Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT (FPP)

ARINATE® 240

Artesunate

1.1. **Strength** 240 mg

1.2. **Pharmaceutical form** Powder, solvent and diluent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 240 mg artesunate powder.

Each ampoule of solvent contains 4 ml of sodium bicarbonate injection 50 mg/ml.

Each ampoule of diluent contains 10 ml of sodium chloride injection 9 mg/ml.

Excipients with known effect

4 ml of solvent contains 55.24 mg (2.4 mmol) of sodium.

20 ml of diluent contains 70.84 mg (3.08 mmol) of sodium.

For the full list of excipients of solvent and of diluent, see section 6.1.

3. PHARMACEUTICAL FORM

Powder, solvent and diluent for solution for injection.

Artesunate powder: sterile, white powder.

Solvent: sterile clear colourless solution

Diluent: sterile clear colourless solution

Reconstituted solution for injection: clear solution free from visible particles.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Arinate (artesunate), administered intravenously or intramuscularly, is indicated in adults and in children for the treatment of severe malaria caused by *Plasmodium falciparum*.

4.2. Posology and mode of administration

4.2.1. Posology

Dose for adults and children weighing more that 20 kg

Arinate is administered at a dose of 2.4 mg of artesunate per kg body weight, by intravenous (IV) or intramuscular (IM) injection at 0,12 and 24 hours.
Thereafter once daily parenteral administration until oral treatment can be substituted.
Arinate should be administered for a minimum period of 24 hours (3 doses) regardless of the patient's ability to tolerate oral medication earlier.
After at least 24 hours administration of Arinate, and when able to tolerate oral administration, the patient should be switched to a complete treatment course of an oral combination antimalarial regimen.

4.2.2. Special populations

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

4.2.3. Paediatric population

Dose for children weighing more than 20 kg : *see section 4.2.1*

Dose for children weighing less than 20 kg

Arinate is administered at a dose of 3 mg of artesunate per kg body weight, by intravenous (IV) or intramuscular (IM) injection at 0,12 and 24 hours.
Thereafter once daily parenteral administration until oral treatment can be substituted.

4.2.4. Method of administration

Preparation /Calculation

Because of the instability of artesunate in aqueous solution the reconstituted solution must be used within one hour of tis preparation. Therefore the required dose of artesunate should be calculate:

- For adults and children weighing more than 20 kg:
  Dose in mg = Patient's weight x 2.4
- For children weighing less than 20 kg
  Dose in mg = patient's weight x 3

The number of vials of artesunate required for the dose should be determined prior to reconstituting the artesunate powder (see SmPC Arinate dosage strengths 60 mg and 120 mg).
Use of the 240 mg vial is especially suited for adult patients.

Patient's weight	< 25 kg	26-50 kg	51-75 kg	> 75 kg
Number of vials of Arinate 240 mg	1	1	1	1

Reconstitution of the artesunate solution for injection

Using a syringe , withdraw 4 ml of the supplied solvent (sodium bicarbonate injection) from the ampoule and inject into the vial containing the artesunate powder.
Shake the vial for several minutes to mix well until the powder is completely dissolved and the solution is clear. If the solution appears cloudy or a precipitate is present, it should be discarded.
The reconstituted solution should always be used immediately and it should be discarded if not used within one hour.

Dilution of the reconstituted artesunate solution

Following reconstitution, the solution must be diluted according to the method of injection, as described below.

Dilution for intravenous (IV) injection

Using a syringe, add 20 ml of the diluent , sodium chloride 0.9% injection, to the vial containing the reconstituted artesunate solution. This will yield 24 ml of a solution containing **artesunate 10mg/ml**. Shake to mix well ensuring that the resulting solution remains clear. If the solution appears cloudy or a precipitate is present , it should be discarded.

The volume (ml) required for injection will be equal to desired dose (mg) divided by 10.

kg	<6	6-7	8-10	11-13	14-16	17-25	26-29	30-33	34-37	38-41	42-45	46-50
ml	1	2	3	4	5	6	7	8	9	10	11	12
kg	51-54	55-58	59-62	63-66	67-70	71-75	76-79	80-83	84-87	88-91	92-95	96-100
ml	13	14	15	16	17	18	19	20	21	22	23	24

Withdraw the required volume of artesunate solution from the vial with a syringe and then inject slowly intravenously , over 1 to 2 minutes or 3 to 4 minutes for larger volume.

Arinate should NOT be administered as an intravenous drip.

Dilution for intramuscular (IM) injection

Using a syringe, add 8 ml of the diluent , sodium chloride 0.9% injection, to the vial containing the reconstituted artesunate solution. This will yield 12 ml of a solution containing **artesunate 20mg/ml.** Shake to mix well ensuring that the resulting solution remains clear. If the solution appears cloudy or a precipitate is present , it should be discarded.

The volume (ml) required for injection will be equal to desired dose (mg) divided by 20.

kg	<8	08-13	14-25	26-33	34-41	42-50	51-58	59-66	67-75	76-83	84-81	92-100
ml	1	2	3	4	5	6	7	8	9	10	11	12

Withdraw the required volume of artesunate solution from the vial with a syringe and then inject slowly intramuscularly; the anterior thigh is usually the preferred site for injection. If the total volume of solution to be injected is large, it may be preferable to divide the volume and inject it at several sites e.g. both thighs.

4.3. Contraindications

Hypersensitivity to the artesunate or to other artemisinin derivates.

4.4. Special warning and precautions for use

4.4.1. General information

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 IV of IM should always be followed by a complete treatment course of an appropriate oral combination antimalarial regimen(see section 4.2)

Resistance to antimalarials

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

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 travellers presenting with sever falciparum malaria. The risk was most pronounce in patient with hyper parasitaemia and in younger children. Some case have been severe and require blood

transfusion. Vigilance for delayed onset anaemia is therefore advised, particularly in hyperparasitemic patients and younger children, and prolonged follow-up until day 28 should be implemented.

Hepatic/renal impairment

Data regarding artesunate pharmacokinetics in patients with hepatic and/or renal impairment are limited.

Based on date from studies in patients with sever malaria, as well as the known metabolism of artesunate , dosage adjustment is not considered necessary in patients with hepatic or renal impairment.

Excipients - sodium

The prepared solution for injection contains sodium (see section 2). It is important to consider the contribution of the amount of sodium from all the medicines that the patient is taking.

4.4.2. Paediatric population

In clinical trails, the efficacy and safety of intravenous and intramuscular artesunate have been similar in adults and in paediatric patients.

4.5. Interactions 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 (half-life approximately 45 minutes) and the potential drug-drug interactions appear 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 DHA was observes when artesunate is given with ritonavir.

4.6. Fertility, pregnancy and lactation

4.6.1. 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 these findings for humans is unknown.

4.6.2. Pregnancy

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

In animal studies, artesunate has been associated with foetal 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 derivates in the second and their trimester , do not indicate adverse effects of artesunate on pregnancy or on the health of the foetus/new-born child.

4.6.3. Lactation

Limited information indicates that dihydroartemisinin (DHA) , the active metabolite of artesunate , is present a low levels in breast mil0 The drug levels are not expected to cause any adverse effect in breastfed infants. The amount of drug present in breast milk doesn't protect the infant from malaria.

4.7. Effects on the ability to drive and use machines

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

4.8. Undesirable effects

Summary of the safety profile

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

More common minor side effects associated with intravenous administration have included dizziness, light-headiness, 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.

Tabulated summary of adverse reaction

Adverse evens considered at least possibly related to artesunate are listed by body system organ class and absolute frequency.

Very common (≥1/10) – Common (1/100-1/10)- Uncommon(1/1 000-1/100),

Rare (1/10 000-1/1 000) – Very rare (≤ 1/10 000) - Frequency not known (cannot be estimated from the available data)

Body system organ class	**Adverse effect**	**Frequency**
Blood and lymphatic system disorders	Neutropenia and anaemia (both occasionally severe), thrombocytopenia	Uncommon
	Pure red cell aplasia	Very rare
	Post-Artesunate Delayed Haemolysis (PADH)* mild and transient decrease in reticulocyte count	Not known
Nervous system disorders	Dizziness, light-headiness, headache, insomnia, tinnitus (with or without decrease I auditory function)	Common
	Peripheral neuropathy	Very rare
Respiratory disorders	Cough, nasal symptoms	Common
Gastro-intestinal disorder	Altered taste, nausea, vomiting, abdominal pain or cramps, diarrhoea	Common
	Raised serum amylase, pancreatitis	Rare
Hepatobiliary disorders	Transient rises in liver transaminases (AST, ALT)	Uncommon
	Hepatitis	Rare
Skin and subcutaneous tissue disorders	Rash, alopecia	Common
Musculoskeletal and connective tissue disorders	Arthralgia, muscle disorders	Common
General disorders and administration site conditions	Fatigue, malaise, fever, pain at injection site	Common
Immune system disorders	Hypersensitivity	Uncommon

Description of selected adverse reaction

*Post-Artesunate Delayed Haemolysis (PADH) -see section 4.4 –

Cases of delayed haemolytic anaemia have been identified in non-immune travellers 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 72 children (7%) experienced delayed haemolytic anaemia following

treatment with injectable artesunate and one child required transfusion. Onset of haemolysis and anaemia was evident by 14-28 days after artesunate treatment. Vigilance for this adverse events is required.

Adverse reaction in paediatric population
The safety profile of injectable artesunate is similar in children and adults.

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.
In case of accidental overdosage, symptomatic treatment in a Specialized Centre is required.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group and ATC code**:** Antimalarial ATC code P01BE03

Mechanism of action
Artesunate is a hemi succinate derivative of dihydroartemisinin (DHA), 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 cyto-adherence.
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.

5.2. Pharmacokinetic properties

Intravenous
After intravenous injection artesunate is very rapidly biotransformed to its active metabolite, dihydroartemisinin (DHA). Consequently, artesunate half-life (t1/2) 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 administrations. In the above studies (adult and paediatric), the range of values for the estimated time to maximum concentration (Tmax) and t1/2 for DHA were 05-15 minutes and 21-64 minutes, respectively, while DHA Cmax values ranged from 5.3-1.6 µmol/L.

Intramuscular
Artesunate is rapidly absorbed following intramuscular injection, and peak plasma levels are generally achieved within 30 minutes of administration. Thus, after IM injection of 2.4 mg/kg of artesunate, absorption was rapid in Gabonese children and Vietnamese adults, with Tmax values of 8 minutes and 12 minutes, respectively. The corresponding artesunate $t^{1}/^{2}$ values were estimated to be 48 minutes in children and 41 minutes in adults, and Cmax values were 1.7 and 2.3 µmol/L, for children and adults, respectively.
After IM injection artesunate Cmax values were therefore lower by roughly 45-fold in children and 20-fold in adults when compared to IV injection. However, rates of artesunate elimination in children and adults were 32-fold and 13-fold slower, respectively, following IM injection, compared to IV administration.

Distribution

DHA has been shown to substantially accumulate in P. falciparum-infected erythrocytes. Plasma protein binding of dihydroartemisinin (DHA) 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, account 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; α-dihydroartemisinin-β-glucuronide has been identified as the major urinary product in patients with falciparum malaria.

Special populations

No pharmacokinetic data are available for patients with impaired renal or hepatic function.

However, based on the known mechanisms of metabolism and elimination of artesunate, combined with clinical data from patients with severe malaria and accompanying renal and/or hepatic compromise of various degrees, no dose modifications are considered necessary in renal or hepatic impairment.

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 hematopoietic 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 foetal toxicity in rats, rabbits and monkeys, resulting in foetal 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-foetuses were most sensitive from gestational days 9-14; at other times embryotoxicity was significantly reduced.

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, 50, 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

Solvent : sodium bicarbonate - edetate disodium -water for injections

Diluent: sodium chloride -water for injections

6.2. Incompatibilities

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

6.3. Shelf life

24 months

6.4. Special precautions for storage

Store below 30°C, in a dry place.

Store in the original package to protect from light or moisture.

For single use.

The reconstituted solution should be kept below 30° and should be used within one hour of its preparation.

6.5. Nature and contents of container

Artesunate 240 mg powder for injection is filled in a clear glass vial of 30 ml (USP Type III glass). The vial is closed with a grey rubber closure and sealed with an aluminium flip-off seal with green coloured disc.

Solvent (sodium bicarbonate injection 5% w/v) ; colourless ampoule of Type I glass with black snap-off ring filled with 4 ml solution.

Diluent (sodium chloride 0.9% w/v): colourless ampoules of Type I glass with blue snap-off ring each filled with 10 ml solution.

Box containing one vial of powder (A), one ampoule of solvent (B) and two ampoules of diluent (C) placed in a plastic tray along with a patient leaflet.

6.6. Special precautions for disposal and other handlings

For preparation an handling of injectable solution: see section 4.2.4.

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

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE ADDRESS

7.1. Marketing Authorisation Holder

Dafra Pharma GmbH, Mühlenberg 7, 4052 Basel, Switzerland.

7.2. Manufacturer

Systacare Remedies
Village Bal Kalan Crossing, Majitha Road, Amritsar, India

8. MARKETING AUHORISATION NUMBER

See list of MAs per country

9. DATE OF FIRST REGISTRATION

See list of MAs per country

10. PRODUCT SUPPLY CATEGORY

Prescription Only Medicine (POM)

11. DATE OF REVISION OF TEXT

08/2022