IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0970/029/001
Case No: 2060697

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

AstraZeneca UK Limited

600 Capability Green, **Luton**, **LU1 3LU**, **United Kingdom**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Avloclor Tablets 250 mg

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **30/01/2009**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Avloclor Tablets 250 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 250 mg chloroquine phosphate which is equivalent to 155 mg chloroquine base.

For a full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Tablets.

Avloclor Tablets are white in colour, round, biconvex with a breakline and on either side of the line an 'A' intagliation is present. The reverse face of the tablet is plain.

The breakline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

a) Treatment of malaria.

b) Prophylaxis and suppression of malaria.

c) Treatment of amoebic hepatitis and abscess.

d) Treatment of discoid lupus erythematosus.

e) Treatment of systemic lupus erythematosus.

f) Treatment of rheumatoid arthritis.

4.2 Posology and method of administration

The dose should be taken after food.

a) Treatment of malaria

i) P. falciparum and P. malariae infections

Adults: The initial dose is four tablets which is followed by two tablets six hours after and then two tablets a day for two days.

Children: A single dose of 10mg base/kg, followed six hours later by 5mg base/kg and 5mg base/kg a day for two days.

ii) P. vivax and P. ovale infections

Adults: The initial dose is four tablets which is followed by two tablets six hours later and then two tablets a day for two days. Follow with a course of treatment with primaquine if a radical cure is required.

Children: A single dose of 10mg base/kg followed six hours later by 5 mg base/kg and 5mg base/kg for two days. Follow with a course of treatment with primaquine if a radical cure is required.

b) Prophylaxis and suppression of malaria

Adults: Two tablets taken once a week, on the same day each week, starting one week before exposure to risk, continued during exposure and for four weeks after leaving the malarious area.

Children: A single dose of 5mg chloroquine base/kg per week, on the same day each week starting one week before exposure to risk, continued during exposure and for four weeks after leaving the malarious area.
For practical purposes, children aged over 14 years may be treated as adults. The dose given to infants and children should be calculated on their body weight and must not exceed the adult dose regardless of weight.
A dose of 5mg chloroquine base/kg in children can be approximated from the table.

Under 1 year	1/8 adult dose [0.25 tablet]
1 - 4 years	1/4 adult dose [0.5 tablet]
5 - 8 years	1/2 adult dose [1 tablet]
9 - 14 years	3/4 adult dose [1.5 tablets]

c) Amoebic hepatitis

Adults: Four tablets daily for two days followed by one tablet twice daily for two or three weeks.

d) Lupus erythematosus

Adults: One tablet twice daily for one to two weeks followed by a maintenance dosage of one tablet daily.

e) Rheumatoid arthritis

Adults: The usual dosage is one tablet daily.

Elderly patients: There are no special dosage recommendations for the elderly, but it may be advisable to monitor elderly patients so that optimum dosage can be individually determined.

4.3 Contraindications

There are no known absolute contraindications to the use of Avloclor.

4.4 Special warnings and precautions for use

In any locality where drug resistant malaria is known or suspected, it is essential to take professional advice on what prophylactic regimen or treatment regimen is appropriate.
Caution is necessary when giving Avloclor to patients with impaired hepatic function, particularly when associated with cirrhosis. Caution is also necessary in patients with porphyria. Avloclor may precipitate severe constitutional symptoms including abdominal and neuropsychiatric disturbances, hepatic impairment and photosensitivity. Avloclor may also cause an increase in the amount of porphyrins excreted in the urine especially in patients with high alcohol intake.

Caution is necessary when giving Avloclor to patients with renal disease.

Avloclor should be used with care in patients with a history of epilepsy. Potential risks and benefits should be carefully evaluated before use in subjects taking anti-convulsant therapy or with a history of epilepsy as, rarely, cases of convulsions have been reported in association with chloroquine.

Considerable caution is needed in the use of Avloclor for long-term high dosage therapy and such use should only be considered when no other drug is available.

Prolonged therapy with high doses may lead to occasional development of irreversible retinal damage.

Patients receiving Avloclor continuously at higher dose levels for periods longer than 12 months should undergo ophthalmic examination before treatment and at three monthly intervals. This also applies to patients receiving Avloclor at weekly intervals for a period of more than 3 years or if the total consumption is expected to exceed 1.6g/kg.

Full blood counts should be carried out regularly during extended treatment as bone marrow suppression may occur rarely.

The use of Avloclor in patients with psoriasis may precipitate a severe attack of psoriasis.

4.5 Interaction with other medicinal products and other forms of interaction

Chloroquine may potentiate the neuromuscular blocking effects of aminoglycosides or other neuromuscular blocking drugs.

If the patient is taking ciclosporin then chloroquine may cause an increase in ciclosporin levels.

When rabies vaccine is injected into the skin chloroquine may reduce its effectiveness.

Chloroquine significantly reduces levels of praziquantel. Caution is therefore advised during co-administration. Prescribers may consider increasing the dose of praziquantel if the patient does not respond to the initial dose.

Caution is necessary when Avloclor is administered with known hepatotoxic drugs.

Antacids (aluminium, calcium and magnesium salts) and adsorbents (eg kaolin) may reduce the absorption of chloroquine, so should be taken well separated from Avloclor (at least four hours apart).

4.6 Pregnancy and lactation

Pregnancy: Malaria in pregnant women increases the risk of maternal death, miscarriage, still-birth and low birth weight with the associated risk of neonatal death. Malarial prophylaxis is therefore strongly advised in pregnant women at risk of catching malaria. It is therefore acceptable to take the recommended dosage of Avloclor during all stages of pregnancy. Medical advice should be sought by subjects during the first trimester.

There is evidence to suggest that Avloclor given to women in high doses throughout pregnancy can give rise to foetal abnormalities including ocular or cochlear damage.

Lactation: Although Avloclor is excreted in breast milk, the amount is insufficient to confer any benefit on the infant. Separate chemoprophylaxis for the infant is required.

4.7 Effects on ability to drive and use machines

Defects in visual accommodation may occur on first taking Avloclor and patients should be warned regarding driving or operating machinery

4.8 Undesirable effects

The adverse reactions which may occur at doses used in the prophylaxis or treatment of malaria are generally not of a serious nature. Where prolonged high dosage is required, i.e. in the treatment of rheumatoid arthritis, adverse reactions can be of a more serious nature.

Adverse reactions reported after 'Avloclor' use are:
Headache
Gastro-intestinal disturbances
Skin eruptions
Pruritus
Exfoliative dermatitis,
Photosensitivity
Ototoxicity
Slate-grey pigmentation of the nails and mucosae
Occasional depigmentation or loss of hair
Difficulty in accommodation
Blurring of vision
Corneal opacities
Retinal degeneration
Electrocardiographic changes
Neurological and psychiatric changes, including convulsions and psychosis
Thrombocytopenia
Agranulocytosis
Aplastic anaemia
Allergic reactions - manifested as anaphylactic reactions, urticaria, angioedema and vasculitis
Toxic epidermal necrolysis
Erythema multiforme
Stevens-Johnson syndrome
Cardiomyopathy
Neuromyopathy
Myopathy
Proteinuria

4.9 Overdose

Chloroquine is highly toxic in overdose and children are particularly susceptible. The chief symptoms of overdosage include circulatory collapse due to a potent cardiotoxic effect, respiratory arrest and coma. Overdose may lead to multiorgan failure including liver failure, pancreatitis and rhabdomyolysis. Symptoms may progress rapidly after initial nausea and vomiting. Cardiac complications may occur without progressively deepening coma.
Death may result from circulatory or respiratory failure or cardiac dysrhythmia. If there is no demonstrable cardiac output due to dysrhythmias, asystole or electromechanical dissociation, external chest compression should be persisted with for as long as necessary, or until adrenaline (epinephrine) and diazepam can be given (see below).
Gastric lavage should be carried out urgently, first protecting the airway and constituting artificial ventilation where necessary. There is a risk of cardiac arrest following aspiration of gastric contents in more serious cases. Activated charcoal left in the stomach may reduce absorption of any remaining chloroquine from the gut.
Circulatory status (with central venous pressure measurement), respiration, plasma electrolytes and blood gases should be monitored, with correction of hypokalaemia and acidosis if indicated. Cardiac dysrhythmias should not be treated unless life threatening; drugs with quinidine-like effects should be avoided. Intravenous sodium bicarbonate 1-2mmol/kg over 15 minutes may be effective in conduction disturbances, and DC shock is indicated for ventricular tachycardia and ventricular fibrillation.
Early administration of the following has been shown to improve survival in cases of serious poisoning:

1. Adrenaline (epinephrine) infusion 0.25 micrograms/kg/min initially, with increments of 0.25 micrograms/kg/min until adequate systolic blood pressure (more than 100mmHg) is restored; adrenaline (epinephrine) reduces the effects of chloroquine on the heart through its inotropic and vasoconstrictor effects.

2. Diazepam infusion (2mg/kg over 30 minutes as a loading dose, followed by 1-2 mg/kg/day for up to 2-4 days). Diazepam may minimise cardiotoxicity. Acidification of the urine, haemodialysis, peritoneal dialysis or exchange transfusion have not been shown to be of value in treating chloroquine poisoning. Chloroquine is excreted very slowly, therefore symptomatic cases merit observation for several days.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Avloclor is an anti-malarial drug of the 4-aminoquinoline group.
The mode of action of chloroquine on plasmodia has not been fully elucidated. Chloroquine binds to and alters the properties of DNA. Chloroquine also binds to ferriprotoporphyrin IX and this may lead to lysis of the plasmodial membrane.
In suppressive treatment, chloroquine inhibits the erythrocytic stage of development of plasmodia. In acute attacks of malaria, it interrupts erythrocytic schizogony of the parasite. Its ability to concentrate in parasitised erythrocytes may account for the selective toxicity against the erythrocytic stages of plasmodial infection.

5.2 Pharmacokinetic properties

Studies in volunteers using single doses of chloroquine phosphate equivalent to 300mg base have found peak plasma levels to be achieved within one to six hours. These levels are in the region of 54-102 microgram/litre, the concentration in whole blood being some 4 to 10 times higher. The elimination half-life of chloroquine is dose dependent and is approximately one hundred hours. Following a single dose, chloroquine may be detected in plasma for more than four weeks. Mean bioavailability from tablets of chloroquine phosphate is 89%. Chloroquine is widely distributed in body tissues such as the eyes, kidneys, liver and lungs where retention is prolonged. The elimination of chloroquine is slow, with a multi exponential decline in plasma concentration. The initial distribution phase has a half-life of 2 – 6 days while the terminal elimination phase is 10-60 days. Approximately 50-70% of chloroquine in plasma is bound to the plasma proteins.

The principal metabolite is monodesethylchloroquine, which reaches a peak concentration of 10-20 microgram/litre within a few hours. Mean urinary recovery, within 3-13 weeks, is approximately 50% of the administered dose, most being unchanged drug and the remainder as metabolite. Chloroquine may be detected in urine for several months.

5.3 Preclinical safety data

Avloclor has been widely used for many years in clinical practice. There is no animal data which adds significant information relevant to the prescriber, to that covered elsewhere in this document.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Magnesium Stearate
Maize Starch

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

5 years.

6.4 Special precautions for storage

Do not store above 30°C. Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

PVC/Aluminium Foil Blister Pack of 20 Tablets.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

AstraZeneca UK Limited
600 Capability Green
Luton LU1 3LU
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 970/29/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1st April 1977
Date of last renewal: 1st April 2007

10 DATE OF REVISION OF THE TEXT

January 2009