiomyopathy which may result in cardiac failure and in some cases a fatal outcome. Chronic toxicity should be considered when conduction disorders (bundle branch block/atrioventricular heart block) as well as biventricular hypertrophy are found. Drug withdrawal may lead to recovery.

Eye disorders – *Common:* Blurring of vision due to a disturbance of accommodation which is dose dependent and reversible; *Uncommon*: Retinopathy with changes in pigmentation and visual field defects can occur, but appears to be uncommon if the recommended daily dose is not exceeded. In its early form it appears reversible on discontinuation of hydroxychloroquine. If allowed to develop, there may be a risk of progression even after treatment withdrawal. Patients with retinal changes may be asymptomatic initially, or may have scotomatous vision with paracentral, pericentral ring types, temporal scotomas and abnormal colour vision. Corneal changes including oedema and opacities have been reported. They are either symptomless or may cause disturbances such as haloes, blurring of vision or photophobia. They may be transient and are reversible on stopping treatment; Non-proliferative diabetic retinopathy has also been observed with hydroxychloroquine. *Not known:* Cases of maculopathies and

macular degeneration have been reported (the onset ranging from 3 months to several years of exposure to hydroxychloroquine) and may be irreversible.

Ear and labyrinth disorders - *Uncommon:* Vertigo, tinnitus; *Not known:* Hearing loss

Gastrointestinal disorders - *Very common:* Abdominal pain, nausea; *Common:* Diarrhoea, vomiting. These symptoms usually resolve immediately on reducing the dose or on stopping treatment; *Uncommon:* Dyspepsia

Hepatobiliary disorders - *Uncommon:* Abnormal liver function tests; *Not known:* Fulminant hepatic failure

Immune system disorders - *Not known:* Urticaria, angioedema, bronchospasm

Investigations – *Uncommon:* Rise in CPK level

Metabolism and nutrition disorders - *Common:* Anorexia; *Uncommon:* Dyslipidemia; *Not known:* Hypoglycemia. Hydroxychloroquine may precipitate or exacerbate porphyria, weight loss, lassitude.

Nervous system disorders - *Common*: Headache; *Uncommon*: Dizziness; *Not known*: Convulsions, ataxia, nystagmus

Musculoskeletal and connective tissue disorders - *Uncommon:* Sensory motor disorders; *Not known:* Skeletal muscle myopathy or neuromyopathy leading to progressive weakness and atrophy of proximal muscle groups. Myopathy may be reversible after drug discontinuation, but recovery may take many months. Depression of tendon reflexes and abnormal nerve conduction.

Psychiatric disorders - *Common:* Affect lability; *Uncommon:* Nervousness; *Not known:* Psychosis, irritability, emotional changes, nightmares, suicidal behaviour

Respiratory, thoracic and mediastinal disorders – *Uncommon:* Nasopharyngitis, cough

Renal and urinary disorders – *Uncommon:* Urinary tract infection

Reproductive system and breast disorders – *Uncommon:* Dysfunctional uterine bleeding

Skin and subcutaneous tissue disorders - *Common:* Skin rash, pruritus; *Uncommon:* Pigmentation disorders in skin and mucous membranes, bleaching of

hair, alopecia. These usually resolve readily on stopping treatment; *Not known:* Bullous eruptions including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS syndrome) photosensitivity, exfoliative dermatitis, acute generalised exanthematous pustulosis (AGEP). AGEP has to be distinguished from psoriasis, although hydroxychloroquine may precipitate attacks of psoriasis. It may be associated with fever and hyperleukocytosis. Outcome is usually favourable after drug withdrawal; Skin eruptions (urticarial, morbilliform, lichenoid, maculopapular, purpuric, erythema annulare centrifugum).

4.9 OVERDOSAGE:

Overdosage with the 4-aminoquinolines is dangerous particularly in infants, as little as 1-2g having proved fatal. Death can occur within 2h of overdosage. An adult male is reported to have survived an overdose of 36 tablets (200mg per tablet) and a plasma level of 6.1mg/L.

The 4-aminoquinoline compounds are very rapidly and completely absorbed after ingestion, and in accidental overdosage, or rarely with lower doses in hypersensitive patients, toxic symptoms may occur within 30 minutes.

The symptoms of massive overdose may include headache, drowsiness, visual , cardiovascular collapse and convulsions, hypokalaemia and rhythm and conduction disorders including QT prolongation, Torsade de Pointes, ventricular tachycardia and ventricular fibrillation, followed by sudden potentially fatal respiratory and cardiac arrest. The electrocardiogram may reveal atrial standstill, nodal rhythm, prolonged intraventricular conduction time, and progressive bradycardia leading to ventricular fibrillation and/or arrest.

Since these effects may appear soon after taking a massive dose, treatment should be prompt and symptomatic. The stomach should be immediately evacuated either

by emesis or by gastric lavage. Finely powdered charcoal in a dose at least five times of the overdose may inhibit further absorption if introduced into the stomach by tube following lavage and within 30 minutes of ingestion of the overdose.

Convulsions, if present, should be controlled before attempting gastric lavage. If due to cerebral stimulation, cautious administration of an ultrashort-acting barbiturate may be tried but, if due to anoxia, it should be corrected by oxygen administration, artificial respiration or, in shock with hypotension, by vasopressor therapy. Because of the importance of supporting respiration, tracheal intubation or tracheostomy, followed by gastric lavage, may also be necessary. Exchange transfusions have been used to reduce the level of 4-aminoquinoline drug in the blood.

Consideration should be given to administration of parenteral diazepam in cases of overdosage. It has been shown to be beneficial in reversing chloroquine cardiotoxicity.

Respiratory support may be needed and the need for intubation or tracheostomy considered. Shock should be treated by the administration of fluid (with plasma expanders if necessary) with central venous pressure monitoring. In severe cases, the administration of dopamine should be considered.

A patient who survives the acute phase and is asymptomatic should be closely observed for at least 6 hours. If serious toxic symptoms occur from overdosage or sensitivity, it has been suggested that ammonium chloride (8 g daily in divided doses for adults) be administered orally three or four days a week for several months after therapy has been stopped, as acidification of the urine increases renal excretion of the 4-aminoquinoline compounds by 20 to 90 percent. However,

caution must be exercised in patients with impaired renal function and/or metabolic acidosis.

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties:

Hydroxychloroquine has been found to be useful as an anti-inflammatory, antiplatelet and anti-thrombotic agent. It also produces beneficial effects in conditions associated with light sensitivity. It has also been shown to have favourable effect on glycemic control.

The cellular and molecular mechanisms involved in all these recognised pharmacological actions of hydroxychloroquine are largely unknown.

In rheumatoid arthritis, hydroxychloroquine acts as a DMARD (disease modifying antirheumatic agent). Hydroxychloroquine is thought to act as a mild immunosupressant, inhibiting the production of rheumatoid factor and acute phase reactants. It has several pharmacological actions, which may be involved in their therapeutic effect in the treatment of rheumatoid disease, but the role of each is not known. These include interaction with sulphydryl groups, interference with enzyme activity (including phospholipase, NADH-cytochrome C reductase, cholinesterase, collagenase, proteases and hydrolases), DNA binding, stabilisation of lysosomal membranes, inhibition of prostaglandin formation, inhibition of polymorphonuclear cell chemotaxis and phagocytosis, possible interference with interleukin 1 production from monocytes and inhibition of neutrophil superoxide release.

Hydroxychloroquine therapy may lead to the regression of the skin lesions of discoid or systemic lupus erythematosus.

Hydroxychloroquine is thought to have useful photoprotective properties by suppressing abnormal responses to ultraviolet light in sunlight.

Although the mechanism by which hydroxychloroquine improves glucose control remains unclear, experimental studies have shown that hydroxychloroquine, being an acidotropic agent concentrates intracellularly in very high concentration. This high intracellular concentration may inhibit endosomal degradation of the insulin internalized with its receptor. A preclinical study in diabetic rats has demonstrated beneficial effects of hydroxychloroquine on glucose homeostasis due to reduction in insulin degradation at post-receptor level.

The mechanisms of hypoglycemia with hydroxychloroquine can be inferred from studies of chloroquine, a structurally similar compound. Chloroquine concentrates in endosomes, which may result in inhibition of endosomal degradation of insulin internalized with its receptor. Accumulation of chloroquine in endosomes causes an increase in pH, which may then lead to inhibition of proteolytic enzymes responsible for degradation of insulin. *In vitro* studies on chloroquine suggest that chloroquine may reduce intracellular insulin degradation at the post-receptor level and slow receptor recycling, resulting in intracellular insulin accumulation. The drug also appears to enhance binding of insulin to its membrane receptor in lymphocytes.

It has been proposed that the dissociation of insulin from its receptor appears to be the rate limiting step in the degradation process of insulin. Thus, a direct interaction of chloroquine or hydroxychloroquine with the insulin receptor reduces the rate of dissociation of insulin from its receptor. This condition might increase the biological half-life of the receptor-insulin complex and consequently prolong the action of insulin. A pharmacodynamic study conducted in obese, non-diabetic subjects demonstrated that use of hydroxychloroquine for 6 weeks is associated with significant increase in insulin sensitivity index and a trend towards reduced insulin resistance and insulin secretion.

Type 2 diabetes mellitus is characterized by several degrees of insulin resistance and relative deficiency in its secretion. Insulin resistance has been attributed to adipose tissue activation associated with an increased release of various inflammatory cytokines. IL-6 and C-reactive protein are 2 sensitive physiological markers of sub-clinical inflammation, and their elevated levels are associated with hyperglycemia, insulin resistance, and overt T2DM. In *in vitro* studies on stimulated peripheral blood mononuclear cells, hydroxychloroquine has been shown to inhibit production of various inflammatory markers such as tumor necrosis factor-alpha (TNF-alpha), interleukin 6 (IL-6), and interferon-gamma (IFN-gamma).

Studies also suggest that the parent drug chloroquine may increase LDL receptor levels, possibly by its effect on intracellular lysosomes. Such a mechanism may explain the consistent reduction in LDL and/or total cholesterol levels seen with hydroxychloroquine.

Hydroxychloroquine has been found to be useful as an anti-inflammatory, antiplatelet and anti-thrombotic agent.

5.2 Pharmacokinetics Properties:

Hydroxychloroquine is rapidly and almost completely absorbed orally. Bioavailability is approximately 74%. It is widely distributed in body tissues and concentrates in the spleen, kidneys, liver, melanin containing tissues, lungs to a lesser extent, the spinal cord and brain. Concentrations are 2-5 times higher in erythrocytes than in plasma. Very low concentration is seen in intestinal wall. The drug crosses placenta also. It has moderate protein binding (approximately 45%). It is metabolized in liver, to active de-ethylated metabolites. Hydroxychloroquine has a terminal elimination half-life of approximately 50 days in blood and approximately 32 days in plasma. 23-25% of hydroxychloroquine excreted in urine in unchanged form. Hydroxychloroquine is excreted very slowly; may persist in urine for months or years after medication is discontinued. It is also

excreted in bile. Hemodialysis does not remove appreciable amount of hydroxychloroquine from blood.

5.3 CLINICAL EXPERIENCE:

A study was conducted to compare efficacy and safety of hydroxychloroquine with pioglitazone in type 2 diabetes mellitus (T2DM). This double-blind study randomized 267 uncontrolled type 2 diabetes patients (HbA1c ≥7.5% and ≤11.5%), post 3 months treatment with glimepiride/gliclazide and Metformin, to additionally receive hydroxychloroquine 400 mg/day (n = 135) or pioglitazone 15 mg/day (n=132) for 24 weeks. Efficacy was assessed by changes in HbA1c, fasting (FBG) and post-prandial (PPG) blood glucose at Week 12 and Week 24. At Week 12 and Week 24, HbA1c, FBG and PPG significantly reduced from baseline in both groups. Mean reduction in glycemic parameters at Week 12 (HbA1c: -0.56% vs -0.72%, p = 0.394; FBG: -0.99 mmol/L vs -1.05 mmol/L, p = 0.878; PPG: -1.93 mmol/L vs -1.52 mmol/L, p = 0.423) and Week 24 (HbA1c: -0.87% vs -0.90%, p = 0.909; FBG: -0.79 mmol/L vs -1.02 mmol/L, p = 0.648; PPG: -1.77 mmol/L vs -1.36 mmol/L, p = 0.415) was not significantly different between the hydroxychloroquine and pioglitazone groups. Change in total cholesterol (TC) and LDL-C was significant in favor of hydroxychloroquine (TC: -0.37 mmol/L vs 0.03 mmol/L, p = 0.002; LDL-C: -0.23 mmol/L vs 0.09 mmol/L, p=0.003). Triglycerides significantly reduced in both groups at Week 24. Mean HDL-C remained unchanged. Study treatments were well tolerated. Hydroxychloroquine had favourable effects on glycemic parameters and lipids.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

Polysorbate 80, Dibasic Calcium Hydrogen Phosphate Dihydrate, Colloidal Silicon dioxide, Maize starch, Purified Water, Purified Talc, Magnesium Stearate, Hydroxy Propyl Methyl Cellulose, Titanium Dioxide and Polyethylene Glycol – 6000.

6.2 Incompatibilities:

None

6.3 Shelf – life:

48 months

6.4 Special precautions for storage:

"Store below 30°C in a dry place, away from light".

Keep out of reach of children

6.5 Nature and contents of container:

Blisters of 10 tablets. 3 such blisters are packed in a printed showbox alongwith the leaflet. The blisters are constructed of PVC (192 mm thickness) and Aluminium Foil (188 mm thickness).

6.6 Special precautions for disposal:

None

7.0 Applicant/Holder of Certificate of Product Registration

Name of the Applicant:

Ipca Pharma Nigeria Limited.

2nd Floor (Left Wing, Front 0 ice)

Olajire

House - 3, tlupeju

Bye Pass, llupeju Lagos, Nigeria

8. Drug Product Manufacture

Ipca Laboratories Ltd
P .O. Sejavta, District : Ratlam
Madhya Pradesh
Pin – 457001, India
Phone No.: 91-7412-278000/8099
Unit/Block – Pharma-III Block

9. NAFDAC Registration No:

04-7590