SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Co-Arinate® Junior

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet Co-Arinate® Junior contains 100 mg artesunate, 250 mg sulfamethoxypyrazine and 12,5 mg pyrimethamine.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Box containing 1 blister of 3 tablets.

Other pharmaceutical form: Co-Arinate® Adult: each tablet contains 200 mg artesunate, 500 mg sulfamethoxypyrazine and 25 mg pyrimethamine.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Co-Arinate® is used as curative treatment for all forms of malaria, including severe malaria caused by multi drug-resistant strains of Plasmodium falciparum. In case of P. vivax addition of primaquine may be required. Co-Arinate® has been especially designed to treat malaria in children, adolescents and adults.

4.2 Posology and method of administration:

The dose for this treatment is based on body weight at 4 mg / kg of artesunate combined with sulfamethoxypyrazine and pyrimethamine.

Three consecutive intakes of this dose must be given during 48 hours:

- A first tablet is taken upon confirmation of malaria diagnosis (at Time 0)
- A second tablet is taken 24 hours later
- The final tablet is taken after a further 24 hours have passed; therefore there is an interval of 24 hours between doses which must be adhered to.

Dosage scheme for the 48 hour treatment:

Presentation	Weight (kg) Age (in years)	Number of tablets			Total course
		0 h	24 h	48 h	
Co-Arinate® Junior	≥ 10 – < 18 kg (1 - 5 years)	1/2	1/2	1/2	1,5 tablets
	≥ 18 – < 36 kg (6 – 13 years)	1	1	1	3 tablets

The tablets should be taken with fluid such as drinking water. In order to facilitate administration they may be crushed if necessary.

Note: A full course of therapy is essential to avoid recrudescence.
In case of vomiting within 30 minutes after intake of the tablet, the full dose should be re-administered. Vomiting within 1 hour after intake requires re-administering half the dose.

Additional information: A further course of Co-Arinate® may be necessary if the malaria infection returns (relapse) or if you are re-infected with Plasmodium parasites after having been cured**.**

4.3 Contraindications

Co-Arinate® is contra-indicated in individuals hypersensitive to artesunate, sulfamethoxypyrazine, pyrimethamine or any of the other ingredients of this medication.
The use of this medicine is contra-indicated in case of severe hepatic or renal insufficiency and in case of severe blood dyscrasias or documented megaloblastic anaemia due to folate deficiency.

4.4 Special warnings and precautions for use

In case other medicines are taken or other medical problems are present, mention it to the doctor. It is essential for patients to complete the full treatment to avoid recrudescence. In case of complicated malaria, general medical supportive care should be provided to patients.

4.5 Interactions with other medicinal products

Artesunate:
No clinically significant adverse drug interactions with artesunate have been reported to date. The activity of other anti-malarials may be potentiated by artesunate.

Sulfamethoxypyrazine and pyrimethamine:
Antifolic acid drugs such as other sulfonamides or trimethoprim-sulfamethoxazole combinations should not be used while the patient is receiving sulfamethoxypyrazine in combination with pyrimethamine (Co-Arinate®) for antimalarial treatment.

4.6 Pregnancy and lactation

Pregnancy:
Use of the product is not recommended during the first trimester (organogenesis period) unless, in the doctor's opinion, the benefits outweigh the risks, as is often encountered with complicated and cerebral malaria. No cases of human embryotoxicity or teratogenicity have been reported.

Breastfeeding:
Women should not breast feed their infants during Co-Arinate® therapy.
Sulfamethoxypyrazine and Pyrimethamine are both excreted into maternal milk.
Artesunate does not appear in the breast milk of lactating mothers, and its metabolite Dihydroartemisinin is present in insignificant amounts.

4.7 Effects on ability to drive and to use machines

No reactions are noted to date.

4.8 Undesirable effects

The disease is characterized by unpleasant symptoms and these should not be confused with side effects of the drug.

Undesirable effects from artesunate are generally rare at the therapeutic dose. In very rare cases, slight changes in haematologic values have been seen, including a reduction in the number of reticulocytes as well as a slight increase in transaminases. These signs however, do not generally give rise to any noticeable clinical manifestations.
In rare cases, a slight, but transient reduction in sinus heart rate has been observed, and the QTc interval is not affected.
Abdominal cramps and mild diarrhoea have been reported at elevated doses, these symptoms are transient.

Side effects with sulfamethoxypyrazine are extremely rare and the syndrome of Stevens-Johnson or the syndrome of Lyell have never been described. In theory, the syndrome of Stevens-Johnson or the syndrome of Lyell may occur although this has not been reported to date.
Crystalluria due to the use of sulfamethoxypyrazine does not occur because of the excellent solubility of the related compound and its acetylated metabolite.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

4.9 Overdose

The recommended dose should not be exceeded. In case of accidental over-dosage, symptomatic treatment in a specialized centre is required.

5. PHARMACOLOGIC PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutical class: Antimalarial drug.

Artesunate is a very active derivative of the artemisinins, a new class of antimalarial drugs derived from Artemisinin. The latter compound is extracted from the plant Artemisia annua and artesunate is prepared semi-synthetically.

Sulfamethoxypyrazine is a long-acting sulphonamide that acts as a folic acid biosynthesis inhibitor.

Pyrimethamine is also a folic acid biosynthesis antagonist (reductase inhibitor).

Co-Arinate® is an artemisinin based combination therapy (ACT) which contains three medicaments active against malaria parasites. In this combination the drug artesunate kills the parasites very fast and potentiates the effects of the other two drugs sulfamethoxypyrazine and pyrimethamine which have a long elimination half-life. This combination therapy permits a shorter duration of treatment, thereby improving compliance.
The theoretical risk for drug resistance is significantly reduced by using combination therapy.

5.2. Pharmacokinetic properties

Artesunate administered in caplets give rise to therapeutic levels in a short time and the peak levels are reached after 4 to 9 hours.
Artesunate is rapidly converted to its main metabolite dihydroartemisinin. Further processes of oxidation and consequent conjugation occur. The elimination of the

compound from the body is somewhat slower and follows first order kinetics. Since the drug is only given for a short period of time, accumulation in the body is unlikely. Further degradation of dihydroartemisinin takes place and the metabolites formed are eliminated by the kidneys and excreted in the bile.

As part of the combination sulfamethoxypyrazine/pyrimethamine are present which are both long acting medicinal products.
The absorption is fast and the peak levels are reached within 1.5 to 8 hours.
Their metabolism or biotransformation is very slowly.
The elimination by the kidneys is practically the only way, therefore the administration of water is important to avoid cristalluria.
Sulfamethoxypyrazine penetrates into the red globules in a rate equal to his liposolubility and inverse to his protein bound quantity. The half-life time is about 65 hours and 60 % is bound to proteins.
Pyrimethamine diffuses into many tissues, including red globules. His protein bounding rate is high, 87 % and his half-life time ranges from 54 to 148 hours.

5.3. Pre-clinical safety data

The cytotoxicity of artesunate does not affect human beings and high-dose animal toxicity studies did not reveal any particular lesions. Electron microscopic studies have shown that membranous structures of the parasites are progressively disintegrated in the presence of artesunate.
Artesunate does not possess pharmacodynamic activities apart from a lowering of sinus heart rate. Studies in catheterised anaesthetised pigs show that high doses administered i.m. do not affect cardiovascular variables. The drug has no effect on contractility, not on conduction and not on repolarisation. The drug does not prolong the QTc interval. Only a slight reduction in sinus heart rate has been observed. What was seen in anaesthetised pigs is similar to observations in human beings.
Recent studies in man indicate that artesunate is effective in the prevention and the cure of infestations caused by Schistozoma of the types mansoni, japonica and haematobium. However, higher doses are needed.

Pyrimethamine was not found carcinogenic in female mice or in male and female rats. The carcinogenic potential of pyrimethamine in male mice could not be assessed from the study because of markedly reduced life-span. Pyrimethamine was found to be mutagenic in laboratory animals and also in human bone marrow following 3 or 4 consecutive daily doses totalling 200 mg to 300 mg. Pyrimethamine was not found mutagenic in the Ames test. Testicular changes have been observed in rats treated with 105 mg/kg/day of sulfadoxine/pyrimethamine and with 15 mg/kg/day of pyrimethamine alone. Fertility of male rats and the ability of male or female rats to mate were not adversely affected at dosages of up to 210 mg/kg/day

of sulfadoxine/pyrimethamine. The pregnancy rate of female rats was not affected following their treatment with 10.5 mg/kg/day, but was significantly reduced at dosages of 31.5 mg/kg/day or higher, a dosage approximately 30 times the weekly human prophylactic dose or higher.

6. PHARMACEUTICAL PARTICULARS S

6.1. List of excipients

Maltodextrin
Microcrystalline cellulose
Sodium starch glycolate
Colloidal anhydrous silica
Magnesium stearate

6.2. Shelf life

2 years

6.3. Special precautions for storage

Store below 30°C, in the original package, protected from light and humidity.
Keep out of reach and sight of children. Do not use after the expiry date, stated on the packaging (Exp.). The expiry date refers to the last day of that month.

7. NAME OF MANUFACTURER

FAMAR Italia S.p.A., 25 Via Zambeletti, Baranzate (Milan), Italy.

8. REGISTRATION/LICENCE HOLDER:

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

9. DATE OF REVISION OF THE TEXT: 03/2018.