1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

1. Name of the medicinal product

Product name: DIPAKSO Tablets

Approved generic name: Dihydroartemisinin and Piperaquine Phosphate Tablets

2. Qualitative and quantitative composition

Strength: Each tablet contains Dihydroartemisinin 40mg and Piperaquine Phosphate 320mg

Pharmaceutical form: Oral tablets

3. Pharmaceutical form

This product is a film-coated tablet, which is almost white to light yellow after removing the coating.

4. Clinical particulars

4.1 Therapeutic indications

Treatment of clinical attacks of Malaria caused by P. falciparum, P, Vivax and P. malariae

4.2 Posology and method of administration

Dihydroartemisinin and Piperaquine Phosphate Tablets should be administeted once daily over three consecutive days taken orally with water and without food. Each dose should be taken not less than 3 hours after the last food intake and no food should be taken within 3 hours after each dose. Patients should follow doctor's instruction. The recommended dosage is as shown in the table below:

Age(Years)	<6	6 - 11	11 - 16	>16
Body weight (kg)	13 - 24	24 - 30	30 - 36	>36
Day 1	1 tablet	1½ tablets	2 tablets	3 tablets
Day 2	1 tablet	1½ tablets	2 tablets	3 tablets
Day 3	1 tablet	1½ tablets	2 tablets	3 tablets
Total	3 tablets	4½ tablets	6 tablets	9 tablets

4.3 Contraindication

The product is not recommended for use in women during the first 3 months of pregnancy.

4.4 Special warnings and precautions for use

Do not exceed the stated dosage.

4.5 Interaction with other medical products and other forms of interaction

Dihydroartemisinin and Piperaquine Phosphate Tablets is contraindicated in patients already taking other medicinal products that are known to prolong the QTc interval due to the risk of a pharmacodynamic interaction leading to an additive effect on the QTc interval.

4.6 Pregnancy and lactation

There are insufficient data on the use of dihydroartemisinin and piperaquine in pregnant women, however, Dihydroartemisinin and Piperaquine Phosphate Tablets should not be used during the first trimester of pregnancy.

Animal data suggest excretion of piperaquine into breast milk but no data are available in humans. Women taking Dihydroartemisinin and Piperaquine Phosphate Tablets should not breast-feed during their treatment.

4.7 Effects on ability to drive and use machines

Patients should know that mild dizziness, vertigo, headache, nausea, vomiting and abdominal discomfort may occur, and so should stop driving and operating machinery during the treatment.

4.8 Undesirable effects

1. Nausea or vomiting may occur occasionally with incidence of less than 6%

2. No noticeable side effect of Dihydroartenisinin is reported. The Dihydroartemisinin would, for certain individuals, bring effects of greater or lesser severity: for example, a reversible reduction in reticulocyte counts.

3. Possible side-effect of PQP include mild dizziness, vertigo, headache, nausea, vomiting and abdominal discomfort. Reversible leucopenia was infrequently reported; dyspnea and palpitations were also reported but not further specified.

4.9 Overdose

In cases of suspected overdose, symptomatic and supportive therapy should be given as appropriate, including ECG monitoring because of the possibility of QTc interval prolongation.

5. Pharmacological properties

5.1 Pharmacotherapeutic group: Antimalarial

This product is a compound preparation composed of dihydroartemisinin and piperaquine phosphate.

Dihydroartemisinin is a derivative of artemisinin and the active substance of artemisinin. It has a strong killing effect on plasmodium anasexuals, and can quickly kill the plasmodium, thereby controlling symptoms. Drug resistance breeding experiments show that Plasmodium is not easily resistant to dihydroartemisinin.

Piperaquine phosphate is a 4-aminoquinoline antimalarial drug. Its antimalarial effect is similar to that of chloroquine. It affects the ultrastructure of plasmodium schizont in the red stage, and can mainly swell the trophozoite food bubble membrane and mitochondria, leading to its physiological The function is destroyed, thereby killing the malaria parasite. Piperquine phosphate has no cross-resistance to chloroquine.

In vitro pharmacodynamic studies have shown that the combined use of dihydroartemisinin and piperaquine phosphate has a synergistic effect and can delay the development of resistance to malaria parasites.

5.2 Pharmacokinetic properties

Mode of action of Dihydroartemisinin:

Dihydroartemisinin mainly interferes with the membrane structures of trophozoites (erythrocytic asexual forms), i.e. whorled food vacuole membrane, distended mitochondria, swollen unclear membranes, dissociation of ribosomes from endoplasmic reticulum leading to cytoplasmic vacuolization and autophagocytosis- In addition, biochemical depression of protein synthesis and nucleic acid synthesis are exhibited.

Upon oral administration Dihydroartemisin is rapidly absorbed and maximum blood concentration attained 1 hour afterwards, with a half-life of about 4 hours. It is widely distributed in the liver, kidneys and bile. Approximately 80% is excreted through the

urine and feces within 24 hrs after administration It is metabolized to two inactive metabolites, deoxydihydroartemisinin and dihydroxydihydroartemisinin.

Mode of action of Piperaquine Phosphate:

Experimental results show that PQP interferes with physiological function of the food vacuole membrane of the trophozoites leading to autophagocytosis of the parasites. It has no marked effect on the ring forms, immature or mature schizonts and the male or female gametocytes. Upon oral administration about 80-90% is absorbed within 24 hrs. It is widely distributed in the body mainly in the liver, kidneys, lungs and spleen. About 25% of the total dose is partitioned in the liver within 8 hrs of intake. Elimination is very slow with the half-life of about 9.4 days. It is excreted through bile by hepatoenteral circulation.

5.3 Preclinical safety data

Dihydroartemisinin:

Genetic toxicity: The results of Ames test, CHL chromosome aberration test, and micronucleus test were all negative.

Reproductive toxicity: It has embryotoxic effects on pregnant mice, which can increase embryo absorption in a dose-dependent manner; no teratogenic effects are seen.

Piperaquine phosphate:

Repeated administration toxicity: Beagle dogs were given oral administration once a week, 100mg/Kg for 14 weeks, or 25mg/Kg for 26 weeks, the liver was found to be the main target organ for toxicity.

Genotoxicity: Ames test, bone marrow cell chromosome analysis and sister chromatid exchange rate (SCE) test results were all negative.

Reproductive toxicity: no embryo toxicity and teratogenic effects have been found in animal experiments.

Dihydroartemisinin and piperaquine phosphate are used in combination, which is additive in toxicity and has no toxic effect.

6. Pharmaceutical particulars

6.1 List of excipients

Low-Substituted Hydroxypropyl Cellulose, Microcrystalline cellulose, Pregelatinized Starch, Hypromellose, Ethanol (95%), Purified water, Sodium Starch Glycolate, Magnesium stearate, Gastric soluble film coating powder

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store in a cool and dry place below 30°C. Protect from light.

6.5 Nature and contents of container

Blister(Aluminum foil-PVC).

Packs of 9 tablets per blister, 1 blisters per packs.

6.6 Marketing authorization holder

Manufacturer name: FRONT Pharmaceutical PLC

Physical address: Economic and Technical Development Zone, Xuancheng, China

Tel: 86-0563-2625199

Fax: 86-0563-2625199

E-mail: export@frontpharm.com

6.7 Marketing authorization numbers

6.8 Date of first authorization/renewal of the authorization

Date of first authorization: August 05, 2020

6.9 Date of revision of the text

August 05, 2020