1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

Attached

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. NAME OF THE MEDICINAL PRODUCT

LOKART 60 Injection (Artesunate for Injection 60 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains:

Artesunate… 60mg

3. PHARMACEUTICAL FORM

Dry Powder for Injection

4. Clinical particulars

4.1 Therapeutic indications

Artesunate for Injection is administered intravenously or intramuscularly, is indicated for the treatment of severe malaria caused by *Plasmodium falciparum*, in adults and children. Consideration should be given to official treatment guidelines for malaria (e.g. by WHO).

4.2 Posology and method of administration

Adults and children weighing 20 kg or more:

Artesunate for Injection is administered at a dose of 2.4 mg of artesunate / kg body weight, by intravenous (IV) or intramuscular (IM) injection, at 0, 12 and 24 hours, then once daily until oral treatment can be substituted.

Children weighing less than 20 kg:

Artesunate for Injection is administered at a dose of 3 mg of artesunate / kg body weight, by intravenous (IV) or intramuscular (IM) injection, at 0, 12 and 24 hours, then once daily until oral treatment can be substituted (see section 5.1).

Artesunate for Injection should be administered for a minimum of 24 hours (3 doses), regardless of the patient's ability to tolerate oral medication earlier. After at least 24 hours of Artesunate for Injection, and when able to tolerate oral medication, the patient should be switched to a complete treatment course of an oral combination antimalarial regimen.

Hepatic and renal impairment:

Dose adjustment is not necessary in patients with hepatic or renal impairment (see Sections 4.4 and 5.2).

Method of administration: I.M. or I.V.

4.3 Contraindications

Artesunate for Injection is contraindicated in patients with hypersensitivity to artesunate or other artemisinins or to any of the components of the formulation listed in section 6.1.

4.4 Special warnings and precautions for use

Non-falciparum malaria

Artesunate has not been evaluated in the treatment of severe malaria due to *Plasmodium vivax, Plasmodium malariae* or *Plasmodium ovale.*

Resistance to antimalarials

Local information on the prevalence of resistance to antimalarials should be considered in choosing the appropriate combination antimalarial regimen for use with Artesunate for Injection.

Post-treatment haemolytic anaemia

Delayed haemolytic anaemia following treatment with injectable artesunate has been observed in children in malaria endemic areas and in non-immune travelers presenting with severe falciparum malaria. The risk was most pronounced in patients with hyperparasitaemia and in younger children. Some cases have been severe and required blood transfusion. Vigilance for delayed onset anaemia is therefore advised, particularly in hyperparasitaemic patients and younger children, and prolonged follow-up should be considered (e.g. 14-28 days). As the overall benefit-risk ratio remains highly favourable for injectable artesunate in the treatment of severe malaria, WHO strongly recommends its continued use.

Hepatic / renal impairment:

Data regarding artesunate pharmacokinetics in patients with hepatic and/or renal impairment are limited. Based on data from studies in patients with severe malaria, as well as the known metabolism of artesunate (see Section 5.2), dosage adjustment is not considered necessary in patients with hepatic or renal impairment.

Paediatric population

In clinical trials, the efficacy and safety of intravenous and intramuscular artesunate have been similar in adult and paediatric populations.

4.5 Interaction with other medicinal products and other forms of interaction

Artesunate is rapidly and extensively converted to dihydroartemisinin (DHA), the active metabolite, primarily by plasma and erythrocyte esterases. DHA elimination is also rapid (half-life approximately 45 minutes) and the potential for drug-drug interactions appears

limited. *In vitro* drug-interaction studies have demonstrated minimal effects of artesunate on cytochrome P450 isoenzymes. Few clinical drug-drug interaction studies have been performed. An increase in plasma concentrations of artesunate was observed with nevirapine and a reduced plasma concentration of dihydroartemisinin was observed when artesunate is given with ritanovir.

4.6 Pregnancy and Lactation

Pregnancy

Severe malaria is especially hazardous during pregnancy, therefore full dose parenteral artesunate treatment should be administered at any stage of pregnancy without delay.

In animal studies, artesunate has been associated with fetal toxicity during the first trimester of pregnancy. Limited clinical experience with the use of artesunate in the first trimester of pregnancy as well as clinical data from more than 4,000 pregnant women, treated with artemisinin derivatives in the second and third trimester, do not indicate adverse effects of artesunate on pregnancy or on the health of the fetus/newborn child.

Breastfeeding

Limited information indicates that dihydroartemisinin, the active metabolite of artesunate, is present at low levels in breast milk. The drug levels are not expected to cause any adverse effects in breastfed infants. The amount of drug present in breast milk does not protect the infant from malaria.

Fertility

No specific studies with artesunate in humans have been conducted to evaluate effects on fertility. In a reproduction toxicity study in rats, testicular and epididymal lesions were seen, but there were no effects on fertility (see section 5.3). The relevance of this finding for humans is unknown.

4.7 Effects on ability to drive and use machines

There is no information on the effect of artesunate on the ability to drive or use machines. The patient's clinical status should be considered when assessing ability to drive or operate machinery.

4.8 Undesirable effects

The most important reported side effect of artesunate is a rare severe allergic reaction (estimated risk approximately 1 in 3000 patients), which has involved urticarial rash as well as other symptoms, including hypotension, pruritus, oedema, and/or dyspnoea.

More common minor side effects associated with IV administration have included dizziness, light-headedness, rash, and taste alteration (metallic/ bitter taste). Nausea, vomiting, anorexia and diarrhea have also been reported, however it is uncertain whether such events have been symptoms of severe malaria.

Adverse events considered at least possibly related to artesunate are listed below by body system, organ class and absolute frequency. Frequencies are defined as very common (≥ 1/10), common (1/100–1/10), uncommon (1/1000–1/100), rare (1/10 000–1/1000), and very rare (< 1/10 000).

Blood and lymphatic systems disorders

Uncommon: Neutropenia and anaemia (both occasionally severe), thrombocytopenia

Very rare: Pure red cell aplasia

Frequency unknown: Post-treatment haemolyticanaemia,*, mild and transient decrease in reticulocyte count

Nervous system disorders

Common: Dizziness, light-headedness, headache, insomnia, tinnitus (with or without decrease in auditory function)

Very rare: Peripheral neuropathy (or paraesthesia)

Respiratory disorders

Common: Cough, nasal symptoms

Gastrointestinal disorders

Common: Altered taste, nausea, vomiting, abdominal pain or cramps, diarrhoea

Rare: Raised serum amylase, pancreatitis

Hepatobiliary disorders

Uncommon: Transient rises in liver transaminases (AST, ALT)

Rare: Hepatitis

Skin and subcutaneous tissue disorders

Common: Rash, alopecia

Musculoskeletal and connective tissue disorders

Common: Arthralgia, muscle disorders

General disorders and administration site conditions

Common: Fatigue, malaise, fever, pain at injection site

Immune system disorders

Uncommon: hypersensitivity

**Post-treatment anaemia*

Cases of delayed haemolytic anaemia have been identified in non-immune travelers following treatment of severe malaria with injectable artesunate. Some were severe and required blood transfusions. In a study in African children aged 6 months to 10 years of age in malaria endemic areas, 5 out of 72 children (7%) experienced delayed haemolytic anaemia following treatment with injectable artesunate, and one child required transfusion. Risk was increased with hyperparasitaemia in all age groups and with younger age in children. Onset of haemolysis and anaemia was evident by 14-28 days after artesunate treatment. Vigilance for this adverse event is advised.

Paediatric population:

The safety profile of injectable artesunate is similar in children and adults.

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. Healthcare professionals are asked to report any suspected adverse reactions to the marketing authorisation holder, or, if available, via the national reporting system.

4.9 Overdose

Experience of acute overdose with artesunate is limited. A case of overdose has been documented in a 5 year-old child who was inadvertently administered rectal artesunate at a dose of 88 mg/kg/day over 4 days, representing a dose more than 7-fold higher than the highest recommended artesunate dose. The overdose was associated with pancytopenia, melena, seizures, multi-organ failure and death.

Treatment of overdose should consist of general supportive measures.

5.0 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: Antimalaria, ATC code: P01BE03

Mechanism of action

Artesunate is a hemisuccinate derivative of dihydroartemisinin, which is itself formed by the reduction of artemisinin. Artemisinin is a sesquiterpene lactone endoperoxide extracted from qinghao (sweet wormwood, *Artemisia annua L.*), a plant which has been used for centuries in traditional Chinese medicine.

The mechanism of action of the artemisinins likely involves cleavage of the internal endoperoxide bridge through reaction with haeme within the infected erythrocyte, thereby

generating free radicals which alkylate vital parasite proteins. However, artemisinins have also been reported to inhibit an essential parasite calcium adenosine triphosphatase.

The artemisinins are distinguished from other antimalarials by their ability to kill all erythrocytic stages of the malaria parasite, including the relatively inactive ring stage and late schizonts, as well as the gametocytes responsible for malaria transmission. Artesunate and the artemisinins are the most rapid acting of the antimalarials, and they have also been shown to enhance splenic clearance of infected erythrocytes by reducing cytoadherence.

In vitro, dihydroartemisinin (DHA), the active metabolite of artesunate, exhibits similar potency against chloroquine-resistant and chloroquine-sensitive clones of *P. falciparum.*

Artesunate and the other artemisinins are essentially inactive against extra-erythrocytic forms, sporozoites, liver schizontes or merozoites.

Clinical efficacy and safety

In the SEAQUAMAT (South East Asian Quinine Artesunate Malaria Trial), an international randomised, open-label, multicenter trial conducted in Bangladesh, India, Indonesia and Myanmar, 1461 patients with severe malaria (including 1259 adults) were treated intravenously with either artesunate or quinine. Artesunate was administered at 2.4 mg/kg IV at 0, 12 and 24 h and then every 24 h until the patient could tolerate oral medication. Quinine was given IV at 20 mg/kg over 4 hours, followed by 10 mg/kg over 2-8 hours, 3 times daily until oral therapy could be started. Mortality in the artesunate group was 15% versus 22% in the quinine group, for a reduction in risk of death of 34.7% (p=0.0002). Subgroup analysis suggested a greater benefit of artesunate versus quinine in patients with parasitaemia>10%. The reduction in mortality observed in the 202 paediatric patients (<15 years of age) appeared consistent with the overall results, however the number of children was too small to demonstrate statistical significance. Post-treatment hypoglycaemia was more common in the quinine-treated group.

Paediatrics

The AQUAMAT (African Quinine Artesunate Malaria Trial) was an international, randomized open-label multicenter trial which sought to extend the results of the SEAQUAMAT study by comparing parenteral artesunate versus IV quinine for severe malaria in 5425 African children (< 15 years) in 9 African countries (Mozambique, The Gambia, Ghana, Kenya, Tanzania, Nigeria, Uganda, Rwanda, and Democratic Republic of the Congo). Dosing was similar to SEAQUAMAT, except that both artesunate and

quinine could be administered either intravenously or intramuscularly, using the same doses for IM and IV administration for each drug. Roughly one third of patients received study drug by intramuscular injection. Mortality in the artesunate group was 8.5% compared to 10.9% in the quinine group, resulting in a relative risk reduction for death of 22.5% (p=0.0022); the risk reduction was similar for IV and IM administration. In addition, although the risk of neurological sequelae in survivors in both groups did not differ significantly by 28 days following treatment, in-hospital coma, convulsions, and deterioration of coma were all less frequent in the artesunate-treated patients. As in the SEAQUAMAT, post-treatment hypoglycaemia was more common in the quinine-treated group.

5.2 Pharmacokinetic properties

Pharmacokinetics of Artesunate

Absorption	
Oral bioavailability	Not applicable
Food effect	Not applicable
Distribution	
Volume of distribution (mean)	Artesunate:15 L/kg Dihydroartemisinin: 1.6-2.6 L/kg
Plasma proteinbinding*in vitro*	Artesunate: 75% Dihydroartemisinin:80-90% with decreased binding at higher concentrations
Tissue distribution	Dihydroartemisinin
	accumulates substantially in *P.falciparum*-infected erythrocytes
Metabolism	
Extensively hydrolysed by plasma esterases and perhaps also by CYP2A6.	
Active metabolite(s)	Dihydroartemisinin is further metabolised through glucuronidation
Elimination	
Elimination half life	Artesunate: 3–29 minutes Dihydroartemisinin: 40–95 minutes
Mean systemic clearance (Cl/F)	Artesunate: 20 L/kg/h Dihydroartemisinin: 1.4 – 2.7 L/kg/h

% of dose excreted in urine	NA*
% of dose excreted in faeces	NA*

*Information not available.

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. approximately 10 and 17 times the proposed maximal therapeutic dose in man, evidence of toxicity was observed in the haematopoietic organs, the immune system and response, the liver and kidneys.

Genotoxicity

Artesunate did not show any mutagenic or clastogenic potential in *in vitro* and *in vivo* tests (Ames, mouse micronucleus).

Carcinogenesis

No studies of the carcinogenic potential of artesunate have been conducted.

Reproductive toxicology studies

Oral artesunate caused dose-dependent fetal toxicity in rats, rabbits and monkeys, resulting in fetal resorption and abortion, as well as a low incidence of cardiac and skeletal defects. The no-observed-adverse-effect-level (NOAEL) was 12 mg/kg in pregnant monkeys (3 and 7 day exposures) and the no or low adverse effects level was 5-7 mg/kg in pregnant rats or rabbits (12 day exposures), both of which are above the therapeutic dose range (2.4-4.8 mg/kg) and expected duration of exposure for treatment of severe malaria in humans. In rats, the embryo-fetuses were most sensitive from gestational days 9-14; at other times embryotoxicity was significantly reduced. A study of artesunate administered to male rats daily for 6 weeks noted testicular and epididymal lesions, although these lesions did not affect fertility. The lesions were reversible after cessation of treatment.

Safety pharmacology studies

A slight sedative effect, decrease in body temperature, mild natriuretic effect and a decrease in creatinine clearance were observed with artesunate after single intravenous doses of 200 mg/kg (mice), 450 mg/kg (rats, rabbits and dogs) and following single oral

doses of 180 mg/kg in male rats. Beagle dogs administered IV artesunate at 10, 20 and 50 mg/kg for 14 days did not display significant clinical effects, including any signs of neurotoxicity, effects on body weight, ECG abnormalities (including QT interval changes), heart rate, blood pressure, or respiratory rate.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Artesunate for injection: No excipients

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months from the date of manufacturing

6.4 Special precautions for storage

Store in a cool, dry and dark place below 30^{o}C.

6.5 Nature and contents of container

A combipack containing dry powder for injection filled in 5 ml labeled glass vial with pack insert and 1 glass ampoule each of Sodium Bicarbonate 5% w/v (1 ml) and Sodium Chloride Injection 9% w/v (5 ml).

6.6 Special precautions for disposal

No special requirements.

7.0 APPLICANT/MANUFACTURER

IMPORTED AND MARKETED IN NIGERIA BY:

MANUFACTURED BY:

ANCALIMA LIFESCIENCES LTD.

50TH K.M. Stone National Highway 44

Murthal, Sonepat- 131039 (India)