Drugfield **PHARMACEUTICALS LIMITED**

SUMMARY OF PRODUCT CHARACTERISTICS

Resoquine® Injection (Chloroquine 40mg/ml)

1. NAME OF THE MEDICINALPRODUCT

Resoquine® (Chloroquine 40mg/ml) Injection

2. QUALITATIVE AND QUANTITATIVECOMPOSITION

Each ml contains 40mg chloroquine in form of chloroquine phosphate

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Injection

4. Clinical particulars

4.1 Therapeutic indications

Resoquine injection is indicated for the suppressive treatment and for acute attacks of malaria due to P. vivax, P.malariae, P. ovale, and susceptible strains of P. falciparum. The drug is also indicated for the treatment of extraintestinal amebiasis. Ressoquine injection does not prevent relapses in patients with vivax or malariae malaria because it is not effective against exoerythrocytic forms of the parasite, nor will it prevent vivax or malariae infection when administered as a prophylactic. It is highly effective as a suppressive agent in patients with vivax or malariae malaria, in terminating acute attacks, and significantly lengthening the interval between treatment and relapse. In patients with falciparum malaria it abolishes the acute attack and effects complete cure of the infection, unless due to a resistant strain of P. falciparum

4.2 Posology and method of administration

Posology

Important Dosage and Administration Instructions

Use as directed by a physician.

Initial Dosage

When given parentally, an initial dose of 10 mg base/kg should be given over a period of 8 hours by slow intravenous infusion.

Subsequent infusions of 5 mg base /kg should be given every 8 hours up to a total dose of 25 mg base/kg.

Chloroquine can be administered by intramuscular or subcutaneous injection at a dose of 3.5 mg base/kg 6-hourly up to a total dose of 25 mg base/kg.

Method of administration

Intramuscular Injection

4.3 Contraindications

Use of this drug is contraindicated in the presence of retinal or visual field changes either attributable to 4-aminoquinoline compounds or to any other etiology, and in patients with known hypersensitivity to 4-aminoquinoline compounds. However, in the treatment of acute attacks of malaria caused by susceptible strains of plasmodia, the physician may elect to use this drug after carefully weighing the possible benefits and risks to the patient.

4.4 Special warnings and precautions for use

It has been found that certain strains of P. falciparum have become resistant to 4-aminoquinoline compounds (including chloroquine and hydroxychloroquine). Chloroquine resistance is widespread and, at present, is particularly prominent in various parts of the world including sub-Saharan Africa, Southeast Asia, the Indian subcontinent, and over large portions of South America, including the Amazon basin1. Before using chloroquine for prophylaxis, it should be ascertained whether chloroquine is appropriate for use in the region to be visited by the traveler. Chloroquine should not be used for treatment of P. falciparum infections acquired in areas of Chloroquine resistance or malaria occurring in patients where Chloroquine prophylaxis has failed. Patients infected with a resistant strain of plasmodia as shown by the fact that normally adequate doses have failed to prevent or cure clinical malaria or parasitemia should be treated with another form of antimalarial therapy.
Irreversible retinal damage has been observed in some patients who had received long-term or high-dosage 4-aminoquinoline therapy. Retinopathy has been reported to be dose related. When prolonged therapy with any antimalarial compound is contemplated, initial (base line) and periodic ophthalmologic examinations (including visual acuity, expert slit-lamp, funduscopic, and visual field tests) should be performed. If there is any indication (past or present) of abnormality in the visual acuity, visual field, or retinal macular areas (such as pigmentary changes, loss of foveal reflex), or any visual symptoms (such as light flashes and streaks) which are not fully explainable by difficulties of accommodation or corneal opacities, the drug should be discontinued immediately and the patient closely observed for possible progression. Retinal changes (and visual disturbances) may progress even after cessation of therapy. All patients on long-term therapy with this preparation should be questioned and examined periodically, including testing knee and ankle reflexes, to detect any evidence of muscular weakness. If weakness occurs, discontinue the drug. A number of fatalities have been reported following the accidental ingestion of chloroquine, sometimes in relatively small doses (0.75 g or 1 g chloroquine phosphate in one 3-year-old child). Patients should be strongly warned to keep this drug out of the reach of children because they are especially sensitive to the 4-aminoquinoline compounds. Use of Resoquine injection in patients with psoriasis may precipitate a severe attack of psoriasis. When used in patients with porphyria the condition may be exacerbated. The drug should not be used in these conditions unless in the judgment of the physician the benefit to the patient outweighs the potential risks. Usage in Pregnancy: Radioactively tagged chloroquine administered intraveneously to pregnant pigmented CBA mice passed rapidly across the placenta and accumulated selectively in the melanin structures of the fetal eyes. It was

retained in the ocular tissues for five months after the drug had been eliminated from the rest of the body2. There are no adequate and well-controlled studies evaluating the safety and efficacy of chloroquine in pregnant women. Usage of chloroquine during pregnancy should be avoided except in the suppression or treatment of malaria when in the judgment of the physician the benefit outweighs the potential risk to the fetus.

PRECAUTIONS

Hematological Effects/Laboratory Tests Complete blood cell counts should be made periodically if patients are given prolonged therapy. If any severe blood disorder appears which is not attributable to the disease under treatment, discontinuance of the drug should be considered. The drug should be administered with caution to patients having G-6-PD (glucose-6 phosphate dehydrogenase) deficiency. Auditory Effects In patients with preexisting auditory damage, chloroquine should be administered with caution. In case of any defects in hearing, chloroquine should be immediately discontinued, and the patient closely observed
(see ADVERSE REACTIONS).
Hepatic Effects Since this drug is known to concentrate in the liver, it should be used with caution in patients with hepatic disease or alcoholism or in conjunction with known hepatotoxic drugs. Central Nervous System Effects Patients with history of epilepsy should be advised about the risk of chloroquine provoking seizures

Dosage and Administration.
Geriatric Use Clinical studies of Aralen did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. However, this drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function.

4.5 Interaction with other medicinal products and other forms of interaction

Antacids and kaolin: Antacids and kaolin can reduce absorption of chloroquine; an interval of at least 4 hours between intake of these agents and chloroquine should be observed.
Cimetidine: Cimetidine can inhibit the metabolism of chloroquine, increasing its plasma level. Concomitant use of cimetidine should be avoided.
Ampicillin: In a study of healthy volunteers, chloroquine significantly reduced the bioavailability of ampicillin. An interval of at least two hours between intake of this agent and chloroquine should be observed.
Cyclosporin: After introduction of chloroquine (oral form), a sudden increase in serum cyclosporin level has been reported. Therefore, close monitoring of serum cyclosporin level is recommended and, if necessary, chloroquine should be discontinued.

4.6 Pregnancy and Lactation

Pregnancy

Radioactively tagged chloroquine administered intraveneously to pregnant pigmented CBA mice passed rapidly across the placenta and accumulated selectively in the melanin structures of the fetal eyes. It was retained in the ocular tissues for five months after the drug had been eliminated from the rest of the body2. There are no adequate and well-controlled studies evaluating the safety and efficacy of chloroquine in pregnant women. Usage of chloroquine

during pregnancy should be avoided except in the suppression or treatment of malaria when in the judgment of the physician the benefit outweighs the potential risk to the fetus.

Lactation

Because of the potential for serious adverse reactions in nursing infants from chloroquine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the potential clinical benefit of the drug to the mother.

Females and Males of Reproductive Potential

Chloroquine should be used with caution, chronic (suppressive) treatment and abuses of the drug should be avoided as the arbitrary use may result in reproductive health dysfunctions. This may be evidenced in the effects such as reduction in sperm count, weight of testes and epididymis.

4.7 Effects on ability to drive and use machines

At start of treatment chloroquine has a temporary effect on visual accommodation, causing blurred and/or double vision. Therefore patients should be advised that the product may affect their ability to drive or operate machinery.

4.8 Undesirable effects

Special Senses:

Ocular: Irreversible retinal damage in patients receiving long-term or high-dosage 4-aminoquinoline therapy; visual disturbances (blurring of vision and difficulty of focusing or accommodation); nyctalopia; scotomatous vision with field defects of paracentral, pericentral ring types, and typically temporal scotomas, e.g., difficulty in reading with words tending to disappear, seeing half an object, misty vision, and fog before the eyes.

Auditory: Nerve type deafness; tinnitus, reduced hearing in patients with preexisting auditory damage. Musculoskeletal system: Skeletal muscle myopathy or neuromyopathy leading to progressive weakness and atrophy of proximal muscle groups, which may be associated with mild sensory changes, depression of tendon reflexes and abnormal nerve conduction, have been noted.

Gastrointestinal system: Anorexia, nausea, vomiting, diarrhea, abdominal cramps.

Skin and appendages: Pleomorphic skin eruptions, skin and mucosal pigmentary changes; lichen planus-like eruptions, pruritus, photosensitivity and hair loss and bleaching of hair pigment.

Hematologic system: Rarely, aplastic anemia, reversible agranulocytosis, thrombocytopenia and neutropenia.

Central Nervous system: Convulsive seizures. Mild and transient headache. Neuropsychiatric changes including psychosis, delirium, personality changes and depression.

Cardiovascular system: Rarely, hypotension, electrocardiographic change (particularly, inversion

or depression of the T-wave with widening of the QRS complex), and cardiomyopathy.

4.9 Overdose

Symptoms:

Chloroquine is very rapidly and completely absorbed after ingestion. Toxic doses of chloroquine can be fatal. As little as 1 g may be fatal in children. Toxic symptoms can occur within minutes. These consist of headache, drowsiness, visual disturbances, nausea and vomiting, cardiovascular collapse, shock and convulsions followed by sudden and early respiratory and cardiac arrest. The electrocardiogram may reveal atrial standstill, nodal rhythm, prolonged intraventricular conduction time, and progressive bradycardia leading to ventricular fibrillation and/or arrest.

Treatment:

Treatment is symptomatic and must be prompt with immediate evacuation of the stomach by emesis (at home, before transportation to the hospital) or gastric lavage until the stomach is completely emptied. If finely powdered, activated charcoal is introduced by stomach tube, after lavage, and within 30 minutes after ingestion of the ant malarial, it may inhibit further intestinal absorption of the drug. To be effective, the dose of activated charcoal should be at least five times the estimated dose of chloroquine ingested. Convulsions, if present, should be controlled before attempting gastric lavage. If due to cerebral stimulation, cautious administration of an ultra short-acting barbiturate may be tried but, if due to anoxia, it should be corrected by oxygen administration and artificial respiration. Monitor ECG. In shock with hypotension, a potent vasopressor should be administered. Replace fluids and electrolytes as needed. Cardiac compressing or pacing may be indicated to sustain the circulation. Because of the importance of supporting respiration, tracheal intubation or tracheostomy, followed by gastric lavage, may also be necessary. Peritoneal dialysis and exchange transfusions have also been suggested to reduce the level of the drug in the blood. A patient who survives the acute phase and is asymptomatic should be closely observed for at least six hours. Fluids may be forced, and sufficient ammonium chloride (8 g daily in divided doses for adults) may be administered for a few days to acidify the urine to help promote urinary excretion in cases of either overdosage or sensitivity.

5. PHARMACOLOGICALPROPERTIES

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: Anti malarial, ATC code: NO2ADO1

Pharmacodynamics

Chloroquine inhibits the action of heme polymerase, which causes the buildup of toxic heme in *Plasmodium* species. It has a long duration of action as the half life is 20-60 days. Patients should be counselled regarding the risk of retinopathy with long term usage or high dosage, muscle weakness, and toxicity in children.

5.2 Pharmacokinetic properties

Mechanism of Action

The major action of chloroquine is to inhibit the formation of hemozoin (Hz) from the heme released by the digestion of hemoglobin (Hb). The free heme then lyses membranes and leads to parasite death.

Chloroquine inhibits the action of heme polymerase in malarial trophozoites, preventing the conversion of heme to hemazoin. *Plasmodium* species continue to accumulate toxic heme, killing the parasite.

Chloroquine passively diffuses through cell membranes and into endosomes, lysosomes, and Golgi vesicles; where it becomes protonated, trapping the chloroquine in the organelle and raising the surrounding pH. The raised pH in endosomes, prevent virus particles from utilizing their activity for fusion and entry into the cell.

Chloroquine does not affect the level of ACE2 expression on cell surfaces, but inhibits terminal glycosylation of ACE2, the receptor that SARS-CoV and SARS-CoV-2 target for cell entry. ACE2 that is not in the glycosylated state may less efficiently interact with the SARS-CoV-2 spike protein, further inhibiting viral entry.

Absorption: Absorbed readily and almost completely.
Distribution: 55% bound to plasma proteins. Concentrated in erythrocytes, liver, spleen, kidneys, heart, and brain and is strongly bound in melanin-containing cells.
Metabolism: About 30% of an administered dose is metabolized by the liver to monodesethyl-chloroquine and bidesethylchloroquine.
Excretion: About 70% of dose is excreted unchanged in urine; unabsorbed drug is excreted in feces. Small amounts of the drug may be present in urine for months after the drug is discontinued. Renal excretion is enhanced by urinary acidification.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Dihydrogen Phosphate, Micotinamide, Benzyl Alcohol

6.2 Incompatibilities

None have been reported or are known

6.3 Shelf-life

36 Months

6.4 Special precautions for storage

Store below 30°C in tight container protected from light and moisture.

6.5 Nature and contents of container and special equipment for use, administration or implantation

Resoquine Injection is presented in 30ml amber glass vials as a clear pale yellow, odourless liquid. 50 vials are then packed in a hard board packaging.

6.6 Special precautions for disposal and other handling

No special requirements.

7. APPLICANT/MANUFACTURER

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