Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT (FPP)

Artesiane® Suppogel

Artemether

1.1. Strength

40 mg

1.2. Pharmaceutical form

Rectal capsule[1]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1. Qualitative declaration

Artemether

Excipients with known effect : Refined soy-bean oil

2.2. Quantitative declaration

Each rectal capsule contains 40 mg artemether.

3. PHARMACEUTICAL FORM

Rectal capsule

Transparent oblong, soft capsule with a light yellow oily content.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Treatment of malaria caused by all forms of Plasmodium, including the most resistant strains. Artesiane Suppogel is specifically indicated in the treatment of severe malaria and in pre-transfer treatment. In the treatment of simple forms of malaria Artesiane Suppogel can be used in case applying an oral form is difficult or impossible.

Treatment of acute malaria attacks due to Plasmodium falciparum. Rectal capsules /suppogels are intended for emergency treatment, at a time when the administration of other forms is difficult or impossible. This medication is

[1] Rectal capsule is the pharmacopoeial name for this dosage form. Suppogel is a more common name applied for the patients.

available to mothers to treat their adolescents in the absence of medical help. This presentation applies in particular to rural areas of developing countries. In case of P. vivax infection, resurgence is frequently shown, repeat treatment by combination therapy is recommended.

According to the recommendations, a monotherapy treatment with Artesiane Suppogel should be followed by a complete cure with an effective oral CTA.

Artesiane Suppogel is specifically indicated in the pre-transfer treatment of severe malaria. In the case of a suspected severe malaria, and when the time between the transfer of the patient to the care unit and the start of treatment is more than 6 hours, pre-transfer treatment is recommended. If a transfer is impossible the treatment should take its course until the patient is able to take oral treatment and complete a cure with an effective CTA.

4.2. Posology and mode of administration

4.2.1. Posology

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

Usual dose: Dose of 4 mg/kg bodyweight on the first day
Dose of 2mg/kg bodyweight from day 2 off.

4.2.2. Special populations

Rectal capsules (suppogels) are generally administered to children and adolescent and to elderly having difficulties of swallowing oral forms, or having gastro-intestinal problems , as well as in severe cases such as neuromalaria, with decreased consciousness or in the event of a coma. When the patient regains consciousness or, in the absence of gastrointestinal problems, treatment will be followed by oral treatment with an effective CTA.

4.2.3. Pediatric population

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

Usual dose: Dose of 4 mg/kg bodyweight on the first day
Dose of 2mg/kg bodyweight from day 2 off.

A full treatment course runs over five days .

4.2.4. Method of administration

Rectal administration. The capsule is inserted in the anus and pushed into the rectum. In case needed, the patient is kept lying down avoiding that the capsule is pushed out.

4.3. Contraindications

- Patients with known hypersensitivity to the active substance artemether
- Patients with known hypersensitivity to peanut or soya or to any other ingredient of the capsule shell , described 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 Plasmodium. (opening of a peroxide bridge).An apparent resistance is sometimes seen but this is mainly due to multiple broods of Plasmodium developing at different times in the same patient. In controlled studies , recrudescent does not exceed 3%. In case of recrudescence (real or apparent) a complete new treatment of 5 days is required.

4.4.2. Pediatric population

Administration of artemether via the rectal route to infants and children is foreseen when vomiting is a present as an eminent symptom of the disease.

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

4.5.1. General information

- No specific drug interaction were observed during clinical studies with Artesiane® (artemether).
- Artemether potentiates the antimalarial effect of other antimalarials having a different mode of action.
- Artemether is metabolised primarily by the cytochrome enzyme CYP3A4, but does not inhibit this enzyme at therapeutic concentrations.
- The combined use with CYP3A4 inhibitors and/or inductors will not affect antimalarial activity, but may moderate the relationship between artemether and dihydroartemisin.

4.5.2. Additional information on special populations

See 4.5.1

4.5.3. Pediatric population

See 4.5.1

4.6. Pregnancy, lactation and fertility

4.6.1. Pregnancy

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

Given the high risk of malaria during pregnancy, for mother and the fetus, the responsible physician should consider use of artemether 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 schizonticides. In cerebral as well as in complicated malaria, general supportive therapy is required.

4.6.2. Lactation

Data on excretion in breast milk are not available.

4.6.3. Fertility

No data are available on the effects of artemether on human fertility.

4.7. Effects on the ability to drive and use machines

No effects on the ability to drive and use machines have been reported following administration of artemether.

4.8. Undesirable effects

Artemether administered via the rectal route is generally well-tolerated.
In rare case , an local rectal irritation is observed.

Undesirable effects taking into account all available pharmaceutical forms of artemether

Biological changes, such as an increase in transaminases and a decrease in the number of reticulocytes, are rare and transient and are not accompanied by clinical manifestation.

A decrease in sinus heart rate, without any change in the electrocardiogram, was reported.

At high doses, transient abdominal pain, tinnitus and diarrhea have been reported.

4.9. Overdose

No serious side effects were reported during repeated administration of the therapeutic dose.
No specific antidote is known.
In the case of accidental and severe overdose, symptomatic treatment in a specialised center 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.

The clinical and parasitological findings of rectal artemether and intravenous quinine, in a study with 103 children with malaria, show similarity in efficacy.

5.2. Pharmacokinetic properties

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

The rectal administration pathway provides a bioavailability similar to intramuscular injection, but there is great variability in absorption after both pathways. Although interindividual variability in bioavailability is reported, rectal administration has shown it to generate an acceptable efficacy.

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

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

Content of the capsule

Refined soy-bean oil

Shell of the capsule

Glycerol

Gelatine

Purified water

6.2. Incompatibilities

Not applicable

6.3. Shelf life

3 years

6.4. Special precautions for storage

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

6.5. Nature and contents of container

Blister of PVC/PE/PVDC – Aluminum with 6 units.

Box with 6 rectal capsules.

6.6. Special precautions for disposal and other handlings

No special requirements for disposal.

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

Manufacturer of the rectal capsules (bulk)

A.R.C.O-Chemie GmbH, Wetterstrasse 33-37, 58313 Herdecke, Germany

Packager

Tjoapack Netherlands B.V, Nieuwe Donk 9, Etten->Leur, 4879 AC- The Netherlands

8. MARKETING AUHORISATION NUMBER

See list of MAs per country

9. DATE OF FIRST REGISTRATION

See list of MAs per country

10. DATE OF REVISION OF TEXT

02/2020