

1. Name of medicinal product

Chloroquine phosphate tablet 250mg

2. Qualitative and quantitative composition

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

For full list of excipients, see section 6.1.

3. Pharmaceutical form

Tablets

4. Clinical particulars

4.1 Therapeutic indications

- Treatment of amoebic hepatitis and abscess.
- Treatment of discoid and systemic lupus erythematosus.
- Treatment of rheumatoid arthritis.

4.2 Posology and method of administration

The dose should be taken after food.

Amoebic hepatitis

Adults: Four tablets daily for two days followed by one tablet twice daily for two or three weeks.

Elderly Patients: There are no special dosage recommendations for the elderly, but it may be advisable to monitor elderly patients so that optimum dosage can be individually determined.

Hepatic or Renally Impaired Patients: Caution is necessary when giving Chloroquine phosphate tablets to patients with renal disease or hepatic disease.

Lupus erythematosus

Adults: One tablet twice daily for one to two weeks followed by a maintenance dosage of one tablet daily.

Elderly Patients: There are no special dosage recommendations for the elderly, but it may be advisable to monitor elderly patients so that optimum dosage can be individually determined.

Hepatic or Renally Impaired Patients: Caution is necessary when giving Chloroquine phosphate tablet to patients with renal disease or hepatic disease.

Rheumatoid arthritis

Adults: The usual dosage is one tablet daily.

Elderly Patients: There are no special dosage recommendations for the elderly, but it may be advisable to monitor elderly patients so that optimum dosage can be individually determined.

Hepatic or Renally Impaired Patients: Caution is necessary when giving Chloroquine phosphate tablet to patients with renal disease or hepatic disease.

4.3 Contraindications

Known hypersensitivity to chloroquine or any other ingredients of the formulation. Concomitant use with amiodarone.

4.4 Special warnings and precautions 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 hypoglycemia including loss of consciousness that could be life threatening in patients treated with and without

medications. Patients treated with chloroquine should be warned about

the risk of hypoglycemia and the associated clinical signs and symptoms. Patients presenting with clinical symptoms suggestive of hypoglycemia 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 dyarrhythmia
- uncorrected hypokalemia and/or hypomagnesemia
- and during concomitant administration with QT interval prolonging agents 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 Chloroquine phosphate 250mg tablet to patients with impaired hepatic function, particularly when associated with cirrhosis.

Caution is also necessary in patients with porphyria. Chloroquine phosphate 250mg tablet 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 (DRESS) 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 Chloroquine phosphate 250mg tablet to patients with renal disease.

Chloroquine phosphate 250mg tablet 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. Considerable caution is needed in the use of Chloroquine phosphate 250mg tablet 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 Chloroquine phosphate 250mg tablet 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 hemolysis.

Acute extrapyramidal disorders have been reported during treatment with chloroquine, usually disappearing on discontinuation of treatment and/or on symptomatic treatment.

4.5 Interaction with other medicinal products 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. Halofantrine should not be administered with chloroquine. In particular, amiodarone should not be used and its use is contraindicated. Antacids (aluminum, calcium and magnesium salts) and adsorbents (e.g. kaolin) may reduce the absorption of chloroquine, so should be taken well separated from Chloroquine phosphate 250mg tablet (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. Para sympathomimetics: 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).

4.6 Fertility, pregnancy and lactation

Pregnancy

Chloroquine phosphate 250mg tablet 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, stillbirth 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 Chloroquine phosphate 250mg tablet given to women in high doses throughout pregnancy can give rise to fetal abnormalities including visual loss, ototoxicity and cochlear-vestibular dysfunction.

Lactation

Although Chloroquine phosphate 250mg tablet 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 Chloroquine phosphate 250mg tablet and patients should be warned regarding driving or operating machinery.

4.8 Undesirable effects

The adverse reactions which may occur at doses used in the prophylaxis or treatment of malaria are generally not of a serious nature. Where prolonged high dosage is required, i.e. in the treatment of rheumatoid arthritis, adverse reactions can be of a more serious nature.

Undesirable effects are listed by MedDRA System Organ Classes.

Assessment of undesirable effects is based on the following frequency groupings:

Very common: $\geq 1/10$

Common: $\geq 1/100$ to $< 1/10$

Uncommon: $\geq 1/1,000$ to $< 1/100$

Rare: $\geq 1/10,000$ to $< 1/1,000$

Very rare: $< 1/10,000$

Not known: cannot be estimated from the available data

System Organ Class	Undesirable Effect and Frequency
Blood and lymphatic system disorders	Not known Bone marrow failure Aplastic anaemia Agranulocytosis Thrombocytopenia Neutropenia Pancytopenia
Immune system disorders	Not known Hypersensitivity and anaphylactic reactions, including urticaria, angioedema and vasculitis.
Metabolism and nutrition disorders	Not known Hypoglycaemia
Psychiatric Disorders	Rare Hallucinations Not known Psychotic disorder including anxiety, personality change Insomnia Confusion Depression Suicidal behavior Psychosis Aggression Delusion Paranoia Mania Attention deficit Sleep disorder
Nervous system disorders	Not known Convulsion Visual field defects Headache Neuromyopathy Acute extrapyramidal disorders (such as dystonia, dyskinesia, tongue protrusion, torticollis)
Eye disorders	Not known Retinal degeneration Macular defects of color vision Pigmentation Optic atrophy scotomas Blindness Corneal opacity and pigmented deposits Vision blurred Accommodation disorder Diplopia
Ear and labyrinth disorders	Not known Tinnitus Hypoacusis Deafness neurosensory
Cardiac disorders	Rare Cardiomyopathy Not known Atrioventricular block, QT-prolongation
Vascular Disorders	Not known Hypotension
Respiratory, thoracic and mediastinal	Not known

	Diffuse parenchymal lung disease
Gastrointestinal disorders	Not known Gastrointestinal disorder Nausea Vomiting Diarrhea Abdominal pain
Hepatobiliary disorders	Rare Changes in liver function, including hepatitis and abnormal liver function tests
Skin and subcutaneous tissue disorders	Not known Macular, urticarial and purpuric skin eruptions Alopecia Erythema multiforme Drug reaction with eosinophilia and systemic symptoms syndrome (DRESS) Stevens-Johnson syndrome (SJS) Toxic epidermal necrolysis (TEN) Precipitation of psoriasis Pruritus Photosensitivity reaction Lichenoid keratosis Pigmentation disorder * Exfoliative dermatitis Acute generalized exanthematous pustulosis (AGEP)
Musculoskeletal and connective tissue disorders	Not known Myopathy
Investigations	Not known Electrocardiogram change**

* Long term use

**At high doses

Reporting of suspected adverse reactions

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

4.9 Overdose

Features

Undesirable effects

The adverse reactions which may occur at doses used in the prophylaxis or treatment of malaria are generally not of a serious nature. Where prolonged high dosage is required, i.e. in the treatment of rheumatoid arthritis, adverse reactions can be of a more serious nature.

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.

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 hypokalemia is essential but it may have a protective effect and should not be corrected in the early stages of poisoning. The degree of hypokalemia 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 hyperkalemia 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:

- Adrenaline infusion until adequate systolic blood pressure (more than 100mmHg) 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, hemodialysis, 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 Pharmacodynamic properties

Pharmacotherapeutic group: Antiprotozoals, Antimalarials

ATC code: P01BA01

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 parasitized erythrocytes may account for the selective toxicity against the erythrocytic stages of plasmodial infection.

5.2 Pharmacokinetic properties

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.

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.

5.3 Preclinical safety data

Chloroquine phosphate 250mg tablet 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

- Lactose
- Maize starch.
- Povidone
- Methyl Paraben
- Propyl Paraben
- Purified Talc
- Magnesium stearate

6.2 Incompatibilities

None have been reported or are known.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30°C. Protect from light and moisture.

6.5 Nature and contents of container

PVC/Aluminum Foil Blister Pack of 10 x 10 tablets

6.6 Special precautions for disposal and other handling

No special instructions.

7. Marketing authorization holder

Emzor Pharmaceuticals Industries limited.

Sagamu/Benin Expressway, Makun, Sagamu Local Govt, Nigeria.

8. Marketing authorization number(s)

N/A

9. Date of first authorization/renewal of authorization

N/A

10. Date of revision of text

N/A