SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Hydroxychloroquine sulfate 200mg film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Hydroxychloroquine sulfate 200 mg

Excipient with known effect

Each tablet contains 47.5 mg of lactose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film Coated Tablet

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults

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

Paediatric Population

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

4.2 Posology and method of administration

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, 300mg 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 300mg or 400mg daily if the response lessens.
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.
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.

The tablets are for oral administration.

4.3 Contraindications

- hypersensitivity to hydroxychloroquine or to any of the excipients
- known hypersensitivity to 4-aminoquinoline compounds
- pre-existing maculopathy of the eye

4.4 Special warnings and precautions for use

Retinopathy

The occurrence of retinopathy is very uncommon if the recommended daily dose is not exceeded. The administration of doses in excess of the recommended maximum is likely to increase the risk of retinopathy, and accelerate its onset.

Patients who take hydroxychloroquine should be referred for annual retinopathy monitoring once they have been taking the medication for 5 years. Patients who have additional risk factors, should be referred for retinopathy monitoring once they have been taking the medication for 1 year.

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

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.

Hydroxychloroquine sulfate should be discontinued immediately in any patient who develops a pigmentary abnormality, visual field defect, or any other abnormality not explainable by difficulty in accommodation or presence of corneal opacities. Patients should continue to be observed for possible progression of the changes.

Patients should be advised to stop taking the drug immediately and seek the advice of their prescribing doctor if any disturbances of vision are noted, including abnormal colour vision.

Chronic cardiac toxicity

Cases of cardiomyopathy resulting in cardiac failure, in some cases with fatal outcome, have been reported in patients treated with hydroxychloroquine sulfate (see section 4.8 and 4.9). Clinical monitoring for signs and symptoms of cardiomyopathy is advised and hydroxychloroquine sulfate should be discontinued if cardiomyopathy develops. Chronic toxicity should be considered when conduction disorders (bundle branch block / atrio-ventricular heart block) as well as biventricular hypertrophy are diagnosed (see section 4.8).

Hepatitis B reactivation

Reactivation of hepatitis B virus has been reported in patients treated with hydroxychloroquine in combination with other immunosuppressants.

Caution is required in the following circumstances

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

Carefully consider the benefits and risks before prescribing hydroxychloroquine for any patients taking azithromycin or other macrolide antibiotics, because of the potential for an increased risk of cardiovascular events and cardiovascular mortality (see section 4.5).

Caution should also be applied when it is used in the following:

- patients with hepatic or renal disease, and in those taking drugs known to affect those organs. Estimation of plasma hydroxychloroquine levels should be undertaken in patients with severely compromised renal or hepatic function and dosage adjusted accordingly.
- patients with severe gastrointestinal, neurological or blood disorders.
- patients with a sensitivity to quinine, those with glucose-6-phosphate dehydrogenase deficiency, those with porphyria cutanea tarda which can be exacerbated by hydroxychloroquine and in patients with psoriasis since it appears to increase the risk of skin reactions.
- patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Bone Marrow Depression

Although the risk of bone marrow depression is low, periodic blood counts are advisable as anaemia, aplastic anaemia, agranulocytosis, a decrease in white blood cells, and thrombocytopenia have been reported. Hydroxychloroquine sulfate should be discontinued if abnormalities develop.

Paediatric population

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

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 the 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.

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.

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.

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 Hydroxychloroquine.

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.

Severe cutaneous adverse reactions (SCARs)

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

Extrapyramidal disorders

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

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.

4.5 Interaction with other medicinal products and other forms of interaction

Digoxin

Hydroxychloroquine sulfate has been reported to increase plasma digoxin levels: serum digoxin levels should be closely monitored in patients receiving combined therapy.

Chloroquine

Hydroxychloroquine sulfate may also be subject to several of the known interactions of chloroquine even though specific reports have not appeared. These include: potentiation of its direct blocking action at the neuromuscular junction by aminoglycoside antibiotics; inhibition of its metabolism by cimetidine which may increase plasma concentration of the antimalarial; antagonism of effect of neostigmine and pyridostigmine; reduction of the antibody response to primary immunisation with intradermal human diploid-cell rabies vaccine.

Antacids

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

Anti-diabetics

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

Drugs known to prolong the 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.

There may be an increased risk of inducing ventricular arrhythmias if hydroxychloroquine is used concomitantly with other arrhythmogenic drugs, such as amiodarone and moxifloxacin.

Ciclosporin

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

Tamoxifen

Concomitant use of drugs known to induce retinal toxicity, e.g. tamoxifen and hydroxychloroquine sulfate, is not recommended (see section 4.4).

Antimalarials

Hydroxychloroquine can lower the convulsive threshold. Co-administration of hydroxychloroquine with other antimalarials known to lower the convulsion threshold (e.g mefloquine) may increase the risk of convulsions.

Antiepileptics

Also, the activity of antiepileptic drugs might be impaired if co-administered with hydroxychloroquine.

Praziquantil

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.

Agalsidase

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

Azithromycin and macrolide antibiotics

Observational data have shown that co-administration of hydroxychloroquine with azithromycin in patients with rheumatoid arthritis is associated with an increased risk of cardiovascular events and cardiovascular mortality. Carefully consider the balance of benefits and risks before prescribing hydroxychloroquine for any patients taking azithromycin. Similar careful consideration of the balance of benefits and risks should also be undertaken before prescribing hydroxychloroquine for any patients taking other macrolide antibiotics, such as clarithromycin or erythromycin, because of the potential for a similar risk when hydroxychloroquine is co-administered with these medicines.

4.6 Fertility, pregnancy and lactation

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).

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) at doses higher than those normally used in rheumatological conditions. For a daily dose of ≥ 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).

In SLE there is evidence that hydroxychloroquine reduces disease activity during pregnancy reinforcing the importance of continuing this therapy. Pregnancy itself can induce lupus flares which has the potential to harm the fetus. Preliminary studies have suggested that hydroxychloroquine can reduce the risk of neonatal lupus and congenital heart block in lupus patients who are anti-Ro positive. A recently published study of pregnant patients with antiphospholipid syndrome found that exposure to hydroxychloroquine was linked to a significantly higher live birth rate.

Taken together in autoimmune diseases such as lupus and anti-phospholipid syndrome the balance of benefit outweighs any potential harm to the foetus and therefore hydroxychloroquine should be continued. A dose below 400mg should be considered if thought sufficiently effective by the physician. In other diseases the prescribing physician should assess the risk/benefit ratio for hydroxychloroquine and act accordingly.

In case of prolonged treatment during pregnancy, hydroxychloroquine safety profile in particular ophthalmological side effects should be taken into account for child monitoring. Available evidence does not show an increased risk of retinal toxicity in infants after maternal hydroxychloroquine therapy.

Lactation:

Data on safety during breastfeeding are limited but no harmful effects have been observed. Hydroxychloroquine is excreted in small amounts in breast milk, with estimates of exposure to infants ranging from <1% to about 3% of the adult dose. All infants exposed to hydroxychloroquine during pregnancy will also have been exposed during breastfeeding because the half-life of hydroxychloroquine is more than 40 days. Hydroxychloroquine seems to carry a low risk of harm to the infant. A careful benefit-risk assessment should be made whether to take hydroxychloroquine therapy whilst breastfeeding, taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

4.7 Effects on ability to drive and use machines

Impaired visual accommodation soon after the start of treatment has been reported and patients should be warned regarding driving or operating machinery. If the condition is not self-limiting, it will resolve on reducing the dose or stopping treatment.

4.8 Undesirable effects

The following CIOMS frequency rating is used, when applicable:

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).

Tabulated list of adverse reactions

System Organ class	**Frequency**	**Adverse reaction**
Immune system disorders	Not known	Urticaria, angioedema, bronchospasm
Eye disorders	Common	Blurring of vision due to a disturbance of accommodation which is dose dependent and reversible
	Uncommon	Retinopathy with changes in pigmentation and visual field defects can occur, but appears to be uncommon if the recommended daily dose is not exceeded. In its early form it appears reversible on discontinuation of hydroxychloroquine sulfate. If allowed to develop, there may be a risk of progression even after treatment withdrawal. Patients with retinal changes may be asymptomatic initially, or may have scotomatous vision with paracentral, pericentral ring types, temporal scotomas and abnormal colour vision. Corneal changes including oedema and opacities have been reported. They are either symptomless or may cause disturbances such as haloes, blurring of vision or photophobia. They may be transient and are reversible on stopping treatment.
	Not known	Cases of maculopathies and macular degeneration have been reported (the onset ranging from 3 months to several years of exposure to hydroxychloroquine) and may be irreversible
Skin and subcutaneous tissue disorders	Common	Skin rash, Pruritus
	Uncommon	Pigmentary disorders in skin and mucous membranes, bleaching of hair, alopecia These usually resolve readily on stopping treatment.

	Not known	Bullous eruptions including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS syndrome), Sweet's syndrome and Severe cutaneous adverse reactions (SCARs), photosensitivity, exfoliative dermatitis, acute generalised exanthematous pustulosis (AGEP). 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 disorders	Very common	Abdominal pain, nausea
	Common	diarrhoea, vomiting These symptoms usually resolve immediately on reducing the dose or on stopping treatment.
Nervous system disorders	Common	Headache
	Uncommon	Dizziness
	Not known	Convulsions have been reported with this class of drugs. Extrapyramidal disorders such as dystonia, dyskinesia, tremor (see section 4.4).
Cardiac disorders	Not known	QT interval prolongation in patients with specific risk factors, which may lead to arrhythmia (torsade de pointes, ventricular tachycardia) (see sections 4.4 and 4.9). Cardiomyopathy which may result in cardiac failure and in some cases a fatal outcome (see SPC section 4.4 and 4.9) Chronic toxicity should be considered when conduction disorders (bundle branch block/atrioventricular heart block) as well as biventricular hypertrophy are found. Drug withdrawal may lead to recovery.
Musculoskeletal and connective tissue disorders	Uncommon	Sensory motor disorders
	Not known	Skeletal muscle myopathy or neuromyopathy leading to progressive weakness and atrophy of proximal muscle groups. Myopathy may be reversible after drug discontinuation, but recovery may take many months. Depression of tendon reflexes and abnormal nerve conduction studies.

Blood and lymphatic system disorders	Not known	Bone-marrow depression, anaemia, aplastic anaemia, agranulocytosis, leucopenia and thrombocytopenia
Hepatobiliary disorders	Uncommon	Abnormal liver function tests
	Not known	Drug-induced liver injury (DILI) including hepatocellular injury, cholestatic liver injury, acute hepatitis, mixed hepatocellular/cholestatic liver injury and fulminant hepatic failure
Metablism and nutrition disorders	Not known	Hypoglycaemia (see section 4.4), Hydroxychloroquine may precipitate or exacerbate porphyria.
	Common	Anorexia
Ear and labyrinth disorders	Uncommon	Vertigo, tinnitus
	Not known	Hearing loss
Psychiatric disorders	Common	Affect lability
	Uncommon	Nervousness
	Not known	Psychosis, suicidal behavior, depression, hallucinations, anxiety, agitation, confusion, delusions, mania and sleep disorders.

Reporting of side effects

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 the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

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 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 by gastric lavage. Activated charcoal in a dose at least five times of the overdose may inhibit further

absorption if introduced into the stomach by tube following lavage and within 30 minutes of ingestion of the overdose.

Consideration should be given to administration of parenteral diazepam in cases of 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

ATC Code: P01BA02

Pharmacotherapeutic group: Anti rheumatic

Antimalarial agents like chloroquine and hydroxychloroquine have several pharmacological actions which may be involved in their therapeutic effect in the treatment of rheumatic disease, but the role of each is not known. These include interaction with sulphydryl groups, interference with enzyme activity (including phospholipase, NADH - cytochrome C reductase, cholinesterase, proteases and hydrolases), DNA binding, stabilisation of lysosomal membranes, inhibition of prostaglandin formation, inhibition of polymorphonuclear cell chemotaxis and phagocytosis, possible interference with interleukin 1 production from monocytes and inhibition of neutrophil superoxide release.

5.2 Pharmacokinetic properties

Hydroxychloroquine has actions, pharmacokinetics and metabolism similar to those of chloroquine. Following oral administration, hydroxychloroquine is rapidly and almost completely absorbed. In one study, mean peak plasma hydroxychloroquine concentrations following a single dose of 400mg in healthy subjects ranged from 53-208ng/ml with a mean of 105ng/ml. The mean time to peak plasma concentration was 1.83 hours. The mean plasma elimination half-life varied, depending on the post-administration period, as follows: 5.9 hours at C_{max}-10 hours), 26.1 hours (at 10-48 hours) and 299 hours (at 48-504 hours). The parent compound and metabolites are widely

distributed in the body and elimination is mainly via the urine, where 3% of the administered dose was recovered over 24 hours in one study.

5.3 Preclinical safety data

Carcinogenicity

Animal studies concerning a cancerogenic potential of hydroxychloquine are not available.

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

Developmental and reproductive toxicity

Hydroxychloroquine passes the placenta and can induce damage to organs of the fetus. In studies with mice and monkeys, chloroquine, a substance related to hydroxychloroquine, resulted in transplacental transfer and accumulation in the adrenal cortex and the retina. High maternal doses of chloroquine were fetotoxic 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose Monohydrate

Maize Starch

Hypromellose

Croscarmellose Sodium

Magnesium Stearate

Talc

Titanium Dioxide

Macrogol 6000

Iron Oxide Yellow E172

Polysorbate 80

6.2 Incompatibilities

No incompatibilities are known.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

250µm clear PVC/20µm aluminium foil blister pack containing 10 tablets.

The blister packs are packed in a outer cardboard carton containing 28, 30 or 60 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

None

7 MARKETING AUTHORISATION HOLDER

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United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

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