Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Plaquenil 200mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:
Hydroxychloroquine sulphate 200 mg
Excipients: Lactose monohydrate 35.25mg tablet

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated Tablet
white, biconvex tablets with flat sides, marked HCQ on one side and 200 on the reverse.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Adults
Plaquenil tablets are recommended for the 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

Plaquenil 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.

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. The 400mg tablet should not be used in adults with an ideal body weight of less than 62kg.

Paediatric Population

The minimum effective dose 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 31kg.

4.3 Contraindications

- known hypersensitivity to 4-aminoquinoline compounds
- pre-existing maculopathy of the eye
- below 6 years of age (200mg tablets not adapted for weight <35kg) or for ideal body weight < 31 kg (see section 4.2)

4.4 Special warnings and 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 200 g.

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 drugs known to induce retinal toxicity, such as tamoxifen, is not recommended.

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 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).

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).

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.

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

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, 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.

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

Extrapyramidal disorders may occur with Plaquenil (See Section 4.8).

4.5 Interaction with other medicinal products and other forms of interactions

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

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.

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 4.4 and 4.9). Halofantrine should not be administered with hydroxychloroquine.

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

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

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

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

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.

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

Concurrent use with drugs with oculotoxic or haemotoxic potential should be avoided if possible.

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

4.6 Fertility, pregnancy and lactation

Pregnancy:
Only limited non-clinical data are available for hydroxychloroquine. In animal studies, reproduction toxicity was found with chloroquine, a substance related to hydroxychloroquine, following high maternal exposure. Chloroquine preclinical data show a potential risk of genotoxicity in some test systems (see section 5.3)

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 crosses the placenta. 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 hemorrhages and abnormal retinal pigmentation. These effects were not confirmed in larger series/observational studies. 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

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

Fertility
There is no information available on the effect of Hydroxychloroquine sulfate on human fertility. In animal studies, chloroquine, a substance related to hydroxychloroquine, showed adverse effects on male fertility (see section 5.3).

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.

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*	*Uncommon*	*Rare*	*Very rare*	*Not known*

	common					
Blood and lymphatic system disorders						Bone marrow depression, anemia, aplastic anemia, agranulocytosis, leucopenia, thrombocytopenia.
Immune system disorders						Urticaria, angioedema, bronchospasm
Metabolism and nutrition disorders		Anorexia				Hypoglycemia Hydroxychloroquine may exacerbate porphyria
Psychiatric disorders		Affect lability	Nervousness			Psychosis, suicidal behaviour
Nervous system disorders		Headache	Dizziness			Convulsions have been reported with this class of drugs. 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
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. Drug 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. Outcome is usually favourable after drug 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 drug discontinuation, but recovery may take many months. Depression of tendon reflexes and abnormal nerve conduction studies

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 HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

Overdosage with the 4-aminoquinolines is dangerous particularly in infants, as little as 1-2g 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 by gastric lavage. Activated charcoal in a dose at least five times that of the overdosage 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

Hydroxychloroquine is rapidly absorbed following oral administration. Mean bioavailability is approximately 74%. It is widely distributed throughout the body, accumulating within blood cells and other tissues such as liver, lungs, kidneys and eyes. It is partially converted to active ethylated metabolites in the liver and eliminated principally via the kidney, 23 to 25% unchanged, but also via the bile. Excretion is slow, the terminal elimination half-life being approximately 50 days (whole blood) and 32 days (plasma).

Hydroxychloroquine crosses the placenta and is likely to resemble chloroquine in entering breast milk.

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.

Genotoxicity/Carcinogenicity
There are limited data on hydroxychloroquine genotoxicity or carcinogenicity. Chloroquine, a substance related to hydroxychloroquine was genotoxic in non-GLP in-vitro tests. A non-GLP 2-year dietary administration carcinogenicity study of chloroquine in rats did not show any carcinogenic potential.
Reproductive and developmental toxicity
Hydroxychloroquine crosses the placenta. In non-GLP studies with mice and monkeys, transplacental transfer 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 microophthalmia. 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 SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose Monohydrate
Maize starch
Magnesium stearate
Povidone
Opadry OY-L-28900
(Containg Hypromellose, Macrogol 4000, Titanium Dioxide (E171), Lactose Monohydrate)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

i) Amber glass bottle with tin plate screw cap. Pack size 100 tablets.

ii) HDPE bottle with LDPE cap. Pack size 56 tablets.

iii) PVC/aluminium foil blister pack. Pack size 56 or 60 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Ireland Limited T/A SANOFI
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0540/155/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1st April 1977

Date of last renewal: 1st April 2007.

10 DATE OF REVISION OF THE TEXT

March 2020