Artesunate and Amodiaquine Tablets 25/67.5 mg, 50/135 mg, 100/270 mg

SUMMARY OF PRODUCT CHARACTERISTIC

1. Name of the Medicinal Product

Artesunate and Amodiaquine Tablets 25/67.5 mg

Artesunate and Amodiaquine Tablets 50/135 mg

Artesunate and Amodiaquine Tablets 100/270 mg

2. Qualitative and Quantitative Composition

COMPOSITION:

Each Bilayered tablet contains:
Artesunate ……..……25/50/100mg
Amodiaquine USP
Equivalent to Amodiaquine USP ……..…67.5 /135/270 mg

Excipient (s):

For a full list of excipients, see section 6.1.

3. Pharmaceutical Form

Bilayered Tablet

Artesunate and Amodiaquine Tablets 25/67.5 mg

Bilayered, round flat, bevelled edged, uncoated tablets having plain surface on both sides, one layer is yellow coloured; the other one is white to off white coloured.

Artesunate and Amodiaquine Tablets 50/135 mg

Bilayered, round flat, bevelled edged, uncoated tablets having plain surface on both sides, one layer is yellow coloured; the other one is white to off white coloured.

Artesunate and Amodiaquine Tablets 100/270 mg

Bilayered, round flat, bevelled edged, uncoated tablets having plain surface on both sides, one layer is yellow coloured; the other one is white to off white coloured.

4. Clinical Particulars

4.1 Therapeutic indications

Artesunate & Amodiaquine is indicated for the treatment of uncomplicated cases of malaria due to Plasmodium falciparum strains which are susceptible to amodiaquine as well as to artesunate.

4.2 Posology and method of administration

Oral use

The dosage of artesunate and amodiaquine is:

- 4 mg/kg (range 2 to 10 mg/kg) body weight of artesunate and

- 10 mg/kg (range 7.5 to 15 mg/kg) body weight of amodiaquine base once daily for 3 days.

Weight range (approximate age range)	**1st day of treatment**	**2nd day of treatment**	**3rd day of treatment**
≥ 4.5kg to < 9 kg (2 to 11 months)*	25 mg AS 67.5 mg AQ	25 mg AS 67.5 mg AQ	25 mg AS 67.5 mg AQ
≥9kg to <18kg (1 to 5 years)*	50 mg AS 135 mg AQ	50 mg AS 135 mg AQ	50 mg AS 135 mg AQ
≥18kg to <36kg (6 to 13 years)*	100 mg AS 270 mg AQ	100 mg AS 270 mg AQ	100 mg AS 270 mg AQ
≥ 36kg (14 years and above)*	200 mg AS 540 mg AQ	200 mg AS 540 mg AQ	200 mg AS 540 mg AQ

* if a weight-age mismatch occurs, dosing should be weight-based.

AS: artesunate

AQ: amodiaquine

Artesunate & Amodiaquine should not be taken with a high-fat meal.

The tablets should be swallowed with water.

For patients unable to swallow the tablets whole, e.g. very young children, the tablets can be dissolved in water before administration. The tablets can also be crushed and administered with water.

Should vomiting occur within half an hour after dosing, a repeated dose of Artesunate & Amodiaquine is to be taken. In case of further vomiting, treatment for severe malaria should be considered.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients,
- History of liver injury during treatment with amodiaquine,
- Previous haematological event during treatment with amodiaquine,
- Retinopathy (in case of frequent treatment).

Artesunate & Amodiaquine must not be used for malaria prophylaxis, since it may result in agranulocytosis and severe hepatotoxicity.

4.4 Special warnings and precautions for use

- Artesunate & Amodiaquine is not recommended:
  - for the treatment of complicated malaria
  - treatment of malaria due to *Plasmodium vivax, Plasmodium malariae* or *Plasmodium ovale*
  - Artesunate & Amodiaquine has not been evaluated for malaria prophylaxis. The use of amodiaquine for prophylaxis results in an unacceptably high risk of agranulocytosis and liver toxicity and is contraindicated. Therefore, the combination of amodiaquine and artesunate is also contraindicated for malaria prophylaxis
  - Caution should be exercised in patients with renal or hepatic impairment.
- Symptoms suggestive of the following diseases should be carefully monitored:
- Hepatitis, pre-icteric phase and especially when jaundice has developed,
- Agranulocytosis (as suggested, for instance, by a clinical condition including fever and/or tonsillitis and/or mouth ulcers).

When these symptoms develop or exacerbate during the course of therapy with Artesunate & Amodiaquine, laboratory tests for liver function and/or blood cell counts should be performed at once. Immediate discontinuation of treatment may be required. In such cases, continuation of treatment with amodiaquine increases the risk of death.

- The combination of artesunate and amodiaquine may induce neutropenia and increase the risk of infection.
- Caution is advised when combining artesunate and amodiaquine tablets with drugs inhibiting, inducing or competing for CYP2C8.

- Co-administration of artesunate and amodiaquine tablets and efavirenz should be avoided, since this combination has been noted to cause marked hepatotoxicity.

- Cardiovascular effects have been reported with other amino-4-quinoline derivatives during high dose treatment. There is no evidence that an overdose of amodiaquine causes any of the life-threatening cardiovascular complications often seen after an overdose of chloroquine. However, by chemical class analogy, caution should be exercised, especially with patients who have recently taken other antimalarial drug with cardiovascular side effects (quinine, quinidine, halofantrine, lumefantrine, mefloquine) or those who are under treatment with cardiovascular drugs or other drugs with the potential to prolong the QT interval.

Artesunate & Amodiaquine should not be used in regions where amodiaquine resistance is widespread, as the treatment with the combination under such conditions may mean effectively a treatment with artesunate alone with an insufficient duration and decreased plasma concentrations as compared to artesunate alone. As a result, the risk of development of resistance of *P.falciparum* to artesunate increases significantly.

Amodiaquine is effective against some chloroquine-resistant strains of *P.falciparum*, although there is cross-resistance.

Amodiaquine and artesunate have not been studied specifically in patients with thalassaemia, sickle cell anaemia or G6PD deficiency.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions with drugs used for treatment of HIV and/or tuberculosis may occur, though little clinical data is available. Prescriber should be vigilant for adverse events potentially related to such interactions, including liver toxicity and neutropenia.

Artesunate & Amodiaquine is not recommended to be administered concomitantly with drugs known to inhibit the liver enzymes cytochrome (CYP) 2A6 (e.g. methoxsalen, pilocarpine, tranylcypromine) and/or CYP2C8 (e.g. trimethoprim, ketoconazole, ritonavir, saquinavir, lopinavir, gemfibrozil, montelukast,).

No pharmacokinetic interactions of artesunate with other antimalarial drugs of importance have been identified. However, concomitant administration of Artesunate & Amodiaquine with other antimalarial treatments is not recommended, as no data on efficacy and safety are available.

A statistically significant decrease in dihydroartemisinin (DHA), the main active metabolite of artesunate, occurs with concomitant use of artesunate and amodiaquine (Cmax decreased 47%, AUC_{0-inf} decreased 17%).

Agranulocytosis and hepatitis have been reported following the use of amodiaquine in long term prophylaxis treatments. Therefore, caution should be taken whilen prescribing amodiaquine-containing products, such as Artesunate & Amodiaquine, concurrently with other drugs with a potential for liver and/or haematological toxicity.

Though no pharmacokinetic interactions have been documented, amodiaquine and desethylamodiaquine inhibit CYP 2D6 in vitro and may cause clinically significant interactions with some β-blockers, anti-depressants, and antipsychotics drugs. Caution should be exercised when co-administration of these agents with Artesunate & Amodiaquine tablets is deemed necessary.

4.6 Pregnancy and Lactation

Pregnancy

Malaria is known to be particularly hazardous during pregnancy. The benefits and risks of therapy with Artesunate & Amodiaquine to mother and foetus must be assessed by the prescriber.

The safety of amodiaquine in pregnant women has not been conclusively established, although many years of experience with the drug have not indicated any teratogenicity.

Data on a limited number of exposed pregnant women do not indicate any adverse effect of artemisinins on pregnancy or on the health of the foetus/newborn child.

During 1^{st} trimester of pregnancy, Artesunate & Amodiaquine should not be used unless clearly necessary e.g. if treatment is life-saving for the mother, and if another antimalarial is not suitable or not tolerated.

During 2^{nd} or 3^{rd} trimesters of pregnancy, Artesunate & Amodiaquine may be used with caution, only if other antimalarials are unsuitable.

Lactation:

The amounts of antimalarials in breast milk are small. Therefore, lactating women can receive artemisinin-based combination therapies for malaria treatment.

4.7 Effects on ability to drive and use machines

Patients receiving Artesunate & Amodiaquine should be warned that somnolence, dizziness or asthenia may occur, in which case they should not drive or use machines.

4.8 Undesirable effects

The most frequent adverse reactions observed were: anorexia, abdominal pain, nausea, asthenia, somnolence, insomnia and cough.

The most serious adverse reactions observed were: asthenia, anaemia and vertigo.

The adverse reactions are ranked under body-system and frequency using the following convention: very common: ≥1/10; common: ≥ 1/100 to <1/10; uncommon: ≥ 1/1000 to < 1/100; rare: ≥1/10,000 to < 1/1000; very rare : < 1/10,000; not known: cannot be estimated from the available data.

Class-organ	**Frequency**	**Adverse reactions**
Infections and infestations	Uncommon	Bronchitis acute, gastroenteritis, oral candidiasis
Blood and lymphatic system disorders	Uncommon	Anaemia
Metabolism and nutrition disorders	Uncommon	Hypoglycaemia
Psychiatric disorders	Common Uncommon	Anorexia, insomnia Hallucination
Nervous system disorders	Common Uncommon	Somnolence Paraesthesia
Eye disorders	Uncommon	Ocular icterus
Ear and labyrinth disorders	Uncommon	Vertigo
Cardiac disorders	Uncommon	Arrhythmia, bradycardia
Respiratory, thoracic, and mediastinal disorders	Common	Cough
Gastro-intestinal disorders	Common Uncommon	Nausea, abdominal pain Diarrhoea, vomiting
Skin and subcutaneous tissue disorders	Uncommon	Pruritus, rash, face oedema, skin disorders
Musculoskeletal and connective tissue disorders	Uncommon	Arthralgia
General disorders and administration site conditions	Common Uncommon	Asthenia Oedema peripheral, pyrexia

Post-marketing experience

Frequency not known: Acute extrapyramidal disorders (such as dystonia, dyskinesia, tongue protrusion, torticollis). These adverse reactions usually resolved after discontinuation of Artesunate & Amodiaquine and appropriate medical treatment.

In published literature data, generated mostly during post-approval use of amodiaquine and/or artesunate, additional types of events have been reported. For some of these events, it is unclear whether they are related to amodiaquine/artesunate or occur as a result of the underlying disease process:

- headache, dizziness
- cold, flu, rhinitis, shivering, sore throat
- convulsion
- splenomegaly, jaundice
- allergic reaction

The following adverse reactions may occur with amodiaquine, especially at higher doses and/or during prolonged treatment; their frequency is not known:

- Blood and lymphatic system disorders: cases of leucopenia and neutropenia (agranulocytosis)
- Nervous system disorders: rare neuromyopathy
- Eye disorders, varying in type and severity: transient accommodation disorders, corneal opacifications regressive once treatment is stopped, very rarely, irreversible retinopathy justifying specialist ophthalmic attention
- Hepato-biliary disorders: severe and sometimes fatal hepatitis
- Skin and subcutaneous disorders: slate-grey pigmentation, notably affecting the fingers and mucous membranes.

4.9 Overdose

In cases of suspected overdose, the patient should be urgently transferred to a specialized unit where appropriate monitoring and symptomatic and supportive therapy should be applied.

Artesunate

No cases of overdose have been reported to date.

Amodiaquine

- The dangerous dose of amodiaquine cannot be stated precisely because of the low number of known cases; by analogy with chloroquine, it can be estimated at around 2 grams as a single administration in adults,
- Symptoms: headache, dizziness, visual disorders, cardiovascular collapse and convulsions, followed by early respiratory and cardiac arrest.

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Artemisinin and derivatives, combinations;

ATC code: P01BF03

Artesunate & Amodiaquine is an artemisinin-based combination therapy which consists of two blood schizonticides, with independent modes of action and different intraparasitic biochemical targets.

Artesunate: Artesunate is a hemisuccinate derivative of dihydroartemisinin, which is obtained by the reduction of artemisinin, a sesquiterpene lactone endoperoxide extracted from a plant used in traditional Chinese medicine, known as sweet or annual wormwood (*Artemisia annua*).

The mechanism of action of artesunate has been widely studied and appears well established. The artesunate endoperoxide bridge is split by haeme within the infected erythrocyte, generating singlet oxygen. Parasite proteins, particularly in membranous structures, are thus alkylated, leading to parasite death.

In-vitro experiments in *P. falciparum* have shown that artemisinin derivatives are active against a broad spectrum of the life cycle of the parasite, from the relatively inactive ring stage to late schizonts. The schizonticidal and gametocytocidal activities of artesunate, administered orally have been demonstrated in vivo on chloroquine-sensitive strains of Plasmodium (*P. berghei* in mice and *P. knowlesi* in monkeys) and on chloroquine-resistant strains (*P. berghei* in mice).

In-vitro, artesunate appears to be inactive against extra-erythrocyte forms, sporozoites, liver schizontes or merozoites.

Amodiaquine: Amodiaquine is a synthetic 4-aminoquinoline antimalarial. Its activity is characterized by a schizonticidal action on *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale* and *Plasmodium malaria* by destroying intraerythrocytic forms.

The mechanism of action of 4-aminoquinoline derivatives against plasmodium is not yet completely known. It is nonetheless accepted that these derivatives, one of which is amodiaquine, penetrate the infected red blood cells and prevent the parasite from polymerizing haeme into an insoluble product called haemozoin, leading to parasite death. Strains of *Plasmodium falciparum* resistant to 4-aminoquinolines (chloroquine, amodiaquine) are present in many areas, and their geographical distribution is constantly

changing.However, amodiaquine remains active against some chloroquine-resistant *P. falciparum* strains.

5.2 Pharmacokinetic properties

Artesunate

Absorption

After oral administration, absorption is rapid. Most of the artesunate is promptly biotransformed, mainly through plasma esterases, into the active metabolite dihydroartemisinin (DHA).

After administration of two Artesunate & Amodiaquine 100mg/270mg tablets (i.e total dose of 540 mg amodiaquine and 200 mg artesunate) in healthy volunteer, the mean (CV) artesunate C_{max} value was 162.9 ng/ml (75%), and the corresponding value for AUC was 89.9 ng.h/ml (51%). The median (range) artesunate t_{max} value was 0.25 hours (0.25-1.33 h).

The mean (CV) DHA C_{max} value was 460.4 ng/ml (3 %), and the corresponding value for AUC was 712.2 ng.h/ml (36%). The median (range) DHA t_{max} value was 0.75 hours (0.5-1.33 h).

Distribution

DHA has been shown to substantially accumulate in *P. falciparum*-infected erythrocytes. Artesunate is not significantly protein-bound.

Metabolism

Artesunate is extensively hydrolysed by plasma esterases and perhaps also by CYP2A6. Its main metabolite, DHA is presumed to account for most of the in vivo antimalarial activity. DHA is further metabolised through glucuronidation prior to excretion.

Elimination

Artesunate has a plasma half-life of 3-29 minutes. The active metabolite DHA has a plasma half-life of 40 to 95 minutes. The modes of excretion of DHA have not been fully elucidated.

Amodiaquine

Absorption

After oral administration of amodiaquine is quickly absorbed and biotransformed into its main active form, desethylamodiaquine. The absolute bioavailability of amodiaquine is not known. After administration of two Artesunate & Amodiaquine 100mg/270mg tablets (i.e total dose of 540 mg amodiaquine and 200 mg artesunate) in healthy volunteers, the mean (CV) amodiaquine C_{max} value was 9.2 ng/ml (33%), and the corresponding value for AUC was 65.7 ng.h/ml (45%). The median (range) amodiaquine t_{max} value was 0.79 hours (0.48-8 h).

The mean (CV) desethylamodiaquine C_{max} value was 147.9 ng/ml (41%), and the corresponding value for AUC was 9947.8 ng.h/ml (43%). The median (range) desethylamodiaquine t_{max} value was 2 hours (1.33- 8 h).

Distribution

The volume of distribution of amodiaquine is estimated at 20 to 40 l/kg. Desethylamodiaquine, the main metabolite of amodiaquine, is assumed to be the main active form after oral administration. It is mainly found in blood, at much higher concentrations than unchanged amodiaquine. Its concentration in whole blood is 4-6 times higher than in plasma.

Metabolism

The hepatic first pass metabolism of amodiaquine is high, with formation of the active metabolite, desethylamodiaquine, presumably via the CYP2C8 isoenzyme. Further metabolism includes oxidation and glucuronoconjugation.

Elimination

Amodiaquine is eliminated principally through biotransformation with only around 2% excreted unchanged in urine. Desethylamodiaquine is slowly eliminated with a terminal half-life of 9-18 days.

5.3 Preclinical safety data

No studies of the carcinogenic potential of the combination of artesunate and amodiaquine or the individual agents have been conducted.

Artesunate did not show any mutagenic or clastogenic potential in *in vitro* and *in vivo* tests (Ames, mouse micronucleus). Although amodiaquine, like chloroquine, has shown both mutagenic and clastogenic potential, studies with the artesunate amodiaquine

combination in the Ames test and micronucleus in rat did not demonstrate any evidence of genotoxicity.

Reproductive toxicology studies, conducted in rats and rabbits, confirmed the known embryotoxic and teratogenic potential of artesunate and the maternal toxicity associated with amodiaquine. The combination did not demonstrate any particular effects on fertility or associated parameters. In the peri-postnatal study, the offspring from the F1 generation did not show any effect on sexual development, and despite an early slowing of bodyweight increases with some effect on testicular and epididymal weights, no sequelae were noted on reproductive capacity.

No new toxicity was induced through the administration of the two substances in combination.

6. Pharmaceutical Particulars

6.1 List of Excipients

Calcium Carbonate and maize starch
Povidone
Croscarmellose sodium
Silicon dioxide
Magnesium Stearate
Microcrystalline Cellulose

6.2 Incompatibilities

None

6.3 Shelf life

24 months from the manufacturing date.
Never use after the expiry date clearly indicated on the outer packaging.

6.4 Special precautions for storage

Store below 30ºC, in dry place and protect from light.

6.5 Nature and contents of container

Artesunate and Amodiaquine Tablets 25/67.5 mg
Alu/Alu Blister pack Alu / Alu Cold form blister pack of 10 tablets, such 10 blisters in a carton along with pack insert.

Artesunate and Amodiaquine Tablets 50/135 mg
Alu/Alu Blister pack Alu / Alu Cold form blister pack of 10 tablets, such 10 blisters in a carton along with pack insert

Artesunate and Amodiaquine Tablets 100/270 mg
Alu/Alu Blister pack Alu / Alu Cold form blister pack of 10 tablets, such 10 blisters in a carton along with pack insert

6.6 Special Precaution for disposal

None

7. Supplier

Macleods Pharmaceuticals Ltd.
304, Atlanta Arcade, Marol Church Road,
Andheri (East), Mumbai- 400 059,
India
Phone: +91-22-66762800
Fax: +91-22-2821 6599

Contact:
Sandhya Jadhav
Tel: 0091 22 28314611/28258944/28302293/
28208971
Fax: 0091 28216599
Email: sjadhav@macleodspharma.com

8. Who Reference Number (Prequalification Programme)

9. Date of first Prequalification/ last renewal

10. Date of Revision of the Text:

References:

- http://apps.who.int/prequal/WHOPAR/WHOPARPRODUCTS/MA097part4v1.pdf
- http://apps.who.int/prequal/WHOPAR/WHOPARPRODUCTS/MA056-57-58part4v3.pdf