1.3 Product Information

1.3.1 Summary of product characterization

1. Name of the Medicinal Product

(a) Product Name : Kafi Meter Injection (Artemether Injection)
(b) Strength : 80 mg
(c) Pharmaceutical Dosage Form : Injection

2. Quality and Quantitative Composition

(a) Qualitative Declaration, the active substance should be declared by its recommended INN. Accompanied by its salt or hydrate form if relevant.

Composition:

Each ml contains:
Artemether 80 mg

(b) Quantitative Declaration, the quantity of the active substance must be expressed per dosage unit

Sr. No.	Name of the Materials	Specification	Label Claim	Quantity (mg/mL)	Active/ Inactive
1	Artemether	I.H.	80 mg	80 mg	Active

3. Pharmaceutical Form Visual description of the appearance of the product (colour, markings, etc.) e.g.: Clear colourless oily solution filled in amber glass ampoule.

4. Clinical Particulars

4.1 Therapeutic Indications:

Kafi Meter Injection is indicated for the treatment of all kinds of malaria including the chloroquine-resistant subtertian malaria and the first line aid of critical malaria.

4.2 Posology and method of administration:

Kafi Meter injection when used as monotherapy, a minimum 6-day course is required to prevent recrudescence. If regimens of less than 6 days are employed, combination with oral Lumefantrine or Mefloquine or another effective blood schizonticide should be employed.

Kafi Meter Injection is for intramuscular use only. The daily dose can be given as a single injection.

Severe malaria and complicated malaria including cerebral malaria.

Adults:
One ampoule (80 mg) twice on the first day then followed by one ampoule (80 mg) daily for the subsequent 5 days.

Children:

1.6 mg/kg body weight twice on the first day then followed by 1.6 mg/kg body weight daily for the subsequent 5 days. In children the use of tuberculin syringe is advisable since the injection volume will be small.

3.2 mg/kg by the intramuscular route as a loading dose on the first day, followed by 1.6 mg/kg daily for a minimum of 3 days or until the patient can take oral therapy to complete a 7-day course. The daily dose can be given as a single injection. In children, the use of a tuberculin syringe is advisable since the injection volume will be small.

4.3 Contraindications:
Kafi Meter Injection is contraindicated in patients with hypersensitivity to artemether or other artemisinin compounds.

Kafi Meter Injection is not recommended in the first trimester of pregnancy because of limited data.

4.4 Special warning and precautions for use:
Warming and shaking the ampoule before use will redissolve any crystal that may have been formed during storage at low temperatures.

Care should be taken when using to treat the women being pregnant within three months or patients with vomiting severely.

For the first aid of severe malaria Artemether Injection is preferred.

4.5 Interaction with other medicinal products and other forms of interactions:
Since electrocardiographic QT prolongation has been reported in some patients treated with Artemether, it is recommended to avoid prescription of medications known to produce a prolongation of QT interval or patients receiving such medication: erythromycin, terfenadine, astemizole, probucol, class Ia antiarrhythmic agents (quinidine, procainamide, disopyramide), Class III anti-arrhythmic agents (amiodarone, bretylium), bepridil, sotalol, tricyclic antidepressants, some neuroleptics and phenothiazines are to be monitored closely.

4.6 Fertility, Pregnancy and lactation:
As per information available from World Health Organisation, little experience has been gained with the use of this drug in pregnancy but it should not be withheld if it is considered life-saving to the mother.

Artemisinin and its derivatives can be used for treatment of uncomplicated malaria during the second and third trimester of pregnancy in areas of multidrug resistance. Owing to lack of data, use in the first trimester of pregnancy is not recommended.

Artemisinin and its derivatives have not been measured in the milk of nursing mothers. It is very likely that these are present in milk and nursing mothers should not be given artemisinin if they are suffering from uncomplicated malaria either in multidrug resistant or drug sensitive situations. If the nursing mother is suffering from complicated and serious malaria induced by multidrug-resistant *P. falciparum* and artemisinin is indicated, breast feeding should be stopped.

4.7 Effects on ability to drive and use machine:
None Known

4.8 Undesirable effects

Artemether has been remarkably well-tolerated, and appears less toxic than quinine or chloroquine; adverse effects include bradycardia, electrocardiogram abnormalities, dizziness, injection site pain, skin reactions, and fever. Transient decreases in neutrophils and reticulocytes have been reported in some patients treated with artemether.

Drug induced fever has been observed with artemether. Mild reactions were seen in patients to whom artemether had been administered intramuscularly. These included nausea, hypotension, dizziness and tinnitus. These side effects were also reported: dark urine, sweating, somnolence, and jaundice. There were no deaths or any other side effects. No irreversible side effects were seen.

Slight rise of SGOT and SGPT may occur in individual cases. Neurological side effects have not yet been observed in clinical use but clinical trials suggest that coma may be prolonged in patients treated with artemether and there was an increased incidence of convulsions in one trial in cerebral malaria. Transient first degree heart block has been documented in three patients receiving artemether.

Neurotoxicity has been observed in animal studies but not in humans. Cardiotoxicity has been observed following administration of high doses of Artemether.

4.9 Overdose:

There is no experience with overdosage with artemether. There is no specific antidote known for the artemisinin derivatives.

However, experimental toxicological results obtained with large doses of artemisinin on the cardiovascular system and the CNS should be considered. Overdosage could bring on cardiac irregularities. An ECG should be taken before initiating treatment in cardiac patients. Irregularities in the pulse should be looked for and cardiac monitoring carried out if necessary. The animal results on the CNS suggest that overdose could result in changes in brain stem function. Clinicians treating cases of overdosage should look for changes in gait, loss of balance, or changes in ocular movements and reflexes.

5 Pharmacological Properties

5.1 Pharmacodynamic Properties:

Pharmacotherapeutic group: Artemisinin and derivatives, plain ATC code: P01BE02

The Artemether is a strong schizontocide and can bring about rapid control of symptoms by destroying plasmodium. It is equally effective against chloroquine resistant strains of subtertian malaria but ineffective in gametocytes. It is shown by animal experiments that this drug has low toxicity, however, it is fetal toxic which mainly causes fetus absorption. When the drug was administered I.M. to mice, rats or rabbits at a dose of 10.7mg / kg body wt., the rate of absorption was 30%, 90.7%, or 100% respectively.

5.2 Pharmacokinetic Properties:

Artemether is rapidly and completely absorbed from the site of I.M. injection, the maximum blood concentration of the drug is reached in 7 hours after I.M. injection of 10 mg/kg. The peak value is about 0.8mcg/ml with a half-life of about 13 hours. The drug is widely distributed in the body. Among them, the highest level is achieved in the liver and kidneys. The drug is mainly excreted in the faeces with a part in urine.

5.3 Preclinical Safety Data:

General toxicity

The main changes observed in repeat-dose toxicity studies were associated with the expected pharmacological action on erythrocytes, accompanied by responsive secondary haematopoiesis.

Neurotoxicity

Studies in dogs and rats have shown that intramuscular injections of artemether resulted in brain lesions mainly in brainstem nuclei. Changes observed mainly in brainstem nuclei included chromatolysis, eosinophilic cytoplasmic granulation, spheroids, apoptosis and dark neurons. Lesions were observed in rats dosed for at least 7 days and dogs for at least 8 days, but lesions were not observed after shorter intramuscular treatment courses or after oral dosing. The estimated artemether 24 h AUC after 7 days of dosing at the no observed effect level is approximately 7-fold greater or more than the estimated artemether 24 h AUC in adult humans. The hearing threshold was affected at 20 dB by oral artemether administration to dogs at a dose of about 29 times the highest artemether clinical dose (160 mg/day) based on body surface area comparisons. Most nervous system disorder adverse events in the studies of the 6-dose regimen were mild in intensity and resolved by the end of the study.

Reproductive toxicity studies

Embryotoxicity was observed in rat and rabbit reproductive toxicity studies conducted with artemether, a derivative of artemisinin. Artemisinins are known to be embryotoxic.

Artemether caused increases in post-implantation loss and teratogenicity (characterised as a low incidence of cardiovascular and skeletal malformations) in rats and rabbits. The embryotoxic artemether dose in the rat yields artemether and dihydroartemisinin exposures similar to those achieved in humans based on AUC.

Juvenile toxicity studies

A study investigated the neurotoxicity of oral artemether in juvenile rats. Mortality, clinical signs and reductions in body weight parameters occurred most notably in younger rats. Despite

the systemic toxicity noted, there were no effects of artemether on any of the functional tests performed and there was no evidence of a direct neurotoxic effect in juvenile rats.

Very young animals are more sensitive to the toxic effect of artemether than adult animals. There is no difference in sensitivity in slightly older animals compared to adult animals. Clinical studies have established the safety of artemether and lumefantrine administration in patients weighing 5 kg and above.

Cardiovascular Safety Pharmacology

In toxicity studies in dogs at doses >600 mg/kg/day, there was some evidence of prolongation of the QTc interval (safety margin of 1.3-fold to 2.2-fold for artemether using calculated free Cmax), at higher doses than intended for use in man.

In vitro hERG assays showed a safety margin of >100 for artemether and dihydroartemisinin. The hERG IC50 was 8.1 μM for lumefantrine and 5.5 μM for its desbutyl metabolite.
Based on the available non-clinical data, a potential for QTc prolongation in the human cannot be discounted.

6 Pharmaceutical Particulars

6.1 List of excipients:

Sr. No.	Name of the Materials	Specification
1	Butylated Hydroxyanisole	B.P.
2	Butylated Hydroxytoluene	B.P.
3	Propyl gallate	B.P.
4	Ethyl alcohol	B.P.
5	Benzyl Alcohol	B.P.
6	Ethyl Oleate	B.P.

6.2 Incompatibilities:
Not applicable.

6.3 Shelf life:
36 Months

6.4 Special precautions for storage: Store in cool, dark & dry place.
Store below 30°C. Protect from light and moisture.
Do not freeze. Keep out of the reach of children.

6.5 Nature and contents of container:
1.0 mL Amber glass ampoule. Such 6 ampoules in a plastic Tray packed in printed carton with pack Insert.

6.6 Special precaution for disposal
No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7.0 Applicant/Manufacturer

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