SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Hydroxychloroquine Sulfate 200 mg Film – Coated Tablets
Quinoric 200mg Film-Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 200 mg Hydroxychloroquine Sulfate B.P.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film coated tablet (tablet)

White, circular, biconvex film coated tablets debossed with 'BL' on one face and '200' on the other.

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

Posology

Adults (including the elderly)

The minimum effective dose should be employed. This dose should not exceed 6.5 mg/kg/day (calculated from ideal body weight and not actual body weight) and will be either 200 mg or 400 mg per day.

In patients able to receive 400mg daily:

Initially 400 mg daily in divided doses. The dose can be reduced to 200 mg when no further improvement is evident. The maintenance dose should be increased to 400 mg daily if the response lessens.

Paediatric population

The minimum effective dose should be employed and should not exceed 6.5 mg/kg/day based on ideal body weight. The 200 mg tablet is therefore not suitable for use in children with an ideal body weight of less than 31kg.

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.

Method of administration

The tablets are for oral administration. Each dose should be taken with a meal or glass of milk.

4.3 Contraindications

- Hypersensitivity to the active substance, 4-aminoquinoline compounds or to any of the excipients listed in section 6.1
- Pre-existing maculopathy of the eye
- Pregnancy (see section 4.6).

4.4. Special warnings and precautions for use

Visual effects

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.

All patients should have an ophthalmological examination before initiating treatment with Hydroxychloroquine. Thereafter, ophthalmological examinations must be repeated at least every 12 months.

The examination should include testing visual acuity, careful ophthalmoscopy, fundoscopy and 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 200 g.

Hydroxychloroquine 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.

Concomitant use of hydroxychloroquine with medicinal products known to have a toxic effect on the retina (e.g. tamoxifen) is not recommended.

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.

Cardiac effects

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 with 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).

Caution is required in the following conditions

Hydroxychloroquine 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 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.

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.

Blood disorders

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 should be discontinued if abnormalities develop.

Toxic effects in children

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

Musculoskeletal effects

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.

Dermatological reactions

Life-threatening cutaneous reactions Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with the use of Hydroxychloroquine.

Patients should be advised of the signs and symptoms and monitored closely for skin reactions. The highest risk for occurrence of SJS or TEN is within the first weeks of treatment.

If symptoms or signs of SJS or TEN (e.g. progressive skin rash often with blisters or mucosal lesions) are present, Hydroxychloroquine treatment should be discontinued.

The best results in managing SJS and TEN come from early diagnosis and immediate discontinuation of any suspect drug. Early withdrawal is associated with a better prognosis.

If the patient has developed SJS or TEN with the use of Hydroxychloroquine, Hydroxychloroquine must not be re-started in this patient at any time.

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

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 concomitant 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 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.

Halofantrine

Halofantrine prolongs the QT interval and should not be administered with other drugs that have the potential to induce cardiac arrhythmias, including hydroxychloroquine. Also, 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.

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.

Anti-epileptics

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

Agalsidase

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

Tamoxifen

Concomitant use of drugs with known toxic effects on the retina (e.g. tamoxifen) and hydroxychloroquine is not recommended.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is insufficient clinical data on use of hydroxychloroquine during pregnancy. Hydroxychloroquine crosses the placenta. 4-aminoquinolines in therapeutic doses caused damage to the central nervous system, including ototoxicity (auditory and vestibular toxicity, congenital deafness), retinal haemorrhages and abnormal retinal pigmentation.

In animal studies, reproduction toxicity was found with chloroquine, a substance related to hydroxychloroquine, following high maternal exposition (see section 5.3).

Hydroxychloroquine is contraindicated during pregnancy (see section 4.3). Before treatment is started a pregnancy has to be excluded.

Breast-feeding

Hydroxychloroquine is excreted in small amounts in human breast milk. Neonates are extremely sensitive to the toxic effects of 4-aminoquinolines.Because of the long half-life and the daily high dosage of hydroxychloroquine an accumulation must be expected. Hydroxychloroquine is contraindicated during lactation (see section 4.3).

Fertility

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

Contraception

During treatment with hydroxychloroquine and for at least 3 months after treatment termination, a pregnancy should be strictly avoided.

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) 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	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	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

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.

4.9 Overdose

Overdosage with the 4-aminoquinolines is particularly dangerous in infants, as little as 1-2g having proved fatal.

Symptoms

The symptoms of overdosage may include headache, visual disturbances, cardiovascular collapse,convulsions and hypokalaemia. Rhythm and conduction disorders, including QT prolongation, Torsade de Pointes, ventricular tachycardia and ventricular fibrillation, followed by sudden and early respiratory and cardiac arrest. Immediate medical attention is required, as these effects may appear shortly after the overdose.

Management

The stomach should be immediately evacuated, either by emesis or gastric lavage. Finely powdered 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 may be needed and the need for incubation or tracheotomy considered. Shock should be treated by administration of fluid (with plasma expanders if necessary) with central venous pressure monitoring. In severe cases, the administration of dopamine should be considered.

A patient who survives the acute phase and is asymptomatic should be closely observed for at least 6 hours.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti -rheumatic

ATC Code: P01BA02

Mechanism of action

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 sulphadryl groups, interference with enzyme activity (including phospholipase, NADH- cytochrome C reductase, cholinestrase, proteases and hydrolases) , DNA binding , stabilisation of lysosomal membranes, inhibition of prostagalandin 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, 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.

Distribution

The parent compound and metabolites are widely distributed in the body.

Metabolism

The metabolism of Hydroxychloroquine is similar to that of Chloroquine.

Elimination

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 229 hours (at 48-504 hours). 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

Animal studies concerning a cancerogenic potential of hydroxychloquine are not available. A mutagenic potential could not be excluded.

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

Maize starch
Calcium Hydrogen Phosphate dihydrate
Colloidal anhydrous silica
Polysorbate 80
Purified Talc
Magnesium stearate
Hypromellose
Titanium dioxide
Macrogol 6000

6.2. Incompatibilities

Not applicable

6.3 Shelf life

Containers: 3 years

Blisters: 4 years

6.4 Special precautions for storage

Store in the original package.

6.5 Nature and contents of container

Al/PVC blister, pack sizes of 30, 60 and 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Bristol Laboratories Ltd.
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8 MARKETING AUTHORISATION NUMBER(S)

PL 17907/0017

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04/07/2018