Plaquenil-Hydroxychloroquine sulfate 200mg Film-coated Tablets

Summary of Product Characteristics Updated 10-Mar-2020 | Zentiva

1. Name of the medicinal product

Plaquenil 200 mg Film-coated Tablets

Hydroxychloroquine sulfate 200 mg film-coated Tablets

2. Qualitative and quantitative composition

Hydroxychloroquine Sulfate 200 mg

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Film coated tablet.

White, round, film-coated tablets marked 'HCQ' on one side and '200' on the other side.

4. Clinical particulars

4.1 Therapeutic indications

Adults

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

Paediatric population

Treatment of juvenile idiopathic arthritis (in combination with other therapies), discoid and systemic lupus erythematosus.

4.2 Posology and method of administration

Posology

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.

4.3 Contraindications

- Known hypersensitivity to 4-aminoquinoline compounds or to any of the excipients listed in section 6.1.
- Pre-existing maculopathy of the eye.

4.4 Special warnings and precautions for use

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... target, and colour vision.

...is 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.

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.

Extrapyramidal disorders

Extrapyramidal disorders may occur with hydroxychloroquine sulfate (see section 4.8).

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.

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 (see sections 4.8 and 4.9). 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/atrio-ventricular heart block) as well as biventricular hypertrophy are diagnosed (see section 4.8).

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 (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).

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 (see section 5.3). In humans, there are insufficient data to rule out an increased risk of cancer in patients receiving long-term treatment.

Hydroxychloroquine sulfate should be used with caution in patients taking medicines which may cause adverse 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.

Lactose intolerance

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

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.

4.5 Interaction with other medicinal products and other forms of interaction

Hydroxychloroquine sulfate has been reported to increase plasma digoxin levels. Serum digoxin levels should be closely monitored in patients receiving concomitant treatment.

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.

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

As hydroxychloroquine may enhance the effects of a hypoglycaemic treatment, a decrease in doses of insulin or anti-diabetic drugs may be required.

Halofantrine prolongs the QT interval and should not be administered with other drugs that have the potential to induce cardiac arrhythmias, including hydroxychloroquine. Also, there may be an increased risk of inducing ventricular arrhythmias if hydroxychloroquine is used concomitantly with other arrhythmogenic drugs, such as amiodarone and moxifloxacin.

An increased plasma ciclosporin level was reported when ciclosporin and hydroxychloroquine were co-administered.

Hydroxychloroquine can lower the convulsive threshold. Co-administration of hydroxychloroquine with other anti-malarials known to lower the convulsion threshold (e.g mefloquine) may increase the risk of convulsions. Also, the activity of anti-epileptic drugs might be impaired if co-administered with hydroxychloroquine.

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.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

A moderate amount of data on pregnant women (between 300 – 1000 pregnancy outcomes), including prospective studies in long-term use with large exposure, have not observed a significant increased risk of congenital malformations or poor pregnancy outcomes.

Hydroxychloroquine crosses the placenta.

Only limited non-clinical data are available for hydroxychloroquine, data on chloroquine have shown developmental toxicity at high supratherapeutic doses and a potential risk of genotoxicity in some test systems (see section 5.3).

Therefore hydroxychloroquine sulfate should be avoided in pregnancy except when, in the judgement of the physician, the individual potential benefits outweigh the potential hazards.

Breast-feeding

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.

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

Impaired visual accommodation soon after the start of treatment 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.

4.8 Undesirable effects

The following CIOMS frequency rating is used, when applicable:

V... y common ≥ 10 %; Common ≥ 1 and <10 %; Uncommon ≥ 0.1 and < 1 %; Rare ≥ 0.01 and < 0.1 %; Very rare ... 0.0... Not known (frequency cannot be estimated from available data).

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: hypoglycemia

Hydroxychloroquine may precipitate or exacerbate porphyria.

Psychiatric disorders

Common: affect lability

Uncommon: nervousness

Not known: psychosis

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).

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, peri-central 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 (the onset ranging from 3 months to several years of exposure to hydroxychloroquine) and may be irreversible.

Ear and labyrinth disorders

Uncommon: vertigo, tinnitus

Not known: hearing loss

Cardiac disorders

Not known: cardiomyopathy which may result in cardiac failure and in some cases a fatal outcome (see sections 4.4 and 4.9)

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: 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:

• 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 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.

Metabolism and nutrition disorders

Not known: hypoglycaemia (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

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

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, followed by sudden potentially fatal respiratory and cardiac arrest. Immediate medical attention is required, as these effects may appear shortly after the overdose.

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.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimalarials, Aminoquinolines, ATC code: P01B A02.

Mechanism of action

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 sulphydryl 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.

5.2 Pharmacokinetic properties

Hydroxychloroquine has actions, pharmacokinetics and metabolism similar to those of chloroquine. Following oral administration, hydroxychloroquine is rapidly and almost completely absorbed. In one study, mean peak plasma

hydroxychloroquine concentrations following a single dose of 400 mg in healthy subjects ranged from 53 – 208 ng/ml with a mean of 105 ng/ml. The mean time to peak plasma concentration was 1.83 hours. The mean plasma elimination half-life varied, depending on the post administration period, as follows: 5.9 hours at C_{max} – 10 hours), 26.1 hours (at ... – 48 hours and 299 hours (at 48 – 504 hours). The parent compound and metabolites are widely distributed in the body and elimination is mainly via the urine, where 3% of the administered dose was recovered over 24 hours in one study.

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 two products.

Genotoxicity

There are limited data on hydroxychloroquine genotoxicity. Chloroquine is reported in the literature to elicit both gene mutations and chromosomal/DNA breaks in some *in vitro* systems but not in others and in *in vivo* studies using rodents when dosed via the intraperitoneal route. Chromosomal effects were not observed *in vivo* when chloroquine was administered orally.

Carcinogenicity

There are no data on hydroxychloroquine carcinogenicity.

In a limited 2-years study in rats with chloroquine, no increase in neoplastic or proliferative changes was observed.

Developmental and reproductive toxicity

There are limited data on hydroxychloroquine teratogenicity. Chloroquine is teratogenic in rats after administration at very high, supratherapeutic doses, i.e. between 250 – 1500 mg/kg/day, showing a fetal mortality rate of 25% and ocular malformations (anophthalmia and microophthalmia) in 45% of foetuses in the 1000 mg/kg/day group. Auto-radiographic studies have shown that when administered at the start or the end of gestation, chloroquine accumulates in the eyes and ears of fetuses.

A study in male rats after 30 days of oral treatment at 5 mg/day of chloroquine showed a decrease in fertility rate, and in testosterone levels, weight of testes, epididymis, seminal vesicles and prostate.

6. Pharmaceutical particulars

6.1 List of excipients

- Lactose monohydrate
- Maize starch
- Magnesium stearate
- Polyvidone
- Opadry OY-L-28900 (containing hypromellose, macrogol 4000, titanium dioxide (E171), lactose)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

Amber glass bottles with a tin plate screw cap containing 100 tablets.

HDPE bottle with LDPE cap containing 56 tablets.

250 µm clear PVC/20 µm aluminium foil blister pack containing 56 or 60 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Not applicable.

7. Marketing authorisation holder

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8. Marketing authorisation number(s)

PL 17780/0748

9. Date of first authorisation/renewal of the authorisation

30/09/1994

10. Date of revision of the text

02/03/2020

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