Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

Artesunate Amodiaquine 25mg/ 67.5mg Bilayer Tablets

Artesunate Amodiaquine 50mg/135mg Bilayer Tablets

Artesunate Amodiaquine 100mg/270mg Bilayer Tablets

2. Qualitative and quantitative composition

- *Artesunate Amodiaquine* bilayer tablets is a fixed dose combination of artesunate and amodiaquine (as hydrochloride).

  Artesunate Amodiaquine 25mg/ 67.5mg Bilayer Tablets

- Each bilayer tablets contains 25mg of artesunate and 67.5mg amodiaquine (as amodiaquine hydrochloride)
- Each tablet contains about 71mg of Mannitol

Artesunate Amodiaquine 50mg/135mg Bilayer Tablets

Each bilayer tablets contains 50mg of artesunate and 135mg of amodiaquine (as amodiaquine hydrochloride)

- Each tablet contains about 142mg of Mannitol

Artesunate Amodiaquine 100mg/270mg Bilayer Tablets

Each bilayer tablets contains 100mg of artesunate and 270mg of amodiaquine (as amodiaquine hydrochloride)

- Each tablet contains about 283mg of Mannitol

  Excipients with known effects: Mannitol

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Bilayer tablets

Artesunate Amodiaquine Bilayer Tablets 25mg/67.5mg is a capsule shaped, biconvex, bilayer tablets, one layer is yellow colored and the other one is white to slight yellow colored. One face plain which is yellow in color and a break line on the other face which is white in color. The face with the break line having engravings “AA” on one side and ” 25” on the other side of break line.

Artesunate Amodiaquine Bilayer Tablets 50mg/135mg is a capsule shaped, biconvex, bilayer tablets; one layer is yellow colored and the other one is white to slight yellow colored. One face plain which is yellow in color and a break line on the other face which is a white in color. The face with the break line having engravings “AA” on one side and “50” on the other side of break line.

Artesunate Amodiaquine Bilayer Tablets 100mg/270mg is a Capsule shaped, biconvex, bilayer tablets; one layer is yellow colored and the other one is white to slight yellow colored. One face plain which is yellow in color and a break line on the other face which is a white in color. The face with the break line having engravings “AA” on one side and “100” on the other side of break line.

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

4. Clinical particulars

4.1 Therapeutic indications

Artesunate Amodiaquine Bilayer Tablets 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.

The most recent official guidelines on the appropriate use of antimalarial agents and local information on the prevalence of resistance to antimalarial drugs must be taken into consideration for deciding on the appropriateness of therapy with Artesunate Amodiaquine Bilayer Tablets.

Official guidance will normally include WHO (http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf) and public health authorities guidelines (see also sections 4.4 and 5.1).

Artesunate Amodiaquine Bilayer Tablets should not be used in regions where amodiaquine resistance is widespread. (See also Sections 4.4 and 5.2 regarding pharmacokinetic interactions between artesunate and amodiaquine).

4.2 Posology and method of administration

Oral use. Swallow the tablets whole with water.

- 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 treament**	**2nd day of treatment**	**3rd day of treatment**
≥ 4.5 kg 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
≥ 9 kg to < 18 kg (1 to 5 years)*	50 mg AS 135 mg AQ	50 mg AS 135 mg AQ	50 mg AS 135 mg AQ
≥18 kg to <36 kg (6 to 13 years)*	100 mg AS 270 mg AQ	100 mg AS 270 mg AQ	100 mg AS 270 mg AQ
≥ 36 kg (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

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 Bilayer Tablets must not be used for malaria prophylaxis, since it may result in agranulocytosis and severe hepatotoxicity (see section 4.4).

Artesunate Amodiaquine Bilayer Tablets should not be taken with a high-fat meal (see section 5.2).

4.4 Special warnings and precautions for use

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

Artesunate Amodiaquine Bilayer Tablets 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 (see section 4.5). 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.

Artesunate Amodiaquine Bilayer Tablets has not been evaluated for the treatment of complicated malaria and is therefore not recommended.

Artesunate Amodiaquine Bilayer Tablets 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 (see section 4.3).

Artesunate Amodiaquine Bilayer Tablets has not been studied specifically in patients with thalassaemia, sickle cell anaemia or G6PD deficiency.

In the absence of specific clinical studies, 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 Bilayer Tablets, 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.

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 (see section 4.9 overdosage).

The combination of artesunate and amodiaquine may induce neutropenia (see section 4.8) and increase the risk of infection.

Acute extrapyramidal disorders may occur with Artesunate Amodiaquine Bilayer Tablets, even after administration of a single dose (see section 4.8). These adverse reactions usually resolve after treatment discontinuation of Artesunate Amodiaquine Bilayer Tablets and appropriate medical treatment of the neurological condition. Alternative antimalarial therapy should be instituted.

Caution is advised when combining Artesunate Amodiaquine Bilayer Tablets with drugs inhibiting, inducing or competing for CYP2C8 (see section 4.5).
Co-administration of Artesunate Amodiaquine Bilayer Tablets and efavirenz should be avoided, since this combination has been noted to cause marked hepatotoxicity

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. Prescribers should be vigilant for adverse events potentially related to such interactions, including liver toxicity and neutropenia.

In the absence of clinical data, Artesunate Amodiaquine Bilayer Tablets 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,) (see section 5.2).

No pharmacokinetic interactions of artesunate with other antimalarial drugs of importance have been identified. However, concomitant administration of Artesunate Amodiaquine Bilayer Tablets 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%, AUC0-inf decreased 17%).

Agranulocytosis and hepatitis have been reported following the use of amodiaquine in long term prophylaxis treatments (see section 4.8). Therefore, caution should be observed when prescribing amodiaquine-containing products, such as Artesunate Amodiaquine Bilayer Tablets, 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, antidepressants, and antipsychotics drugs. Caution should be exercised when co-administration of these agents with Artesunate Amodiaquine Bilayer 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 Bilayer Tablets 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. Animal data indicate a limited embryotoxic effect at doses of 6 mg/kg/day or more (see section 5.3).

During 1st trimester of pregnancy, Artesunate Amodiaquine Bilayer Tablets 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 2nd or 3rd trimesters of pregnancy, Artesunate Amodiaquine Bilayer Tablets 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 (including ARTESUNATE AMODIAQUINE) for malaria treatment.

4.7 Effects on ability to drive and use machines

Patients receiving Artesunate Amodiaquine Bilayer Tablets 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 tolerability to the fixed-dose combination Artesunate Amodiaquine Bilayer Tablets was evaluated through two comparative pivotal studies involving 1003 patients treated with the fixed dose combination: one conducted in Burkina-Faso, and another one conducted in Senegal, Cameroon, Mali, and Madagascar.The tolerability was evaluated as comparable to reference treatments.

About 30% of treated patients receiving one single treatment course experienced adverse reactions in the two pivotal studies. Most of the reported adverse reactions were similar to symptoms usually seen during a malaria attack.

The most frequent adverse reactions observed were:

anorexia, abdominal pain, nausea, asthenia, somnolence, insomnia and cough (see hereafter).

The most serious adverse reactions observed in these pivotal studies were:

asthenia, anaemia and vertigo.

The adverse events considered at least possibly related to the treatment (= adverse reactions) are listed hereafter by body system, organ class and absolute frequency.

Tabulated list of adverse reactions

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.

The type and frequencies of all adverse reactions observed from the two pivotal studies are summarised hereafter:

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	Hypoglycemia
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
Musculosketal and connective tissue disorders	Uncommon	Arthralgia
General disorders and administration site conditions	Common Uncommon	Asthenia Oedemia peripheral, pyrexia

Post-marketing experience

Frequency not known: Acute extrapyramidal disorders (such as dystonia, dyskinesia, tongue protrusion, torticollis) have been reported. These adverse reactions usually resolved after discontinuation of Artesunate Amodiaquine Bilayer Tablets and appropriate medical treatment (see section 4.4).
In published literature data, generated mostly during post-approval use of amodiaquine and/or artesunate, additional types of events have been reported. Since frequency estimates are highly variable across the studies, no frequencies are given for these events. 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 have been reported 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.

If any of the side effects is serious or unexpected, you should inform the supplier (see section 7) and/or health authority, as per local regulation.

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board; Pharmacovigilance Electronic Reporting System (PvERS)
https://pv.pharmacyboardkenya.org

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.

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. Cases of extrapyramidal disorders have been reported.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Artesunate Amodiaquine Combination (ATC code P01BF03)

- Artesunate Amodiaquine Bilayer Tablets 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 chemical 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.
- When administered orally, artesunate consistently acts more quickly than orally administered chloroquine and intravenous quinine in all animal models studied, regardless of the strain or dose tested. In macaques (the animal model most similar to humans) infected with a chloroquine-resistant strain of P. knowlesi, cure was obtained with the same dose of artesunate and quinine.
- *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.

  Clinical efficacy and safety

- Artesunate Amodiaquine Bilayer Tablets is indicated in areas where parasite resistance rate to amodiaquine remains below the threshold defined by WHO.
- Efficacy and safety of Artesunate Amodiaquine Bilayer Tablets in uncomplicated *P. falciparum* malaria have been demonstrated in clinical trials in various settings in Africa. Also, published trials suggest adequate efficacy and safety from use in countries of South-East Asia and Latin America.

  Efficacy and safety in children and adults
- The efficacy and safety of the fixed combination Artesunate Amodiaquine Bilayer Tablets in uncomplicated *P.falciparum* malaria were demonstrated in two pivotal studies (Burkina-Faso study and ATAQ-EASY multinational study) conducted in children and adults (see below) as well as in 13 other supportive studies.
- A randomised, controlled, open-label, parallel group study conducted in Burkina-Faso compared the efficacy and safety of Artesunate Amodiaquine Bilayer tablets to an almost equivalent regimen of the individual drugs administered together in 750 children from 6 months to 5 years. The PCR-corrected parasitological cure rates at Day 28 were the same (92.1%) in both treatment groups. The analysis of clinical as well as parasitological data demonstrated the non-inferiority of the fixed-dose combination artesunate and amodiaquine combination compared to separate drugs administered concomitantly in children aged 6 months to 5 years.
- A multinational, randomised, blinded, comparative study (ATAQ EASY) of the efficacy and safety of Artesunate Amodiaquine Bilayer tablets vs artemether lumefantrine tablets in the treatment of uncomplicated *P.falciparum* malaria was conducted in four countries (Cameroon, Madagascar, Mali and Senegal) in 941 adults and children.

- Adequate Clinical and Parasitological cure Rates (ACPR) in the Intent To Treat (ITT) population on Day 28 after PCR correction were 95.2% in the artesunate amodiaquine fixed dose combination once a day (n=310)

and 95.5% in the artemether lumefantrine twice daily group (n=311). In children less than 5 years, ACPR in the ITT population on Day 28 after PCR correction were 94.4% in the artesunate amodiaquine group (n=143) and 93.7 % in the artemether lumefantrine group (n=142). The administration of artesunate amodiaquine fixed-dose combination was non-inferior to artemether lumefantrine in terms of clinical and parasitological efficacy.

- *Efficacy and safety in infants and children treated for repeated malaria attacks*
- A 2-year, randomised, single-centre, open study, comparing the efficacy of the ARTESUNATE AMODIAQUINE (ASAQ) tablets and artemether lumefantrine (AL) tablets in uncomplicated *P.falciparum* malaria was conducted in Uganda in 416 children from 6 to 59 months treated for repeated malaria attacks. Over this 2-year period, a total of 6033 episodes were monitored.

- The 28-day parasitological (PCR-corrected) cure rate was 97.5 % for ASAQ vs 97.0 % for AL for the first attack and PCR-corrected cure rates for subsequent malaria episodes that had over 100 cases (episodes 2-18) ranged from 88.1% to 98.9 % per episode, with no clear difference between the treatment arms.

- ACPR rates remained stable in both treatment groups over time during the 23 months of the study.
- The non-inferiority of a 3-day administration of ARTESUNATE AMODIAQUINE vs artemether lumefantrine in children less than 5 years of age presenting with a first uncomplicated episode of Plasmodium falciparum malaria was demonstrated.
- Repeated administration of ASAQ and AL from 2 to 26 times (median: 15 times) over a 2-year period in this study did not lead to unexpected safety issues. Safety profiles for both ACTs were good and comparable, and there was no evidence of emerging toxicity due to repeated use.

- Serious adverse events (SAE) per malaria attack over the first 23 malaria episodes ranged from 0 to 2% with ASAQ vs 0 to 0.6% with AL. Only one SAE in each group was considered to be related to study treatment. In both cases, increases in hepatic enzymes were reported and patients recovered spontaneously.

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 volunteers (n=32), the mean (CV) artesunate Cmax value was 162.9 ng/ml (75%), and the corresponding value for AUC was 89.9 ng.h/ml (51%). The median (range) artesunate tmax value was 0.25 hours (0.25-1.33 h).

- The mean (CV) DHA Cmax value was 460.4 ng/ml (3 %), and the corresponding value for AUC was 712.2 ng.h/ml (36%). The median (range) DHA tmax 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 in healthy subjects, 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 (n=32), the mean (CV) amodiaquine Cmax value was 9.2 ng/ml (33%), and the corresponding value for AUC was 65.7 ng.h/ml (45%). The median (range) amodiaquine tmax value was 0.79 hours (0.48-8 h).
- The mean (CV) desethylamodiaquine Cmax value was 147.9 ng/ml (41%), and the corresponding value for AUC was 9947.8 ng.h/ml (43%). The median (range) desethylamodiaquine tmax 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.

Artesunate Amodiaquine

Artesunate and amodiaquine interaction

- Single dose data have shown that the co-administration of artesunate and amodiaquine leads to a 47% decrease in the Cmax of dihydroartimisinin, and a 17% decrease of its AUC0-inf, relative to what is seen when artesunate is administered alone. If Artesunate Amodiaquine Bilayer Tablets is used in the presence of amodiaquine resistance, this might further compromise the antimalarial activity of Artesunate Amodiaquine Bilayer Tablets (see also sections 4.1, 4.4 and 5.1).

Special populations

- For the combined use of artesunate and amodiaquine, no pharmacokinetic data are available for patients with impaired renal or hepatic function.

Food effect

- When Artesunate Amodiaquine Bilayer Tablets was taken with a high fat meal in healthy volunteers, the Cmax and AUC(0-t) of amodiaquine increased 23% and 58% respectively, compared to fasting. The Cmax and AUC(0-t) of the active metabolite desethylamodiaquine (DeAQ) increased 18% and 12% respectively with a high-fat meal, compared to fasting.
- Conversely, when Artesunate Amodiaquine Bilayer Tablets was taken with a high fat meal in healthy volunteers, the Cmax and AUC(0-t) of artesunate decreased 66% and 13% respectively, compared to fasting. The Cmax and AUC(0-t) of the active metabolite dihydroartemisinin (DHA) decreased 48% and 5% respectively with a high-fat meal, compared to fasting.

5.3 Preclinical safety data

General toxicity

- Artesunate presents low acute toxicity. After repeated administration of 50 mg/kg/day in rats and 82.5 mg/kg/day in dogs, i.e. 5 and 8.25 times the proposed maximal therapeutic dose in man it is potentially toxic to the haematopoietic organs, the immune system and response, the liver and kidneys.
- For amodiaquine histopathological changes (pigmentation) were seen in the heart at 30 mg/kg/day in rats. The statistically significant effects seen in vitro on ion channels in the heart at 0.1 µM in the hERG current (expressed in Human Embryonic Kidney cells) as well as the increase in QRS complex and QT interval durations at concentrations higher than 0.1µM in the isolated rabbit Purkinje fibres appeared to be due to a non-specific multi-ion channel blockade. Pigmentations were also seen in liver, kidney and thyroid glands in rats as well as in kidneys, liver and lymph nodes in dogs (at doses of 25mg/kg/day). Also an increase in haemosiderosis in the spleen and bone marrow as well as thymus lymphoid depletion were observed.

- The toxicity after acute and chronic administration of the combination artesunate/amodiaquine was similar to that of artesunate and amodiaquine, when administered alone. In repeated dose toxicity studies, the incidence and the severity of lesions were generally related to the dose levels. Amodiaquine given alone at 30 mg/kg/day induced effects very similar to those of the 12/30 mg/kg/day artesunate amodiaquine combination.

  Genotoxicity:

  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.
- Carcinogenesis:

- No studies of the carcinogenic potential of the combination of artesunate and amodiaquine or the individual agents have been conducted.
- Toxicity to Reproduction:
- 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.

  Safety pharmacology studies:
- Slight sedative effect, a decrease in body temperature, a slight natriuretic effect and a decrease in endogenous creatinine clearance were observed with artesunate after single intravenous doses of 200 mg/kg (mice), 450 mg (rats, rabbits and dogs) and after single oral doses of 180 mg/kg in male rats. In conscious telemetered dogs, atrio-ventricular blocks and depressant effects on smooth muscles were reported from 10 mg/kg (single oral dose). Since these effects were observed only in female animals, at a low incidence and without relation to dose, the relationship to artesunate administration remains to be confirmed. Neither neurotoxicity nor prolongation of QT(c) interval were shown.

- Amodiaquine is likely to induce cardiovascular adverse effects, particularly transient prolongation of QT interval duration at 30 mg/kg administered orally. This dose level corresponds to approximately 2-fold the maximum recommended therapeutic dose. At the dose level of 100 mg/kg administered orally (about 6.7 fold the maximum recommended

therapeutic dose), also slight respiratory depressant and natriuretic effects were noted.

- Oral administration of both agents, amodiaquine followed by artesunate, was safe for the CNS, the cardiovascular and respiratory systems at dose levels of artesunate/amodiaquine corresponding to approximately 1.67 / 1.81 fold the maximum therapeutic dose levels (15/5.5 mg/kg amodiaquine/artesunate). The observed natriuretic effect on the kidney was very slight and transient.

6. Pharmaceutical Particulars

6.1 List of Excipients

- Colloidal anhydrous silica
- Croscamellose sodium
- Hydroxy propylcellulose
- Magnesium stearate
- Mannitol
- Pregelatinised starch (Starch 1500)
- Polysorbate 80

6.2 Incompatibilities

Not applicable.

6.3 Shelf-Life

24 months

6.4 Special Precautions for storage

Do not store above 30°C

Store tablets in blisters in the provided carton

6.5 Nature and Content of container

❖ ARTESUNATE AMODIAQUINE BILAYER TABLETS 25mg/67.5mg are presented in following packs

- PVC/EVOH -Aclar Blister Pack : 3 tablets packaged in a PVC/EVOH-Aclar blister pack. Box containing 1, 10 or 25 blisters in a carton

- Aluminum – Aluminum Blister Pack:. 3 tablets packaged in an aluminium/aluminium blister pack. Box containing 1, 10 or 25 blisters in a carton

❖ ARTESUNATE AMODIAQUINE BILAYER TABLETS 50mg/135mg

- PVC/EVOH -Aclar Blister Pack : 3 tablets packaged in a PVC/EVOH-Aclar blister pack. Box containing 1, 10 or 25 blisters in a carton
- Aluminum – Aluminum Blister Pack:. 3 tablets tablets packaged in an aluminium/aluminium blister pack. Box containing 1, 10 or 25 blisters in a carton

6.6 Special precautions for disposal and other handling

- Do not store above 30°C
- Store tablets in blisters in the provided carton

7. Marketing Authorization Holder

Micro Labs Limited
27, Race Course Road
Bangalore-560001
Karnataka,
India
Tel: +91-80-22370451-57
Fax: +91-80-22370463

8. Marketing Authorization Number

Artesunate25mg + Amodiaquine 67.5mg Bilayer Tablets- CTD11532
Artesunate 50mg + Amodiaquine 135mg Bilayer Tablets- CTD11289
Artesunate 100mg + Amodiaquine 270mg Bilayer Tablets - CTD11290

9. Date of first authorization/renewal of the authorization

14/10/2008

10. Date of revision of the text

06/05/2025