**Indications**

- Rheumatic and dermatological conditions
  - Systemic lupus erythematosus.
  - Discoid lupus erythematosus.
  - Rheumatoid arthritis.
  - Juvenile chronic arthritis.
  - Dermatological conditions caused or aggravated by sunlight.

**Malaria**

- For the treatment of acute attacks and for the suppression of malaria due to Plasmodium vivax, P. ovale and P. malariae and sensitive strains of P. falciparum.
- For the radical cure of malaria due to sensitive strains of P. falciparum.

**Contraindications**

- Known hypersensitivity to 4-aminoquinoline compounds.
- Pre-existing maculopathy of the eye.

**Side Effects**

**Ocular Effects**

Retinopathy with changes in pigmentation and visual field defects can occur but is rare. In its early form, it appears reversible on discontinuation of hydroxy-chloroquine. If allowed to develop, there may be a risk of progression even after treatment withdrawal. Patients with retinal changes may be asymptomatically initially, or may have scotomatos vision with paracentral, pericentral ring types and temporal scotomas.

Corneal changes including edema and opacities have been reported. They are either asymptomatic or may cause disturbances such as halos, blurring of vision, or photophobia. They may be transient or are reversible on stopping treatment.

Blurring of vision due to a disturbance of accommodation, which is dose dependent and reversible, may occur.

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**Composition**

Hydroxychloroquine sulfate, 200 mg and 400 mg, tablets; each 200 mg of hydroxychloroquine sulfate salt is equivalent to 155 mg of hydroxychloroquine base.

**Properties**

**Pharmacodynamics**

Hydroxychloroquine, a 4-aminoquinoline antimalarial which combines rapid blood schizonticidal activity with some gametocyticidal activity, is also classified as a slow-acting antirheumatic drug.

Hydroxychloroquine has several pharmacological actions that may be involved in its therapeutic effects. These include interaction with sulphidryl groups; modulation of enzyme activity (including phospholipase, NADH-cytochrome C reductase, cholinesterase, proteases, and hydrolases); binding to DNA; stabilization of lysosomal membranes; inhibition of prostaglandin formation, polymorphonuclear cell chemotaxis and phagocytosis; possible interference with interleukin1 production from monocytes, and inhibition of neutrophil superoxide release. Concentration within and raising the pH of intracellular acidic vesicles may well explain both the antiprotozoal and antirheumatic effects.

**Pharmacokinetics**

Hydroxychloroquine is rapidly absorbed following oral administration. Mean bioavailability is approximately 74%. It is widely distributed throughout the body, accumulating within blood cells and other tissues such as liver, lungs, kidneys and eyes. It is partially converted to active-ethylated metabolites in the liver and eliminated principally via the kidney, 23% to 25% unchanged, but also via the bile. Excretion is slow, the terminal elimination half-life being approximately 50 days (whole blood) and 32 days (plasma). Hydroxychloroquine crosses the placenta and is likely to resemble chloroquine in entering breast milk.
**Liver Effects**
Isolated cases of abnormal liver function tests have been reported and a few cases of fulminant hepatic failure have been published.

**Warnings and Precautions**
General: Before starting a long term treatment, both eyes should be examined by careful ophthalmoscopy for visual acuity, central visual field and color vision, and fundoscopy. Then, the examination should be repeated at least annually. This examination should be more frequent and adapted to the patient, in the following situations: - daily dosage exceeding 6.5 mg/kg ideal (lean) body weight. Absolute body weight used as a guide to dosage, could result in an overdosage in the obese; renal insufficiency; cumulative dose more than 200 g; elderly; impaired visual acuity. If any visual disturbance occurs (visual acuity, color vision...), the drug should be immediately discontinued and the patient closely observed for possible progression of the abnormality. Retinal changes (and visual disturbances) may progress even after cessation of the therapy. The risk of retinopathy with 4-aminoquinolines appears to be dose related and is likely to be increased if recommended dosages are exceeded.

Observe caution in patients with hepatic or renal disease, in whom a reduction in dosage may be necessary, as well as in those taking medicines known to affect these organs.

Observe caution also in patients with gastrointestinal, neurological, or blood disorders, in those with a sensitivity to quinine, and in glucose-6-phosphate dehydrogenase deficiency, porphyria and psoriasis. Patients on long-term therapy should have periodic full blood counts, and hydroxychloroquine should be discontinued if abnormalities develop.

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

All patients on long-term therapy should undergo periodic examination of skeletal muscle function.
and tendon reflexes. If weakness occurs, the drug should be withdrawn.

Malaria: Hydroxychloroquine is not effective against chloroquine-resistant strains of P. falciparum, and is not active against the exo-erythrocytic forms of P. vivax, P. ovale and P. malariae and therefore will neither prevent infection due to these organisms when given prophylactically, nor prevent relapse of infection due to these organisms.

**Pregnancy and Lactation**
Hydroxychloroquine should be avoided in pregnancy except for the suppression or treatment of malaria when, in the judgement of the physician, the potential benefits outweigh the potential hazards. 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.

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.

**Effects on Ability to Drive and Operate Machinery**
Patients should be warned about driving and operating machinery since hydroxychloroquine can impair accommodation and cause blurring of vision. If the condition is not self-limiting, dosage may need to be temporarily reduced.

**Overdosage**
Overdosage with the 4-aminoquinolines is dangerous particularly in infants, as little as 1-2 grams have proved fatal. The symptoms of overdose may include headache, visual disturbances, cardiovascular collapse, convulsions, and rhythm and conduction disorders, followed by sudden early respiratory and cardiac arrest. Since these effects may appear soon after taking a massive dose, treatment should be prompt. The stomach should be immediately evacuated, either by emesis or gastric lavage. Activated charcoal in a dose of at least five times that 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. Consideration should be given to administering diazepam parenterally, since studies have reported it beneficial in reversing chloroquine cardiotoxicity. Respiratory support and shock management should be instituted as necessary.

**Storage**
Tablets should be stored at room temperature (<25°C) and protected from humidity.

**Drug Interactions**
Concomitant hydroxychloroquine and digoxin therapy may result in increased serum digoxin levels: serum digoxin levels should be closely monitored in patients receiving combined therapy.

**Dosage and Administration**
For oral administration only. Each dose should be taken with a meal or glass of milk.
Note: all dosages refer to hydroxychloroquine sulfate not the base equivalent.

**Rheumatic Diseases**
Hydroxychloroquine is cumulative in action and will require several weeks to exert its beneficial therapeutic effects, whereas minor side effects may occur relatively early. If objective improvement does not occur within six months, the drug should be discontinued.

**Rheumatoid Arthritis:** In adults, initially 400 mg to 600 mg daily. For maintenance therapy, 200 mg to 400 mg daily.

**Juvenile Chronic Arthritis:** Doses should not exceed 6.5 mg per kg body weight or 400 mg per day, whichever is smaller.

**Systematic and Discoid Lupus Erythematosus**
In adults initially 400 mg to 800 mg daily. For maintenance therapy 200 mg to 400 mg daily.
**Light-sensitive Disease**

Treatment should be restricted to periods of maximum exposure to light. In adults, 400 mg per day may suffice.

**Malaria**

*Suppression of Malaria:* In adults, 400 mg on the same day of each week. In infants and children, the weekly suppressive dose is 6.5 mg per kg of body weight, but should not exceed the adult dose, regardless of weight. If circumstances permit, suppressive therapy should begin two weeks prior to exposure. However, failing in this, in adults an initial double (loading) dose of 800 mg, or in children 12.9 mg per kg (but not exceeding 800 mg), may be taken in two divided doses, six hours apart. The suppressive therapy should be continued for eight weeks after leaving the endemic area.

*Treatment of the Acute Attack of Malaria:* In adults, an initial dose of 800 mg followed by 400 mg in six to eight hours and 400 mg on each of two consecutive days (total 2 grams of hydroxychloroquine sulfate).

An alternative method, employing a single dose of 800 mg, has also proved effective. The dosage for adults may also be calculated on the basis of body weight as for infants and children (see below).

In infants and children, a total dose of 32 mg per kg of body weight (but not exceeding 2 grams) is administered over three days, as follows:
- First dose: 12.9 mg per kg (but not exceeding a single dose of 800 mg).
- Second dose: 6.5 mg per kg (but not exceeding 400 mg) six hours after the first dose.
- Third dose: 6.5 mg per kg (but not exceeding 400 mg) 18 hours after the second dose.
- Fourth dose: 6.5 mg per kg (but not exceeding 400 mg) 24 hours after the third dose.