

QUINNEL 200 mg Film-coated Tablet

COMPOSITION

Each film-coated tablet contains Hydroxychloroquine sulfate 200 mg.

DESCRIPTION

White round biconvex film-coated tablet debossed with "H, 200" on one side and plain on the other.

PHARMACODYNAMICS

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, inhibition of prostaglandin formation, inhibition of polymorphonuclear cell chemotaxis and phagocytosis, possible interference with interleukin 1 production from monocytes and inhibition of neutrophil superoxide release.

PHARMACOKINETICS

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

Absorption: Following oral administration, peak plasma or blood concentrations is achieved in approximately 3 to 4 hours. Mean absolute oral bioavailability is 79% (SD 12%) in fasting conditions. Food does not modify the oral bioavailability of hydroxychloroquine.

Distribution: Hydroxychloroquine has a large volume of distribution (5500 L when assessed from blood concentrations, 44000 L when assessed from plasma concentrations), due to extensive tissue accumulation (such as eyes, kidney, liver and lungs) 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-desethyl-hydroxychloroquine, and two other metabolites in common with chloroquine, desethylchloroquine and bidesethylchloroquine. *In vitro*, hydroxychloroquine is metabolized mainly by CYP2C8, CYP3A4 and CYP2D6 as well as by FMO-1 and MAO-A, with no major involvement of a single CYP or enzyme.

Elimination: Hydroxychloroquine presents a multi-phasic elimination profile with a long terminal half-life ranging from 30 to 50 days. Approximately 20-25% of the hydroxychloroquine dose is eliminated as unchanged drug in the urine.

INDICATION

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

RECOMMENDED DOSAGE

Adults (including the elderly)

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

In patients able to receive 400 mg daily

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

Paediatric population

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

Method of Administration

The tablets are for oral administration.

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 no improvement by 6 months. In light-sensitive diseases, treatment should only be given during periods of maximum exposure to light.

CONTRAINDICATIONS

- Known hypersensitivity to 4-aminoquinoline compounds.
- Pre-existing maculopathy of the eye.
- Children below 6 years of age (200 mg tablets not adapted for weight <31 kg).

WARNINGS AND PRECAUTIONS

Retinopathy

The occurrence of retinopathy is very uncommon if the recommended daily dose is not exceeded. The administration of doses in excess of the recommended maximum is likely to increase the risk of retinopathy, and accelerate its onset.

All patients should have an ophthalmological examination before initiating treatment with hydroxychloroquine sulfate. Thereafter, ophthalmological examinations must be repeated at least every 12 months.

The examination should include testing visual acuity, careful ophthalmoscopy, fundoscopy, central visual field testing with a red target, and colour vision. This examination should be more frequent and adapted to the patient in the following situations:

- daily dosage exceeds 6.5 mg/kg lean body weight. Absolute body weight used as a guide to dosage could result in an overdose in the obese.
- renal insufficiency
- visual acuity below 6/8
- age above 65 years
- cumulative dose more than 200 g

- concomitant use of hydroxychloroquine sulfate with drugs known to induce retinal toxicity, such as tamoxifen.

Hydroxychloroquine sulfate should be discontinued immediately in any patient who develops a pigmentary abnormality, visual field defect, or any other abnormality not explainable by difficulty in accommodation or presence of corneal opacities. Patients should continue to be observed for possible progression of the changes.

Patients should be advised to stop taking the drug immediately and seek the advice of their prescribing doctor if any disturbances of vision are noted, including abnormal colour vision.

Hypoglycaemia

Hydroxychloroquine 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 hydroxychloroquine 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 hydroxychloroquine should have their blood glucose level checked and treatment reviewed as necessary.

QT interval prolongation

Hydroxychloroquine has the 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 hypokalaemia and/or hypomagnesaemia
- during concomitant administration with QT interval prolonging agents 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.

Chronic cardiac toxicity

Cases of cardiomyopathy resulting in cardiac failure, in some cases with fatal outcome, have been reported in patients treated with hydroxychloroquine sulfate. Clinical monitoring for signs and symptoms of cardiomyopathy is advised and hydroxychloroquine sulfate should be discontinued if cardiomyopathy develops. Chronic toxicity should be considered when conduction disorders (bundle branch block/ atrioventricular heart block) as well as biventricular hypertrophy are diagnosed.

Bone marrow depression

Although the risk of bone marrow depression is low, periodic blood counts are advisable as anaemia, aplastic anaemia, agranulocytosis, a decrease in white blood cells, and thrombocytopenia have been reported. Hydroxychloroquine sulfate should be discontinued if abnormalities develop.

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.

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.

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 is insufficient data to rule out an increased risk of cancer in patients receiving long-term treatment.

Extrapyramidal disorders

Extrapyramidal disorders may occur with hydroxychloroquine sulfate.

Suicidal behaviour and psychiatric disorders

Suicidal behaviour and psychiatric disorders have been reported in some patients treated with hydroxychloroquine. Psychiatric side effects typically occur within the first month after the start of treatment with hydroxychloroquine and have been reported also in patients with no prior history of psychiatric disorders. Patients should be advised to seek medical advice promptly if they experience psychiatric symptoms during treatment.

Severe cutaneous adverse reactions (SCARs)

Cases of severe cutaneous adverse drug reactions (SCAR), including drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported during treatment with hydroxychloroquine. Patients with serious dermatological reactions may require hospitalization, as these conditions may be life-threatening and may be fatal. If signs and symptoms suggestive of severe skin reactions appear, hydroxychloroquine should be withdrawn at once and alternative therapy should be considered.

Carefully consider the benefits and risks before prescribing hydroxychloroquine for any patients taking azithromycin or other macrolide antibiotics, because of the potential for an increased risk of cardiovascular events and cardiovascular mortality.

Hydroxychloroquine should be used with caution in patients taking medicines which may cause adverse ocular or skin reactions. Caution should also be applied when it is used in the following:

- Patients with a sensitivity to quinine, those with glucose-6-phosphate dehydrogenase deficiency, those with porphyria cutanea tarda which can be exacerbated by hydroxychloroquine and in patients with psoriasis since it appears to increase the risk of skin reactions.
- Patients with hepatic or renal disease, and in those taking drugs known to affect those organs. Estimation of plasma hydroxychloroquine levels should be undertaken in

patients with severely compromised renal or hepatic function and dosage adjusted accordingly.

- Patients with severe gastrointestinal, neurological or blood disorders.

Hepatotoxicity

Serious cases of drug-induced liver injury (DILI) including hepatocellular injury, cholestatic liver injury, acute hepatitis, mixed hepatocellular/cholestatic liver injury and fulminant hepatic failure (including fatal cases) have been reported during use of hydroxychloroquine sulfate.

Risk factors may include pre-existing liver disease, or predisposing conditions such as uroporphyrinogen decarboxylase deficiency or concomitant hepatotoxic medications. Prompt clinical evaluation and measurement of liver function tests should be performed in patients who report symptoms that may indicate liver injury. For patients with significant liver function abnormalities, physicians should assess the benefits / risk of continuing the treatment.

Hepatitis B reactivation

Reactivation of hepatitis B virus has been reported in patients treated with hydroxychloroquine in combination with other immunosuppressants.

Paediatric population

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

Excipients

QUINNEL contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Effects on ability to drive and use machines

Impaired visual accommodation soon after the start of treatment, which can cause blurring of vision, has been reported and patients should be warned regarding driving or operating machinery. If the condition is not self-limiting, it will resolve on reducing the dose or stopping treatment.

DRUG INTERACTIONS

Drugs known to prolong the 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 (e.g. macrolides including azithromycin) due to increased risk of ventricular arrhythmia. Halofantrine should not be administered with hydroxychloroquine. There may be an increased risk of inducing ventricular arrhythmias if hydroxychloroquine is used concomitantly with other arrhythmogenic drugs, such as amiodarone and moxifloxacin.

Antidiabetic drugs: As hydroxychloroquine may enhance the effects of a hypoglycaemic treatment, a decrease in doses of insulin or antidiabetic drugs may be required.

Tamoxifen: Concomitant use of drugs known to induce retinal toxicity, e.g. tamoxifen and hydroxychloroquine sulfate, is not recommended.

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

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: The activity of antiepileptic drugs might be impaired if co-administered with hydroxychloroquine.

Hydroxychloroquine sulfate 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.

Antacids: As with chloroquine, antacids may reduce absorption of hydroxychloroquine so it is advised that a 4 hour interval be observed between hydroxychloroquine and antacid dosing.

Azithromycin and macrolide antibiotics: Observational data have shown that co-administration of hydroxychloroquine with azithromycin in patients with rheumatoid arthritis is associated with an increased risk of cardiovascular events and cardiovascular mortality. Carefully consider the balance of benefits and risks before prescribing hydroxychloroquine for any patients taking azithromycin. Similar careful consideration of the balance of benefits and risk should also be undertaken before prescribing hydroxychloroquine for any patients taking other macrolide antibiotics, such as clarithromycin or erythromycin, because of the potential for a similar risk when hydroxychloroquine is co-administered with these medicines.

Praziquantel: 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.

CYP inhibitors or inducers: *In vitro*, hydroxychloroquine is metabolized mainly by CYP2C8, CYP3A4 and CYP2D6, with no major involvement of a single CYP. Concomitant use of cimetidine, a CYP-pan inhibitor, resulted in a 2-fold increase of chloroquine exposure. In the absence of *in vivo* drug interaction studies, caution is advised (e.g. monitoring for adverse reactions) when cimetidine or CYP2C8 and/or CYP3A4 or CYP2D6 strong inhibitors (such as gemfibrozil, clopidogrel, ritonavir, itraconazole, clarithromycin, grapefruit juice, fluoxetine, paroxetine, quinidine) 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/or CYP3A4 strong inducers (such as rifampicin, St. John's Wort, carbamazepine, phenobarbital, phenytoin) are concomitantly administered.

P-glycoprotein (P-gp) substrates: Hydroxychloroquine inhibits P-gp *in vitro* at high concentrations. Therefore, there is a potential for increased concentrations of P-gp substrates when hydroxychloroquine is concomitantly administered. Increased digoxin serum levels were reported when digoxin and hydroxychloroquine were co-administered. 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, dabigatran) are concomitantly administered.

CYP2D6 substrates: Hydroxychloroquine inhibits CYP2D6 *in vitro*. In patients receiving hydroxychloroquine and a single dose of metoprolol, a CYP2D6 probe, the C_{max} and AUC of metoprolol were increased by 1.7-fold, which suggests that hydroxychloroquine is a mild inhibitor of CYP2D6. Caution is advised (e.g. monitoring for adverse reactions or for plasma concentrations as appropriate) when CYP2D6 substrates with narrow therapeutic index (such as flecainide, propafenone) are concomitantly administered.

CYP3A4 substrates: Hydroxychloroquine inhibits CYP3A4 *in vitro*. An increased plasma level of ciclosporin (a CYP3A4 and P-gp substrate) was reported when ciclosporin and hydroxychloroquine were co-administered. In the absence of *in vivo* interaction studies with sensitive CYP3A4 substrates, caution is advised (e.g. monitoring for adverse reactions) when CYP3A4 substrates (such as ciclosporin, statins) are concomitantly administered with hydroxychloroquine.

PREGNANCY AND LACTATION

Pregnancy

Animal studies with the structurally related chloroquine, have shown reproduction toxicity at high maternal exposure. In humans, hydroxychloroquine crosses the placenta and blood concentrations in the foetus are similar to maternal blood concentrations. 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 haemorrhages and abnormal retinal pigmentation.

Therefore, hydroxychloroquine sulfate should be avoided in pregnancy except when, in the judgement of the physician, the individual potential benefits outweigh the potential hazards. If treatment with hydroxychloroquine is necessary during pregnancy, the lowest effective dose should be used. In case of prolonged treatment during pregnancy, hydroxychloroquine safety profile in particular ophthalmological side effects should be taken into account for child monitoring.

Lactation

Hydroxychloroquine is excreted in breast milk (less than 2% of the maternal dose after body weight correction). Careful consideration should be given to long-term treatment with hydroxychloroquine during lactation because of the slow elimination rate and the potential for accumulation of a toxic amount in the infant. It is known that infants are extremely sensitive to the toxic effects of 4-aminoquinolines.

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.

SIDE EFFECTS

Blood and lymphatic system disorders

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

Immune system disorders

Not known: Urticaria, angioedema, bronchospasm

Metabolism and nutrition disorders

Common: Anorexia

Not known: Hypoglycaemia

Hydroxychloroquine may precipitate or exacerbate porphyria.

Psychiatric disorders

Common: Affect lability

Uncommon: Nervousness

Not known: Suicidal behaviour, psychosis, depression, hallucinations, anxiety, agitation, confusion, delusions, mania and sleep disorders.

Nervous system disorders

Common: Headache

Uncommon: Dizziness

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

Extrapyrarnidal disorders such as dystonia, dyskinesia, tremor.

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 form, it appears reversible on discontinuation of hydroxychloroquine sulfate. If allowed to develop, there may be a 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.

Ear and labyrinth disorders

- Uncommon: Vertigo, tinnitus
Not known: Hearing loss

Cardiac disorders

- Not known: QT interval prolongation in patients with specific risk factors, which may lead to arrhythmia (torsade de pointes, ventricular tachycardia). Cardiomyopathy which may result in cardiac failure and in some cases a fatal outcome. Chronic toxicity should be considered when conduction disorders (bundle branch block/atrioventricular heart block) as well as biventricular hypertrophy are found. Drug withdrawal may lead to recovery.

Gastrointestinal disorders

- Very common: Abdominal pain, nausea
Common: Diarrhoea, vomiting
These symptoms usually resolve immediately on reducing the dose or on stopping treatment.

Hepatobiliary disorders

- Uncommon: Abnormal liver function tests
Not known: Drug-induced liver injury (DILI) including hepatocellular injury, cholestatic liver injury, acute hepatitis, mixed hepatocellular / cholestatic liver injury and fulminant hepatic failure.

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: Erythema multiforme, photosensitivity, exfoliative dermatitis, Sweet's syndrome and Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug rash with eosinophilia and systemic symptoms (DRESS), acute generalised 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.

Musculoskeletal and connective tissue disorders

- Uncommon: Sensory motor 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.

SYMPTOMS AND TREATMENT OF OVERDOSE

Overdose with the 4-aminoquinolines is dangerous particularly in infants, as little as 1 – 2 g having proved fatal.

Symptoms: The symptoms of overdose may include headache, visual disturbances, cardiovascular collapse, convulsions and 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 and 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 by gastric lavage. Activated charcoal in a dose at least five times 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 administration of parenteral diazepam in cases of overdose; it has been shown to be beneficial in reversing chloroquine cardiotoxicity. Respiratory support and shock management should be instituted as necessary.

PACK SIZE

Aluminium-white PVC blister pack of 10 tablets.
Each box contains 10 blisters of 10's.

STORAGE CONDITION

Store below 30°C.
Keep out of reach of children.
Jauhi daripada kanak-kanak.

SHELF LIFE: Please refer to the outer box label.

MANUFACTURED BY:

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