Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Hydroxychloroquine sulfate Accord 200 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:
Hydroxychloroquine sulfate 200 mg

Excipient(s) with known effect
Each tablet contains 35.50 mg of lactose monohydrate

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 dimension of 12.80 ± 0.05 mm × 6.10 ± 0.05 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults
Hydroxychloroquine sulfate Accord tablets are recommended for the treatment of rheumatoid arthritis, discoid and systemic lupus erythematosus, and photodermatoses.

This product is also indicated in adults for prevention and treatment of uncomplicated malaria caused by *Plasmodium vivax*, *P. ovale*, *P. malariae* and chloroquine sensitive *P. falciparum*.

Paediatric population (≥ 6 years and ≥ 31 kg)
Treatment of juvenile idiopathic arthritis (in combination with other therapies), discoid and systemic lupus erythematosus.
Also indicated for prevention and treatment of uncomplicated malaria, caused by *Plasmodium vivax*, *P. malariae*, *P. ovale* and chloroquine-sensitive *P. falciparum*.

Chloroquine-resistant *P. falciparum*, and increasingly chloroquine-resistant *P. vivax*, are found in many areas which limits the usefulness of hydroxychloroquine in these areas. Official guidelines andlocal information on the occurrence of resistance to anti-malaria agents must be observed (e.g. WHOand public health directives).

4.2 Posology and method of administration

Hydroxychloroquine works cumulatively and needs a few weeks in order to attain its therapeutic effect for rheumatoid diseases, whereas minor side effects may occur relatively early.

For rheumatic diseases, treatment should be discontinued if there is no improvement by 6 months.

Rheumatoid arthritis
Adults (including the elderly)
Initial dose: 400 mg (2 tablets) once a day, either as a single dose or in two divided doses.
The treatment needs to be continued for 6-8 weeks before assessing the effect. With a good response, the daily dose can be reduced after three months.
Maintenance dose: 200 mg (1 tablet) per day, and later possibly 200 mg (1 tablet) every other day.

Juvenile idiopathic arthritis
Paediatric population

The minimum effective dose should be employed which should not exceed 6.5 mg/kg/day based on ideal body weight and should not exceed 400 mg/day. The 200 mg tablet is therefore not suitable for use in children with an ideal body weight of less than 31 kg (see section 4.3).

Systemic and discoid lupus erythematosus

Adults

Initial dose: 400 mg (2 tablets, as a single dose or in two divided doses) to 600 mg (3 tablets, as a single dose or in two or three divided doses) once a day (for several weeks if necessary). The maximum dose should not exceed 6.5 mg/kg body weight daily.

Maintenance dose: 200 mg (1 tablet) to 400 mg (2 tablets) per day, as a single dose or in two divided doses.

Paediatric population

The minimum effective dose should be employed which should not exceed 6.5 mg/kg/day based on ideal weight and should not exceed 400 mg/daily. The 200 mg tablet is therefore not suitable for use in children with an ideal body weight of less than 31 kg (see section 4.3).

Photodermatoses

Adults

400 mg (2 tablets) once a day, either as a single dose or in two divided doses, is usually enough. Treatment should only be given during periods of maximum exposure to light.

Malaria

Prophylaxis of malaria

Prophylaxis should start one week before arrival in an area with malaria and continue for four weeks after departure from that area.

Adults

400 mg (2 tablets) per week on the same day of each week.

Children

The weekly prophylactic dose is 6.5 mg per kg body weight but may not exceed the maximum adult dosage regardless of body weight. The 200 mg tablet is therefore not suitable for use in children with an ideal body weight of less than 31 kg (see section 4.3).

Treatment of uncomplicatedmalaria

Adults

Initial dose of 800 mg followed 6-8 hours later by 400 mg, and then 400 mg on each of the next two days (total of 2 grams- 10 tablets of hydroxychloroquine sulfate).

For the treatment of an attack of a *Plasmodium falciparum* infection and an acute attack of *Plasmodium vivax* infection to suppress, a single dose of 800 mg is sufficient.

When prescribing a treatment, official guidelines and local information about the occurrence of resistance to anti-malarial medicines should be considered. Examples of this include WHO and public health guidelines.

Treatment of infection with *P. vivax* and *P.ovale* should be completed with treatment with an 8-aminoquinoline for the extra-erythrocytic phase of the plasmodium cycle to eliminate.

Children

13 mg/kghydroxychloroquine sulfate in children is comparable to 800 mg in adults and 6.5 mg/kg hydroxychloroquine sulfate in children is comparable to 400 mg in adults.

A total dose of up to 2 grams is administered over three days, as follows:

- First dose: 13 mg/kg (maximum 800 mg once only).
- Second dose: 6.5 mg/kg (maximum 400 mg) 6 hours after the first dose.
- Third dose: 6.5 mg/kg (maximum 400 mg) 18 hours after the second dose.
- Fourth dose: 6.5 mg/kg (maximum 400 mg) 24 hours after the third dose.

Special population

Patients with reduced kidney and liver function

Caution should be exercised in patients with impaired renal or hepatic function. A reduction in dosage may be required (see section 4.4).

Method of administration

For oral use. 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
- myasthenia gravis
- pre-existing maculopathy of the eye
- retinitis pigmentosa
- below 6 years of age (200 mg tablets not adapted for weight < 31 kg (see section 4.2)

4.4 Special warnings and precautions for use

Suicidal behavior and psychiatric disorders
Suicidal behavior 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.

Retinopathy

- All patients should have an ophthalmological examination before treatment with Hydroxychloroquine sulfate Accord is initiated. Thereafter, ophthalmological examinations must be repeated at least every 6 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 6.5 mg/kg lean body weight. Absolute body weight used as a guide to dosage could result in an overdosage in the obese.
- renal insufficiency
- decreased visual acuity
- age above 65 years
- cumulative dose more than 200 g.

Hydroxychloroquine sulfate Accord 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.

Extrapyramidal disorders

Extrapyramidal disorders may occur with hydroxychloroquine (see section 4.8).

Prolongation of QTc interval

Hydroxychloroquine has potential to prolong the QTc interval in patients with specific risk factors.

Hydroxychloroquine should be used with caution in patients with congenital or documented acquired QT prolongation and/orknown 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 active substance. 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 hydroxychloroquine (see sections 4.8 and 4.9). Clinical monitoring for signs and symptoms of cardiomyopathy is advised. If signs and symptoms of cardiomyopathy occur during treatment with hydroxychloroquine, treatment should be stopped.

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).

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.

Other monitoring with long term use

In long-term treatments, the daily dose needs to be kept as low as possible. The upper limit is 400 mg/day/year, which corresponds with 6 mg/kg

Hydroxychloroquine sulfate Accord 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. Dosage should be 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.

Other monitoring on long-term treatments

Patients on long-term therapy should have periodic full blood count (FBC) and if abnormalities develop, treatment with hydroxychloroquine should be discontinued (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 medicine should be withdrawn (see section 4.8).

Ototoxicity

Ototoxicity from hydrodroxychloroquine is very rare but can be irreversible (see section 4.8). Physicians should inform all patients at initiation of the risks, and consider monitoring those with previous or concomitant causes of audiovestibular impairment.

Malaria

Hydroxychloroquine is not effective against chloroquine-resistant strains of *P. falciparum* and *P. vivax* and is not active against the exoerythrocytic forms *P. vivax, P. ovale* and *P. malariae*.

A long-term use as malaria prophylaxis for children should be avoided.

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 <Invented Name>.

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.

Hepatitis B reactivation

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

Children

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

The medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

There are indications that 4-aminoquinolines, such as hydroxychloroquine, are pharmacologically incompatible with mono-amino oxidase inhibitors.

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

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.

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

Hydroxychloroquine can increase sensitivity to epileptic episodes. 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 or haemotoxic potential should be avoided if possible, because of potential additive effect (please also see section 4.4 and 4.8).

There is a theoretical risk of inhibition of intra-cellular α-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: antagonism of effect of neostigmine and pyridostigmine; reduction of the antibody response to primary immunisation with intradermal human diploid-cell rabies vaccine. Both chloroquine derivatives and aminoglycoside antibiotics may have an effect on the neuromuscular junction; a potential additive effect cannot be ruled out.

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 or 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.

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 . 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.

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 Cmax 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 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.

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

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 ≥ 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).

Rheumatoid arthritis, lupus erythematosus, photodermatoses
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.

Malaria prophylaxis
Hydroxychloroquine may be used for malaria prophylaxis during pregnancy, because malaria itself can cause damage to the foetus.

Breast-feeding
Hydroxychloroquine is excreted in breast milk; the dose received by infants via lactation has been shown to correspond to ca. 2-3% of the maternal dose (corrected for body weight). However, presently no effects on development, or motor, visual and hearing impairment have been reported in infants exposed to hydroxychloroquine via breastfeeding and followed for a period of up to 2 years. The prescriber should consider possible risks and benefits of use during breast-feeding, taking indication and treatment duration into consideration.

Malaria prophylaxis
For use as malaria prophylaxis, hydroxychloroquine may be used during breast-feeding. However, the amount excreted is insufficient to achieve any prophylactic effect on the child.

Fertility
There are no data available on the effect of hydroxychloroquine sulfate on human fertility. Animal studies showed an impairment of male fertility for chloroquine (see section 5.3).

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

Adverse reactions are listed according to the MedDRA system organ class and are ranked by their frequencies. Frequency categories for each adverse reaction are based on the following convention:

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 (frequency cannot be estimated from the available data).

System organ class	Very Common	Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic system disorders				Myelosuppresion		Anaemia, aplastic anaemia, granulocytosis, leukopenia, thrombocytopenia, precipitate or exacerbate porphyria
Metabolism and nutrition disorders		Anorexia				Hypoglycaemia (see section 4.4)
Psychiatric disorders		Affect lability	Nervousness			Drowsiness, suicidal behaviour, psychosis, depression, hallucinations, anxiety, agitation, confusion, delusions, mania and sleep disorders.
Nervous system disorders				Convulsions		Emotional disorders, headache, extrapyramidal phenomena like dystonia, dyskinesia, tremor (see section 4.4)
Eye disorders				Retinopathy with changes in pigmentation and effects of visual fields[1]		Patients with retinal changes may be asymptomatic initially, or may have scotomatous vision with paracentral, pericentral ring types, temporal scotomas and abnormal colour vision. Changes of the cornea, including edema and opacities[2] Blurring of vision due to a disturbance of accommodation[3]
Ear and labyrinth disorders					Hearing loss (irreversible)	Vertigo and tinnitus
Cardiac disorders				Cardiomyopathy, which can result in heart failure, in a few cases with fatal outcome. T-top deviations in ECG.		Conduction disturbance and (bundle branch block/atrioventricular heart block) (see section 4.4) Biventricular hypertrophy (see section 4.4) QT-prolongation in patients who are at risk, which can lead to arrhythmia

						(torsades de pointes, ventricular tachycardia) (see sections 4.4 and 4.9)
Gastrointestinal disorders			Nausea, diarrhoea, abdominal pain[4]	Vomiting[4]		
Hepatobiliary disorders						Abnormal liver function tests, Drug-induced liver injury (DILI) including hepatocellular injury, cholestatic liver injury, acute hepatitis, mixed hepatocellular/cholestatic liver injury and fulminant hepatic failure
Skin and subcutaneous tissue disorders			Rash			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.
Musculoskeletal and connective tissue disorders						Myopathy,[5] neuromyopathy leading to progressive weakness and atrophy of proximal muscle groups. Associated mild sensory changes, depression of tendon reflexes and abnormal nerve conduction may be observed.
General disorders						Urticaria, angioedema and bronchospasm.

and administration site conditions						
Renal and urinary disorders					During long-term therapy with the structurally related chloroquine phosphate a reversible phospholipidosis occurred (increased accumulation of intracellular phospholipids), including renal phospholipidosis. An impaired kidney function can be intensified in this case.	

[1]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.
[2]The changes are symptomless or may cause disturbances such as haloes, blurring of vision or photophobia. They may be transient and are reversible on stopping treatment.
[3]This is dose-dependent and reversible.
[4]These symptoms usually disappear after reduction of dose or after discontinuation of treatment.
[5]This can be reversible if the treatment is terminated, however recovery may take many months.

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

4.9 Overdose

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

Symtoms
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.

Measures
Within one hour of ingestion, 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: Antiprotozoals, aminoquinolines
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. Concentration in intracellular vesicles and increase in pH in these vesicles can be a cause for the antiprotozoal and antirheumatic activity.

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.

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core
Lactose monohydrate
Maize starch
Povidone (E1201)
Magnesium stearate (E470b)

Coating
Polyvinyl alcohol (E1203),
Talc (E553b)
Macrogol
Titanium dioxide (E171)

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 Healthcare Ireland Ltd.
Euro House
Euro Business Park
Little Island
Cork T45 K857
Ireland

8 MARKETING AUTHORISATION NUMBER

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24th April 2020

10 DATE OF REVISION OF THE TEXT

November 2023