National Agency for Food & Drug Administration & Control (NAFDAC)

Registration & Regulatory Affairs (R & R) Directorate

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) TEMPLATE

SUMMARY OF PRODUCT CHARACTERISTICS (SMPC)

1. Name of the Medical Product

1.1 Product Name:

APMOD 50/135 (Artesunate 50 mg + Amodiaquine 135 mg Tablets)

1.2 Strength:

Each bilayered tablet contains:
Artesunate Ph.Int ……. 50 mg
Amodiaquine Hydrochloride
equivalent to Amodiaquine ….. 135 mg

1.3 Pharmaceutical Dosage Form:

Tablets

2. Qualitative & Quantitative Composition

Each bilayered tablet contains:
Artesunate Ph.Int ……. 50 mg
Amodiaquine Hydrochloride
equivalent to Amodiaquine ….. 135 mg
For a full list of excipients, see section 6.1 of SmPC

3. Pharmaceutical Form

Tablet
Circular, bilayered, beveled edged tablet. One layer is yellow in colour with score line and the other layer is white to slightly yellow. The tablet is debossed with 'A' on one side of score line and '2' on the other side of score line.

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

4. Clinical Particulars

4.1 Therapeutic Indications:

Apmod 50/135 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 Apmod 50/135.

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

Apmod 50/135 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
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

Apmod 50/135 should not be taken with a high-fat meal (see section 5.2).
The tablets should be swallowed with water.

For very young children or patients not able to swallow the tablets whole, the tablets may be crushed and added to a small amount of semi-solid food or liquid, all of which should be consumed immediately.

Should vomiting occur within half an hour after dosing, a repeated dose of Apmod 50/135 is to be taken. In case of further vomiting, treatment for severe malaria should be considered.

Renal/hepatic impairment:
No data are available on dosing in hepatically or renally impaired patients (see section 4.4).

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).

Apmod 50/135 must not be used for malaria prophylaxis, since it may result in agranulocytosis and severe hepatotoxicity (see section 4.4).

4.4 Special warning and precautions for use:
Apmod 50/135 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.

Apmod 50/135 has not been evaluated for the treatment of complicated malaria and is therefore not recommended.

Apmod 50/135 has not been evaluated in the treatment of malaria due to *Plasmodium vivax, Plasmodium malariae* or *Plasmodium ovale* and is therefore not recommended.

Apmod 50/135 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).

It is not known, whether the toxicity of amodiaquine, observed with prophylactic use (i.e. agranulocytosis, hepatotoxicity), may also develop after repeated cycles of curative treatment.
Apmod 50/135 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.
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 Apmod 50/135, 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 over dosage).

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 Apmod 50/135, even after administration of a single dose (see section 4.8). These adverse reactions usually resolve after treatment discontinuation of Apmod 50/135 and appropriate medical treatment of the neurological condition. Alternative antimalarial therapy should be instituted.

Caution is advised when combining Apmod 50/135 with drugs inhibiting, inducing or competing for CYP2C8 (see section 4.5).

Co-administration of Apmod 50/135 and efavirenz should be avoided, since this combination has been noted to cause marked hepatotoxicity.

4.5 Interactions with other medicinal products and other forms of Interactions:
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, Apmod 50/135 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 Apmod 50/135 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 Apmod 50/135, 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 antipsychotic drugs. Caution should be exercised when co-administration of these agents with Apmod 50/135 is deemed necessary.

4.6 Fertility, pregnancy and lactation:
Pregnancy
Malaria is known to be particularly hazardous during pregnancy. The benefits and risks of therapy with Apmod 50/135 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, Apmod 50/135 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, Apmod 50/135 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 Apmod 50/135) for malaria treatment.

Fertility
No specific studies with Apmod 50/135 in humans have been conducted to evaluate effects on fertility. Studies in animals showed effects on fertility (see section 5.3). The significance for human is unknown.

4.7 Effects on ability to drive and use machine:
Patients receiving Apmod 50/135 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 combination amodiaquine and artesunate has been evaluated through two 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 experienced adverse reactions. 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 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.
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	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) have been reported. These adverse reactions usually resolved after discontinuation of Apmod 50/135 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.

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.

Artesunate
No cases of overdose have been reported to date.

5. Pharmacological Particulars

5.1 Pharmacodynamic properties:

Pharmacotherapeutic group: Artemisinin and derivatives, combinations
ATC code: P01BF03

Apmod 50/135 is an artemisinin-based combination therapy which consists of two blood schizonticides, with independent modes of action and different intraparasitic biochemical targets.

Apmod 50/135 is indicated in areas where parasite resistance rate to amodiaquine remains below the threshold defined by WHO.

Efficacy and safety of amodiaquine + artesunate in uncomplicated *P. falciparum* malaria have been demonstrated in clinical trials in West and Central Africa and in Madagascar. Inconsistent results have been seen in some areas where combinations of artesunate and amodiaquine have been studied, probably due to a higher prevalence of amodiaquine resistance.

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.

5.2 Pharmacokinetics 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).

A bioequivalence study was conducted with a fixed dose combination product containing 135mg amodiaquine and 50mg artesunate.

After administration of 4 tablets containing amodiaquine and artesunate (135 mg and 50 mg respectively) in healthy volunteers, the mean (± SD) artesunate Cmax value was 278 ng/ml (±122), and the corresponding value for AUC was 201 ng.h/ml (±71). The mean (±SD) artesunate tmax value was 0.37 hours (±0.08). The mean (±SD) DHA Cmax value was 740 ng/ml (±277), and the corresponding value for AUC was 1591 ng.h/ml (±487). The mean (±SD) DHA tmax value was 0.73 hours (± 0.44).

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.

A bioequivalence study was conducted with a fixed dose combination product containing 135mg amodiaquine and 50mg artesunate. After administration of 4 tablets containing amodiaquine and artesunate (135 mg and 50 mg respectively) in healthy volunteers, the mean (±SD) amodiaquine Cmax value was 13.0 ng/ml (±4.4), and the corresponding value for AUC was 131 ng.h/ml (±44). The mean (± SD) amodiaquine tmax value was 0.91 hours (±0.59). The mean (±SD) desethylamodiaquine Cmax value was 111 ng/ml (±36), and the corresponding value for AUC was 3365 ng.h/ml (±1042). The mean (± SD) desethylamodiaquine tmax value was 2.5 hours (± 1.5).

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 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 fixed dose

combination of Apmod 50/135 is used in the presence of amodiaquine resistance, this might further compromise the antimalarial activity of Apmod 50/135 (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 fixed combination of amodiaquine/artesunate 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 fixed combination of amodiaquine/artesunate 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 increases 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. Subclinical artesunate exposure of male guinea pigs caused decreases in total sperm count and sperm motility and an increase in abnormal sperm cells.

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 was 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:

Calcium Carbonate, Colloidal Anhydrous Silica, Croscarmellose Sodium, Magnesium Stearate, Maize Starch, Microcrystalline Cellulose and Povidone.

6.2 Incompatibilities:

Not applicable

6.3 Shelf life:

36 months

6.4 Special Precautions for storage:

Store below 30°C.

6.5 Nature and contents of container:

3 tablets in Alu-OPA/Alu/PVC blister pack, 1 such blisters packed in a carton along with Patient Information Leaflet.

6.6 Special precautions for disposal and other handling:

Not applicable

7. Marketing authorization holder and manufacturing site addresses:

Market Authorization Holder

Ajanta Pharma Limited
Ajanta House,
Charkop, Kandivli (West),
Mumbai- 400 067,
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Manufacturing site address:

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8. Marketing authorization number : B4-1011

9. Date of first registration/ renewal of the registration: Nov 28, 2013

10. Date of revision of text: September 2014
Section 6 updated in February 2018
Section 6 updated in February 2019