1. NAME OF THE MEDICINAL PRODUCT

Hydroxychloroquine Sulfate 200mg Film-coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200mg of hydroxychloroquine sulfate

Excipient(s) with known effect

Each tablet contains 35.5mg of lactose
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated Tablet
White to off white, peanut shaped, biconvex, film-coated tablets debossed with "H11" on one side and plain on the other side with approximate dimensions 12.80 ± 0.05mm X 6.10 ± 0.05mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults
Hydroxychloroquine Sulfate 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

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.

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 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

- known hypersensitivity to 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 Pregnancy and lactation)

4.4 Special warnings and precautions for use

General

- All patients should have an ophthalmological examination before treatment with Hydroxychloroquine Sulfate Tablets 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 6.5mg/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 200g.

Hydroxychloroquine Sulfate Tablets 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 or presence of corneal opacities (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).

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.

Concomitant use of hydroxychloroquine with drugs known to induce retinal toxicity, such as tamoxifen, is not recommended.

Cases of cardiomyopathy resulting in cardiac failure, in some cases with fatal outcome, have been reported in patients treated with Hydroxychloroquine (see Section 4.8 and Section 4.9). Clinical monitoring for signs and symptoms of cardiomyopathy is advised and Hydroxychloroquine Sulfate Tablets 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).

Hydroxychloroquine Sulfate Tablets should be used with caution in patients taking medicines which may cause adverse ocular or skin reactions. Caution should also be applied when it is used in the following:

- patients with hepatic or renal disease, and in those taking medicines known to affect those organs. Estimation of plasma hydroxychloroquine levels should be undertaken in patients with severely compromised renal or hepatic function, and dosage adjusted accordingly.
- patients with severe gastrointestinal, neurological or blood disorders.

Caution is also advised in patients with a sensitivity to quinine, those with glucose-6-phosphate dehydrogenase deficiency, those with porphyria cutanea tarda which can be exacerbated by hydroxychloroquine, and in patients with psoriasis since it appears to increase the risk of skin reactions.

Although the risk of bone-marrow depression is low, periodic blood counts are advisable in all patients on long-term therapy and Hydroxychloroquine Sulfate Tablets should be discontinued if abnormalities develop.

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

All patients on long-term therapy should undergo periodic examination of skeletal muscle function and tendon reflexes.If weakness occurs, the drug should be withdrawn.

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

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.

Extrapyramidal disorders may occur with Hydroxychloroquine (See Section 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

Hydroxychloroquine sulfate has been reported to increase plasma digoxin levels. Serum digoxin levels should be closely monitored in patients receiving concomitant treatment.

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.

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

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

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

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

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

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.

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

Concurrent use with drugs with oculotoxic or haemotoxic potential should be avoided if possible.

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

4.6 Fertility, pregnancy and lactation

Pregnancy
Hydroxychloroquine crosses the placenta. Data are limited regarding the use of hydroxychloroquine during pregnancy. It should be noted that 4-aminoquinolines in therapeutic doses have been associated with central nervous system damage, including, ototoxicity (auditory and vestibular toxicity, congenital deafness), retinal hemorrhages and abnormal retinal pigmentation. Therefore Hydroxychloroquine should not be used in pregnancy unless considered essential by the physician.

Lactation
Careful consideration should be given to using hydroxychloroquine during lactation, since it has been shown to be excreted in small amounts in human breast milk, and it is known that infants are extremely sensitive to the toxic effects of 4-aminoquinolines.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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).

Blood and lymphatic system disorders
Not known: Bone marrow depression, anemia, aplastic anemia, agranulocytosis, leucopenia, thrombocytopenia.

Immune system disorders
Not known: Urticaria, angioedema, bronchospasm

Metabolism and nutrition disorders
Common: Anorexia

Not known: Hypoglycemia
Hydroxychloroquine may exacerbate porphyria.

Psychiatric disorders
Common: Affect lability
Uncommon: Nervousness
Not known: Psychosis

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).

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. 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 photophobia. They may be transient or are reversible on stopping treatment.
Not known: Cases of maculopathies and macular degeneration have been reported and may be irreversible.

Ear and labyrinth disorders
Uncommon: Vertigo, tinnitus
Not known: Hearing loss

Cardiac disorders
Not known:
Cardiomyopathy which may result in cardiac failure and in some cases a fatal outcome (see Section 4.4 and Section 4.9). Chronic toxicity should be considered when conduction disorders (bundle branch block / atrio-ventricular heart block) as well as biventricular hypertrophy are found. Drug withdrawal may lead to recovery.

Gastrointestinal disorders
Very common: Abdominal pain, nausea

Common: Diarrhoea, vomiting
These symptoms usually resolve immediately on reducing the dose or on stopping the treatment.

Hepatobiliary disorders
Uncommon: Abnormal liver function tests

Not known: Fulminant hepatic failure

Skin and subcutaneous tissue disorders
Common: Skin rash, pruritus

Uncommon: Pigmentation 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 generalized exanthematous pustulosis (AGEP). 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.

Musculoskeletal and connective tissue disorders
Uncommon: Sensorymotor 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.

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 the Yellow Card Scheme, Website: 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 pointe, ventricular tachycardia and ventricular fibrillation, 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

Pharmacotherapeutic group: Anti rheumatic
ATC code: P01BA02

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

formation, inhibition of polymorphonuclear cell chemotaxis and phagocytosis, possible interference with interleukin 1 production from monocytes and inhibition of neutrophil superoxide release.

5.2 Pharmacokinetic properties

Hydroxychloroquine is rapidly absorbed following oral administration. Mean bioavailability is approximately 74%. It is widely distributed throughout the body, accumulating within blood cells and other tissues such as liver, lungs, kidneys and eyes. It is partially converted to active ethylated metabolites in the liver and eliminated principally via the kidney, 23 to 25% unchanged, but also via the bile. Excretion is slow, the terminal elimination half-life being approximately 50 days (whole blood) and 32 days (plasma).

Hydroxychloroquine crosses the placenta and is likely to resemble chloroquine in entering breast milk.

5.3 Preclinical safety data

There are no preclinical safety data of relevance to the prescriber, which are additional to that already included in other sections of the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core
Lactose Monohydrate
Maize Starch
Povidone
Magnesium Stearate

Coat
Polyvinyl alcohol,
Talc,
Polyethyleneglycol
Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/aluminium foil blister pack. Pack size 20, 30, 50, 60, 90 or 100 tablets
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Accord-UK Ltd
(Trading style: Accord)
Whiddon Valley
Barnstaple
Devon
EX32 8NS

8. MARKETING AUTHORISATION NUMBER(S)

PL 0142/1254

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25/03/2020

10. DATE OF REVISION OF THE TEXT

31/03/2020