SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Hydroxychloroquine sulfate 300mg Film-Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 300mg of hydroxychloroquine sulfate

Excipient with known effect
Each tablet contains 71.25 mg of lactose.
For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film Coated Tablet

Hydroxychloroquine sulfate 300mg Film Coated Tablets are 15 mm x 6.5 mm white, capsule shaped, film coated tablets (caplets) having a score line on one face. The score line is to facilitate the intake and is not intended to break the tablet in equal doses.

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 6.5/kg/day (calculated from ideal body weight) and will be either 200mg, 300mg or 400mg per day.

In patients able to receive 300mg daily:
Initially 300mg daily in a single dose. The dose can be reduced to 200mg when no further improvement is evident. The maintenance dose should be increased to 300mg 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 300mg tablet is therefore not suitable for use in children with an ideal body weight of less than 46kg. 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
For oral administration.

Each dose should be taken with a meal or glass of milk.

4.3 Contraindications

- hypersensitivity to hydroxychloroquine or to any of the excipients listed in section 6.1
- known hypersensitivity to 4-aminoquinoline compounds
- pre-existing maculopathy of the eye

Please also refer to ‘Drug Interactions’ section 4.5

4.4 Special warnings and precautions for use

Visual effects

The occurrence of retinopathy is 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.

Other risk factors are concomitant tamoxifen use and impaired renal function (estimated glomerular filtration rate of less than 60ml/min/1.73m2).

Patients should be referred to a hospital eye department to have a baseline ocular examination within 6 to 12 months after initiation of therapy to screen for hydroxychloroquine retinopathy. Subsequent follow-up should be directed by an Ophthalmologist.

It should be emphasized that the lowest effective dose should be used to minimize the risk of ocular toxicity.

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.

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 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 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.
- 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.

- patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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 sulfate out of the sight and 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).

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.

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.

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 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:

Although able to cross the placenta, the use of HCQ in pregnancy is now considered to convey a low risk of harm to the foetus with no significant increase in congenital malformations. In SLE there is evidence that HCQ

reduces disease activity during pregnancy reinforcing the importance of continuing this therapy. Indeed, pregnancy itself can induce lupus flares, which can be prevented by HCQ. Preliminary studies have suggested that HCQ 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 HCQ 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 HCQ should be continued. In other diseases the prescribing physician should assess the risk/benefit ratio for HCQ and act accordingly.

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 MedDRA frequency convention is used to evaluate adverse reactions, when applicable:

Very common(>1/10); Common (>1/100, <1/10); Uncommon (>1/1,000, <1/100); Rare >1/10,000, <1/1000); Very rare (<1/10,000) including isolated reports.

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	Not known	Cardiomyopathy which may result in cardiac failure

disorders		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
Metabolism and nutrition disorders	Common	Anorexia
	Not known	Hypoglycaemia (see section 4.4), Hydroxychloroquine may precipitate or exacerbate porphyria.
Ear and labyrinth disorders	Uncommon	Vertigo, tinnitus
	Not known	Hearing loss
Psychiatric disorders	Common	Affect lability
	Uncommon	Nervousness
	Not known	Psychosis, suicidal behaviour, psychosis, depression, hallucinations, anxiety, agitation, confusion, delusions, mania and sleep disorders.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization 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 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

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 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.

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.

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 299 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 epidedymis 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
Polysorbate 80

6.2 Incompatibilities

Not applicable.

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 an outer cardboard carton containing 30 or 60 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Blackrock Pharmaceuticals Ltd.

The Old Barrel Store

Brewery Courtyard

Draymans Lane

Marlow

SL7 2FF

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL33271/0009

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20/03/2020

10 DATE OF REVISION OF THE TEXT

14/11/2022