PLAQUENIL®

HYDROXYCHLOROQUINE SULFATE, USP

WARNING

PHYSICIANS SHOULD COMPLETELY FAMILIARIZE THEMSELVES WITH THE COMPLETE CONTENTS OF THIS LEAFLET BEFORE PRESCRIBING HYDROXYCHLOROQUINE.

DESCRIPTION

Hydroxychloroquine sulfate is a colorless crystalline solid, soluble in water to at least 20 percent, chemically the drug is 2-[4-[7-Chloro-4-quinolylamino]pentyl]ethylamino] ethanol sulfate (1:1). PLAQUENIL (hydroxychloroquine sulfate) tablets contain 200 mg hydroxychloroquine sulfate, equivalent to 155 mg base, and are for oral administration.

Inactive Ingredients: Dibasic Calcium Phosphate, Hydroxypropyl Methylcellulose, Magnesium Stearate, Polyethylene glycol 400, Polyisorbate 80, Corn Starch, Titanium Dioxide.

ACTIONS

The drug possesses antimalarial actions and also exerts a beneficial effect in lupus erythematosus (chronic discoid or systemic) and acute or chronic rheumatoid arthritis. The precise mechanism of action is not known.

INDICATIONS

PLAQUENIL is indicated for the suppressive treatment and treatment of acute attacks of malaria due to Plasmodium vivax, P. malariae, P. ovale, and susceptible strains of P. falciparum. It is also indicated for the treatment of discoid and systemic lupus erythematosus, and rheumatoid arthritis.

CONTRAINDICATIONS

Use of this drug is contraindicated (1) in the presence of retinal or visual field changes attributable to any 4-aminoquinoline compound, (2) in patients with known hypersensitivity to 4-aminoquinoline compounds, and (3) for long-term therapy in children.

WARNINGS, General

PLAQUENIL is not effective against chloroquine-resistant strains of P. falciparum.

Before starting a long-term treatment, both eyes should be carefully examined for visual acuity, central visual field and color vision. Examination should also include fundoscopy. These examinations should be repeated at least annually. Retinal toxicity is largely dose-related. The risk of retinal damage is small with daily doses of up to 6.5 mg/kg body weight. Exceeding the recommended daily dose increases the risk of retinal toxicity. This examination should be more frequent and adapted to the patient in the following situations:

- daily dosage exceeding 6.5 mg/kg ideal body weight. Absolute body weight used as a guide to dosage, could result in an overdose 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. (See ADVERSE REACTIONS section)

Suicidal behavior has been reported in very rare cases in patients treated with hydroxychloroquine. Children are especially sensitive to the 4-aminoquinoline compounds. A number of fatalities have been reported following the accidental ingestion of chloroquine, sometimes in relatively small doses (0.75 g or 1 g in one 3-year-old child). Patients should be strongly warned to keep these drugs out of the reach of children.

Use of PLAQUENIL in patients with porphyria may precipitate a severe attack of porphyria. When used in patients with porphyria the condition may be exacerbated. The preparation should not be used in patients with porphyria.

Usage in Pregnancy

Usage of this drug during pregnancy should be avoided except in the suppression or treatment of malaria. 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. Cases of maculopaties and macular degeneration have been reported and may be irreversible.

SKIN AND SUBCUTANEOUS TISSUE DISORDERs: Bullous eruptions including very rare cases of Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, photosensitivity and exfoliative dermatitis have been reported.

OVERDOSE

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 overdose may include headache, drowsiness, visual disturbances, cardiovascular collapse, convulsions, hypokalemia, rhythm and conduction disorders including QT prolongation, toraside de pointes, ventricular tachycardia and ventricular fibrillation, followed by sudden potential collapse. Intravenous calcium and cardiac arrest. Immediate medical attention is required, as these effects may appear shortly after the overdose. Treatment is systematic and must be prompt with immediate evacuation of the stomach by emesis (at home, before transportation to the hospital) or gastric lavage until the stomach is completely emptied. If finely powdered, activated charcoal is introduced by the stomach tube, after lavage, and within 30 minutes after ingestion of the tablets, it may inhibit further intestinal absorption of the drug. To be effective, the dose of activated charcoal should be at least five times the estimated dose of hydroxychloroquine ingested. 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 oxitoxia, it should be controlled by oxygen administration, artificial respiration, or in shock with hypothermia and 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. A patient who survives the acute phase and is asymptomatic should be closely observed for at least 6 months. Fluids may be forced, and sufficient ammonium chloride (8 g daily in divided doses for adults) may be administered for a few days to acidify the urine to help promote urinary excretion in cases of both overdosage and sensitivity.

MALARIA

Actions

Like chloroquine phosphate, USP, PLAQUENIL is highly active against the erythrocytic forms of P. vivax and P. malariae and most strains of P. falciparum (but not the gametocytes of P. falciparum).

PLAQUENIL does not prevent relapses in patients with P. vivax or P. malariae malaria because it is not effective against exo-erythrocytic forms of the parasite, nor will it prevent P. vivax or P. malariae infection when administered as a prophylactic. It is highly effective as a suppressive agent in patients with P. vivax or P. malariae malaria, in terminating acute attacks, and significantly lengthening the interval between treatment and relapse. In patients with P. falciparum malaria, it abolishes the acute attack and effects complete cure of the infection, unless due to a resistant strain of P. falciparum.

Indications

PLAQUENIL is indicated for the treatment of acute attacks and suppression of malaria.

In recent years, it has been found that certain strains of P. falciparum have become resistant to 4-aminoquinoline compounds (including hydroxychloroquine) as shown by the fact that normally adequate doses have failed to prevent or cure clinical malaria or parasitemia. Treatment with quinine or other specific forms of therapy is therefore advised for patients infected with a resistant strain of parasites.

Before starting a long-term treatment, both eyes should be carefully examined for visual acuity, central visual field and color vision. Examination should also include fundoscopy. These examinations should be repeated at least annually. 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. Exceeding the recommended daily dose sharply increases the risk of retinal toxicity. This examination should be more frequent and adapted to the patient in the following situations:

- daily dosage exceeding 6.5 mg/kg ideal body weight. Absolute body weight used as a guide to dosage, could result in an overdose 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. (See ADVERSE REACTIONS)

Suicidal behavior has been reported in very rare cases in patients treated with hydroxychloroquine.

ADVERSE REACTIONS

Following the administration in doses adequate for the treatment of an acute malarial attack, mild and transient headache, dizziness, and gastrointestinal complaints (diarrhea, anorexia, nausea, abdominal cramps and, on rare occasions, vomiting) may occur. Cardiomyopathy has been rarely reported with daily dosages of hydroxychloroquine.

Psychiatric disorders: Nervousness, emotional lability, psychosis, suicidal behavior.

Nervous system disorders: Dizziness, headache, convulsions have been reported with this class of drugs.

Eye disorders: Retinopathy with changes in pigmentation and visual field defects have been reported. 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. Cases of maculopaties and macular degeneration have been reported and may be irreversible.

Skin and subcutaneous tissue disorders: Bullous eruptions including very rare cases of Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, photosensitivity and exfoliative dermatitis have been reported.

Dosage and Administration

One tablet of 200 mg of hydroxychloroquine sulfate is equivalent to 155 mg base.

Malaria

Suppression

In adults, 400 mg (=310 mg base) on exactly the same day of each week. In infants and children, the weekly suppressive dose is 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 this, in adults an initial double (loading) dose of 800 mg (=620 mg base), or in children 10 mg base per kg body weight 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

In adults, an initial dose of 800 mg (=620 mg base) followed by 400 mg (=310 mg base) in six to eight hours and 400 mg (=310 mg base) on each of two consecutive days (total 2 g hydroxychloroquine sulfate or 1.55 g base). An alternative method, employing a single dose of 800 mg (=620 mg base), has also proved effective. The dosage for adults may also be calculated on the basis of body weight; this method is preferred for infants and children. A total dose representing 25 mg of base per kg of body weight is administered in three days, as follows:

First dose: 10 mg base per kg (but not exceeding a single dose of 620 mg base).

Second dose: 5 mg base per kg (but not exceeding a single dose of 310 mg base) 6 hours after first dose.

Third dose: 5 mg base per kg 18 hours after second dose.

Fourth dose: 5 mg base per kg 24 hours after third dose.

For radical cure of vivax and malariae malaria concomitant therapy with an 8-aminoquinoline compound is necessary.
LUPUS ERYTHEMATOSUS AND RHEUMATOID ARTHRITIS

Indications
PLAQUENIL is useful in patients with the following disorders who have not responded satisfactorily to drugs with less potential for serious side effects: lupus erythematosus (chronic discoid and systemic) and acute or chronic rheumatoid arthritis.

Warnings
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Irreversible retinal damage has been observed in some patients who had received long-term or high-dosage 4-aminoquine therapy for discoid and systemic lupus erythematosus, or rheumatoid arthritis.

When prolonged therapy with any Antimalarial compound is contemplated, initial (base line) and periodic (every three months) ophthalmologic examinations (including visual acuity, expert slit-lamp, funduscopic and visual field tests) should be performed.

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 ofaccommodation or corneal opacities, the drug should be discontinued and the patient closely observed for possible progression.

Retinal changes (and visual disturbances) may progress even after cessation of therapy (see ADVERSE REACTIONS).

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. Exceeding the recommended daily dose sharply increases the risk of retinal toxicity. This examination should be more frequent and adapted to the patient in the following situations:

- daily dosage exceeding 6.5 mg/kg ideal body weight. Absolute body weight used as a guide to dosage, could result in an overdose in the obese;
- renal failure;
- cumulative dose more than 200 g;
- elderly;
- impaired visual acuity.

All patients on long-term therapy with this preparation 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 drug.

In the treatment of rheumatoid arthritis, 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 arthritis has not been established.

Suicidal behavior has been reported in very rare cases in patients treated with hydroxychloroquine.

Precautions
Dermatologic reactions to PLAQUENIL may occur and, therefore, proper care should be exercised when administered to any patient receiving a drug with a significant tendency to produce dermatitis. The methods recommended for early diagnosis of "chloroquine retinopathy" consist of (1) funduscopic examination of the macula for fine pigmentary disturbances or loss of the foveal reflex and (2) examination of the central visual field with a small red test object for pericentral or paracentral scotoma or determination of retinal thresholds to red. Any unexplained visual symptoms, such as light flashes or streaks should also be regarded with suspicion as possible manifestations of retinopathy. If serious toxic symptoms occur from overdosage or sensitivity, it has been suggested that ammonium sulfate or salicylates may be used to reduce the retinopathy (macular pigmentation sometimes with central field defects) diminished or regressed completely after therapy was discontinued. If allowed to develop, there may be a risk of progression even after treatment withdrawal. Paraocular scotoma to red targets (sometimes called "premaculopathy") is indicative of early retinal dysfunction which is usually reversible with cessation of therapy.

A small number of cases of retinal changes have been reported as occurring in patients who received only hydroxychloroquine. These usually consisted of alteration in retinal pigmentation which was detected on periodic ophthalmologic examination; visual field defects were also present in some instances. A case of delayed retinopathy has been reported with loss of vision starting one year after administration of hydroxychloroquine had been discontinued.

Dermatologic Reactions: Bleaching of hair, alopecia, pruritus, skin and mucosal pigmentation, photosensitivity, and skin eruptions (urticarial, morbilliform, lichenoid, maculopapular, purpuric, erythema multiforme, erythema annularis centrifugum, Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, and exfoliative dermatitis).

Hematologic Reactions: Various blood dyscrasias such as aplastic anemia, agranulocytosis, leukopenia, anemia, thrombocytopenia (hemolysis in individuals with glucose-6-phosphate dehydrogenase (G-6-PD) deficiency).

Gastrointestinal Reactions: Anorexia, nausea, vomiting, diarrhea, and abdominal cramps. Isolated cases of abnormal liver function and fulminant hepatic failure.

Allergic reactions: Urticaria, angioedema and bronchospasm have been reported.

Miscellaneous Reactions: Weight loss, lassitude, exacerbation or precipitation of porphyria and photosensitive porosias.

Cardiomyopathy has been rarely reported with high daily dosages of hydroxychloroquine.

Dosage and Administration
One tablet of hydroxychloroquine sulfate, 200 mg, is equivalent to 155 mg base.

Lupus Erythematosus
Initially, the average adult dose is 400 mg (=310 mg base) once or twice daily. This may be continued for several weeks or months, depending on the response of the patient. For prolonged maintenance therapy, a smaller dose, from 200 mg to 400 mg (=155 mg to 310 mg base) daily will frequently suffice. The incidence of retinopathy has been reported to be higher when this maintenance dose is exceeded.

Rheumatoid Arthritis
The cumulative dose is in active use and will require several weeks to exert its beneficial therapeutic effects, whereas 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.

Periodic (every three months) ophthalmologic examinations (including visual acuity, expert slit-lamp, funduscopic and visual field tests) should be performed.

Adverse Reactions
Not all of the following reactions have been observed with every 4-aminoquinoline compound during prolonged therapy with any Antimalarial compound. However, caution must be exercised in patients with impaired renal function and/or metabolic acidosis.

Rheumatoid Arthritis
- elderly;
- cumulative dose more than 200 g;
- daily dosage exceeding 6.5 mg/kg ideal body weight. Absolute body weight used as a guide to dosage, could result in an overdose in the obese;
- renal failure;
- macular changes; depression of tendon reflexes and abnormal nerve conduction.

Miscellaneous Reactions:
- Anorexia, nausea, vomiting, diarrhea, and abdominal cramps. Isolated cases of abnormal liver function and fulminant hepatic failure.
- Gastrointestinal Reactions: Weight loss, lassitude, exacerbation or precipitation of porphyria and photosensitive porosias.
- Cardiomyopathy has been rarely reported with high daily dosages of hydroxychloroquine.

Dermatologic Reactions:
- Bleaching of hair, alopecia, pruritus, skin and mucosal pigmentation, photosensitivity, and skin eruptions (urticarial, morbilliform, lichenoid, maculopapular, purpuric, erythema multiforme, erythema annularis centrifugum, Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, and exfoliative dermatitis).

Hematologic Reactions:
- Various blood dyscrasias such as aplastic anemia, agranulocytosis, leukopenia, anemia, thrombocytopenia (hemolysis in individuals with glucose-6-phosphate dehydrogenase (G-6-PD) deficiency).

Gastrointestinal Reactions:
- Anorexia, nausea, vomiting, diarrhea, and abdominal cramps. Isolated cases of abnormal liver function and fulminant hepatic failure.

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- Urticaria, angioedema and bronchospasm have been reported.

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Rheumatoid Arthritis
The cumulative dose is in active use and will require several weeks to exert its beneficial therapeutic effects, whereas 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 (=310 mg to 465 mg base) daily, 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 optimum response level, often without return of side effects.

Maintenance dosage
When a good response is obtained (usually in four to twelve weeks), the dosage is reduced by 50 percent and continued at a usual maintenance level of 200 mg to 400 mg (=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.

Should a 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 this compound, and they can generally be decreased gradually in dosage or eliminated after the drug has been used for several weeks. When gradual reduction of steroid dosage is indicated, it may be done by reducing every four to five days the dose of cortisone by no more than from 5 mg to 15 mg; of hydrocortisone from 5 mg to 10 mg; of prednisolone and prednisone from 1 mg to 2.5 mg; of methylprednisolone and triamcinolone from 1 mg to 2 mg; and of dexamethasone from 0.25 mg to 0.5 mg.

HOW SUPPLIED PLAQUENIL tablets are white, to off-white, film coated tablets imprinted "PLAQUENIL" on one face in black ink. Each tablet contains 200 mg hydroxychloroquine sulfate (equivalent to 155 mg base). Bottles of 100 tablets (NDC 0024-1560-10).

Dispense in a tight, light-resistant container as defined in the USP/NF. Store at room temperature up to 30° C (86° F).

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A SANOFI COMPANY

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