Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT (FPP)

Artesiane®
Artemether

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

- Artesiane 20: each ampoule (1 ml) contains 20 mg artemether
- Artesiane 40: each ampoule (1 ml) contains 40 mg artemether
- Artesiane 80: each ampoule (1 ml) contains 80 mg artemether
- Artesiane 100: each ampoule (1 ml) contains 100 mg artemether
- Artesiane 300: each ampoule (3 ml) contains 300 mg artemether

3. PHARMACEUTICAL FORM

Solution for injection
Sterile, clear, colourless to slightly yellow oily solution

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Artesiane is indicated for the treatment of malaria in children and in adults caused by all species of Plasmodium, including severe malaria caused by multiple drug resistant strains of Plasmodium falciparum.

Artesiane 20 and Artesiane 40 are indicated for use in children. Artesiane 80 is indicated for use in children and adults.
Artesiane 100 and Artesiane 300 are indicated for use in adults.

4.2. Posology and mode of administration

4.2.1. Posology

The dosage depends on the severity of the case and the clinical state of the patient.

Loading dose for children and adults:
3.2 mg/kg body weight administered as a single intramuscular injection on the first day.

Maintenance dose for children and adults:
1.6 mg/kg/day administered as intramuscular injection once a day during the following four days.
Maintenance treatment can also be continued by oral artemisinin-based combination therapy (ACT), if the patient's condition does not require injections.

Period of use
A full course therapy of five days is essential in order to avoid recrudescence. In case of severe malaria it may be necessary to increase the loading dose and to prolong treatment for seven days if parasitaemia is not cleared during the first few days.

4.2.2. Special populations

see posology 4.2.1.
Patients with acute renal failure might reach higher maximal concentrations ; in these patients the elimination half-life of artemether could be longer.

4.2.3. Paediatric population

As indicated under 4.2.1 Posology.
Rectal administration of artemether (Artesiane suppogel) for children and babies can be considered when vomiting is a prominent symptom of malaria, or when levels of consciousness are diminishing, or in comatose states.

4.2.4. Method of administration

Artesiane solution is given by intramuscular injection in the gluteal muscle or the quadriceps.

Combining other substances in the same syringe should be not be done.
Aseptic conditions must be respected when injecting the solution.

4.3. Contraindications

Artesiane is contra-indicated in
-patients with known hypersensitivity to the active substance artemether, to any other artemisinin derivative or to the excipient listed in section 6.1

4.4. Special warning and precautions for use

4.4.1. General information

Resistance of Plasmodium to artemether has not been observed. Resistance is unlikely to occur in view of the specific mechanism of action of artemether which is very cytotoxic for the Plasmodia (opening of a peroxide bridge). An apparent resistance is sometimes seen but it is mainly due to multiple broods of Plasmodia developing at different times in the same patient.
In controlled studies, recrudescence does not exceed 3%. In case of recrudescence (real or apparent) a complete new treatment of 5 days is recommended.

Caution is advised in treating patients with signs of meningitis as a marked increase in the concentration of artemether in the cerebrospinal fluid of patients with meningitis has been observed.

4.4.2. Pediatric population

Rectal administration of artemether (Artesiane suppogel) for children and babies can be considered when vomiting is a prominent symptom of malaria, or when levels of consciousness are diminishing, or in comatose states.

4.5. Interactions with other medicinal products and other forms of interactions

4.5.1. General information

- In studies performed with Artesiane,, no specific drug interactions were observed.
- Artemether potentialises the antimalarial activity of other antimalarials.
- Artemether is metabolised predominantly by the cytochrome enzyme CYP3A4, but does not inhibit this enzyme at therapeutic concentrations.
- Combined use with inhibitors and/or inducers of CYP3A4 will not have an effect on the antimalarial activity but could alter the ratio of artemether to dihydroartemisinin.

4.5.2. Additional information on special populations

No additional information

4.6. Fertility, pregnancy and lactation

4.6.1. Fertility

There is no information of the effects of artemether on human fertility.

2. Pregnancy

The use of artemether should be avoided during pregnancy, particularly during the first trimester.

Given the high risk of malaria during pregnancy, for mother and foetus, the responsible physician should consider artemether's use essential, particularly in cases of cerebral malaria. Rapid clearance of parasites is essential in severe malaria and the artemisinin derivatives (artemether) achieve this by being the fastest acting schizontocides. In cerebral as well as in complicated malaria, general supportive therapy is required.

3. Lactation

Data on excretion in breastmilk are not available.

7. Effects on the ability to drive and use machines

An influence on the ability to drive or to use machines has not been reported following administration of artemether.

8. Undesirable effects

Intramuscular artemether is generally well-tolerated and, at the recommended dose, adverse events are usually not reported.

Laboratory abnormalities such as increase in transaminases and decrease in reticulocyte count are rare and transient and usually without clinical manifestations.

A decrease in sinus frequency without changes in the electrocardiogram has also been reported.

At high doses, transient abdominal pain, tinnitus and diarrhoea have been described.

9. Overdose

The administration of several times the therapeutic dose was not reported to cause serious adverse events.
A specific antidote is not known.

In case of accidental and severe overdose, symptomatic treatment in a specialised centre is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Antimalarials, Artemisinin and derivatives, plain.
ATC code: P01BE02.
Artemether is a artemisinin derivative.

Artemether has broad stage specificity against blood-stage parasites, from the ring stages through early schizonts. It also reduces gametocyte carriage, limiting malaria transmission from the treated infection.

Artemether is rapidly metabolised into an active metabolite dihydroartemisinin (DHA). The antimalarial activity of artemether and DHA has been attributed to

endoperoxide moiety. The presence of the endoperoxide bridge (generating singlet oxygen and free radicals) appears to be essential for the antimalarial activity.

The site of antiparasitic action of artemether and its metabolite DHA is the food vacuole of the malarial parasite, where they are thought to interfere with the conversion of haem, a toxic intermediate produced during haemoglobin breakdown, to the nontoxic haemozoin, malaria pigment.

5.2. Pharmacokinetic properties

Intramuscular artemether is fairly rapid absorbed, reaching therapeutic levels within the first hour and C_{max} within 4–9 hours.

In patients with severe malaria, artemether seems to be absorbed more slowly and more erratically.

The intramuscular injection of artemether will give a therapeutic plasma level for at least 24 hours, because it is rather slowly released from the muscle deport.

The distribution of radioactive marked artemether was found to be equal between cells and plasma.

The degree of binding to plasma proteins varied markedly according to the studied species, and it is about 50% or more in man.

Artemether is metabolised in the liver, primarily by CYP3A4, to the demethylated derivative dihydroartemisinin (DHA). Dihydroartemisinin is further converted to inactive metabolites.

The elimination is rapid with a $T_{1/2}$ of 1–3 hours. Dihydroartemisinin, itself a potent antimalarial, has a $T_{1/2}$ of about 1 – 3 hours.

5.3. Preclinical safety data

Reproductive toxicity studies
Embryotoxicity was observed in rat and rabbit reproductive toxicity studies conducted with artemether. Artemisinins are known to be embryotoxic

Neurotoxicity

Unlike parenteral artemether showing neurotoxicity in experimental animals, these findings have not been seen in clinical, neurophysiological and pathological studies in humans.

Cardiovascular Safety Pharmacology

Based on the available non-clinical data, a potential for QTc prolongation in the human cannot be excluded.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Medium Chain Triglycerides (MCT) *also described as Fractionated coconut oil*

6.2. Incompatibilities

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

6.3. Shelf life

- Artesiane 20: 36 months.
- Artesiane 40: 36 months.
- Artesiane 80: 48 months
- Artesiane 100: 36 months
- Artesiane 300: 36 months

6.4. Special precautions for storage

Store below 30°C , in the original package to protect from light.

6.5. Nature and contents of container

- Artesiane 20: Type I glass ampoule with 1 ml sterile, colourless to slightly yellow solution containing 20 mg Artemether .
  Boxes with with 10 ampoules.

- Artesiane 40: Type I glass ampoule with 1 ml sterile, colourless to slightly yellow solution containing 40 mg Artemether .
  Box with 10 ampoules.
- Artesiane 80: Type I glass ampoule with 1 ml sterile, colourless to slightly yellow solution containing 80 mg Artemether .
  Box with 5 ampoules.
- Artesiane 100: Type I glass ampoule with 1 ml sterile, colourless to slightly yellow solution containing 100 mg Artemether .
  Box with 10 ampoules.
- Artesiane 300: Type I glass ampoule with 3 ml sterile, colourless to slightly yellow solution containing 300 mg Artemether .
  Box-ready to use kit with 1 ampoule, 1 syringe with needle and 1 pre-injection cleansing swab.

6.6. Special precautions for disposal and other handlings

Aseptic conditions must be respected when injecting the solution.

Any unused product or waste material should be disposed of in accordance with the regulations in force.

7. MARKETING AUTHORISATION HOLDER AND MANUFACURING SITE ADDRESS

7.1. Marketing Authorisation Holder

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

7.2. Manufacturer

Anfarm Hellas S.A., 61st km. Nat. Rd., Athens, Lamia, Schimatari Viotias, 32009, Greece.

8. MARKETING AUHORISATION NUMBER

TAN 22 HM 0261

9. DATE OF FIRST REGISTRATION

19th July, 2022

10. DATE OF REVISION OF TEXT