

## **1 NAME OF MEDICINAL PRODUCT**

Plaquenil 200mg Film-coated Tablets

## **2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each tablet contains 200 mg Hydroxychloroquine sulphate.

### Excipient with known effect

Lactose monohydrate 35.25 mg per tablet

For the 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

#### 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 Plaquenil. 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 (see section 4.8), physicians should assess the benefits/risk of continuing the treatment.

#### Reactivation of infections

Reactivation of hepatitis B virus, varicella zoster virus and tuberculosis has been reported in patients treated with hydroxychloroquine in combination with other immunosuppressants.

#### 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 medicines 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 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).

#### Aggravation of Myasthenia Gravis

Aggravation of symptoms of myasthenia gravis (generalized weakness including shortness of breath, dysphagia, diplopia, ptosis etc.) have been reported in myasthenic patients receiving hydroxychloroquine therapy. Discontinue Plaquenil if aggravation of symptoms related to Myasthenia Gravis is suspected.

#### Severe cutaneous adverse reactions (SCARs)

Cases of severe cutaneous adverse drug reactions (SCARs), 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.

#### Drug Induced Phospholipidosis

Cases of Hydroxychloroquine induced phospholipidosis have been reported during use of Plaquenil (see section 4.8). Drug-induced phospholipidosis may occur in different organ systems such as cardiac, renal, or muscle. Monitoring for toxicity is advised. Discontinue Plaquenil if cardiac, renal, or muscle toxicity related to drug induced phospholipidosis is suspected or demonstrated by tissue biopsy.

#### 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.

#### Macrolide antibiotics

Chloroquine and Hydroxychloroquine should be used with caution in patients receiving these medicines known to prolong the QT interval due to the potential to induce serious adverse cardiovascular events (including QT prolongation, cardiac arrhythmias and Torsade de Pointes) and to increase the risk of cardiovascular mortality.

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

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

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

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).

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

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

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.

##### Effects of hydroxychloroquine on other medicinal products:

###### P-glycoprotein 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 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, 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<sub>max</sub> 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.

#### 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 Fertility, pregnancy and lactation

#### Pregnancy:

Data from a population-based cohort study including 2045 hydroxychloroquine exposed pregnancies suggests a small increase in the relative risk (RR) of congenital malformations associated with hydroxychloroquine exposure in the first trimester (n = 112 events). For a daily dose of  $\geq 400$  mg the RR was 1.33 (95% CI, 1.08 – 1.65). For a daily dose of  $< 400$  mg the RR was 0.95 (95% CI, 0.60 – 1.50). 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 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.

#### 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.

#### 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 ( $\geq 1/10$ ), Common ( $\geq 1/100$  to  $< 1/10$ ), Uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), Rare ( $\geq 1/10,000$  to  $< 1/1,000$ ), Very rare ( $< 1/10,000$ ), not known (cannot be estimated from the available data).*

|                                             | <i>Very common</i> | <i>Common</i>                                                                                   | <i>Uncommon</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | <i>Rare</i> | <i>Very rare</i> | <i>Not known</i>                                                                                                                                 |
|---------------------------------------------|--------------------|-------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|
| <i>Blood and lymphatic system disorders</i> |                    |                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |             |                  | Bone marrow depression, anemia, aplastic anemia, agranulocytosis, leucopenia, thrombocytopenia.                                                  |
| <i>Immune system disorders</i>              |                    |                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |             |                  | Urticaria, angioedema, bronchospasm                                                                                                              |
| <i>Metabolism and nutrition disorders</i>   |                    | Anorexia                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |             |                  | Hypoglycemia<br>Hydroxychloroquine may exacerbate porphyria<br>Phospholipidosis*                                                                 |
| <i>Psychiatric disorders</i>                |                    | Affect lability                                                                                 | Nervousness                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |             |                  | Psychosis, suicidal behaviour, depression, hallucinations, anxiety, agitation, confusion, delusions, mania and sleep disorders.                  |
| <i>Nervous system disorders</i>             |                    | Headache                                                                                        | Dizziness                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |             |                  | Convulsions have been reported with this class of medicines.<br>Extrapyramidal disorders such as dystonia, dyskinesia, tremor (see section 4.4). |
| <i>Eye disorders</i>                        |                    | 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 |             |                  | Cases of maculopathies and macular degeneration have been reported and may be irreversible.                                                      |

|                                    | <i>Very common</i>     | <i>Common</i>                                                                                                        | <i>Uncommon</i>                                                             | <i>Rare</i> | <i>Very rare</i> | <i>Not known</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|------------------------------------|------------------------|----------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|-------------|------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                    |                        |                                                                                                                      | photophobia. They may be transient or are reversible on stopping treatment. |             |                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| <i>Ear and labyrinth disorders</i> |                        |                                                                                                                      | Vertigo, tinnitus                                                           |             |                  | Hearing loss                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <i>Cardiac disorders</i>           |                        |                                                                                                                      |                                                                             |             |                  | QT interval prolongation in patients with specific risk factors, which may lead to arrhythmia (torsade de pointes, ventricular tachycardia)<br>Cardiomyopathy which may result in cardiac failure and in some cases a fatal outcome (see Section 4.4 and Section 4.9).<br>Chronic toxicity should be considered when conduction disorders (bundle branch block / atrio-ventricular heart block) as well as biventricular hypertrophy are found.<br>Hydroxychloroquine withdrawal may lead to recovery. |
| <i>Gastrointestinal disorders</i>  | Abdominal pain, nausea | Diarrhoea, vomiting<br>These symptoms usually resolve immediately on reducing the dose or on stopping the treatment. |                                                                             |             |                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| <i>Hepatobiliary disorders</i>     |                        |                                                                                                                      | Abnormal liver function tests                                               |             |                  | Drug-induced liver injury (DILI) including hepatocellular injury, cholestatic liver injury, acute                                                                                                                                                                                                                                                                                                                                                                                                      |

|                                                        | <i>Very common</i> | <i>Common</i>       | <i>Uncommon</i>                                                                                                                          | <i>Rare</i> | <i>Very rare</i> | <i>Not known</i>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|--------------------------------------------------------|--------------------|---------------------|------------------------------------------------------------------------------------------------------------------------------------------|-------------|------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                        |                    |                     |                                                                                                                                          |             |                  | hepatitis, mixed hepatocellular/cholestatic liver injury and fulminant hepatic failure                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| <i>Skin and subcutaneous tissue disorders</i>          |                    | Skin rash, pruritus | Pigmentation disorders in skin and mucous membranes, bleaching of hair, alopecia<br>These usually resolve readily on stopping treatment. |             |                  | 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 generalized exanthematous pustulosis (AGEP) (see section 4.4). 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 hydroxychloroquine withdrawal. |
| <i>Musculoskeletal and connective tissue disorders</i> |                    |                     | 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                                                                                                                                                                                                                                                                                                                          |

|  |                    |               |                 |             |                  |                                   |
|--|--------------------|---------------|-----------------|-------------|------------------|-----------------------------------|
|  | <i>Very common</i> | <i>Common</i> | <i>Uncommon</i> | <i>Rare</i> | <i>Very rare</i> | <i>Not known</i>                  |
|  |                    |               |                 |             |                  | abnormal nerve conduction studies |

\* Cases of hydroxychloroquine induced phospholipidosis have been reported. Drug-induced phospholipidosis may occur in different organ systems such as cardiac, renal, or muscle causing toxicity (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 HPRA Pharmacovigilance, Website: [www.hpra.ie](http://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 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.

### **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%) 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, 44 000 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.

#### Biotransformation

Hydroxychloroquine is mainly metabolized to N-desethylhydroxychloroquine, 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 product in the urine. 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.

The pharmacokinetics of hydroxychloroquine appears to be linear in the therapeutic dose range of 200 to 500 mg/day.

#### Pharmacokinetic interactions

##### Effect of hydroxychloroquine on other medicinal products

In vitro, hydroxychloroquine has no potential to inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9 and CYP2C19. Hydroxychloroquine inhibits CYP2D6 and CYP3A4 in vitro. An interaction study has shown that hydroxychloroquine is a mild inhibitor of CYP2D6 (see section 4.5).

In vitro, hydroxychloroquine has no significant potential to induce CYP1A2, CYP2B6 and CYP3A4. In vitro, hydroxychloroquine did not significantly inhibit the main transporters BCRP, OATP1B1, OATP1B3, OAT1 and OAT3. Hydroxychloroquine inhibited P-gp at high concentrations (see section 4.5). In vitro, hydroxychloroquine has a potential to inhibit OCT1, OCT2, MATE1 and MATE2-K transporters.

#### Renal impairment

Renal impairment is not expected to significantly modify the pharmacokinetics of hydroxychloroquine in patients with renal impairment because hydroxychloroquine is mainly metabolized and only 20-25% of the hydroxychloroquine dose is eliminated as unchanged drug in the urine. Hydroxychloroquine exposure can increase by up to 46% in patients with moderate and severe renal impairment (see section 4.4).

#### Hepatic impairment

The effect of hepatic impairment on hydroxychloroquine pharmacokinetics has not been evaluated in a specific PK study. Given that hydroxychloroquine is mainly metabolized, hydroxychloroquine exposure is expected to increase in patients with hepatic impairment (see section 4.4).

#### Elderly

The limited data available in elderly rheumatoid arthritis patients suggest that hydroxychloroquine exposures remain in the same range as those observed in younger patients.

#### Paediatrics

The pharmacokinetics of hydroxychloroquine in children aged below 18 years of age have not been established.

### **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 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 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**

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**

No special requirements

## **7. MARKETING AUTHORISATION HOLDER**

sanofi-aventis Ireland Limited T/A SANOFI  
Citywest Business Campus  
Dublin 24  
Ireland

**8. MARKETING AUTHORISATION NUMBER**

PA 540/155/1

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION**

Date of first authorisation: 1st April 1977

Date of last renewal: 1st April 2007

**10. DATE OF (PARTIAL) REVISION OF TEXT**

March 2025.