PLAQUENIL ®

Hydroxychloroquine Sulphate

SANOFI

1 Name of the Medicinal Product

Plaquenil Tablets

2 Qualitative and Quantitative Composition

Hydroxychloroquine Sulphate BP 200mg

3 Pharmaceutical Form

Film coated tablet.

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 (see section 4.2)

4.4 Special Warning and Special Precautions for Use

Retinopathy

- All patients should have an ophthalmological examination before treatment with Plaquenil is initiated. Thereafter, ophthalmological examinations must be repeated at least every 12 months.
- 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 dose sharply increases the risk of retinal toxicity.

The examination should include testing visual acuity and colour vision, careful ophthalmoscopy, fundoscopy and central visual field testing with a red target.

This examination should be more frequent and adapted to the patient in the following situations:

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

Plaquenil should be discontinued immediately in any patient who develops a pigmentary abnormality, visual field defect or any other abnormalities not explained by difficulty in accommodation (see also section 4.8). Patients should continue to be observed as retinal changes and visual disturbances may progress even after cessation of therapy (see also section 4.8).

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

Hypoglycemia

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 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 medicine. Therefore, the recommended dose should not be exceeded (see also sections 4.5 and 4.8).

If signs of cardiac arrhythmia occur during treatment with hydroxychloroquine, treatment should be stopped and an ECG should be performed.

Chronic cardiac toxicity
Cases of cardiomyopathy resulting in cardiac failure, in some cases with fatal outcome, have been reported in patients treated with Plaquenil (see section 4.8 and Section 4.9). Clinical monitoring for signs and symptoms of cardiomyopathy is advised and Plaquenil 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 precautions
Plaquenil 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 hepatic or renal disease, and in those taking medicines 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.

Caution is also advised in 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.

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

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, hydroxychloroquine should be withdrawn (see section 4.8).

Potential carcinogenic risk
Animal carcinogenicity data are only available for one species for the parent medicine 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.

Suicidal behaviour and psychiatric disorders
Suicidal behaviour and psychiatric disorders have been reported in some patients treated with hydroxychloroquine (see Section 4.8). 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.

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

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

4.5 Interactions with other medicinal products and other forms of interaction

Pharmacodynamic interactions
Medicines known to prolong QT interval / with potential to induce cardiac arrhythmia:
Hydroxychloroquine should be used with caution in patients receiving medicines known to prolong the QT interval, e.g., Class IA and III antiarrhythmics, tricyclic antidepressants, antipsychotics, some anti-infectives (antibacterials such as fluoroquinolones e.g. moxifloxacin, macrolides e.g. azithromycin, antiretrovirals such as saquinavir, antifungals such as fluconazole, antiparasitic medicines such as pentamidine) due to increased risk of ventricular arrhythmia (see sections 4.4, 4.8 and 4.9). Halofantrine should not be administered with hydroxychloroquine.

Insulin and antidiabetic drugs
As hydroxychloroquine may enhance the effects of a hypoglycemic treatment, a decrease in doses of insulin or antidiabetic medicines may be required (see also section 4.4 "Hypoglycaemia" and section 4.8).

Antimalarials
Administration of hydroxychloroquine with antimalarials known to lower the convulsion threshold (e.g. mefloquine) may increase the risk of convulsions (see section 4.8).

Antiepileptic drugs
The activity of antiepileptic medicines 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.

Others
Concurrent use with medicines with oculotoxic potential (see also 4.4 “retinopathy”) or haemotoxic potential should be avoided if possible, because of potential additive effect (see section 4.8).

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; antagonism of effect of neostigmine and pyridostigmine; reduction of the antibody response to primary immunisation with intradermal human diploid-cell rabies vaccine.

Pharmacokinetic interactions

Effects of other medicinal products on hydroxychloroquine:

Antacids and kaolin

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 mild/moderate inhibitor of several CYPs including CYP2C8 and CYP3A4, 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, phenytoin) are concomitantly administered.

Effects of hydroxychloroquine on other medicinal products:

P-glycoprotein 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.

CYP2D6 substrates

In patients receiving hydroxychloroquine and a single dose of metoprolol, a CYP2D6 probe, the Cmax 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 such as flecainide, propafenone) 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 coadministered. 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

A moderate amount of data in pregnant women (between 300-1000 prospective pregnancies) from observational studies, as well as a meta-analysis with high and long-term exposure (mainly in the indication autoimmune disease) do not show a statistically significant increased risk of congenital malformations or feto/neonatal toxicity related to hydroxychloroquine. Animal studies with the structurally related chloroquine, have shown reproduction toxicity at high maternal exposure (see section 5.3). In humans, hydroxychloroquine crosses the placenta and blood concentrations in the foetus are similar to maternal blood concentrations.

Hydroxychloroquine sulfate should be avoided in pregnancy except when, in the judgment 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 bodyweight 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.

Fertility

Animal studies showed an impairment of male fertility for chloroquine (see section 5.3). There are no data on the effects of hydroxychloroquine on fertility in humans.

4.7 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.

4.8 Undesirable Effects

The following CIOMS frequency rating is used, when applicable:
Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000), Very rare (<1/10,000), Not known (cannot be estimated from the available data).

	Very common	*Common*	*Uncommon*	*Rare*	*Very rare*	*Not known*
Blood and lymphatic system disorders						Bone marrow depression, anemia, aplastic anemia, agranulocytosis, leucopenia, thrombocytopenia.

	Very common	*Common*	*Uncommon*	*Rare*	*Very rare*	*Not known*
Immune system disorders						Urticaria, angioedema, bronchospasm
Metabolism and nutrition disorders		Anorexia				Hypoglycemia Hydroxychloroquine may exacerbate porphyria
Psychiatric disorders		Affect lability	Nervousness			Psychosis, suicidal behaviour, depression, hallucinations, anxiety, agitation, confusion, delusions, mania and sleep disorders.
Nervous system disorders		Headache	Dizziness			Convulsions have been reported with this class of medicines. Extrapyramidal disorders such as dystonia, dyskinesia, tremor (see section 4.4).
Eye disorders		Blurring of vision due to a disturbance of accommodation which is dose dependent and reversible	Retinopathy, with changes in pigmentation and visual field defects. 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. 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 edema and opacities have been reported. They are either symptomless or may cause disturbances such as halos, blurring of vision, or photophobia. They may be transient or are reversible on stopping treatment.			Cases of maculopathies and macular degeneration have been reported and may be irreversible.
Ear and labyrinth disorders			Vertigo, tinnitus			Hearing loss

	Very common	*Common*	*Uncommon*	*Rare*	*Very rare*	*Not known*
Cardiac disorders						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 (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. Hydroxychloroquine withdrawal may lead to recovery.
Gastrointestinal disorders	Abdominal pain, nausea	Diarrhoea, vomiting These symptoms usually resolve immediately on reducing the dose or on stopping the treatment.				
Hepatobiliary disorders			Abnormal liver function tests			Fulminant hepatic failure
Skin and subcutaneous tissue disorders		Skin rash, pruritus	Pigmentation disorders in skin and mucous membranes, bleaching of hair, alopecia These usually resolve readily on stopping treatment.			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.

	Very common	*Common*	*Uncommon*	*Rare*	*Very rare*	*Not known*
						Outcome is usually favourable after hydroxychloroquine withdrawal.
Musculoskeletal and connective tissue disorders			Sensorimotor disorders			Skeletal muscle myopathy or neuromyopathy leading to progressive weakness and atrophy of proximal muscle groups. Myopathy may be reversible after hydroxychloroquine discontinuation, but recovery may take many months. Depression of tendon reflexes and abnormal nerve conduction studies

4.9 Overdose

Overdosage with the 4-aminoquinolines is dangerous particularly in infants, as little as 1- 2 g 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 and 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 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 administration of parenteral diazepam in cases of overdosage; 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

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

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%).

Distribution
Hydroxychloroquine has a large volume of distribution due to extensive tissue accumulation (5500 L when assessed from blood concentrations, 44 000 L when assessed from plasma concentrations), 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.

Biotransformation
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.
After chronic repeated oral administration of 200 mg and 400 mg hydroxychloroquine sulfate once a day in adult patients with lupus or rheumatoid arthritis, the average steady-state concentrations were around 450-490 ng/mL and 870-970 ng/mL in blood, respectively.
Predictions from single dose pharmacokinetic studies indicate that steady-state of blood concentrations is reached within 4 months of treatment.

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 product in the urine.

5.3 Preclinical Safety Data
Genotoxicity/Carcinogenicity
Based on the studies conducted, hydroxychloroquine is not found to be genotoxic. No relevant non-clinical carcinogenicity studies on hydroxychloroquine are available.

Reproductive and developmental toxicity
Hydroxychloroquine crosses the placenta. In non-GLP studies with mice and monkeys, transplacental transfer of chloroquine, a substance related to hydroxychloroquine, was demonstrated with accumulation in foetal eye and ear tissue. High maternal doses of chloroquine were foetotoxic in rats and caused anophthalmia and microphthalmia. In studies in rats, chloroquine reduced the testosterone secretion, the weight of the testis and epididymis and caused production of abnormal sperm.

There are no preclinical safety data of relevance to the prescriber, which are additional to that already included in other sections of the package insert.

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), monohydrate lactose).

6.2 Incompatibilities
No incompatibilities are known

6.3 Shelf Life
2 years.

6.4 Special Precautions for Storage
Store below 30ºC.

6.5 Nature and Contents of Container
250µm clear PVC/20 µm aluminium foil blister pack containing 56 or 60 tablets.
Not all presentations may be available locally.

6.6 Special precautions for disposal
None.

7 Product Licence Holder
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