SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Artesunate and Amodiaquine Tablets (50 mg / 135 mg)

1.2 ANATOMIC THERAPEUTIC CHEMICAL CLASSIFICATION AND DISTRIBUTION CATEGORY

P01BF03 – Antimalarial

1..3 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each bilayer tablet contains:
Artesunate Ph. Int. ….50 mg
Amodiaquine Hydrochloride USP
equivaent to Amodiaquine….135 mg

2 PHARMACEUTICAL FORM

Tablets

2.1. CLINICAL PARTICULARS

2.2 THERAPEUTICAL INDICATIONS

Artesunate - Amodiaquine fixed dose combination is indicated in the treatment of acute uncomplicated infection of malaria caused by Plasmodium falciparum.

3. POSOLOGY AND METHOD OF ADMINISTRATION

Dosage for adults: 2 tablets of Artesunate & Amodiaquine Hydrochloride tablets (100+300 mg) per day for 3days. Dosage for children: For children above 6 months of age and above 5Kg bodyweight. the dosage of artesunate is 4mg/Kg bodyweight and of Amodiaquine is 10mg/Kg bodyweight per day for 3 consecutive days. Since it is not possible to give the exact dosage based on solid formulation, the dosage should be rounded off to the nearest strength of the tablet. Weight should be given precedence over age in pa edia trie dosing.

3.1 CONTRAINDICATIONS

Artesunate - amodiaquine fixed close combination is contraindicated in patients with known hypersensitivity to artesunate or artemisinin derivatives and amodiaquine or 4 aminoquinolines. Because of resistance and risk of major toxicity. amodiaquine is not recommended for the prophylaxis of malaria. Amodiaquine is also contraindicated in patients with hepatic disorders

3.2 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

The combination has not been evaluated for the treatment of cerebral malaria or other severe manifestations of complicated malaria, including pulmonary oedema or renal failure.
The combination is not recommended for the treatment of malaria caused by P.vivax, P. ovale and P. malariae since other effective antimalarial drugs are available for this purpose. Amodiaquine is no longer recommended for chernoprophylaxis of falciparum malaria because its use is associated with hepatic toxicity and agranulocytosis
Severe neutropenia can occur. Large doses of amodiaquine have been reported to produce syncope, spasticity. convulsions and involuntary movements.Amodiaquine may cause blood dyscrasias. hepatitis, peripheral neuropathy and haemolytic anaemia. Regular opthalmic examination is recommended in patients receiving amodiaquine for long time. Because amodiaquine may concentrate in the liver, the drug should be used with caution in patients with hepatic disease or alcoholism and in patients receiving hepatotoxic drugs.
Since hemolysis and acute renal failure has been reported to occur in a fewpatients with glucose 6-phosphate dehydrogenase deficiency receiving chloroquine, this should also be considered when using amodiaquine.

Usage In pregnancy and lactation
There is no safety data available on use of artemisinin derivatives during pregnancy and lactation. However, as per information, available from World Health Organisation, artemisinin and its derivatives including artesunate should not be used during the first trimester of pregnancy. Although no data is available for amodiaquine, chloroquine, a structurally similar 4-arninoquinoline with the same spectrum of activity and similar adverse reaction profile is known to cross the placental barrier. Hence, risk benefit ratio should be considered before administering artesunate - amodiaquine fixed dose combination in second and third trimester of pregnancy. Artemisinin and its derivatives have not been measured in the milk of nursing mothers. It is very likely that these are present in milk and nursing mothers should not be given artemisinin if they are suffering from uncomplicated malaria either in multidrug resistance or arug sensitive situations, if the nursing mother is suffering from complicated and serious malana induced by multi drug-resistant P. falcipamm and artemisinin is indicated, breast feeding should be stopped.

Usage in paediatries
Artemisinin derivatives are to be given to children over 6 months of age. Amodiaquine is to be given to children weighing more than 5kg. Hence the combination ts indicated for children over 6 months of age and above 5kg bodyweight.

3.3 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Artesunate

Artesunate has a minimal effect on hepatic cytochrome P450 activity and does not appear to influence the metabolism of mefloquine, a drug likely to be used in combination with artesunate. Artesunate does not inhibit the formation of carboxy-primaquine, a metabolite
of primaquine.

Amodiaquine

The incidence of agranulocytosis is higher when arnodiaquine is combined with other antimalarials. Idiosyncratic drug induced involuntary movements have occurred when amodiaquine is combined with chloroquine.

Since magnesium trisilicate and kaolin are known to decrease the gastrointestinal absorption of chloroquine when administered simultaneously, it is likely that this also followsfor amodiaquine. Concomitant administration of chloroquine at recommended doses for malaria chemoprophylaxis during pre-exposure prophylaxis of rabies with intradermally administered rabies vaccine mayinterfere with the antibody response to the vaccine. However, the clinical significance of this interaction remains to be clearly established but should be considered and may have relevance in the caseof Amodiaquine

3.4 EFFECT ON ABILITY TO DRIVE AND USE MACHAINES

Not Known.

3.5 UNDESIRABLE EFFECTS

Artesunate

Artesunate and other related artemisinin derivatives have been widely used in China, with no reports of any serious adverse reactions. Drug induced fever can occur. Neurotoxicity has been observed in animal studies but not in humans. In view of the uncertainty about toxic effects, caution should be exercised when more than one 3 day treatment is given. Carbiotoxicity has been observed following administration of high doses In healthy volunteers, a reversible reduction in reticulccyte counts was the dose limiting adverse effect of artesunate. occurring with doses of 16.88mg/Kg. Possible drug related adverse effects include dizziness, itching, vomiting, abdominal pain, flatulence, headache, bodyache, diarrhoea, tinnitus and increased hair loss, macular rash, reduction in neutrophil counts and convulsions. However, it is likely that many of these effects are disease-related rather than drug-induced. Occasional skin rash and pruritus has been observed with artesunate.

Amodiaquine

Agranulocytosis and other blood dyscrasias, hepatitis and peripheral neuropathy have been reported occasionally after amodiaquine usage alone. Administration of quinoline type drugs has been associated with hemolytic anaemia. In therapeutic

doses used for malaria, amodiaquine may occasionally cause nausea, vomiting, diarrhoea, vertigo and lethargy. Abdominal pain, headache and photosensttivity have been reported with amodiaquine. When given for long periods, it Prolonged usage of amodiaquine can cause occasional development of irreversible retinopathy. The drug can also cause irregular heart beats and tremors. Prophylactic use of amodiaquine is associated with an unacceptably high incidence of serious toxicity. Approximately 1 in 2000 patients develop agranulocytosis. Serious hepatotoxicity has also been reported. Minor adverse effects are similar to those of chloroquine, although pruritus is less of a problem.

3.6 OVERDOSE

No data is available for overdosage of artesunate. It is mainly pertaining to amodiaquine in the artesunate – Amodiaquine combination. Intoxication with amodiaquine is far less frequent than chloroquine poisoning. However, large doses of amodiaquine have been reported to produce syncope, spasticity, convulsions and involuntary movements. The usual signs and symptoms of an overdose are headache, vertigo and vomiting; the more severe manifestations including cardiac arrhythmias, convulsions and coma. The most dramatic feature is visual disturbance, including sudden ioss of vision, which is usually transitory. Other symptoms include itching, cardiovascular abnormalities, dyskinesia. neuromuscular and haematological disorders and hearing loss. Nausea, vomiting, diarrhoea, headache, drowsiness, blurred vision, blindness, convulsions, coma, hypotension, cardiac arrhythmias, cardiac arrest, and impaired respiration are the characteristic features of amodiaquine poisoning. ECG may show inverted or flattened T waves, widening of QRS, ventricular tachycardia and fibrillation. Hypokalemia may be present.

Treatment of overdosage

Treatment of overdosage is supportive and must be prompt since acute toxicity can progress rapidly, possibly leading to vascular collapse and respiratory and cardiac arrest.

Early endotracheal intubation and mechanical ventilation may be necessary. Eariy gastric lavage followed by administration of activated charcoal may provide benefit in reducing absorption of the drug. These should be preceded by measures to correct cardiac and severe cardiovscular disturbances, if present and by respiratory support. Diazeparn IV may control seizures and other manifestations of CMS stimulation. Seizures caused by anoxia should be corrected by oxygen and other respiratory support. Deflbrillators and cardiac pacemakers may be required.

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4 PHARMACOLOGICAL PROPERTIES

4.1 PHARMACODYNAMIC PROPERTIES

Artesunate

Artesunate is a potent blood schizonticide agent for P. falciparum. Artesunate Dinds tightly to parasitized erythrocyte membranes. The functional group responsible for antimalarial activity of artesunate is endoperoxide bond. Release of an active oxygen species from this bond kills the parasite if accumulated in the erythrocytic cells. It also suppresses the production or activity of antioxidant enzymes in the erythrocytes,

causing lysis of the parasitic cell due to the highly reactive free oxygen radicals. It reduces gamelocytecarriage rate.

Amodiaquine
Amodiaquine is an antimalarial with schizonticidal activity. It is effective against the erythrocytic stages of all 4 species of plasmodium. It is as effective as chloroquine against chloroquine-sensttive strains of Plasmodium falciparum and is also effective against some chloroquine-resistant strains. Amodiaquine accumulates in the lysosomes and brings about loss of function. The parasite is unable to digest haemoglobin on which it depends for its energy. In general, 4-aminoquinoline derivatives appear to bind to nucleoproteins and inhibit DNA and RNA polymerase. High drug concentrations are found in the malaria parasite's digestive vacuoles. Rationale for the fixed dose combination of artesunate and Amodiaquine Compliance to treatment is essential to ensure treatment effectiveness and to prevent future resistance to artemisinin combination therapy. When combinations are provided as two separate drugs, patients might take only one of the two drugs or fail to complete the whole course. Taking one drug without the other increases the risk of resistance. Fixed dose combinations combine two drugs into one tablet to ensure that the patients take both drugs in the right dose. Also many patients do not complete the antimalarial course properly because of large number of tablets. This leaves them vulnerable to recurrences of the disease and also allows the parasite, which often rf not totally killed off. to modify and develop resistance. By reducing the number of tablets and by using 2 active ingredients, the fixed dose combination of amodiaquine and artesunate delays resistance. Other advantages of fixed dose combination include rapid effect, high cure rate and reduction of potential for transmission.

5 PHARMACOKINETIC PROPERTIES

Artesunate
Pharmacokinetic data for artesunate in humans are sparse, with no data demonstrating the rate or extent of absorption or the systemic distribution of artesunate. Artesunate is rapidly and completely hydrolysed to the active metabolite dihydroarternisinin before entering the systemic circulation. Peak serum levels occur within one hour of an oral dose of artesunate and persist for up to 4 hours. Dihydroarternisinin has a plasma elimination half-life of less than 2 hours, which may slow the development of resistance to Artesunate

Amodiaquine
Amodiaquine hydrochloride is readily absorbed from gastrointestinal tract.Amodiaquine is rapidly converted in the liver to the active metabolite desethylamodiaquine, only a negligible amount of amodiaquine is being excreted unchanged in the urine. The plasma elimination half-life of desethylamodiaquine has varied from 1 to 10 days or more. About 5% of the total administered dose is recovered in urine while the rest is metabolised in the body. Amodiaquine and desethylamodiaquine have been detected in the urine several months after administration.

1.3.1 SUMMARY OF PRODUCT CHARACTERISTICS

5.1 PRECLINICAL SAFETY DATA

Preclinical data reveal no special hazard for humans based on conventional studies on safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential and reproductive toxicity.

5.2 SHELF LIFE

24 months

5.3 PECIAL PRECAUTIONS FOR STORAGE

Store below 30ºC, in a dry place.
Keep out of reach of children

5.4 NATURE AND CONTENTS OF CONTAINER

1. Alu Alu Blister of 3 tablets. Such 25 Blister in a printed showbox along with the leaflet.(25 x 3's)

5.8 SPECIAL PRECAUTIONS FOR DISPOSAL

After treatment the remaining tablets should be discarded or returned to the Pharmacist.

5.8 REGISTRANT

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