SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Hydroxychloroquinesulfaat DOC 200 mg filmomhulde tabletten.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

A film-coated tablet contains 200 mg of hydroxychloroquine sulphate, which corresponds to 154.8 mg of hydroxychloroquine.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

White, round, biconvex, film-coated tablets (with a dimension of 9.5 mm) embossed with "200' on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults
- Rheumatoid arthritis
- Systemic lupus erythematosus
- Discoid lupus erythematosus
- Photodermatosis
- Treatment of acute attacks and prophylaxis of malaria caused by *Plasmodium vivax, P. falciparum, P. ovale* and *P. malariae.*

Children
- Juvenile idiopathic arthritis (in association with other treatments)
- Systemic lupus erythematosus
- Discoid lupus erythematosus
- Treatment of acute attacks and prophylaxis of malaria caused by *Plasmodium vivax, P. falciparum, P. ovale* and *P. malariae*.

Chloroquine-resistant *P. falciparum*, and increasingly chloroquine-resistant *P. vivax*, occur in many regions, which limits the usability of hydroxychloroquine in these regions.

Official guidelines and local information about the occurrence of anti-malarial drug resistance need to be taken into account. Examples of this include WHO and public safety guidelines.

4.2 Posology and method of administration

General

Hydroxychloroquine works cumulatively and needs a few weeks in order to attain its therapeutic effect for rheumatoid diseases.

Posology

Rheumatoid arthritis

Adults	Children
Starting dose: 400 mg a day. The treatment needs to be continued for 6-8 weeks before assessing the effect. During this period, Hydroxychloroquine sulphate DOC can be combined with prostaglandin synthetase inhibitors (such as acetylsalicylic acid or indomethacin). Combination therapy with gold or phenylbutazone is discouraged. The daily dose can be decreased after three months if there is a positive response. Maintenance dose: 200 mg a day and later potentially 200 mg every other day.	The minimum effective dose needs to be applied and cannot exceed 6.5 mg/kg based on the so called 'ideal body weight' (IBW). This means the 200 mg tablet is not suitable for children with an IBW of less than 31 kg.

Systemic and Discoid Lupus Erythematosus

Adults	Children
Starting dose: 400 mg to 600 mg a day (for a few weeks if necessary). Maintenance dose: 200 mg to 400 mg a day.	

Polymorphic photodermatosis

Adults	Children
Dosage: 400 mg a day usually suffices. The treatment needs to be limited to periods of maximum exposure to light.	

Malaria

Malaria prophylaxis

Prophylaxis needs to be started one week before arrival in an area with malaria and needs to be continued about four to eight weeks after leaving said area.

Adults	Children
Dosage: 400 mg a week on the same day of each week.	The weekly prophylactic dosage is 6.5 mg per kg of body weight, but this must not exceed the maximum adult dosage, regardless of body weight.

The tablets are not suitable for body weights lower than 35 kg (see section 4.3).

Malaria
Treatment of an acute malaria attack

Adults	Children
Starting dose: 800 mg, followed by 400 mg after 6-8 hours and subsequently 400 mg on each of the two following days (2 grams of hydroxychloroquine sulphate in total). For the treatment of an attack of a *Plasmodium falciparum* infection and to suppress an acute attack of a *Plasmodium vivax* infection a one-time dosage of 800 mg suffices. When prescribing this treatment, official guidelines and local information about the occurrence of antimalarial drug resistance need to be taken into account. Examples of this include WHO and public safety guidelines. Treatment of an infection with *Plasmodium malariae*, *vivax* and *oval* needs to be concluded with an 8-aminoquinoline in order to eliminate the extra-erythrocytic stage of the plasmodium cycle.	**13 mg / kg hydroxychloroquine sulfate** for children is comparable to 800 mg for adults and **6,5 mg / kg hydroxychloroquine sulfate** for children is comparable to 400 mg for adults. A total dose of maximum 2 gram is applied over the course of three days, as outlined: First dose: 13 mg per kg (maximum one-time dosage of 800 mg). Second dose: 6,5 mg per kg (maximum 400 mg) 6 hours after the first dosage. Third dose: 6,5 mg per kg (maximum 400 mg) 18 hours after the second dosage. Fourth dose: 6,5 mg per kg (maximum 400 mg) 24 hours after the third dosage.

Hepatic and renal impairment Caution is advised for patients with an impaired renal or liver function. A reduction in dose may be required (see section 4.4).

Method of administration
Preferably, administer Hydroxychloroquinesulfaat DOC after a meal.

4.3 Contraindications

- Hypersensitivity to the active substance, to 4-aminoquinolines or to any of the excipients listed in section 6.1
- Myasthenia gravis
- Existing maculopathy of the eye
- Retinitis pigmentosa.

The tablets are not suitable for patients with a body weight lower than 35 kg.

4.4 Special warnings and precautions for use

General

Retinopathy
Before starting treatment, the patient's visual acuity, field of vision and colour sight needs to be examined using a careful ophthalmoscopy. A fundoscopy also needs to take place. In case of scotoma, nyctalopia or retinal changes, the examination needs to be repeated every 3 months and treatment with Hydroxychloroquine sulphate DOC needs to be discontinued. In other cases, the examination will need to be repeated every 6 months.
Retinal toxicity is primarily dose related. The risk of retinal damage is low for daily doses up to 6.5 mg/kg of body weight. Exceeding the daily recommended dose sharply increases the risk of retinal toxicity.
Concomitant use of hydroxychloroquine and medicines that are known to induce retinal toxicity, including tamoxifen, is not recommended.

This type of examinations needs to be done more frequently and modified according to the patient, in the

following cases:
- Dose exceeds 6.5 mg/kg lean body weight. Absolute body weight used as a guide to dose could result in an overdose in the obese.
- Renal insufficiency
- Cumulative dose higher than 200 g
- Elderlies
- Visual acuity decreased.

The medicinal product should be discontinued immediately in any patient who develops a visual field defect (visual acuity, colour sight etc.) and the patient should be carefully observed for any further progression of the defect. Retinal changes (and visual disturbances) may progress even after cessation of therapy (see section 4.8).

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.

Hypoglycaemia
This medicine has been shown to cause severe hypoglycaemia including loss of consciousness that could be life threatening in patients treated with and without antidiabetic medications (see section 4.5 and 4.8). 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.

Cardiomyopathy
In patients receiving hydroxychloroquine therapy cases of cardiomyopathy have been reported, leading to heart failure, sometimes with fatal outcome (see sections 4.8 and 4.9). Periodic clinical monitoring for signs/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 /heart block atrioventricular) as well as biventricular hypertrophy are diagnosed. Terminating treatment with this medicine could lead to recovery (see section 4.8).

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.

Other monitoring on long-term treatment
Patients on long term therapy should have periodic full blood counts and hydroxychloroquine should be discontinued if blood abnormalities develop (see section 4.8).
All patients on long-term therapy should undergo periodic examination of skeletal muscle function and tendon reflexes. If weakness occurs, the drug should be withdrawn (see section 4.8).

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

Although the risk of bone marrow depression is low, periodic blood counts are advisable. Use of the medicine should be discontinued if blood abnormalities develop.

Caution should be applied for patients with renal or hepatic disorders. A decrease in dose may be required (see section 4.2).

Hepatotoxicity
Serious cases of drug-induced liver injury (DILI) including hepatocellular injury, cholestatic liver injury, acute hepatitis, mixed hepatocellular/cholestatic liver injury and fulminant hepatic failure (including fatal cases) have been reported during use of hydroxychloroquine.
Risk factors may include pre-existing liver disease, or predisposing conditions such as uroporphyrinogen decarboxylase deficiency or concomitant hepatotoxic medications.
Prompt clinical evaluation and measurement of liver function tests should be performed in patients who report symptoms that may indicate liver injury. For patients with significant liver function abnormalities (see section 4.8), physicians should assess the benefits/risk of continuing the treatment.

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

Caution should also be applied in patients with severe gastrointestinal, neurological or blood disorders, those with a sensitivity to quinine, those with glucose-6-phosphate dehydrogenase deficiency, those with porphyria and psoriasis.

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.

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.*

Prolongation of QTc interval
Hydroxychloroquine has been shown to prolong the QTc interval in some patients.
Hydroxychloroquine should be used with caution in patients with congenital or documented acquired QT prolongation and/or known risk factors for prolongation of the QT interval such as:
- cardiac disease e.g. heart failure, myocardial infarction
- proarrhythmic conditions, e.g bradycardia (< 50 bpm)
- a history of ventricular dysrhythmias
- uncorrected hypokalemia and/or hypomagnesemia
- and during concomitant administration with QT interval prolonging agents (see section 4.5) as this may lead to an increased risk for ventricular arrhythmias, sometimes with fatal outcome.

The magnitude of QT prolongation may increase with increasing concentrations of the drug. Therefore, the recommended dose should not be exceeded (see also sections 4.8 and 4.9).
If signs of cardiac arrhythmia occur during treatment with hydroxychloroquine, treatment should be stopped and an ECG should be performed.

Severe cutaneous adverse reactions (SCARs)
Cases of severe cutaneous adverse drug reactions (SCAR), including drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported during treatment with hydroxychloroquine. Patients with serious dermatological reactions may require hospitalization, as these conditions may be life-threatening and may be fatal. If signs and symptoms suggestive of severe skin reactions appear, hydroxychloroquine should be withdrawn at once and alternative therapy should be considered.

4.5 Interactions with other medicinal products and other forms of interaction

There are indications that 4-aminoquinolines are pharmacologically incompatible with monoamine-oxidase inhibitors.

Pharmacodynamic interactions
Drugs known to prolong QT interval / with potential to induce cardiac arrhythmia
Hydroxychloroquine should be used with caution in patients receiving drugs known to prolong the QT interval e.g. Class IA and III antiarrhythmics, tricyclic antidepressants, antipsychotics, some anti-infectives (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 and 4.9). Halofantrine should not be administered with hydroxychloroquine.

Since hydroxychloroquine boosts the effect of a hypoglycaemic treatment, lowering of the dose of insulin or any other anti-diabetes medication may be required.

Chloroquine can decrease the antibody response to a rabies vaccine. In concurrent use of chloroquine, intradermal application of the rabies vaccine is not advised. The response after intramuscular application is generally regarded as sufficient.

Hydroxychloroquine can increase sensitivity to epileptic episodes. Concurrent use of hydroxychloroquine and antimalarial drugs that also increase sensitivity may trigger convulsions.
The efficacy of anti-epileptic drugs may be affected if they are used concurrently with hydroxychloroquine.

Pharmacokinetic interactions

Effects of other medicinal products on hydroxychloroquine:

Antacids and kaolin
Concomitant administration with magnesium- containing antacids or kaolin may result reduced absorption of chloroquine. Per extrapolation, hydroxychloroquine should therefore be administered at least two hours before or after 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 with hydroxychloroquine, caution is advised (e.g. monitoring for adverse reactions) when cimetidine or CYP2C8 and/or CYP3A4 or CYP2D6 strong 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.

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 with digoxin and hydroxychloroquine were co-administered. Caution is advised

(e.g. monitoring for adverse reactions or for plasma concentrations as appropriate) when P-gp substrates with a 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, suggesting that hydroxychloroquine is a mild inhibitor of CYP2D6.
Caution is advised (e.g. monitoring for adverse reactions or plasma concentrations as appropriate) when CYP2D6 substrates with narrow therapeutic index (e.g. 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 (e.g. ciclosporin, statins) are concomitantly administered with hydroxychloroquine.

4.6 Fertility, pregnancy and breastfeeding

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).

Animal studies with the structurally related chloquine, have shown reproduction toxicity at high maternal exposure (see section 5.3). In humans, hydroxychloroquine crosses the placenta and blood concentration in the foetus are similar to maternal blood concentrations.

Malaria prophylaxis and treatment:
After a risk-benefit analysis, hydroxychloroquine can be used during all stages of pregnancy for the prophylaxis and treatment of malaria infections, as the malaria infection itself is harmful to the foetus.

Rheumatoid arthritis, systemic lupus erythematosus:
Hydroxychloroquine should be avoided in pregnancy except when, in the judgment 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.

Breastfeeding
Hydroxychloroquine is excreted in human milk (less than 2% of the maternal dose after body weight correction).
There is insufficient information on the effects of hydroxychloroquine in newborns/infants.
Hydroxychloroquine has a slow elimination rate and after prolonged exposure during breastfeeding there is a risk of accumulation in specific tissues of the infant, such as the retina. With prolonged daily use of high doses of hydroxychloroquine, breastfeeding should be discontinued.

For use as malaria prophylaxis, Hydroxychloroquinesulfaat DOC can be used during breastfeeding. However, the amount of hydroxychloroquine excreted in breast milk is insufficient to achieve any prophylactic effect on the child.

Fertility
Animal studies showed that chloroquine reduces male fertility (see section 5.3). There are no data on the effects of hydroxychloroquine on fertility in humans.

4.7 Effect on ability to drive and use machines

Hydroxychloroquine can lower accommodation and may cause blurry vision. Additionally, it can cause dizziness (see section 4.8) Because of this, hydroxychloroquine can impair the ability to drive and use machines.

4.8 Undesirable effects

Frequencies are defined as: 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), unknown (frequency cannot be determined based on currently known information).

System/organ class	Common	Uncommon	Rare	Very rare	Unknown
Blood and lymphatic systems disorders			Bone marrow depression		Anaemia and aplastic anaemia Agranulocytosis White blood cell count decreased Thrombocytopenia Porphyria aggravated (see section 4.4)
Metabolism and nutrition disorders	Anorexia				Hypoglycaemia (see section 4.4)
Psychiatric disorders	Emotional lability	Nervousness			Dizziness Anxiety Suicidal behaviour Psychosis Depression Hallucinations Agitation Confusion Delusions Mania Sleep disorders
Nervous system disorders			Convulsions		Vertigo Tinnitus Mood disorder Headache Extrapyramidal disorders such as dystonia, dyskinesia, tremor (see section 4.4)
Eye disorders			Retinopathy and changes in		Patients who experience retinal changes may be

			pigmentation and visual field defect (1)		asymptomatic initially, or have scotomatous vision with paracentral and pericentral ring types, temporary scotomas and deviating colour perception Corneal changes, including oedema and opacity(2) Blurred vision caused by abnormality of accommodation (3)
Ear and labyrinthine disorders				(irreversible) hearing loss	
Cardiovascular disorders			Cardiomyopathy, which may result in cardiac failure, in some cases with fatal outcome. T-top deviations in ECG.		Conduction disorders (bundle branch block / atrioventricular block) (see section 4.4) Biventricular hypertrophy (see section 4.4). QT-prolongation in patients with specific risk factors, which may 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		Skin rash		Erythema multiforme Stevens-Johnson syndrome Toxic epidermal necrolysis Acute generalized exanthematous	Itch (4) Changes in skin and mucosal pigmentation (4) Lightening of hair colour (4) Alopecia (4) Lichen planus-like dermatitis Photosensitivity

				pustulosis (AGEP), which can be accompanied by fever and hyperleukocytosis	Exfoliative dermatitis Psoriasis Drug reaction with eosinophilia and systemic symptoms Sweet's syndrome and Severe cutaneous adverse reactions (SCARs)
Musculoskeletal and connective tissue disorders					Myopathy of the skeletal muscles (5) Neuromyopathy leading to progressive weakness Atrophy of the proximal muscle groups Related mild sensory disturbance Tendon reflex decreased Nerve conduction studies abnormal
General disorders and administration site conditions					Allergic reactions such as urticaria and angioedema Bronchospasm

1. In an early stage, the change is reversible after terminating the hydroxychloroquine therapy. After the development of retinopathy, the symptom can persist or aggravate even after terminating the hydroxychloroquine therapy. Cases of maculopathy and macular degeneration have been observed and can be irreversible.
2. The changes are asymptomatic or could cause visual defects such as halos, blurry vision and photophobia. These changes are transient or reversible after terminating the treatment.
3. This is dosage dependent and reversible.
4. These symptoms usually vanish after lowering the dosage of terminating the treatment.
5. This can be reversible when the treatment is terminated, recovery could take a few 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 the national reporting system listed in Appendix V.

4.9 Overdose

Overdoses involving 4-aminoquinolines are dangerous, in particular for small infants. Amounts of 1-2 grams are proven to be fatal.

Symptoms

The symptoms of an overdose can include: headache, visual defects, cardiovascular insufficiency, convulsions, hypokalaemia and 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 instances of respiratory arrests and cardiac arrests.

These effects will develop shortly after intake of a significant overdose and need to be treated as soon as

possible.

Measures
The stomach needs to be emptied within one hour after ingestion by vomiting or gastric lavage. Activated carbon can counteract further absorption when left in the stomach, by using a probe after a gastric lavage. This can even be of significance for an extended period after ingestion.
Studies show that parenteral administration of diazepam can decrease the cardiotoxicity. Artificial respiration and shock management need to occur as soon as possible.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic category: Antirheumatic and antiprotozoal, ATC-code: P01BA02.

Hydroxychloroquine, an anti-malarial 4-aminoquinoline, has a fast blood schizonticide activity and a limited gametocide activity and is also classified as a slow acting anti-rheumatic drug.

Hydroxychloroquine has several pharmacological effects that could relate to the therapeutic effects and side effects.
These include: interaction with sulfhydryl groups (change in the enzyme activity of phospholipase, NADH-cytochrome C reductase, cholinesterase, proteases and hydrolases), DNA binding, stabilisation of lysosomal membranes, inhibition of prostaglandin synthesis, polymorphonuclear cell chemotaxis and phagocytosis, potential influencing of the interleukin-1 production of monocytes and inhibition of neutrophilic superoxide emission. Concentration in intracellular acid vesicle and pH increases in this vesicle could be an explanation for anti-protozoal and anti-rheumatic effects.

5.2 Pharmacokinetic properties

Absorption
After oral administration, the peak plasma or blood concentration is reached in approximately 3 to 4 hours. Mean absolute oral bioavailability is 79% (SD 12%) in fasting conditions. Food does not alter the oral bioavailability of hydroxychloroquine.

Distribution
Hydroxychloroquine has a high volume of distribution (5500 L when assessed from blood concentrations, 44000 L when assessed from plasma concentrations), due to extensive tissue accumulation (such as eyes, kidneys, 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 mainly metabolized by CYP2C8, CYP3A4 and CYP2D6, as well as by FMO-1 and MAO-A, without major involvement of any single CYP or enzyme.

Elimination
Hydroxychloroquine presents a multi-phasic elimination profile, with a long terminal half-life ranging from 30 to 50 days. About 20-25% of 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 appear to be linear in the therapeutic dose range of 200 to 500 mg/day.

Pharmacokinetic interactions

Effect of hydroxychloroquine on other medicinal products
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 (see section 4.5).
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 the potential to inhibit OCT1, OCT2, MATE1 and MATE2-K transporters.

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. Since hydroxychloroquine is primarily metabolised, 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.

Pediatrics
The pharmacokinetics of hydroxychloroquine in children below 18 years of age have not been established.

5.3 Preclinical safety data

Genotoxicity/carcinogenicity
Based on the studies performed, hydroxychloroquine is not found to be genotoxic. No relevant non-clinical carcinogenicity studies on hydroxychloroquine are available.

Reproductive and developmental toxicity
Data on hydroxychloroquine teratogenicity are limited.
The related compound chloroquine was found teratogenic in rats at high supratherapeutic doses, showing a 25% fetal mortality rate and 45% of fetuses eye malformations.
In animals chloroquine accumulates in eyes and ears when administered early or late in pregnancy.

Fertility
There are no data on the effect of hydroxychloroquine on fertility.
Chloroquine showed in rats a decrease in testosterone levels, testes, epididymis, seminal vesicles and prostate weights after 1 month with low dose. Also in rats, the fertility rate was reduced after 14 days of intraperitoneal treatment at low dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Maize starch
Calcium hydrogen phosphate dihydrate (E341)
Silica, colloidal anhydrous (E551)
Polysorbate 80 (E433)
Dried maize starch
Talc (E553b)
Magnesium stearate (E470b)

Film-coating
Hypromellose (E464)
Talc (E553b)
Titanium dioxide (E171)
Macrogol 6000

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in the original package in order to protect from light.

6.5 Nature and contents of container

Transparent PVC/aluminium blister pack containing 30 tablets.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

DOC Generici S.r.l.
Via Filippo Turati 40,
Milaan 20121
Italië

8. MARKETING AUTHORIZATION NUMBER(S)

RVG 122221

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Datum van eerste verlening van de vergunning: 4 februari 2019
Datum van laatste verlenging: 15 januari 2024

10. DATE OF REVISION OF THE TEXT

Laatst gedeeltelijke wijziging betreft rubriek 4.4, 4.5, 4.6, 4.8, 4.9, 5.2 en 5.3: 12 januari 2024