SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. NAME OF MEDICINAL PRODUCT

Afrab® Chloroquine tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 250 mg chloroquine phosphate, which is equivalent to 155 mg chloroquine base.

{For a full list of excipients, see section 6.1}

3. PHARMACEUTICAL FORM

Tablet

A white round tablet, plain on one side and a mark line on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Afrab®Chloroquine tablet is used in the treatment of extra-intestinal amoebiasis in conjuction with an intestinal amoebicide.

4.2 Posology and method of administration

Extra-intestinal amoebiasis:

10mg (base)/kg. P.O. daily for 2 to 3 weeks, to a maximum dosage of 300mg (base) daily.

Treatment of malaria:

Day 1	4 tablets
Day 2	4 tablets
Day 3	2 tablets

The dose should be taken after food

Method of Administration

Oral administration only

4.3 Contraindications

Known hypersensitivity to chloroquine or any other ingredients of the formulation.

4.4 Special warnings and precaution for use

When used as malaria prophylaxis official guidelines and local information on prevalence of resistance to anti-malarial drugs should be taken into consideration.

Chloroquine 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 chloroquine 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 chloroquine should have their blood glucose level checked and treatment reviewed as necessary.

Prolongation of QTc interval

Chloroquine has been shown to prolong the QTc interval in some patients.

Chloroquine 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,
- proarrhythmic conditions e.g bradycardia (< 50 bpm)
- a history of ventricular dysrhythmias
- uncorrected hypokalemia and/or hypomagnesemia
- and during concomitant administration with QT interval prolonging agents (see section 4.5)

as this may lead to an increased risk for ventricular arrhythmias, sometimes with fatal outcome. The magnitude of QT prolongation may increase with increasing concentrations of the drug.

Therefore, the recommended dose should not be exceeded .

If signs of cardiac arrhythmia occur during treatment with chloroquine, treatment should be stopped and an ECG should be performed.

Cardiomyopathy

In patients receiving chloroquine therapy cases of cardiomyopathy have been reported, leading to heart failure, sometimes with fatal outcome. If signs and symptoms of cardiomyopathy occur during treatment with chloroquine, treatment should be stopped.

Caution is necessary when giving Afrab Chloroquine to patients with impaired hepatic function, particularly when associated with cirrhosis.

Caution is also necessary in patients with porphyria. Afrab Chloroquine may precipitate severe constitutional symptoms and an increase in the amount of porphyrins excreted in the urine. This reaction is especially apparent in patients with high alcohol intake.

A small number of cases of diffuse parenchymal lung disease have been identified in patients taking chloroquine. A response after therapy with steroids has been observed in some of these cases.

Cases of drug rash with eosinophilia and systemic symptoms syndrome have been identified in patients taking chloroquine alone or in combination with proguanil. Recovery after discontinuation of treatment and response after therapy with steroids has been observed.

Caution is necessary when giving Afrab Cloroquine to patients with renal disease.

Avloclor should be used with care in patients with a history of epilepsy. Potential risks and benefits should be carefully evaluated before use in subjects on anticonvulsant therapy or with a history of epilepsy as rare cases of convulsions have been reported in association with chloroquine (see section 4.5).

Considerable caution is needed in the use of Afrab Chloroquine for long-term high dosage therapy and such use should only be considered when no other drug is available. Patients on long-term therapy should also be monitored for cardiomyopathy.

Irreversible retinal damage and corneal changes may develop during long term therapy and after the drug has been discontinued. Ophthalmic examination prior to and at 3–6 monthly intervals during use is required if patients are receiving chloroquine

• at continuous high doses for longer than 12 months

• as weekly treatment for longer than 3 years

• when total consumption exceeds 1.6 g/kg (cumulative dose 100 g)

Full blood counts should be carried out regularly during extended treatment as bone marrow suppression may occur rarely. Caution is required if drugs known to induce blood disorders are used concurrently.

The use of Afrab Chloroquine in patients with psoriasis may precipitate a severe attack.

Caution is advised in patients with glucose-6-phosphate dehydrogenase deficiency, as there may be a risk of haemolysis.

4.5 Interaction with other medicinal product and other forms of interaction.

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

Chloroquine should be used with caution in patients receiving drugs known to prolong the QT interval e.g. Class IA and III antiarrhythmics, tricyclic antidepressants, antipsychotics, some anti-infectives due to increased risk of ventricular arrhythmia (see sections 4.4 and 4.9). Halofantrine should not be administered with chloroquine. In particular, amiodarone should not be used and its use is contraindicated. Antacids (aluminium, calcium and magnesium salts) and adsorbents (e.g. kaolin) may reduce the absorption of chloroquine, so should be taken well separated from Afrab Chloroquine (at least four hours apart).

If the patient is taking ciclosporin then chloroquine may cause an increase in ciclosporin levels.

Pre-exposure intradermal human diploid-cell rabies vaccine should not be administered to patients taking chloroquine as this may suppress the antibody response. When vaccinated against rabies, that vaccine should precede the start of the antimalarial dosing; otherwise the effectiveness of the vaccine might be reduced.

Chloroquine significantly reduces levels of praziquantel. Caution is therefore advised during co-administration. Prescribers may consider increasing the dose of praziquantel if the patient does not respond to the initial dose.

Other antimalarials:	increased risk of convulsion with mefloquine.
Cardiac glycosides:	hydroxychloroquine and possibly chloroquine increase plasma concentration of digoxin.
Parasympathomimetics:	chloroquine and hydroxychloroquine have potential to increase symptoms of myasthenia gravis and thus diminish effect of neostigmine and pyridostigmine.
Ulcer healing drugs:	cimetidine inhibits metabolism of chloroquine (increased plasma concentration).

In vitro work has shown that the concomitant use of drugs such as multidrug and toxin extrusion protein (MATE1) inhibitors (e.g., ciprofloxacin, cimetidine, omeprazole, pyrimethamine) may impact the renal clearance of chloroquine, which could theoretically lead to increased levels of chloroquine and potentially overdosage (see section 4.9). In addition, care should be taken when alkalinization of urine occurs as this may reduce chloroquine renal excretion.

Chloroquine may lower the convulsive threshold and thus antagonise the actions of antiepileptics

(See section 4.4).

Thyroid medication: increased Thyroid Stimulating Hormone levels have been observed with the concomitant use of levothyroxine, dosage adjustment of thyroid medication may be necessary.

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

4.6 Pregnancy and Lactation

Afrab Chloroquine should not be used during pregnancy unless, in the judgement of the physician, potential benefit outweighs the risk.

Short-term malaria prophylaxis:

Malaria in pregnant women increases the risk of maternal death, miscarriage, still-birth and low birth weight with the associated risk of neonatal death. Travel to malarious areas should be avoided during pregnancy but, if this is not possible, women should receive effective prophylaxis.

Long-term high dose:

There is evidence to suggest that Afrab Chloroquine given to women in high doses throughout pregnancy can give rise to foetal abnormalities including visual loss, ototoxicity and cochlear-vestibular dysfunction.

Lactation

Although Afrab Chloroquine is excreted in breast milk, the amount is too small to be harmful when used for malaria prophylaxis but as a consequence is insufficient to confer any benefit on the infant. Separate chemoprophylaxis for the infant is required. However, when long-term high doses are used for rheumatoid disease, breast feeding is not recommended.

4.7 Effects on ability to drive and use machines

Defects in visual accommodation may occur on first taking Afrab Choroquine and patients should be warned regarding driving or operating machinery.

4.8 Undesirable Effects

Ocular reaction: Blurring of vision and difficulty of focusing or accommodation.

Neuromuscular reaction: convulsive seizures.

Auditory reaction: tinnitus, reduced hearing in patients with pre-existing auditory damage.

Gastro-intestinal reactions: anorexia, nausea, vomiting, diarrhea, abdominal cramps.

Dermatological reaction: skin eruption, skin and mucosal pigmentary changes, pruritus, hair loss.

CNS reaction: mild and transient headache, psychic stimulation.

Cardio-vascular reaction: rarely hypotension, electrocardiographic changes.

4.9 Overdose

Features

Chloroquine is highly toxic in overdose and children are particularly susceptible. The chief symptoms of overdosage include circulatory collapse due to a potent cardiotoxic effect, respiratory arrest and coma. Symptoms may progress rapidly and include:

- General features include nausea and vomiting. Hypokalaemia is common in severe poisoning and metabolic acidosis may also develop. Rarely hepatotoxicity, nephritis, gastric haemorrhage, haematological abnormalities and psychiatric features may occur.

- Neurological features include headache, dizziness, drowsiness, blurred vision, diplopia and, rarely, blindness, may precede restlessness, increased excitability and convulsions. Coma is less common.

- Cardiac features often appear at an early stage. Cardiac arrest may be a presenting feature. Hypotension is very common and may progress to cardiogenic shock and pulmonary oedema.

With serious intoxication, width-increased QRS complex, bradyarrhythmias, nodal rhythm, QT prolongation, atrioventricular block, ventricular tachycardia, torsades de pointes, ventricular fibrillation may occur.

Intraventricular conduction defects with a wide QRS, and prolongation of the QT interval are more common than A-V (atrioventricular) conduction defects. Ventricular tachycardia and fibrillation tend to occur early while torsade de pointes develops after about 8 hours.

Management

Acute overdose with chloroquine can be rapidly lethal and intensive supportive treatment should be started immediately.

Death may result from circulatory or respiratory failure or cardiac arrhythmia but is usually due to cardiac arrest related to the direct effects on the myocardium. If there is no demonstrable cardiac output due to arrhythmias, asystole or electromechanical dissociation, external chest compression should be persisted with for as long as necessary, or until adrenaline and diazepam can be given (see below).

Firstly, maintain a clear airway and ensure adequate ventilation. The benefit of gastric decontamination is uncertain, but activated charcoal can be considered for adults and children aged over 5 years, within 1 hour of ingestion of more than 10 mg/kg of chloroquine base as a single dose or for any amount in a child aged 5 years and under, as it may reduce absorption of any remaining chloroquine from the gut. Activated charcoal should also be considered within 1 hour of ingestion of a weekly dose taken on 2 or more consecutive days. Alternatively, gastric lavage may be considered in adults within 1 hour of a potentially life threatening overdose. There is a risk of cardiac arrest following aspiration of gastric contents in more serious cases.

Monitor circulatory status (with central venous pressure measurement), cardiac rhythm, respiration, conscious level and urinary output. Check urea & electrolytes, liver function and full blood count in symptomatic patients. Consider arterial blood gas analysis in patients who have a reduced level of consciousness or have reduced oxygen saturation on pulse oximetry.

It is not clear if correction of hypokalaemia is essential but it may have a protective effect and should not be corrected in the early stages of poisoning. The degree of hypokalaemia may be correlated with the severity of chloroquine intoxication. If it persists beyond 8 hours, cautious correction should be undertaken with frequent biochemical monitoring of progress. Rebound hyperkalaemia is a risk during recovery.

In case of persistent metabolic acidosis consider intravenous sodium bicarbonate. Rapid correction is particularly important if there is prolongation of the QRS interval. DC (direct current) shock is indicated for ventricular tachycardia and ventricular fibrillation.

Cardiac arrhythmias should be treated with caution. The use of anti-arrhythmic drugs (such as those with quinidine-like effects) is best avoided since they may depress the myocardium further and exacerbate hypotension.

Early administration of the following has been shown to improve survival in cases of serious poisoning:

1. Adrenaline infusion until adequate systolic blood pressure (more than 100mg/Hg) is restored; adrenaline reduces the effects of chloroquine on the heart through its inotropic and vasoconstrictor effects.

Diazepam infusion; diazepam may decrease the cardiotoxicity of chloroquine.

Acidification of the urine, haemodialysis, peritoneal dialysis or exchange transfusion have not been shown to be of value in treating chloroquine poisoning. Chloroquine is excreted very slowly; therefore cases of overdosage require observation for several days.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics Properties

Pharmacotherapeutic group: Antiprotozoals, Antimalarials

ATC code: P01BA01

Mechanism of action :

The mode of action of chloroquine on plasmodia has not been fully elucidated. Chloroquine binds to and alters the properties of DNA. Chloroquine also binds to ferriprotoporphyrin IX and this leads to lysis of the plasmodial membrane.

In suppressive treatment, chloroquine inhibits the erythrocytic stage of development of plasmodia. In acute attacks of malaria, it interrupts erythrocytic schizogony of the parasite. Its ability to concentrate in parasitised erythrocytes may account for the selective toxicity against the erythrocytic stages of plasmodial infection.

5.2 Pharmacokinetic properties

Absorption and Bioavailability: Studies in volunteers using single doses of chloroquine phosphate equivalent to 300mg base have found peak plasma levels to be achieved within one to six hours. These levels are in the region of 54 - 102microgram/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.

Distribution: Chloroquine is widely distributed in body tissues such as the eyes, kidneys, liver, and lungs where retention is prolonged.

Metabolism: Approximately 50-70% of chloroquine in plasma is bound to the plasma proteins.

Elimination: The elimination of chloroquine is slow, with a multi exponential decline in plasma concentration

5.3 Preclinical safety data
Chloroquine has been widely used for many years in clinical practice. There is no animal data which adds significant information relevant to the prescriber, to that covered elsewhere in this document.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Corn Starch (Paste)
Corn Starch (Diluent)
Corn Starch (Finalblending)
Magnesium Stearate
Aerosil

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 30^{o}C in a dry place.

6.5 Nature and contents of container

The tablets are packed in ALU/PVC blisters in printed cardboard case.

Pack sizes: 1 X 10 tablets

6.6 Special precautions for disposal and other handling

No special requirements.

7. APPLICANT/MANUFACTURER

Afrab Chem Limited
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