

Package Insert
ACCOQUIN
Hydroxychloroquine Sulfate Tablets 200 mg

1. Name of the Medicinal Product

ACCOQUIN

2. Qualitative and Quantitative Composition

Each film coated tablet contains:

Hydroxychloroquine Sulfate Ph.Eur. 200 mg eq. to Hydroxychloroquine 155 mg

3. Pharmaceutical Form

Film coated tablet.

Description: White to off-white, peanut shaped, biconvex, film-coated tablets debossed with “H11” on one side and plain on the other side.

4. Clinical Particulars

4.1 Therapeutic Indications

Treatment of rheumatoid arthritis, juvenile chronic arthritis, discoid and systemic lupus erythematosus, and dermatological conditions caused or aggravated by sunlight.

4.2 Posology and Method of Administration

Adults (including the elderly)

The minimum effective dose should be employed. This dose should not exceed 6.5mg/kg/day (calculated from ideal body weight and not actual body weight and will be either 200mg or 400mg per day.

In patients able to receive 400mg daily:

Initially 400mg daily in divided doses. The dose can be reduced to 200mg when no further improvement is evident. The maintenance dose should be increased to 400mg daily if the response lessens.

Children:

The minimum effective doses should be employed and should not exceed 6.5mg/kg/day based on ideal body weight. The 200mg tablet is therefore not suitable for use in children with an ideal body weight of less than 31 kg.

Each dose should be taken with a meal or glass of milk.

Hydroxychloroquine is cumulative in action and will require several weeks to exert its beneficial effects, whereas minor side effects may occur relatively early. For rheumatic disease treatment should be discontinued if there is not improvement by 6 months. In light-sensitive diseases, treatment should only be given during periods of maximum exposure to light.

The tablets are for oral administration.

4.3 Contraindications

- known hypersensitivity to 4-aminoquinoline compounds
- pre-existing maculopathy of the eye
- Below 6 years of age (200 mg tablets not adapted for weight <35 kg) or for ideal body weight < 31 kg

4.4 Special Warning and Special Precautions for Use

Retinopathy

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.

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 6.5mg/kg ideal (lean) body weight. Absolute body weight used as a guide to dosage, could result in an overdosage in the obese;
- renal insufficiency;
- impaired visual acuity
- elderly: age above 65 years.
- Cumulative dose more than 200g.

If any visual disturbance occurs (visual acuity, color vision.), Hydroxychloroquine 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 section 4.8).

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

Hypoglycemia

Hydroxychloroquine has been shown to cause severe hypoglycemia including loss of consciousness that could be life threatening in patients treated with and without antidiabetic medications (see section 4.5 and 4.8). Patients treated with hydroxychloroquine 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 hydroxychloroquine should have their blood glucose level checked and treatment reviewed as necessary.

QT interval prolongation

Hydroxychloroquine has potential to prolong the QTc interval in patients with specific risks factors.

Hydroxychloroquine 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
- during concomitant administration with QT interval prolonging agents (see section 4.5) as this may lead to an increased risk for ventricular arrhythmias.

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

Chronic cardiac toxicity

Cases of cardiomyopathy resulting in cardiac failure, in some cases with fatal outcome, have been reported in patients treated with Hydroxychloroquine (see section 4.8 and 4.9). Clinical monitoring for signs and symptoms of cardiomyopathy is advised and Hydroxychloroquine 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 (see section 4.8).

Other monitoring on long-term treatments

Patients on long-term therapy should have periodic full blood counts, and hydroxychloroquine should be discontinued if abnormalities develop (see section 4.8).

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 (see section 4.8).

Hydroxychloroquine should be used with caution in patients taking medicines which may cause adverse ocular or skin reactions.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Potential carcinogenic risk

Experimental data showed a potential risk of inducing gene mutations. Animal carcinogenicity data is only available for one species for the parent drug chloroquine and this study was negative. In humans, there are insufficient data to rule out an increased risk of cancer in patients receiving long term treatment.

Suicidal behavior

Suicidal behavior has been reported in very rare cases in patients treated with hydroxychloroquine (see Section 4.8).

Extrapyramidal disorders

Extrapyramidal disorders may occur with Hydroxychloroquine (see section 4.8).

Other precautions

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.

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

4.5 Interactions with other medicinal products and other forms of interactions

Hydroxychloroquine sulphate may also be subject to several of the known interactions of chloroquine even though specific reports have not appeared. 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.

Pharmacodynamic interactions

Insulin and antidiabetic drugs

As hydroxychloroquine may enhance the effects of a hypoglycemic treatment, a decrease in doses of insulin or antidiabetic drugs may be required

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

Hydroxychloroquine 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 4.3 and 4.9). Halofantrine should not be administered with hydroxychloroquine.

Antimalarials

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

Antiepileptic drugs

Also, the activity of antiepileptic drugs might be impaired if co-administered with hydroxychloroquine.

Agalsidase

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

Effects of other medicinal products on hydroxychloroquine:

Antacids

Concomitant administration with magnesium-containing antacids or kaolin may result in reduced absorption of chloroquine. Per extrapolation, hydroxychloroquine 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. Per extrapolation, due to the similarities in structure and metabolic elimination pathways between hydroxychloroquine and chloroquine, a similar interaction could be observed for hydroxychloroquine. 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.

Lack of efficacy of hydroxychloroquine was reported when rifampicin, a CYP2C8 and CYP3A4 strong inducer, was 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 medicinal products:

P-gp substrates

The inhibitory potential of hydroxychloroquine on P-gp substrates has not been evaluated. In vitro observations show that all other aminoquinolines tested inhibit P-gp. Therefore, there is a potential for increased concentrations of P-gp substrates when hydroxychloroquine is concomitantly administered.

An increased plasma ciclosporin level was reported when ciclosporin and hydroxychloroquine were co-administered. Increased digoxin serum levels were reported when digoxin and hydroxychloroquine were coadministered. 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, dabigatran) are concomitantly administered.

Praziquantel

In a single-dose interaction study, chloroquine has been reported to reduce the bioavailability of praziquantel. It is not known if there is a similar effect when hydroxychloroquine and praziquantel are co-administered. Per extrapolation, due to the similarities in structure and pharmacokinetic parameters between hydroxychloroquine and chloroquine, a similar effect may be expected for hydroxychloroquine.

4.6 Pregnancy, Lactation and Fertility

Pregnancy

Only limited preclinical data are available for hydroxychloroquine, therefore chloroquine data are considered due to the similarity of structure and pharmacological properties between the 2 products.

In animal studies on chloroquine, embryo-fetal developmental toxicity was shown at very high, supratherapeutic doses (ranging from 250 to 1500mg/kg bodyweight). Chloroquine preclinical data show a potential risk of genotoxicity in some test systems.

In humans, at recommended doses for prophylaxis and treatment of malaria with chloroquine: Chloroquine has been safely used in pregnant women. Observational studies, as well as a meta-analysis including prospective studies with large exposure, have shown no increased risk of congenital malformations or poor pregnancy outcomes.

For hydroxychloroquine, when used on long-term therapy with high dosages for auto-immune diseases:

Observational studies, as well as a meta-analysis including prospective studies in long-term use with large exposure have not observed a statistically significant increased risk of congenital malformations or poor pregnancy outcomes.

Hydroxychloroquine should be avoided in pregnancy except when, in the judgment of the physician, the individual potential benefits outweigh the potential hazards.

Lactation

Hydroxychloroquine is excreted in breast milk (less than 2% of the maternal dose after bodyweight correction).

There are very limited data on the safety in the breastfed infant during hydroxychloroquine long-term treatment; the prescriber should assess the potential risks and benefits of use during breastfeeding, according to indication and duration of treatment.

Fertility

Animal studies showed an impairment of male fertility for chloroquine (see section 5.3). 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 hydroxychloroquine can impair accommodation and cause blurring of vision. If the condition is not self-limiting, dosage may need to be temporarily reduced.

4.8 Undesirable Effects

The following CIOMS frequency rating is used, when applicable:

Very common $\geq 10\%$; Common ≥ 1 and $< 10\%$; Uncommon ≥ 0.1 and $< 1\%$;

Rare ≥ 0.01 and $< 0.1\%$; Very rare $< 0.01\%$; Not known (frequency cannot be estimated from available data).

- Eye disorders:

Common:

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

Uncommon:

Retinopathy with changes in pigmentation and visual field defects can occur, but appears to be uncommon if the recommended daily dose is not exceeded. In its early forms it appears reversible on discontinuation of Hydroxychloroquine. If allowed to develop, there may be risk of progression even after treatment withdrawal.

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

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

Not known:

Cases of maculopathies and macular degeneration have been reported and may be irreversible.

- Skin and subcutaneous tissue disorders:

Common: Skin rash, pruritus

Uncommon: Pigmentation disorders in skin and mucous membranes, bleaching of hair, alopecia. These usually resolve readily on stopping treatment.

Not known: Bullous eruptions including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS syndrome, photosensitivity, exfoliative dermatitis, acute generalized exanthematous pustulosis (AGEP). AGEP has to be distinguished from psoriasis, although hydroxychloroquine may precipitate attacks of psoriasis. It may be associated with fever and hyperleukocytosis. Outcome is usually favourable after drug withdrawal.

- Gastrointestinal disorders:

Very common: Abdominal pain, nausea.

Common: Diarrhoea, vomiting.

These symptoms usually resolve immediately on reducing the dose or stopping the treatment.

- Nervous system disorders:

Common: Headache.

Uncommon: Dizziness.

Not known: Convulsions have been reported with this class of drugs.

Extrapyramidal disorders such as dystonia, dyskinesia, tremor (see section 4.4).

- Psychiatric disorders:

Common: Affect lability.

Uncommon: Nervousness.

Not known: Psychosis, suicidal behaviour.

- Ear and labyrinth disorders:

Uncommon: Vertigo, tinnitus.

Not known: Hearing loss.

- Musculoskeletal and connective tissue disorders:

Uncommon: Sensorimotor disorders.

Not known: Skeletal muscle myopathy or neuromyopathy leading to progressive weakness and atrophy of proximal muscle groups.

Myopathy may be reversible after drug discontinuation, but recovery may take many months.

Depression of tendon reflexes and abnormal nerve conduction studies.

- Cardiac disorders:

Not known:

QT interval prolongation in patients with specific risk factors, which may lead to arrhythmia (torsade de pointes, ventricular tachycardia) (see sections 4.3 and 4.8)

Cardiomyopathy which may result in cardiac failure and in some cases a fatal outcome (see section 4.4 and section 4.9).

Chronic toxicity should be considered when conduction disorders (bundle branch block / atrio-ventricular heart block) as well as biventricular hypertrophy are found. Drug withdrawal may lead to recovery.

- Blood and lymphatic system disorders:

Not known: Bone marrow depression, anemia, aplastic anemia, agranulocytosis, leucopenia, thrombocytopenia.

- Metabolism and nutrition disorders:

Common: Anorexia.

Not known: Hypoglycemia.

Hydroxychloroquine may exacerbate porphyria.

- Hepatobiliary disorders:

Uncommon: Abnormal liver function tests.

Not known: Fulminant hepatic failure.

- Immune system disorders:

Not known: Urticaria, angioedema, bronchospasm.

4.9 Overdose

Signs and Symptoms

Overdosage with the 4-aminoquinolines is particularly dangerous in infants, as little as 1- 2 grams having proved fatal

The symptoms of overdosage may include headache, visual disturbances, cardiovascular collapse, convulsions, hypokalaemia rhythm and conduction disorders, including QT prolongation, torsade de pointes, ventricular tachycardia and ventricular fibrillation, width-increased QRS complex, bradyarrhythmias, nodal rhythm, atrioventricular block followed by sudden potentially fatal respiratory and cardiac arrest. Immediate medical attention is required, as these effects may appear shortly after the overdose

Management

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.

5. Pharmacological Properties

5.1 Pharmacodynamic Properties

Antimalarial agents like chloroquine and hydroxychloroquine have several pharmacological actions which may be involved in their therapeutic effect in the treatment of rheumatic disease, but the role of each is not known. These include interaction with sulphhydryl groups, interference with enzyme activity (including phospholipase, NADH – cytochrome C reductase, cholinesterase, proteases and hydrolases), DNA binding, stabilisation of lysosomal membranes, inhibitions of prostaglandin formation, inhibition of polymorphonuclear cell chemotaxis and phagocytosis, possible interference with interleukin 1 production from monocytes and inhibition of neutrophil superoxide release.

5.2 Pharmacokinetic Properties

Hydroxychloroquine has actions, pharmacokinetics and metabolism similar to those of chloroquine.

Absorption

Following oral administration, peak blood concentrations is achieved in approximately 4 hours. Oral absolute bioavailability is 79%.

Distribution

Hydroxychloroquine has a large volume of distribution due to extensive tissue accumulation (5500 L in blood, 44 000 L in plasma), and has been shown to accumulate in blood cells, with a blood to plasma ratio of 7.2. Approximately 50% of hydroxychloroquine is bound to plasma proteins.

Metabolism

Hydroxychloroquine is mainly metabolized to N-desethylhydroxychloroquine, and two other metabolites in common with chloroquine, desethylchloroquine and bidesethylchloroquine. It can be extrapolated from chloroquine, that hydroxychloroquine could be metabolized in vitro by the same CYPs as for chloroquine, i.e. CYP2C8 and CYP3A, and to a lesser extent by CYP2D6.

Elimination

Hydroxychloroquine presents a multi-phasic elimination profile with a long terminal half-life ranging from 30 to 60 days. Approximately 20-25% of the hydroxychloroquine dose is eliminated as unchanged drug in the urine.

5.3 Preclinical Safety Data

Only limited preclinical data are available for hydroxychloroquine, therefore chloroquine data are considered due to the similarity of structure and pharmacological properties between the 2 products.

6 Pharmaceutical Particulars

6.1 List of Excipients

Lactose Monohydrate, Maize Starch, Povidone K30, Magnesium Stearate, Opadry II 85F580019 white (containing Polyvinyl alcohol-part. Hydrolyzed, Talc, Macrogol/PEG, Titanium Dioxide)

6.2 Incompatibilities

No incompatibilities are known

6.3 Shelf Life

2 years.

6.4 Special Precautions for Storage

Store below 30°C.

6.5 Nature and Contents of Container

6 x 10 tablets in clear PVC/aluminium foil blister pack.

6.6 Special precautions for disposal

None.

7 Product Registrant

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