Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Plaquenil 200 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200 mg Hydroxychloroquine sulphate

Excipient: Lactose monohydrate.

For a full list of excipients see 6.1

3 PHARMACEUTICAL FORM

Film-coated Tablet

Product imported from Greece:
White, biconvex tablets with flat sides, marked HCQ on one side and 200 on the reverse.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Plaquenil tablets are recommended for the 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

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.

Children:

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 35kg

4.3 Contraindications

- known hypersensitivity to 4-aminoquinoline compounds
- pre-existing maculopathy of the eye
- pregnancy (see section 4.6 Pregnancy and lactation)
- below 6 years of age (200mg tablets not adapted for weight <35kg)

4.4 Special warnings and precautions for use

General

- 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, 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.

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.

Although the risk of bone-marrow depression is low, periodic blood counts are advisable and Plaquenil should be discontinued if abnormalities develop.

Young 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.

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.

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

4.5 Interaction with other medicinal products and other forms of interaction

Hydroxychloroquine sulphate has been reported to increase plasma digoxin levels. Serum digoxin levels should be closely monitored in patients receiving combined therapy.

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.

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.

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:
Hydroxychloroquine crosses the placenta. Data are limited regarding the use of hydroxychloroquine during pregnancy. 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. Therefore Plaquenil should not be used in pregnancy unless considered essential by the physician.

Lactation:
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.

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

- **Ocular effects:**

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 Plaquenil. 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 visions.

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 or are reversible on stopping treatment. Blurring of vision due to a disturbance of accommodation which is dose dependent and reversible, may also occur.

- **Dermatologic effects:**

Skin rashes sometimes occur; pruritus, pigmentary changes in skin and mucous membranes, bleaching of hair, and alopecia have also been reported. These usually resolve readily on stopping treatment. Bullous eruptions including very rare cases of erythema multiforme and Stevens-Johnson syndrome, photosensitivity and isolated cases of exfoliative dermatitis have been reported.
Very rare cases of acute generalised exanthematous pustulosis (AGEP) has to be distinguished from psoriasis, although hydroxychloroquine may precipitate attacks of psoriasis. It may be associated with fever and hyperleukocytosis. Outcome is usually favourable after drug withdrawal.

- **Gastrointestinal effects:**

Gastrointestinal disturbances such as nausea, diarrhoea, anorexia, abdominal pain and, rarely, vomiting may occur. These symptoms usually resolve immediately on reducing the dose or on stopping treatment.

- **CNS effects:**

Less frequently, dizziness, vertigo, tinnitus, hearing loss, headache, nervousness, emotional lability, toxic psychosis and convulsions have been reported.

- **Neuromuscular effects:**

Skeletal muscle myopathy or neuromyopathy leading to progressive weakness and atrophy of proximal muscle groups have been noted. Myopathy may be reversible after drug discontinuation, but recovery may take many months. Associated mild sensory changes, depression of tendon reflexes and abnormal nerve conduction may be observed.

- **Cardio-vascular effects:**

Cardiomyopathy has been rarely reported.

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

- **Haematologic effects:**

Rarely, there have been reports of bone marrow depression. Blood disorders such as anaemia, aplastic anaemia, agranulocytosis, decrease in white blood cells and thrombocytopaenia have been reported.

Hydroxychloroquine may precipitate or exacerbate porphyria.

- **Liver effects:**

Isolated cases of abnormal liver function tests and rare cases of fulminant hepatic failure have also been reported.

- Allergic reactions:

Urticaria, angioedema and bronchospasm have been reported.

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, and rhythm and conduction disorders, followed by sudden early respiratory and cardiac arrest. Since these effects may appear soon after taking a massive dose, treatment should be prompt and symptomatic. 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 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

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
(Containing hypromellose, macrogol 4000, titanium dioxide (E171), Lactose Monohydrate)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

The shelf life expiry date for this product shall be the date shown on the blister and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Foil blister pack. Pack size 60 tablets.

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 PARALLEL PRODUCT AUTHORISATION HOLDER

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8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA1562/42/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14th January 2011

10 DATE OF REVISION OF THE TEXT