1.3.1.1.1 Professional Information for medicines for human use

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

PLASMOQUINE (200 mg, capsules)

2 QUALITIVE AND QUANTITIVE COMPOSITION

Each capsule contains 200 mg chloroquine sulphate monohydrate equivalent to 146,7 mg chloroquine base.

Sugar free

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

A hard gelatine capsule with a white body and a light blue cap.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Malaria prophylaxis in areas where chloroquine resistance is not encountered.

Treatment of malaria where clinical symptoms and parasitaemia are rapidly controlled, provided that the patient did not contract malaria in a chloroquine-resistant area and was not using chloroquine as prophylaxis for malaria.

4.2 Posology and method of administration

Posology

The dosages for children 6 - 12 years, for malaria prevention and treatment, must be carefully

calculated according to body mass as indicated.

Malaria prevention:

Adults and children over 12 years:

2 capsules per week.

It is advisable to start taking PLASMOQUINE one or two weeks before entering a malaria area. Thereafter repeat dosage at strictly adhered to weekly intervals during exposure to risk and for four to six weeks after exposure. The medicine should be taken on the same day of each week.

Malaria treatment:

Adults and children over 12 years:

4 capsules taken as a single dose followed by 2 capsules six hours later and then 2 capsules daily for the following two days.

Paediatric population

Malaria prevention:

5 mg base per kg body-mass per week.

General guideline for children 6 - 12 years:

1 capsule per week (147 mg base).

Malaria treatment:

10 mg base per kg body-mass, followed by 5 mg per kg after 6 hours, then 5 mg per kg daily for 2 days.

General guideline for children 6 - 12 years:

2 capsules (294 mg base) taken as a single dose followed by 1 capsule (147 mg base) six

hours later and then 1 capsule (147 mg base) daily for the following two days.

Method of administration

For oral use.

4.3 Contraindications

- Hypersensitivity to the active substance, chloroquine or to any of the excipients.
- Patients with pre-existing maculopathy of the eye.
- Patients with known hypersensitivity to 4-aminoquinoline compounds.
- Long-term therapy in children.
- Children under 6 years of age.

4.4 Special warnings and precautions for use

No malaria prophylaxis is fully effective and therefore the prevention of mosquito bites remains the most important malaria preventative measure.

Preventative measures which should be taken are:

- Visit areas, where malaria is prevalent, during the dry season or when rainfall is low.
- Sleep under a mosquito net which is tucked in under the mattress.
- Install screening in doors and windows.
- Regularly apply mosquito repellent to exposed skin.
- Spray living quarters with insecticide in the late afternoon.
- Use mosquito coils or pads.
- Limit outdoor activities after sunset when mosquitoes are more active.
- Wear long-sleeved shirt and trousers when outdoors between dusk and dawn.

High risk persons should avoid malaria areas altogether.

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High risk persons include:

- Babies and children under the age of ~~5~~ 6 years.
- Pregnant women.
- The elderly (older than 65 years).
- Immunocompromised individuals such as cancer patients on chemotherapy, individuals on long term steroid therapy, AIDS patients and persons who have had spleens removed.

Upon returning from a malaria area, be particularly aware of symptoms such as fever, which may alternate with chills and shivers, joint and muscular pains, severe headache, nausea, diarrhoea and fatigue (flu-like symptoms). If these symptoms are experienced, inform your doctor that you have been to a malaria area.

PLASMOQUINE should be used with extreme caution in epileptic patients as chloroquine may interfere with seizure control.

Patients with glucose-6-phosphate dehydrogenase deficiency should be observed for haemolytic anaemia during chloroquine treatment.

PLASMOQUINE is not effective against chloroquine-resistant strains of *Plasmodium falciparum*.

Patients should be warned to keep PLASMOQUINE out of the reach of children, as small children are particularly sensitive to the 4-aminoquinolines.

PLASMOQUINE should be used with caution or not at all in patients with severe gastrointestinal, neurological or blood disorders. Gastrointestinal disturbances such as nausea, anorexia, abdominal cramps or rarely vomiting, occur in some patients. If such severe disorders occur during therapy, the medicine should be stopped. Periodic blood counts are advised.

When used in patients with porphyria or psoriasis, these conditions may be exacerbated. PLASMOQUINE should not be used in these conditions.

Chronic cardiac toxicity

Cases of cardiomyopathy resulting in cardiac failure, in some cases with fatal outcome, have been reported in patients treated with PLASMOQUINE. Clinical monitoring for signs and symptoms of cardiomyopathy is advised and PLASMOQUINE 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.

Hypoglycaemia

PLASMOQUINE has been shown to cause severe hypoglycaemia including loss of consciousness that could be life threatening in patients treated with and without anti-diabetic medications. Patients treated with PLASMOQUINE 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 PLASMOQUINE should have their blood glucose level checked and treatment reviewed as necessary.

QT interval prolongation

PLASMOQUINE prolongs the QTc interval and should not be used in patients receiving medicines known to prolong the QT interval, e.g. class IA and III antidysrhythmics, tricyclic antidepressants, antipsychotics, some anti-infectives due to increased risk of ventricular arrhythmia (see section 4.5 and section 4.9).

PLASMOQUINE should be used with caution in patients with congenital or documented acquired QT prolongation and/or known risk factors for prolongation of the QT interval such as:

- cardiac disease, e.g., heart failure, myocardial infarction;
- prodysrhythmic conditions, e.g., bradycardia (< 50 bpm);
- a history of ventricular dysrhythmias;
- uncorrected hypokalaemia and/or hypomagnesaemia.

The magnitude of QT prolongation may increase with increasing concentrations of the medicine. Therefore, the recommended dose should not be exceeded (see section 4.5 and section 4.8).

Carefully consider before prescribing azithromycin or other macrolide antibiotics for any patients taking PLASMOQUINE, because of the potential for an increased risk of cardiovascular events and cardiovascular mortality (see section 4.5).

Ophthalmological

Irreversible retinal damage has been observed in some patients who had received long-term or high-dosage 4-aminoquinolone therapy for discoid and systemic lupus erythematosus, or rheumatoid arthritis. Retinopathy has been reported to be dose related. Exceeding the recommended daily dose sharply increases the risk of retinal toxicity.

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If there is any indication of abnormality in the visual field, 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, the medicine should be discontinued immediately and the patient closely observed for possible progression. Retinal changes (and visual disturbances) may progress after cessation of therapy (see section 4.8).

Concomitant use of PLASMOQUINE with medicines known to induce retinal toxicity, such as tamoxifen, is not recommended.

Before starting treatment with PLASMOQUINE, all patients should have a careful complete examination of both eyes, which includes slit lamp microscopy for corneal changes, fundoscopy, visual acuity, central visual field and colour vision. A complete eye examination before treatment will determine the presence of any visual abnormalities, either coincidental or due to the disease and establish a baseline for further assessment of the patient's vision.

Ophthalmological testing should be conducted at 6-monthly intervals in patients receiving PLASMOQUINE at a dose of not more than 6 mg per kg body weight per day.
Ophthalmological testing should be conducted at 3-4 monthly intervals in the following circumstances:

- Dose exceeds 6 mg per kg ideal (lean) body weight per day. Absolute body weight used as a guide to dosage, could result in an overdosage in the obese.
- Significant renal impairment.
- Significant hepatic impairment.
- Elderly.

- Complaints of visual disturbances
- Duration of treatment exceeds 8 years.

Corneal changes often subside on reducing the dose or on interrupting therapy for a short period of time, but any suggestion of retinal change or restriction in the visual field is an indication for complete withdrawal of the medicine.

The use of sunglasses in patients exposed to strong sunlight is recommended, as this may be an amplifying factor in retinopathy.

Skin reactions

Pleomorphic skin eruptions (morbilliform, lichenoid or purpuric), itching, dryness and increased pigmentation sometimes appear after a few months of therapy. The rash is usually mild and transient. If a rash appears, PLASMOQUINE should be withdrawn and only started again at a lower dose.

Patients with psoriasis appear to be more susceptible to severe skin reactions than other patients.

Severe cutaneous adverse reactions (SCARs)

Cases of severe cutaneous adverse drug reactions (SCARs), including drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported during treatment with PLASMOQUINE. Patients with serious dermatological reactions may require hospitalisation, as these conditions may be life-threatening and may

be fatal. Patients should be informed about the signs and symptoms of serious skin manifestations and monitored closely. If signs and symptoms suggestive of severe skin reactions appear, PLASMOQUINE should be withdrawn at once and alternative therapy should be considered.

Other monitoring on long-term treatments

Patients on long-term therapy should have periodic full blood counts. If evidence of abnormalities such as agranulocytosis, aplastic anaemia, thrombocytopenia or leukopenia becomes apparent, and cannot be attributed to the disease being treated, PLASMOQUINE should be discontinued.

All patients on long-term therapy with PLASMOQUINE should be questioned and examined periodically, including the testing of knee and ankle reflexes, to detect any evidence of muscular weakness. If weakness occurs, discontinue the medicine.

Miscellaneous

Muscle weakness, vertigo, tinnitus, nerve deafness, headache and nervousness have been reported less frequently.

Suicidal behaviour and psychiatric disorders have been reported in some patients treated with PLASMOQUINE.

Psychiatric side effects typically occur within the first month after the start of treatment with PLASMOQUINE and have been reported also in patients with no prior history of psychiatric

disorders. Patients should be advised to seek medical advice promptly if they experience psychiatric symptoms during treatment.

Extrapyramidal disorders may occur with PLASMOQUINE.

Patients with porphyria cutanea tarda (PCT) are more susceptible to hepatotoxicity (see section 4.8).

Use in hepatic impairment

Use caution in patients with hepatic disease, as well as in those taking medicines known to affect the organ. A reduction in dosage may be necessary.

Use in renal impairment

Use caution in patients with renal disease, as well as in those taking medicines known to affect the organ. A reduction in dosage may be necessary.

4.5 Interaction with other medicines and other forms of Interaction

Pharmacodynamic Interactions

Medicine known to prolong QT interval/with potential to induce cardiac arrhythmia

PLASMOQUINE should not be used in patients receiving medicine known to prolong the QT interval, e.g. Class IA and III antidysrhythmics, tricyclic antidepressants, antipsychotics or some anti-infectives due to increased risk of ventricular arrhythmia (see section 4.4 and section 4.9).

Halofantrine should not be administered with PLASMOQUINE.

Macrolide antibiotics

Observational data have shown that co-administration of PLASMOQUINE with azithromycin in patients with rheumatoid arthritis is associated with an increased risk of cardiovascular events and cardiovascular mortality (see section 4.4). Carefully consider before prescribing azithromycin for any patients taking PLASMOQUINE. Similar careful consideration should also be undertaken before prescribing other macrolide antibiotics for any patients taking PLASMOQUINE because of the potential for a similar risk when PLASMOQUINE is co-administered with these medicines (see section 4.4).

Antidiabetic medicine

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

Antimalarials

PLASMOQUINE can lower the convulsive threshold. Co-administration of PLASMOQUINE with other antimalarials known to lower the convulsion threshold (e.g. mefloquine) may increase the risk of convulsions.

Antiepileptic medicine

The activity of antiepileptic medicines might be impaired if co-administered with PLASMOQUINE.

Others

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

Concurrent use with medicines with oculotoxic or haemotoxic potential should be avoided.

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It has been suggested that 4-aminoquinolines are pharmacologically incompatible with monoamine oxidase inhibitors.

PLASMOQUINE may also be subject to several of the known interactions of chloroquine. These 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 the antimalarial.
- Antagonism of effect of neostigmine and pyridostigmine.
- Reduction of the antibody response to primary immunisation with intradermal human diploid-cell rabies vaccine.

Pharmacokinetic Interactions

Effects of other medicines on PLASMOQUINE:

Antacids and kaolin

Concomitant administration with magnesium-containing antacids or kaolin may result in reduced absorption of chloroquine. Per extrapolation, PLASMOQUINE should therefore be administered at least two hours apart from antacids or kaolin.

CYP inhibitors or inducers

Concomitant use of cimetidine, a moderate CYP2C8 and CYP3A4 inhibitor, resulted in a 2-fold increase of chloroquine exposure. Caution is advised (e.g. monitoring for adverse reactions) when CYP2C8 and CYP3A4 strong or moderate inhibitors (such as gemfibrozil,

clopidogrel, ritonavir, itraconazole, clarithromycin, grapefruit juice) are concomitantly administered.

Caution is advised (e.g. monitoring for efficacy) when CYP2C8 and CYP3A4 strong inducers (such as rifampicin, St John's Wort, carbamazepine, phenobarbital) are concomitantly administered.

Effects of hydroxychloroquine on other medicines:

CYP3A4 substrates

Caution is advised (e.g. monitoring for adverse reactions) when CYP3A4 substrates (such as ciclosporin and statins) are concomitantly administered.

CYP2D6 substrates

Caution is advised (e.g. monitoring of adverse reactions or for plasma concentrations as appropriate) when CYP2D6 substrates with narrow therapeutic index (such as flecainide and propafenone) are concomitantly administered.

P-glycoprotein substrates

Caution is advised (e.g. monitoring for adverse reactions or for plasma concentrations as appropriate) when P-gp substrates with narrow therapeutic index (such as digoxin, ciclosporin and dabigatran) are concomitantly administered.

Praziquantel

In a single-dose interaction study, chloroquine has been reported to reduce the bioavailability of praziquantel.

4.6 Fertility, pregnancy and lactation

Pregnancy

Chloroquine as contained in PLASMOQUINE crosses the placenta. It should be noted 4-aminoquinolines in therapeutic doses have been associated with central nervous system damage, including ototoxicity (auditory and vestibular toxicity and congenital deafness), retinal haemorrhages and abnormal retinal pigmentation.

PLASMOQUINE should be avoided in pregnancy.

Breastfeeding

Chloroquine as contained in PLASMOQUINE is excreted in breast milk and it is known that infants are extremely sensitive to the toxic effects of 4-amonioquinones.
Although chloroquine is excreted in breast milk, the amount is insufficient to confer any protection against malaria to the infant. Separate chemoprophylaxis for the infant is required.

Fertility

A study in male rats showed a decrease in testosterone levels, weight of testes, epididymis, seminal vesicles and prostate after 30 days of oral treatment with chloroquine at 5 mg/day.
In another rat study with chloroquine the male fertility rate was decreased after 14 days of intraperitoneal treatment at 10 mg/kg/day.

There are no data in humans.

4.7 Effects on ability to drive and use machines

Patients should be warned about driving and operating machinery since PLASMOQUINE can impair visual accommodation and cause blurring of vision. If the condition is not self-limiting, the dosage may need to be temporarily reduced.

4.8 Undesirable effects

a) Summary of the safety profile

PLASMOQUINE may exacerbate porphyria.

Blood disorders have been reported, including aplastic anaemia, reversible agranulocytosis, thrombocytopenia and neutropenia.

Prolonged treatment with high doses may lead to visual disturbances such as blurred vision and difficulty in focusing caused by corneal and retinal changes. Corneal opacities are normally reversible upon withdrawal of treatment whereas retinal changes, resulting in severe visual impairment, may progress after discontinuation of treatment and are generally irreversible. The risk of retinal changes occurs when the total cumulative dose ingested exceeds 100 g and especially when high daily dosages are used. Hypotension and ECG changes may occur at higher doses.

Side effects occurring with antimalarial doses are usually reversible upon withdrawal of the medicine and include headache, gastro-intestinal disturbances such as nausea, vomiting and diarrhoea, pruritus and skin eruptions.

Less frequently, a range of mental changes have been reported, including psychotic episodes, anxiety and personality changes.

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Other side effects that may occur after prolonged use: loss of hair, bleaching of hair pigment, blue-black pigmentation of mucous membranes and skin, photosensitivity, neuritis, reduced hearing, nerve deafness, neuromyopathy and myopathy.

b) Tabulated list of adverse reactions

Body System	**Undesirable effect**		
	Frequent	**Less frequent**	**Unknown**
Blood and the lymphatic system disorders		bone marrow depression, anaemia, aplastic anaemia, leukopenia, thrombocytopenia agranulocytosis	
Immune system disorders			urticaria, angioedema, bronchospasm
Metabolism and nutrition disorders	anorexia		hypoglycaemia
Psychiatric disorders	affect lability	psychosis, suicidal behaviour, nightmares, depression, hallucinations, anxiety, agitation, confusion, delusions, mania and sleep disorders	

Nervous system disorders	headache	dizziness, nerve deafness, nervousness, convulsions, neuromyopathy, nystagmus, ataxia	extrapyramidal disorders such as dystonia, dyskinesia, tremor
Eye disorders	blurring of vision	corneal changes, retinal changes, retinopathy with changes in pigmentation and visual field defects	maculopathies and macular degeneration
Ear and labyrinth disorders		vertigo, tinnitus	hearing loss
Cardiac disorders		cardiomyopathy	bundle branch block/atrioventricular heart block, biventricular hypertrophy, QT interval prolongation
Gastrointestinal disorders	abdominal pain, nausea, diarrhoea, vomiting		
Hepato-biliary disorders		abnormal liver function tests Drug-induced liver injury (DILI), hepatocellular	

		injury, acute hepatitis, fulminant hepatic failure	
Skin and subcutaneous tissue disorders	skin rashes, alopecia, pruritus	pigmentary changes, bleaching of hair, erythema multiforme, photosensitivity, exfoliative dermatitis, Sweet's syndrome and severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), toxic epidermal necrolysis (TEN), acute generalised exanthematous pustolosis (AGEP)	
Musculoskeletal, connective tissue and bone disorders		sensorimotor disorders	absent or hypoactive deep tendon reflexes, muscle weakness or neuromyopathy depression of tendon reflexes, abnormal

			nerve conduction studies.
General disorders		exacerbation or precipitation of porphyria and attacks of psoriasis, weight loss, lassitude	

c) Description of selected adverse reactions

Eye Disorders

Before starting treatment with PLASMOQUINE, all patients should have a careful complete examination of both eyes, which includes slit lamp microscopy for corneal changes, fundoscopy, visual acuity, central visual field and colour vision, repeated at six-month intervals during therapy (see section 4.4 – Opthalmological).

Any adverse changes in the ocular findings or the appearance of scotoma, night blindness or other retinal changes require immediate discontinuation of PLASMOQUINE; these patients should not subsequently receive any pharmacologically similar medicines.

Patients with retinal changes may be asymptomatic initially, or may even have scotomatous vision with paracentral, pericentral ring types, temporal scotomas and abnormal colour visions.

Corneal changes including oedema and opacities have occurred from three weeks (infrequently) to some years after the beginning of therapy. They are either symptomless or may cause disturbances such as halos, blurring of vision, or photophobia. They may be

transient or are reversible on stopping treatment. Should these types of corneal changes occur with PLASMOQUINE, it should be either stopped or temporarily withdrawn.

Reversible extra-ocular muscle palsies and temporary blurring of vision due to interference with accommodation have also been noted.

Retinal changes such as abnormal macular pigmentation and depigmentation (sometimes described as a "bull's eye"), pallor of the optic disc, optic atrophy and narrowing of the retinal arterioles have been reported.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Symptoms of overdosage:

Overdosage with chloroquine is dangerous and may lead to death within a few hours.

Small children seem to be particularly sensitive to the adverse effects of chloroquine.

Acute overdosage can cause headache, gastrointestinal disturbances, drowsiness, dizziness, a fall in blood pressure, visual disturbances with sudden loss of vision.

The chief symptom of chloroquine overdosage is cardiovascular collapse progressing to convulsions, cardiac and respiratory arrest, and death.

Cardiac arrhythmias also may occur.

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Treatment of overdosage:

Treatment is symptomatic and supportive.

Overdosage with chloroquine can be rapidly fatal and therefore treatment should be administered promptly.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 20.2.6 Medicines against Protozoa.

Chloroquine sulphate is an anti-malarial agent with rapidly acting blood schizonticidal and some gametocyticidal activity. It is not effective against exoerythrocytic tissue stages of plasmodia.

5.2 Pharmacokinetic properties

Studies in volunteers using single doses of chloroquine phosphate equivalent to 300 mg base have found peak plasma levels to be achieved within one to six hours. These levels are in the region of 54 – 102 microgram/litre, the concentration in whole blood being some 4 to 10 times higher. Following a single dose, chloroquine may be detected in plasma for more than four weeks. Mean bioavailability from tablets of chloroquine phosphate is 89 %.

Chloroquine is widely distributed in body tissues such as the eyes, kidneys, liver, and lungs where retention is prolonged. The elimination of chloroquine is slow, with a multi exponential decline in plasma concentration. The initial distribution phase has a half-life of 2-6 days while the terminal elimination phase is 10-60 days. Approximately 50-70 % of chloroquine in plasma is bound to the plasma proteins.

The principal metabolite is monodesethylchloroquine, which reaches a peak concentration of 10-20 microgram/litre within a few hours. Mean urinary recovery, within 3-13 weeks, is

approximately 50 % of the administered dose, most being unchanged drug and the remainder as metabolite. Chloroquine may be detected in urine for several months.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium sulphate dihydrate (Edible grade E 516), Microcrystalline cellulose (Avicel PH101) Colloidal silicon dioxide (Syloid 244), Magnesium stearate (vegetable grade)

Composition of capsule shell, Blue:

Brilliant blue FCF FD&C Blue 1, Erythrosine FD&C Red 3, Titanium dioxide, Gelatin

Composition of the Body, White:

Titanium dioxide, Gelatin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

60 months

6.4 Special precautions for storage

Store below 25 ºC.

Protect from light.

6.5 Nature and contents of container

The capsules are packed in 20's, 100's and 500's in white polypropylene securitainers with white LDPE lids and a foam insert.

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Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

No special requirements.

7 HOLDER OF THE CERTIFICATE OF REGISTRATION

Medchem Pharmaceuticals (Pty) Ltd

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0181

8 REGISTRATION NUMBER(S)

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