1.3 Product Information

1.3.1 Summary of product characterization

1. Name of the Medicinal Product

(a) Product Name	:	Fexona Artesunate Injection 60 mg (Artesunate Injection 60mg)
(b) Strength	:	60 mg
(c) Pharmaceutical Dosage Form	:	Dry Powder for 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 vial contains:
Artesunate 60 mg

Each ampoule of Solvent contains: Sodium Bicarbonate 50 mg/mL, 1 mL
Each ampoule of Diluent contains: Sodium Chloride 9 mg/mL, 5 mL

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

Sr. No.	Name of the Materials	Specification	Label Claim	Overages (%)	Quantity (mg/vial)	Active/ Inactive
1	Artesunate	In-House	60 mg	8.33 %	65.0 mg	Active

3. Pharmaceutical Form Visual description of the appearance of the product (colour, markings, etc.) e.g.:
Clear glass vial contains white crystalline powder for injection.

4. Clinical Particulars,

4.1 Therapeutic Indications:
Artesunate administered intravenously or intramuscularly, is indicated for the treatment of severe malaria caused by Plasmodium falciparum, in adults and children.

4.2 Posology and method of administration:
Adults and children: Artesunate 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. Artesunate 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, and when able to tolerate oral medication, the patient should be switched to a complete treatment course of an oral combination antimalarial regimen.

4.3 Contraindications:
Artesunate is contraindicated in patients with hypersensitivity to Artesunate or other artemisinins.

4.4 Special warning 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.

Switching to oral treatment regimen:
Acute treatment of severe falciparum malaria with Artesunate should always be followed by a complete treatment course of an appropriate oral combination antimalarial regimen

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. Relevant treatment guidelines should be consulted.

Post-treatment anaemia:
Despite transient decreases in reticulocyte counts, clinically significant anaemia associated with IV Artesunate has not been common in clinical trials. However, occasional cases of post treatment haemolytic anaemia severe enough to require transfusion have been reported. 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 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 interactions:
Artesunate is rapidly and extensively converted to dihydroartemisinin (DHA), the active metabolite, primarily by plasma and erythrocyte esterases. DHA elimination is also rapid (halflife approximately 45 min) 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, however no clinically significant interactions have been identified.

4.6 Pregnancy and lactation:
Pregnancy:
Severe malaria is especially hazardous during pregnancy, therefore full dose parenteral antimalarial treatment should be administered without delay. There has been limited clinical experience with the use of Artesunate in pregnancy.

Breastfeeding/lactation:
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.

4.7 Effects on ability to drive and use machine:
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, prutitus, 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 diarrhoea 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 anaemia (see below), 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:
In general, despite transient decreases in reticulocyte counts, clinically significant anaemia attributed to IV Artesunate has not been common in clinical trials in severe malaria. However, in a case-series of 25 patients in Europe who were treated with IV Artesunate for severe malaria acquired in an endemic area, 6 patients developed significant post-treatment haemolytic anaemia, presenting as late as 3 weeks after treatment, and 5 of them required transfusion. The aetiology of the haemolysis remains unknown.

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, multiorgan failure and death.

Treatment of overdose should consist of general supportive measures.

5. Pharmacological Properties

5.1 Pharmacodynamic Properties:
Pharmacotherapeutic group: Antimalarial, 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.

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

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 parisitemia >10%. The reduction in mortality observed in the 202 paediatric patients.

5.2 Pharmacokinetic Properties:
Intravenous
After intravenous injection Artesunate is very rapidly bio transformed to its active metabolite, dihydroartemisinin (DHA). Consequently, Artesunate half-life (t½) is estimated to be less than 5 minutes. Following a single IV dose of 2.4 mg/kg, maximum Artesunate plasma concentrations (Cmax) were estimated to be 77 μmol/L in a study in Gabonese

children with severe malaria, and 42 and 36 μmol/L in two studies in Vietnamese adults with uncomplicated malaria.

High concentrations of DHA are observed within 5 minutes of Artesunate IV administration. In the above studies (adult and paediatric), the ranges of values for the estimated time to maximum concentration (tmax) and t½ for DHA were 0.5-15 minutes and 21-64 minutes, respectively, while DHA Cmax values ranged from 5.3-10.6 μmol/L.

Distribution DHA has been shown to substantially accumulate in P. falciparum-infected erythrocytes. Plasma protein binding of dihydroartemisinin was determined to be 93% in patients and 88% in healthy volunteers.

Metabolism and elimination Artesunate is extensively and rapidly hydrolysed by plasma esterases, with possible minimal contribution by CYP2A6. The main metabolite, dihydroartemisinin, accounts for most of the in vivo antimalarial activity of oral artesunate, however, following IV administration. Artesunate may contribute more significantly. DHA is further metabolized in the liver via glucuronidation and is excreted in the urine; αdihydroartemisinin-β-glucuronide has been identified as the major urinary product in patients with falciparum malaria.

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.

6.0 Pharmaceutical Particulars

(a) List of excipients:

No excipients used.

(b) Incompatibilities:

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

(c) Shelf life: 36 Months

(d) Special precautions for storage:

Store below 30°C. Protect from light and moisture.

(e) Nature and contents of container:

7.5 mL Clear glass vial, 1 ml FFS ampoule of Sodium Bicarbonate Injection BP 5% w/v & 5 mL FFS ampoule of Sodium Chloride Injection BP 0.9% w/v are packed plastic tray then in printed carton along with package insert.

f) Instructions for use and handling
Not applicable.

7.0 Marketing Authorization Holder

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8.0 Marketing Authorization Numbers

9.0 Date of first authorization/renewal of the authorization

10.0 Date of revision of the text