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
- Photodermatitis
- 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**

<table>
<thead>
<tr>
<th>Adults</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td>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.</td>
</tr>
</tbody>
</table>

**Systemic and Discoid Lupus Erythematosus**

<table>
<thead>
<tr>
<th>Adults</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting dose: 400 mg to 600 mg a day (for a few weeks if necessary). Maintenance dose: 200 mg to 400 mg a day.</td>
<td></td>
</tr>
</tbody>
</table>

**Polymorphic photodermatosis  Polymorphic light eruption**

<table>
<thead>
<tr>
<th>Adults</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage: 400 mg a day usually suffices. The treatment needs to be limited to periods of maximum exposure to light.</td>
<td></td>
</tr>
</tbody>
</table>

**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.

<table>
<thead>
<tr>
<th>Adults</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage: 400 mg a week on the same day of each week.</td>
<td>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.</td>
</tr>
</tbody>
</table>

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

**Treatment of an acute malaria attack**

<table>
<thead>
<tr>
<th>Adults</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>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 <em>Plasmodium falciparum</em> infection and to suppress an acute attack of a <em>Plasmodium vivax</em> 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 <em>Plasmodium malariae</em>, <em>vivax</em> and <em>oval</em> needs to be concluded with an 8-aminoquinoline in order to eliminate the extra-erythrocytic stage of the plasmodium cycle.</td>
<td><strong>13 mg / kg hydroxychloroquine sulfate</strong> for children is comparable to 800 mg for adults and <strong>6.5 mg / kg hydroxychloroquine sulfate</strong> 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.</td>
</tr>
</tbody>
</table>

**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 <Product name> 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**

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.

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

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.

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.

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.

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.

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

**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.

**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).

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). 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.

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.

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.

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.

Concomitant treatment of hydroxychloroquine with digoxin can result in increased plasma digoxin levels. Serum digoxin levels should be closely monitored in patients receiving concomitant treatment.

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

Hydroxychloroquine inhibits CYP2D6. Concurrent use with drugs that inhibit CYP2D6 is not advised.

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.

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 due to increased risk of ventricular arrhythmia (see sections 4.4 and 4.9). Halofantrine should not be administered with hydroxychloroquine.
4.6 Fertility, pregnancy and breastfeeding

Pregnancy
A moderate amount of data on pregnant women (between 300-1000 prospective pregnancies) indicate no malformative or feto/neonatal toxicity of hydroxychloroquine. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). The quinine derivative chloroquine is considered safe for pregnant women at recommended doses for prophylaxis (and treatment) of malaria. After prolonged, daily use of chloroquine in high doses during human pregnancy, sporadic adverse effects have been observed (cochleovestibular and retinal abnormalities) that were not confirmed in larger series. Although these effects have not been described for hydroxychloroquine, the daily use of hydroxychloroquine at high doses (such as for systemic lupus erythematosus, rheumatoid arthritis and treatment of acute attack of malaria) should only be made on strict indication and if the risk of stopping treatment is greater than the possible risk to the fetus.

Hydroxychloroquine may be used for malaria prophylaxis during pregnancy, since no adverse effects on the fetus were demonstrated when using the prophylactic doses.

Lactation
Hydroxychloroquine is excreted in human milk. Because of the slow elimination rate and due to the risk of accumulation of a toxic amount in the infant at prolonged daily use of high doses of hydroxychloroquine, it is recommended to stop breastfeeding. At dosages once a week, such as for malaria prophylaxis, the available amount of hydroxychloroquine for the infant is significantly reduced and the chance of accumulation and toxicity is much lower. Although breastfeeding is not considered to be harmful during treatment for malaria prophylaxis, the amount of excreted is insufficient to achieve any prophylactic effect on the child.

Fertility
There is no information available on the effect hydroxychloroquine sulphate on human fertility (see section 5.3).

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).

<table>
<thead>
<tr>
<th>System/organ class</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Very rare</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic systems disorders</td>
<td></td>
<td></td>
<td>Bone marrow depression</td>
<td></td>
<td>Anaemia and aplastic anaemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Agranulocytosis</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>White blood cell count decreased</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Porphyria aggravated</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Anorexia</td>
<td></td>
<td>Hypoglycaemia (see section 4.4)</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>-------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Emotional lability</td>
<td>Nervousness</td>
<td>Dizziness Anxiety Suicidal behaviour Psychosis Depression Hallucinations Agitation Confusion Delusions Mania Sleep disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Convulsions</td>
<td></td>
<td>Vertigo Tinnitus Mood disorder Headache Extrapyramidal disorders such as dystonia, dyskinesia, tremor (see section 4.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Retinopathy and changes in pigmentation and visual field defect (1)</td>
<td></td>
<td>Patients who experience retinal changes may be 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)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ear and labyrinthine disorders</td>
<td>(irreversible) hearing loss</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disorders</td>
<td>Cardiomyopathy, which may result in cardiac failure, in some cases with fatal outcome. T-top deviations in ECG.</td>
<td></td>
<td>Conduction disorders (bundle branch block / atrioventricular block) (see section 4.4) Biventricular hypertrophy (see section 4.4). QT-prolongation (see sections 4.4 and 4.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea Diarrhoea Abdominal pain</td>
<td>Vomiting (4)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| **Hepatobiliary disorders** |  | Abnormal liver function tests  
Fulminant hepatic failure |
| **Skin and subcutaneous tissue disorders** | Skin rash | Erythema multiforme  
Stevens-Johnson syndrome  
Toxic epidermal necrolysis  
Acute generalized exanathematous pustulosis (AGEP), which can be accompanied by fever and hyperleukocytosis  
Itch (4)  
Changes in skin and mucosal pigmentation (4)  
Lightening of hair colour (4)  
Alopecia (4)  
Lichen planus-like dermatitis  
Photosensitivity  
Exfoliative dermatitis  
Psoriasis  
Drug reaction with eosinophilia and systemic symptoms |
| **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, followed by sudden and potentially fatal instances of respiratory arrests and cardiac arrests.

With serious intoxication, width-increased QRS complex, bradyarrhythmias, nodal rhythm, QT prolongation, atrioventricular block, ventricular tachycardia, torsades de pointes, ventricular fibrillation may occur.

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 sulphhydryl 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**
Hydroxychloroquine is quickly absorbed after oral administration. The average biological availability is approximately 74%.

**Distribution**
Distribution occurs throughout the entire body, accumulation takes place in the blood cells and tissues such as in the liver, kidneys and eyes.

**Biotransformation**
It is partially metabolised in the liver into active ethylated metabolites and elimination predominantly takes
place through the kidneys (23-25% unchanged), but also through the gall bladder.

**Elimination**
Elimination is slow; the terminal elimination half-life is approximately 50 days (total blood) and 32 days (plasma). Hydroxychloroquine passes the placenta and is probably excreted in human breast milk, much likely as chloroquine.

**5.3 Preclinical safety data**

No relevant non-clinical studies are available.

**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**
Hyromellose (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**
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

10. DATE OF REVISION OF THE TEXT

Laatste gedeeltelijke wijziging betreft de rubrieken 4.4 en 4.8: 4 juni 2021