

## WHO-PQ RECOMMENDED SUMMARY OF PRODUCT CHARACTERISTICS

*This summary of product characteristics focuses on uses of the medicine covered by WHO's Prequalification Team - Medicines. The recommendations for use are based on WHO guidelines and on information from stringent regulatory authorities.\**

*The medicine may be authorised for additional or different uses by national medicines regulatory authorities.*

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\*[https://extranet.who.int/pqweb/sites/default/files/documents/75%20SRA%20clarification\\_Feb2017\\_newtempl.pdf](https://extranet.who.int/pqweb/sites/default/files/documents/75%20SRA%20clarification_Feb2017_newtempl.pdf)

## 1. NAME OF THE MEDICINAL PRODUCT

[MA132 trade name]†

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

[MA132 trade name] is a fixed dose combination of amodiaquine and artesunate.

Each tablet contains 67.5 mg amodiaquine (as hydrochloride) and 25 mg artesunate

Each tablet contains about 71mg of mannitol.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Tablets

[MA132 trade name] is a capsule shaped, biconvex, bilayer tablet, one layer is yellow coloured and the other one is white to slightly yellow coloured. One face plain which is yellow in colour and a break line on the other face which is white in colour. The face with the break line having engravings “AA” on one side and “25” on the other side of break line.

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

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

[MA132 trade name] is indicated for the treatment of uncomplicated malaria due to *Plasmodium falciparum* strains which are susceptible to amodiaquine and 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 [MA132 trade name].

[MA132 trade name] should not be used in regions where amodiaquine resistance is widespread because such use significantly increases the risk of developing resistance to artesunate.

### 4.2 Posology and method of administration

*Children 4.5–9 kg*

The doses of [MA132 trade name] are shown below (in terms of tablets as well as the active substances). Information is given for all weights of children in whom the tablets can be used. However, it is important to ensure that the pack size, i.e. the number of tablets in the pack, is sufficient for the full treatment course according to the child's weight.

Child's weight (approximate age)	Dose	
less than 9 kg (up to 11 months)	1 tablet daily for 3 days	amodiaquine 67.5 mg + artesunate 25 mg daily for 3 days
9–18 kg (1–5 years)	2 tablets daily for 3 days	amodiaquine 135 mg + artesunate 50 mg daily for 3 days

† Trade names are not prequalified by WHO. This is the national medicines regulatory agency's responsibility.

18–36 kg (6–13 years)	Use formulations containing higher amounts of amodiaquine and artesunate	amodiaquine 270 mg + artesunate 100 mg daily for 3 days
more than 36 kg (over 14 years)		amodiaquine 540 mg + artesunate 200 mg daily for 3 days

The dosage of [MA132 trade name] is based on the following weight-based doses of the two components:

- amodiaquine 10 mg/kg daily for 3 days
- artesunate 4 mg/kg daily for 3 days.

### **Administration**

[MA132 trade name] is taken orally and the tablets should be swallowed with water. They should not be taken with a meal that contains a high amount of fat (see section 5.2).

For patients unable to swallow the tablets, e.g. very young children, the tablets can be crushed and either mixed in water or taken with water.

If the patient vomits within half an hour after dosing, another dose of [MA132 trade name] should be taken. In case of further vomiting, treatment for severe malaria should be considered.

### **Renal and hepatic impairment**

No data are available on dosing in patients with hepatic or renal impairment (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)

[MA132 trade name] must not be used for malaria prophylaxis since it may result in agranulocytosis and severe hepatotoxicity (see section 4.4).

## **4.4 Special warnings and precautions for use**

[MA132 trade name] should not be used in regions where amodiaquine resistance is widespread, as treatment with the combination may mean effectively a treatment with artesunate alone with an insufficient duration and lower plasma concentrations as compared to treatment with artesunate alone (see section 4.5). As a result, the risk of *P. falciparum* developing resistance to artesunate increases significantly.

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

[MA132 trade name] has not been evaluated for the treatment of complicated malaria and is therefore not recommended.

[MA132 trade name] has not been evaluated in the treatment of malaria due to *P. vivax*, *P. malariae* or *P. ovale* and is therefore not recommended.

[MA132 trade name] 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.

[MA132 trade name] has not been studied in patients with thalassaemia, sickle cell anaemia or glucose-6-phosphate dehydrogenase (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, tonsillitis or mouth ulcers).

When these symptoms develop or worsen during treatment with [MA132 trade name], laboratory tests are required at once for liver function, or blood cell counts, or both. Immediate discontinuation of treatment may be required since continuation of treatment with amodiaquine increases the risk of death.

Cardiovascular effects have been reported with 4-aminoquinoline derivatives. Due to a potential for QT prolongation, amodiaquine should be used with caution in patients with: cardiac disease, a history of ventricular dysrhythmias, uncorrected hypokalaemia or hypomagnesaemia, or bradycardia (< 50 beats per minute), and during concomitant use of substances that prolong the QT interval (see Sections 4.5).

The combination of artesunate and amodiaquine may induce neutropenia and increase the risk of infection.

Acute extrapyramidal side effects may occur with [MA132 trade name], even after a single dose (see section 4.8). These reactions usually resolve after discontinuing treatment with [MA132 trade name] and medical treatment of the neurological condition. Alternative antimalarial therapy should be instituted.

#### *Excipients*

Each tablet contains mannitol, which may have a mild laxative effect.

### **4.5 Interaction with other medicinal products and other forms of interaction**

Interactions may occur with drugs used for treating HIV and tuberculosis, though few clinical data are available. Prescribers should be vigilant for adverse events potentially related to such interactions, including liver toxicity and neutropenia. Concomitant administration of [MA132 trade name] and efavirenz should be avoided, since this combination can cause marked hepatotoxicity.

Concomitant administration is not recommended of [MA132 trade name] with drugs that inhibit the liver enzymes cytochrome (CYP) 2A6 (e.g. methoxsalen, pilocarpine, tranlycypromine) or those that inhibit CYP2C8 (e.g. trimethoprim, ketoconazole, ritonavir, saquinavir, lopinavir, gemfibrozil, montelukast).

No pharmacokinetic interactions of artesunate with other important antimalarial drugs have been identified. However, concomitant administration of [MA132 trade name] with other antimalarial treatments is not recommended, as data on efficacy and safety are not available.

The concentration of dihydroartemisinin (DHA, the main active metabolite of artesunate), decreases when artesunate and amodiaquine are used concomitantly ( $C_{max}$  decreased 47%,  $AUC_{0-\infty}$  decreased 17%).

Agranulocytosis and hepatitis have occurred after long-term use of amodiaquine for prophylaxis. Therefore, caution should be observed when [MA132 trade name] is used concurrently with other drugs that cause liver or haematological toxicity.

Amodiaquine and desethylamodiaquine inhibit CYP 2D6 in vitro and may cause clinically significant interactions with some beta-blockers, antidepressants, and antipsychotics drugs. Caution should be exercised when they are co-administered with [MA132 trade name].

### **4.6 Fertility, pregnancy and breastfeeding**

#### *Pregnancy*

Malaria is particularly hazardous during pregnancy. The healthcare provider must consider the benefits and risks of treatment with [MA132 trade name] for the mother and the fetus.

The safety of amodiaquine in pregnant women has not been formally established, but many years of experience with it does not indicate a risk of 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 baby. Animal data indicate a limited embryotoxic effect at daily doses of 6 mg/kg or more.

During first trimester of pregnancy, [MA132 trade name] 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 is not tolerated.

During second and third trimesters, [MA132 trade name] may be used with caution, only if other antimalarials cannot be used.

#### *Breastfeeding*

The amounts of antimalarials in breast milk are small. Therefore, lactating women can receive [MA132 trade name] for malaria treatment.

#### **4.7 Effects on ability to drive and use machines**

Patients receiving [MA132 trade name] 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 safety of amodiaquine/artesunate was evaluated through two comparative pivotal studies involving 1003 patients treated with the fixed dose combination.

Adverse reactions reported from clinical studies and post-marketing experience are listed below according to system organ class.

Most of the adverse reactions observed in clinical studies were similar to symptoms usually seen during a malaria attack. The most frequent adverse reactions 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.

Adverse reactions are ranked under headings of frequency using the MedDRA frequency convention:

Very common ( $\geq 1/10$ )

Common ( $\geq 1/100$  to  $< 1/10$ )

Uncommon ( $\geq 1/1,000$  to  $< 1/100$ )

Rare ( $\geq 1/10,000$  to  $< 1/1,000$ )

Very rare ( $< 1/10,000$ )

Not known (cannot be estimated from available data).

#### *Infections and infestations*

Uncommon                      bronchitis acute, gastroenteritis, oral candidiasis

#### *Immune system disorders*

Unknown frequency        allergic reaction \*

#### *Blood and lymphatic system disorders*

Uncommon                      anaemia

Unknown frequency        leucopenia \*\*, neutropenia (agranulocytosis), sometimes severe \*\*

#### *Metabolism and nutrition disorders*

Uncommon                      hypoglycaemia

#### *Psychiatric disorders*

Common                        anorexia, insomnia

Uncommon                      hallucination

#### *Nervous system disorders*

Common                        somnolence

Uncommon	paraesthesia
Rare	neuromyopathy**
Unknown frequency	extrapyramidal disorders (such as dystonia, dyskinesia, tongue protrusion, torticollis) *, headache *, dizziness *, convulsions *

*Eye disorders*

Uncommon	ocular icterus
Very rare	irreversible retinopathy (requiring specialist ophthalmic care)**
Unknown frequency	transient accommodation disorders **, corneal opacity (reduces on stopping treatment)**

*Ear and labyrinth disorders*

Uncommon	vertigo
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*Cardiac disorders*

Common	prolonged QT interval (frequency based on studies in 289 patients with ECG recording)*
Uncommon	arrhythmia, bradycardia

*Respiratory, thoracic, and mediastinal disorders*

Common	cough
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*Gastro-intestinal disorders*

Common	nausea, abdominal pain
Uncommon	diarrhoea, vomiting

*Hepatobiliary disorders*

Unknown frequency	severe hepatitis (sometimes fatal)** , splenomegaly* , jaundice*
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*Skin and subcutaneous tissue disorders*

Uncommon	pruritus, rash, face oedema, skin disorders
Unknown frequency	slate-grey pigmentation (notably affecting fingers and mucous membranes)**

*Musculoskeletal and connective tissue disorders*

Uncommon	arthralgia
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*General disorders and administration site conditions*

Common	asthenia
Uncommon	oedema peripheral, pyrexia
Unknown frequency	cold* , flu* , rhinitis* , shivering* , sore throat*

\* Data from post-marketing experience

\*\* Reported in HIV-infected patients, particularly in those on zidovudine and/or cotrimoxazole. Also reported with amodiaquine alone, especially at higher doses and/or during prolonged treatment

***Reporting of suspected adverse reactions***

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Health care providers are asked to report any suspected adverse reactions to the marketing authorisation holder, or, if available, via the national reporting system.

## 4.9 Overdose

In case of suspected overdose, the patient should be urgently transferred to a specialist unit with facilities for clinical monitoring and where symptomatic and supportive therapy can be given.

### *Amodiaquine*

The dose at which amodiaquine can cause serious toxicity is not known; by comparison with chloroquine, it can be estimated at around 2 g as a single dose in adults,

Symptoms and signs: headache, dizziness, visual disorders, QT interval prolongation, cardiovascular collapse and convulsions, followed by respiratory and cardiac arrest. Extrapyraxidal disorders have been reported.

### *Artesunate*

There is limited experience of overdose with artesunate. Artesunate overdose should be treated symptomatically.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Artesunate Amodiaquine Combination (ATC code P01BF03)

[MA132 trade name] is an artemisinin-based combination therapy which consists of two blood schizonticides, with independent modes of action and different biochemical targets in the parasites.

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

In vitro artemisinin derivatives are active against a broad spectrum of the life cycle of the *Plasmodium falciparum* parasite, from the relatively inactive ring stage to late schizonts. The schizonticidal and gametocytocidal activities of orally administered artesunate 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).

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) infection with a chloroquine-resistant strain of *P. knowlesi* was cured with the same doses of artesunate and quinine.

*Amodiaquine*: Amodiaquine is a synthetic 4-aminoquinoline antimalarial. It has schizonticidal action on *P. falciparum*, *P. vivax*, *P. ovale* and *P. malaria* which destroys intraerythrocytic forms.

The mechanism of action of 4-aminoquinoline derivatives against plasmodium has not been established. Amodiaquine can 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***

[MA132 trade name] is for use in areas where parasite resistance to amodiaquine remains low.

Efficacy and safety of [MA132 trade name] in uncomplicated *P. falciparum* malaria have been demonstrated in clinical trials in various settings in Africa. Trials also suggest adequate efficacy in south-east Asia and Latin America.

### *Efficacy and safety in children and adults*

The efficacy and safety of [MA132 trade name] in uncomplicated *P. falciparum* malaria were demonstrated in two pivotal studies (Burkina-Faso study and ATAQ-EASY multinational study) in children and adults, as well as in 13 other supportive studies.

A randomised, controlled, open-label, parallel-group study in Burkina-Faso compared the efficacy and safety of [MA132 trade name] tablets to an almost equivalent regimen of the individual drugs given together in 750 children aged 6 months to 5 years. The parasitological cure rates after 28 days were the same (92%) in both groups. Analysis of both clinical and parasitological data demonstrated the non-inferiority of the artesunate and amodiaquine combination compared to separate drugs used concomitantly.

A multinational, randomised, blinded, comparative study (ATAQ EASY) of the efficacy and safety of [MA132 trade name] tablets vs artemether/lumefantrine tablets in the treatment of uncomplicated *P. falciparum* malaria was conducted in 4 African countries (Cameroon, Madagascar, Mali and Senegal) in 941 adults and children.

Adequate clinical and parasitological cure rates in the intention-to-treat (ITT) population on day 28 were 95.2% with artesunate/amodiaquine fixed-dose combination once a day (n = 310) and 95.5% with the artemether/lumefantrine twice daily group (n = 311). In children aged less than 5 years, in the ITT population on day 28 cure rates were 94.4% in the artesunate/amodiaquine group (n = 143) and 93.7 % in the artemether/lumefantrine group (n = 142). The clinical and parasitological efficacy of artesunate/amodiaquine combination was non-inferior to artemether/lumefantrine.

### *Efficacy and safety in infants and children treated for repeated malaria attacks*

A 2-year, randomised, single-centre, open study, compared the efficacy of the [MA132 trade name] tablets and artemether/lumefantrine tablets in uncomplicated *P. falciparum* malaria in Uganda in 416 children aged from 6 to 59 months for treating repeated malaria attacks. Over this 2-year period, a total of 6033 episodes were monitored.

The 28-day parasitological cure rate was 97.5 % for artesunate/amodiaquine vs 97.0 % for artemether/lumefantrine for the first attack and cure rates for over 100 subsequent malaria episodes ranged from 88.1% to 98.9 % per episode, with no clear difference between the treatment arms.

Cure rates remained stable in both treatment groups over time during the 23 months of the study.

A 3-day course of [MA132 trade name] was non-inferior to artemether/lumefantrine in children aged less than 5 years presenting with a first episode of uncomplicated *Plasmodium falciparum* malaria.

Repeated use of artesunate/amodiaquine and artemether/lumefantrine between 2 to 26 times (median: 15 times) over a 2-year period in this study did not reveal unexpected safety issues. Safety profiles for both were good and comparable, and there was no evidence of emerging toxicity due to repeated use.

Serious adverse events per malaria attack over the first 23 episodes ranged from 0 to 2% with artesunate/amodiaquine vs 0 to 0.6% with artemether/lumefantrine. Only one serious event in each group was considered to be related to treatment. In both cases, increases in hepatic enzymes were reported and patients recovered spontaneously.

## **5.2 Pharmacokinetic properties**

*No pharmacokinetic data are available for [MA132 trade name]. A bioequivalence study was conducted with a fixed dose combination product containing 270mg Amodiaquine (as hydrochloride) and 100mg Artesunate that is essentially the same as [MA132 trade name] in qualitative terms and with respect to the ratio of active and other ingredients.*

The absorption characteristics of 270 mg Amodiaquine (as hydrochloride) and 100 mg Artesunate have been determined in healthy volunteers under fasting conditions as follows:

Pharmacokinetic variable	Arithmetic mean value ( $\pm$ standard deviation)	
	Artesunate	Amodiaquine
Maximum concentration ( $C_{max}$ )	380 $\pm$ 265 ng/mL	20.6 ( $\pm$ 7.3) ng/mL



Area under the curve (AUC <sub>0-∞</sub> ), a measure of the extent of absorption	207 ± 84 ng.h/mL	235 (± 104) ng-h/MI
Time to attain maximum concentration (t <sub>max</sub> )	0.49 ± 0.27 hours	1.32 ± 1.15 hours

	Artesunate	Amodiaquine
<b>General</b>		
C <sub>max</sub> ng/mL	162.9	9.2
AUC <sub>0-∞</sub> ng-hour/mL	89.9	65.7
t <sub>max</sub> hours	0.25 (0.25-1.33)	0.79 (0.48-8)
<b>Absorption</b>		
Absolute bioavailability		The absolute bioavailability of amodiaquine is not known.
Oral bioavailability	Absorption is rapid. Most of the artesunate is promptly biotransformed to the active metabolite dihydroartemisinin (DHA)	Amodiaquine is quickly absorbed and biotransformed to its main active form, desethylamodiaquine.
Food effect	When [MA056] was taken with a high fat meal in healthy volunteers, the C <sub>max</sub> and AUC <sub>(0-t)</sub> of artesunate decreased 66% and 13% respectively, compared to fasting. The C <sub>max</sub> and AUC <sub>(0-t)</sub> of the active metabolite (DHA) decreased 48% and 5% respectively with a high-fat meal, compared to fasting.	When [MA056] was taken with a high fat meal in healthy volunteers, the C <sub>max</sub> and AUC <sub>(0-t)</sub> of amodiaquine increased 23% and 58% respectively, compared to fasting. The C <sub>max</sub> and AUC <sub>(0-t)</sub> of the active metabolite desethylamodiaquine increased 18% and 12% respectively with a high-fat meal, compared to fasting.
<b>Distribution</b>		
Volume of distribution		Amodiaquine: 20–40 L/kg Desethylamodiaquine, the main metabolite of amodiaquine, is found in blood, at much higher concentrations than unchanged amodiaquine. Its concentration in whole blood is 4-6 times higher than in plasma.
Plasma protein binding <i>in vitro</i>	Artesunate is not significantly protein-bound	
Tissue distribution	Active metabolite, DHA, accumulates substantially in <i>P. falciparum</i> -infected erythrocytes	
<b>Metabolism</b>		
	Extensively hydrolysed by plasma esterases and perhaps also by CYP2A6. DHA is further metabolised through glucuronidation before excretion.	The hepatic metabolism of amodiaquine, through the isoenzyme CYP2C8, is high, with formation of the active metabolite, desethylamodiaquine
<b>Elimination</b>		

Plasma half-life	3–29 minutes (artesunate) 40–95 minutes (DHA)	Amodiaquine is eliminated principally through biotransformation with only around 2% excreted unchanged in urine. Desethylamodiaquine is eliminated with a terminal half-life of 9–18 days.
<b>Special populations</b>		
	For the combined use of artesunate and amodiaquine, no pharmacokinetic data are available for patients with impaired renal or hepatic function.	

### 5.3 Preclinical safety data

#### *General toxicity*

*Artesunate* presents low acute toxicity. After repeated doses of 50 mg/kg/day in rats and 82.5 mg/kg/day in dogs, i.e. 5 and 8.25 times the maximal therapeutic dose in humans, it is potentially toxic to the haematopoietic organs, the immune system and response, the liver and kidneys.

For *amodiaquine* pigmentation was seen in the heart at 30 mg/kg/day in rats. The statistically significant *in vitro* effects 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 0.1 µM in the isolated rabbit Purkinje fibres appeared to be due to a non-specific multi-ion channel blockade. Pigmentation was also seen in liver, kidney and thyroid glands in rats as well as in kidneys, liver and lymph nodes in dogs (at doses of 25 mg/kg/day). Also, haemosiderosis increased in the spleen and bone marrow and thymus lymphoid depletion occurred.

Toxicity after acute and chronic administration of the combination artesunate/amodiaquine was similar to that with artesunate and amodiaquine, given alone. In repeated-dose toxicity studies, the incidence and the severity of lesions was 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*

*In vitro* and *in vivo* tests (Ames, mouse micronucleus) did not reveal any mutagenic or clastogenic potential of artesunate. Although amodiaquine, like chloroquine, has both mutagenic and clastogenic potential, studies with the artesunate/amodiaquine combination in the Ames test and micronucleus in rat did not demonstrate 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 in rats and rabbits have confirmed the 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 early slowing of bodyweight increase 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*

Slight sedative effect, decreased body temperature, a slight natriuretic effect and decreased 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 with a single oral dose of 10 mg/kg. Since these effects were observed only in female animals, at a low incidence and without relation to dose, the relationship to artesunate administration cannot 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 with an oral dose of 30 mg/kg. This dose level corresponds to approximately 2-fold the maximum recommended therapeutic dose. Also, slight respiratory depressant and natriuretic effects occurred with an oral dose of 100 mg/kg (about 6.7-fold the maximum therapeutic dose).

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

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Mannitol  
Hydroxypropylcellulose  
Colloidal anhydrous silica  
Magnesium stearate  
Pregelatinized starch  
Croscarmellose sodium  
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 contents of container**

*PVC/EVOH-Aclar blister pack:*

3 tablets are packed in a PVC/EVOH-Aclar blister pack. Such 1, 10 or 25 blisters are contained in a box.

*Aluminium–Aluminium blister pack:*

3 tablets packed in an aluminium-aluminium blister pack. Such 1, 10 or 25 blisters are contained in a box.

### **6.6 Special precautions for disposal and other handling**

No special requirements

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## **7. SUPPLIER**

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## **8. WHO REFERENCE NUMBER (WHO Prequalification Programme)**

MA132

## **9. DATE OF PREQUALIFICATION**

31 October, 2018

## **10. DATE OF REVISION OF THE TEXT**

October 2021

### ***References***

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### *Section 4.5*

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### *Section 4.6*

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### *Section 5.2*

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*Detailed information on this medicine is available on the World Health Organization (WHO) website:*  
<https://extranet.who.int/pqweb/medicines>