SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

A-CQ 100 Chloroquine 100 mg, tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

A-CQ 100 Chloroquine 100 mg tablets containing chloroquine phosphate, equivalent to 100 mg chloroquine per tablet.

Contains 41 mg lactose per tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

Round white tablet with a score line on one side and the inscription 'CQ 100' on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

A-CQ 100 Chloroquine 100 mg is intended for:

- Prophylaxis and treatment of all forms of malaria
    - Treatment of *Plasmodium vivax a*nd *P. ovale* should be followed by treatment with primaquine in order to eliminate the exo-erythrocytic phase of the plasmodium cycle
    - Resistance of *Plasmodium falciparum* to chloroquine is seen in many regions. This limits the applicability of chloroquine in these regions
    - Study WHO and local treatment guidelines before initiating treatment
- Treatment of rheumatoid arthritis, either adult or juvenile, not responding to 6 months' treatment with a prostaglandin synthesis inhibitor
- Treatment of lupus erythematosus
- Treatment of hepatic amoebiasis in combination with a luminal amoebicidal drug
    - in cases which do not respond to treatment with a general amoebicidal drug (metronidazole, tinidazole)
    - in patients for whom general amoebicidal drugs are contraindicated

4.2 Posology and method of administration

The tablets have only a single score line and not a score cross. Dosages less than half a tablet are not possible. The tablets are therefore not suitable for children with a bodyweight less than 10 kg.

<u>Prophylaxis of malaria</u>
Adults and children 13 years and older
Single prophylactic doses of 300 mg are usually given 1-2 weeks before departure to an endemic area or on the first and second day prior to departure. Thereafter 1 dose a week during stay in the endemic area and during 4-8 weeks after return.

Children (bodyweight of 10 kg or more)
For children, it is recommended to use a dosage schedule similar to that described above for older patients. The single doses should however be adjusted as follows:

- 5 mg / kg body weight
- according to age:

11 – 12 years	250 mg
7 – 10 years	150 mg
4 – 6 years	100 mg
Below 3 years	50 mg

A-CQ 100 Chloroquine 100 mg should be taken during or shortly after a meal.

Treatment of malaria
Acute attack:

Adults
Single starting dose of 600 mg, followed by 300 mg 6 hours later. Thereafter, 300 mg per day for 2 days. If necessary, another 300 mg per day for two days. Continue with the prophylactic dose.

Children (bodyweight 10 kg or more)
Starting dose 10 mg/kg, followed by a dose of 5 mg/kg 6 hours later. Thereafter, 5 mg/kg per day for 2 days. Continue with the prophylactic dose.

Other indications
The dosage advice is intended for adults; for children use the adapted lower doses (see "prophylaxis of malaria").

- Hepatic amoebiasis
Start with 300 mg twice a day for two days. Continue with 300 mg once a day for 2-3 weeks.

- Lupus erythematosus
Start with 300-600 mg per day for 8-15 days, followed by 200-300 mg per day for 2-3 weeks; maintenance dose 100-200 mg per day.

- Rheumatoid arthritis
Start with 150-300 mg per day for 7-10 days, maintenance dose 100-200 mg per day, not exceeding 4 mg/kg per day.

4.3 Contraindications

Do not use A-CQ 100 Chloroquine 100 mg:

- In patients with hypersensitivity to chloroquine or any of the excipients listed in section 6.1, or who have hypersensitivity to other 4-aminoquinoline derivatives;
- In patients with myasthenia gravis;
- In patients with retinal or visual field changes. In case of acute attacks of malaria the physician may decide, after careful consideration of the potential benefits and risks, to prescribe this product anyway.

4.4 Special warnings and precautions for use

Suicidal behaviour and psychiatric disorders
Cases of suicidal behaviour and psychiatric disorders have been reported in patients treated with chloroquine (see section 4.8), including 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.

Prolongation of QTc interval
Chloroquine has been shown to prolong the QTc interval in some patients.
Chloroquine 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 chloroquine, treatment should be stopped and an ECG should be performed.

Cardiomyopathy
In patients receiving chloroquine therapy cases of cardiomyopathy have been reported, leading to heart failure, sometimes with fatal outcome (see sections 4.8 and 4.9). If signs and symptoms of cardiomyopathy occur during treatment with chloroquine, treatment should be stopped.

Hypoglycaemia
Chloroquine 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 chloroquine 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 chloroquine should have their blood glucose level checked and treatment reviewed as necessary.

Retinopathy
Irreversible retinal damage may occur in patients treated for a prolonged period. An ophthalmic examination should be performed before starting treatment and at regular intervals during treatment (every 3-6 months). Treatment with chloroquine should be stopped immediately if retinal damage occurs.

Resistance
Resistance of *Plasmodium falciparum* to chloroquine is well documented. Epidemiological data should be considered before starting treatment with chloroquine. Treatment with another antimalarial or combination therapy may be necessary in areas with known or presumed resistance of *Plasmodium falciparum*.

Other
Caution is advised if there is a known history of epilepsy (convulsions have been seen), porphyria (risk of acute episodes), psoriasis (deterioration of lesions), renal and/or hepatic disease, hypersensitivity to quinine, glucose-6-phosphate dehydrogenase deficiency, or severe gastrointestinal, neurological and/or haematological disorders. Blood tests should be performed regularly in cases of prolonged treatment. Treatment with chloroquine should be stopped if haematological disorders occur.

Young children are particularly susceptible to 4-aminoquinoline derivatives. Relatively low dosages may cause severe intoxication (lethal respiratory or circulatory disorders).

Chloroquine is not effective against recurrent tertian malaria infections (cause by *P. vivax* and *P. ovale*). Cross-resistance has been found with mepacrine, proguanil and pyrimethamine.

This product contains lactose. Patients with rare hereditary diseases, such as galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption, should not use this product.

4.5 Interaction with other medicinal products and other forms of interaction

- Drugs known to prolong QT interval / with potential to induce cardiac arrhythmia. Chloroquine 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 chloroquine.
- Activated charcoal, magnesium trisilicate, magnesium-containing antacids and kaolin may lead to reduced absorption of chloroquine. Chloroquine should therefore be administered at least 4 hours before or after taking products.
- Concomitant use of chloroquine with cimetidine, a cytochrome P450 inhibitor, may result in an increased half-life and decreased clearance of chloroquine, resulting in increased plasma concentrations of chloroquine.
- Concomitant administration of ciclosporin and chloroquine may result in increased plasma concentrations of ciclosporin.
- Chloroquine may affect the antibody response to rabies vaccine. Do not administrate the vaccine intradermally. The antibody response following intramuscular administration is considered to be sufficient.
- There are indications that 4-aminoquinoline derivatives are pharmacological incompatible with MAO inhibitors.
- There is a higher risk of dermatitis when chloroquine is used in combination with gold compounds, or with phenylbutazone or oxyphenbutazone. Concomitant use should be avoided.
- Concomitant administration of chloroquine with digoxin or paracetamol may increase plasma concentrations of digoxin or paracetamol.
- Concomitant administration of chloroquine with ampicillin decreases the bio-availability of ampicillin.

4.6 Fertility, pregnancy and lactation

Pregnancy

Chloroquine crosses the placenta, but can be used safely in pregnant women when used for prophylaxis or treatment of malaria. The safety of chloroquine has not been determined in pregnant women treated with high doses for a prolonged period. There is also limited experience with prolonged treatment of chloroquine at anti-rheumatic dosages in pregnant women. Cochlear/vestibular and retinal damage in the foetus has been seen occasionally. Daily treatment with chloroquine as an anti-rheumatic is therefore not recommended during pregnancy, unless the benefits to the mother outweigh the risks to the foetus.

Lactation

Although chloroquine is excreted in breast milk, it can be given safely as prophylaxis for the mother. The amount excreted in breast milk is insufficient to confer protection to the infant. Separate prophylaxis for the infant is required.

4.7 Effects on ability to drive and use machines

Patients should be warned that temporary visual disturbance may occur and they should not drive and use machines when this happens. Dizziness, psychological changes or accommodation disorders may also occur, and this should be taken into account when participating in traffic or operating machinery.

4.8 Undesirable effects

Chloroquine is usually well tolerated.

Skin and subcutaneous tissue disorders
- Rash, pruritus, hair loss, lichen-planus type disorders, blue-black discoloration, especially of nails and mucous membranes, possible exacerbation of psoriasis.
- Rare reports of Toxic Epidermal Necrolysis (TEN), erythema multiforme and Stevens-Johnson syndrome (SJS).

Immune system disorders
- Anaphylactic reactions, including angio-oedema.

Metabolism and nutrition disorders
- Unknown: hypoglycaemia (see section 4.4)

Nervous system disorders
- Convulsions
- Polyneuritis, myopathy and neuropathy.

Musculoskeletal and connective tissue disorders
- Myopathy

General disorders and administration site conditions
- Headache

Psychiatric disorders
- Very common: insomnia
- Common: depression
- Rare: psychiatric disorders such as anxiety, agitation, confusion, hallucinations, delirium
- Unknown: suicidal behaviour, psychosis, aggression, delusion, paranoia, mania, attention deficit, sleep disorders.

Eye disorders
- Retinopathy, in rare cases irreversible following prolonged treatment with high dosages.
- Reversible blurred vision and reversible turbidity of the cornea.

Cardiac disorders
During prolonged treatment with high dosages:
- Rare: Cardiomyopathy
- Possible occurrence of rare cardiac arrhythmias, abnormal T wave in ECGs
- Unknown: Atrioventricular block, QT-prolongation (see sections 4.4 and 4.9).

Blood and lymphatic system disorders
- Bone marrow depression, agranulocytosis, pancytopenia, thrombocytopenia, aplastic anaemia.

Ear and labyrinth disorders
- Tinnitus, reduced hearing, deafness

Gastrointestinal disorders
- Nausea, gastrointestinal disorders, vomiting, anorexia, diarrhoea.

Hepatobiliary disorders
- Hepatic function disorders

- Occasionally abnormal liver function tests and hepatitis.

4.9 Overdose

Chloroquine is rapidly absorbed and is highly toxic in overdose. Children are particularly susceptible to overdose. The chief and most severe symptoms at overdose include convulsions, coma, widening of the QRS complex on ECG with dysrhythmias (ventricular dysrhythmias), bradyarrhythmias, nodal rhythm, QT prolongation, atrioventricular block, ventricular tachycardia, torsades de pointes, ventricular fibrillation, hypotension, cardiac arrest, respiratory insufficiency with respiratory arrest. Severe hypokalaemia may occur. Initially headache, sleeplessness, visual disturbance, nausea and vomiting may occur.

Hospitalisation in an intensive care unit is indicated. Rapid treatment with absorption-inhibiting therapy is important (gastric lavage, activated charcoal, osmotic laxative). Subsequent treatment should be symptomatic. Early mechanic ventilation and concurrent administration of adrenaline (before start of ventricular dysrhythmias) and high dosages of diazepam have been successful in treating severe chloroquine intoxication:

- IV infusion of adrenaline starting with 0.25 µg per kg bodyweight per minute, with an increase of 0.25 µg per kg bodyweight until systolic blood pressure is sufficiently restored (> 100 mmHg); adrenaline reduces the effects of chloroquine on the heart through its inotropic and vasoconstrictor effects.

- IV infusion of diazepam at a dose of 2 mg/kg over 30 minutes followed by 1-2 mg/kg/day for 2 to 4 days; diazepam may minimise cardiotoxicity.

Methods for enhanced elimination such as haemodialysis, haemoperfusion or exchange transfusions have not been shown to be of value in treating chloroquine intoxication. Chloroquine is excreted very slowly; symptomatic cases therefore merit observation for several days.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: antimalarials, aminoquinolines

ATC-code: P01BA01

5.1 Pharmacodynamic properties

Chloroquine is a 4-aminoquinoline derivative. It is active against the erythrocytic forms of all plasmodium species (blood schizonticidal action), but not against the exo-erythrocytic parasitic forms of *P. vivax* and *P. ovale*. The mechanism of action in malaria is unknown. One possible mechanism is that absorption and accumulation of chloroquine in the parasite causes an increase in the pH of the intracellular vacuoles, thereby reducing the parasite's ability to break down haemoglobin. A second possibility is that chloroquine forms a complex by binding to the ferriprotoporphyrin that is released from the haemoglobin of infected erythrocytes. This complex is toxic for the cell membranes of the parasite and the erythrocytes.

Resistance of *Plasmodium falciparum* to chloroquine is seen to a limited extent in some parts of Southeast Asia (the Philippines and parts of Indonesia), but is frequent and widespread in the Amazon basin area of South America, large parts of Southeast Asia and sub-Saharan Africa. Chloroquine resistance has also been described for *Plasmodium vivax*, and occurs in some areas of Southeast Asia and possibly also in South America.

Chloroquine is also effective against the extra-intestinal form of *Entamoeba histolytica* (tissue amoebicidal action). Chloroquine also has anti-inflammatory properties.

5.2 Pharmacokinetic properties

Absorption
Following oral administration approximately 80% of the dose is absorbed. Maximum plasma concentrations of approximately 100 ng/ml will be reached 2-6 hours after administration of 300 mg.

Distribution
Chloroquine is widely distributed throughout the body, to almost all organs. The distribution volume is large (approximately 200 l/kg). Concentrations in the organs are 300-500 times higher than the concentration in plasma. Plasma protein binding of chloroquine is 50%. Chloroquine crosses the placenta and is excreted at low concentrations in breast milk.

Biotransformation and elimination
Chloroquine is metabolised by liver enzymes to the active metabolite desethylchloroquine. Excretion takes place mainly via the urine. Approximately 50-60% of the administered dose is excreted by the kidneys, of which 70% as chloroquine and approximately 23% as desethylchloroquine. The plasma elimination half-time of chloroquine is approximately 2 weeks.

5.3 Preclinical safety data

No special data.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Maize starch
Pregelatinised maize starch
Crospovidone
Magnesium stearate
Colloidal silicon dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

Store below 25°C in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

A-CQ 100 Chloroquine 100 mg tablets are packed per 10 tablets in PVC/Aluminium blister strips. Three PVC/aluminium blister strips are packed with a Patient Information Leaflet in a green and white coloured carton box.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Ace Pharmaceuticals BV, Schepenveld 41, 3891 ZK Zeewolde, the Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

RVG 106659

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

November 2023