# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

D-ARTEPP® Dispersible (Dihydroartemisinin/Piperaquine Phosphate), 20/160mg dispersible tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

**Name of ingredient Qty (SI units)**

Each dispersible tablet contains 20mg dihydroartemisinin (DHA) and 160 mg piperaquine tetraphosphate (as the tetrahydrate).
For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Dipsersible tablet (tablet, without coated).
Almost white or pale yellow round tablet, debossed with “D” on one side and a scoreline on the other side.
The tablet can be divided into equal halves.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

D-ARTEPP® dispersible is indicated for the treatment of uncomplicated *Plasmodium falciparum* malaria in children and infants 6 months and over and weighing 5 kg or more.
Consideration should be given to official guidance on the appropriate use of antimalarial agents.

### 4.2 Posology and method of administration

Posology
D-ARTEPP® dispersible should be administered over three consecutive days for a total of three doses taken at the same time each day.
Dosage
Patient should follow doctor’s instructions. The recommended dosage is listed as following:

| Body weight (kg) | Daily dose (mg) | | Tablet strength and number of tablets per dose |
|---|---|---|---|
| | DHA | PQP | |
| 5to <8 | 20 | 160 | 1 x 20/160mg tablet |
| 8 to<11 | 30 | 240 | $1^1/_2$x 20/160mg tablet |
| 11 to<17 | 40 | 320 | 2 x 20/160mg tablet |
| 17 to<25 | 60 | 480 | $1^1/_2$ x 40/320mg tablets |
| 25 to<36 | 80 | 640 | 2 x 40/320mg tablets |

Do not give this medicine to infants below 5kg in weight.
If a patient vomits within 30 minutes of taking D-ARTEPP, the whole dose should be re-administered; if a patient vomits within 30-60 minutes, half the dose should be re-administered. Re-dosing with D-ARTEPP® dispersible should not be attempted more than once. If the second dose is vomited, alternative antimalarial therapy should be instituted.
If a dose is missed, it should be taken as soon as realised and then the recommended regimen continued until the full course of treatment has been completed.

A second course of D-ARTEPP® dispersible should not be given within 2 months after the first course due to the long elimination half-life of piperaquine (see sections 4.4 and 5.2).

*Hepatic and renal impairment*
D-ARTEPP® dispersible has not been evaluated in subjects with moderate or severe renal or hepatic insufficiency. Therefore, caution is advised when administering D-ARTEPP® dispersible to these patients (see section 4.4).

See posology table above.
The safety and efficacy of Dihydroartemisin/Piperaquine phosphate in children aged less than 6 months and in children weighing less than 5 kg has not been established. No data are available for these paediatric subsets.

*Method of administration*
D-ARTEPP® dispersible should be taken in a small amount of water (Approximately 10ml per tablet) in a cup. Allow the tablet(s) to disintegrate and stir gently before giving the solution to patients to drink immediately. Afterwards, immediately rinse the cup with an additional small amount of water (approximately 10 ml) and give it to patients to drink completely and without food.
Each dose should be taken no less than 3 hours after the last food intake.
No food should be taken within 3 hours after each dose.

## 4.3 Contraindications

- Hypersensitivity to any of the active substances or to any of the excipients in section 6.1
- Severe malaria according to WHO definition.
- Family history of sudden death or of congenital prolongation of the QTc interval.
- Known congenital prolongation of the QTc-interval or any clinical condition known to prolong the QTc interval.
- History of symptomatic cardiac arrhythmias or with clinically relevant bradycardia.
- Any predisposing cardiac conditions for arrhythmia such as severe hypertension, left ventricular hypertrophy (including hypertrophic cardiomyopathy) or congestive cardiac failure accompanied by reduced left ventricle ejection fraction.
- Electrolyte disturbances, particularly hypokalaemia, hypocalcaemia or hypomagnesaemia.
- Taking medicinal products that are known to prolong the QTc interval. These include (but are not limited to):
  - • Antiarrhythmics (e.g. amiodarone, disopyramide, dofetilide, ibutilide, procainamide, quinidine, hydroquinidine, sotalol).
  - • Neuroleptics (e.g. phenothiazines, sertindole, sultopride, chlorpromazine, haloperidol, mesoridazine, pimozide, or thioridazine), antidepressive agents.
  - • Certain antimicrobial agents, including agents of the following classes:
    - macrolides (e.g. erythromycin, clarithromycin),
    - fluoroquinolones (e.g. moxifloxacin, sparfloxacin),
    - imidazole and triazole antifungal agents,
    - and also pentamidine and saquinavir.
  - • Certain non-sedating antihistamines (e.g. terfenadine, astemizole, mizolastine).
  - • Cisapride, droperidol, domperidone, bepridil, diphemanil, probucol, levomethadyl, methadone, vinca alkaloids, arsenic trioxide.
- Recent treatment with medicinal products known to prolong the QTc interval that may still be circulating at the time that Dihydroartemisin/Piperaquine phosphate tablets is commenced

(e.g. mefloquine, halofantrine, lumefantrine, chloroquine, quinine and other antimalarial agents) taking into account their elimination half-life.

### 4.4 Special warnings and precautions for use

D-ARTEPP® dispersible should not be used to treat severe falciparum malaria (see section 4.3) and, due to insufficient data, should not be used to treat malaria due to Plasmodium vivax, Plasmodium malariae or Plasmodium ovale.

The long half-life of piperaquine (about 22 days) should be kept in mind in the event that another anti-malarial agent is started due to treatment failure or a new malaria infection (see below and sections 4.3 and 4.5).
Piperaquine is an inhibitor of CYP3A4. Caution is recommended when co-administering D-ARTEPP® dispersible with medicinal products exhibiting variable patterns of inhibition, induction or competition for CYP3A4 as the therapeutic and/or toxic effects of some co-administered medicinal products could be altered (see sections 4.5 and 5.2).

D-ARTEPP® dispersible should not be used during pregnancy in situations where other suitable and effective antimalarials are available (see section 4.6).

*Effects on cardiac repolarization*
In clinical trials with Dihydroartemisin/Piperaquine phosphate limited ECGs were obtained during treatment. These showed that QTc prolongation occurred more frequently and to a larger extent in association with Dihydroartemisin/Piperaquine phosphate tablets therapy than with the comparators (see section 5.1 for details of the comparators). Analysis of cardiac adverse events in clinical trials showed that these were reported more frequently in Dihydroartemisin/Piperaquine phosphate treated patients than in those treated with comparator antimalarial (see section 4.8). Before the third dose of Dihydroartemisin/Piperaquine phosphate tablets, in one of the two Phase III studies 3/767 patients (0.4%) were reported to have a QTcF value of > 500 ms versus none in the comparator group.

The potential for Dihydroartemisin/Piperaquine phosphate to prolong the QTc interval was investigated in parallel groups of healthy volunteers who took each dose with high (~1000 Kcal) or low (~400 Kcal) fat/calorie meals or in fasting conditions. Compared to placebo, the maximum mean increases in QTcF on day 3 of dosing with Dihydroartemisin/Piperaquine phosphate were 45.2, 35.5 and 21.0 msec under respective dosing conditions. The QTcF prolongation observed under fasting conditions lasted between 4 and 11 hours after the last dose was administered on day 3. The mean QTcF prolongation compared to placebo decreased to 11.8 msec at 24 hours and to 7.5 msec at 48 hours. No healthy subject dosed in fasting conditions showed a QTcF greater than 480 msec or an increase over baseline greater than 60 msec. The number of subjects with QTcF greater than 480 msec after dosing with low fat meals was 3/64, while 10/64 had QTcF values over this threshold after dosing with high fat meals. No subject had a QTcF value greater than 500 msec in any of the dosing conditions.

An ECG should be obtained as early as possible during treatment with Dihydroartemisin/Piperaquine phosphate and ECG monitoring should be applied in patients who may have a higher risk of developing arrhythmia in association with QTc prolongation (see below).

When clinically appropriate, consideration should be given to obtaining an ECG from all patients before the last of the three daily doses is taken and approximately 4-6 hours after the last dose, since the risk of QTc interval prolongation may be greatest during this period (see section 5.2). QTc intervals of more than 500 ms are associated with a pronounced risk for potentially life-threatening ventricular tachyarrhythmias. Therefore, ECG monitoring during the following 24-48 hours should be applied for patients found to have a prolongation to this extent. These patients should not receive

another dose of Dihydroartemisin/Piperaquine phosphate and alternative antimalarial therapy should be instituted.

Compared to adult males, female patients and elderly patients have longer QTc intervals. Therefore, they may be more sensitive to the effects of QTc-prolonging medications such as Dihydroartemisin/Piperaquine phosphate so that special caution is required.

Special precaution is advised in young children when vomiting, as they are likely to develop electrolyte disturbances. These may increase the QTc-prolonging effect of Dihydroartemisin/Piperaquine phosphate (see section 4.3).

Piperaquine is metabolised by and is an inhibitor of CYP3A4. There is a potential for a several-fold increase of piperaquine plasma concentrations when it is co-administered with other CYP3A4 substrates (due to competition) and, especially, with CYP3A4 inhibitors, resulting in an exacerbation of the effect on QTc prolongation (see sections 4.3 and 4.5). Therefore, particular caution is required if D-ARTEPP® dispersible is administered to patients taking such medicinal products, and ECG monitoring is advised due to the risk of higher plasma concentrations of piperaquine (see section 4.5).

Dihydroartemisin/Piperaquine phosphate has not been evaluated in patients with moderate or severe renal or hepatic insufficiency (see section 4.2). Due to the potential for higher plasma concentrations of piperaquine to occur, caution is advised if D-ARTEPP® dispersible is administered to patients with jaundice and/or with moderate or severe renal or hepatic insufficiency, and ECG and blood potassium monitoring are advised.

## 4.5 Interaction with other medicinal products and other forms of interaction

D-ARTEPP® dispersible 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 (see section 4.3 and 4.4).
Drug-drug pharmacokinetic interaction studies with Dihydroartemisin/Piperaquine phosphate have not been performed. The assessment of the potential for drug-drug interactions to occur is based on in vitro studies.

*Effect of D-ARTEPP® dispersible on co-administered medicinal products*
Piperaquine is metabolised by, and is an inhibitor of CYP3A4. Therefore, it has the potential to increase plasma concentrations of other substrates for this enzyme (e.g. HMG CoA reductase inhibitors) with the risk of increased toxicity. Particular attention should be paid when medicinal products that have a narrow therapeutic index (e.g. antiretroviral medicinal products and cyclosporine) are co-administered with D-ARTEPP® dispersible.

Piperaquine undergoes a low level of metabolism by CYP2C19, and is also an inhibitor of this enzyme. There is the potential for reducing the rate of metabolism of other substrates of this enzyme, such as omeprazole, with consequent increase of their plasma concentration, and therefore, of their toxicity. Piperaquine has the potential to increase the rate of metabolism for CYP2E1 substrates resulting in a decrease in the plasma concentrations of substrates such as paracetamol or theophylline, and the anaesthetic gases enflurane, halothane and isoflurane. The main consequence of this interaction could be a reduction of efficacy of the co-administered medicinal products.

DHA administration may result in a slight decrease in CYP1A2 activity. Caution is therefore, advised when D-ARTEPP® dispersible is administered concomitantly with medicinal products metabolised by this enzyme that have a narrow therapeutic index, such as theophylline. Any effects are unlikely to persist beyond 24 hours after the last intake of DHA.

*Effect of co-administered medicinal products on D-ARTEPP® dispersible*

Piperaquine is metabolised by CYP3A4 in vitro. The contribution of CYP3A4 to elimination of piperaquine in vivo is unknown. Concomitant treatment with medicinal products which inhibit CYP3A4 may lead to a marked increase of piperaquine plasma concentration resulting in an exacerbation of the effect on QTc (see section 4.4). Therefore, particular caution is required if D-ARTEPP® dispersible is administered to patients taking such medicinal products (e.g. some protease inhibitors [amprenavir, atazanavir, indinavir, nelfinavir, ritonavir], nefazodone or verapamil), and ECG monitoring should be considered due to the risk of higher plasma concentrations of piperaquine.

All these potential interactions should be kept in mind for patients who require D-ARTEPP® dispersible treatment and, due to the long half-life of piperaquine, for up to 3 months after the treatment.

Enzyme inducing medicinal products such as rifampicin, carbamazepine, phenytoin, phenobarbital, St. John's wort (Hypericum perforatum) are likely to lead to reduced piperaquine plasma concentrations. The concentration of DHA may also be reduced. Concomitant treatment with such medicinal products is not recommended.

*Food interaction*
Absorption of piperaquine is increased in the presence of fatty food (see sections 4.4 and 5.2) which may increase its effect on QTc interval. Therefore, D-ARTEPP® dispersible should be taken with water only as described in section 4.2. D-ARTEPP® dispersible should not be taken with grapefruit juice as it is likely to lead to increased piperaquine plasma concentrations.

## 4.6 Pregnancy and lactation

*Pregnancy:*
There are insufficient data on the use of DHA and piperaquine in pregnant women. Based on animal data, D-ARTEPP® dispersible is suspected to cause serious birth defects when administered during the first trimester of pregnancy (see sections 4.4 and 5.3). Reproductive studies with artemisinin derivatives have demonstrated teratogenic potential with an increased risk during early gestation (see section 5.3). Piperaquine was not teratogenic in the rat or rabbit. In perinatal and postnatal studies in rats, piperaquine was associated with delivery complications. However, there was no delay in neonatal development following exposure in utero or via milk.

D-ARTEPP® dispersible should not be used during pregnancy in situations where other suitable and effective anti- malarials are available (see section 4.4).

*Lactation:*
Animal data suggest excretion of piperaquine into breast milk but no data are available in humans. Women taking D-ARTEPP® dispersible should not breast-feed during their treatment.

*Fertility*
There are no specific data relating to the effects of piperaquine on fertility, however, to date no adverse events have been reported during clinical use. Moreover, data obtained in animal studies show that fertility is unaffected by DHA in both females and males.

## 4.7 Effects on ability to drive and use machines

Adverse event data collected in clinical trials suggest that D-ARTEPP® dispersible has no influence on the ability to drive and operate machines once the patient has recovered from the acute infection.

## 4.8 Undesirable effects

*Summary of the safety profile*

The safety of Dihydroartemisin/Piperaquine phosphate has been evaluated in two phase III open-label studies involving 1,239 paediatric patients up to 18 years and 566 adult patients >18 years treated with Dihydroartemisin/Piperaquine phosphate tablets.

In a randomized trial in which 767 adults and children with uncomplicated P. falciparum malaria were exposed to Dihydroartemisin/Piperaquine phosphate, 25 % of subjects were judged to have experienced an adverse drug reaction (ADR). No single type of ADR occurred at an incidence of ≥ 5%. The most frequent ADRs observed at an incidence ≥1.0% were: Headache (3.9%), Electrocardiogram QTc Prolonged (3.4%), P. falciparum infection (3.0%), Anaemia (2.8%), Eosinophilia (1.7%), Haemoglobin decreased (1.7%), Sinus tachycardia (1.7%), Asthenia (1.6%), Haematocrit [decreased] (1.6%), Pyrexia (1.5%), Red Blood Cell Count decreased (1.4%). A total of 6 (0.8%) subjects had serious ADRs in the study.

In a second randomized trial, 1,038 children, aged between 6 months and 5 years, were exposed to Dihydroartemisin/Piperaquine phosphate and 71% were judged to have experienced an ADR. The following ADRs were observed at an incidence of ≥5.0%: Cough (32%), Pyrexia (22.4%), Influenza (16.0%), P. falciparum infection (14.1%), Diarrhoea (9.4%), Vomiting (5.5%) and Anorexia (5.2%). A total of 15 (1.5%) subjects had serious ADRs in the study.

*Tabulated list of adverse reactions*
In the tables below, ADRs are listed under system organ class (SOC), and ranked by headings of frequency, the most frequent first, using the following convention: Very common (≥ 1/10), common (≥1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data). The table in this section is for adult patients only. A corresponding table for paediatric patients is presented in the specific section below.

Frequency of ADRs in adult patients participating in clinical studies with Dihydroartemisin/Piperaquine phosphate tablets:

| SOC | Very Common | Common | Uncommon |
|---|---|---|---|
| Infections and infestations | | P falciparum infection | Influenza<br>Respiratory tract infection |
| Blood and lymphatic system disorders | | Anaemia | |
| Metabolism and nutrition disorders | | | Anorexia |
| Nervous system disorders | | Headache | Dizziness<br>Convulsion |
| Cardiac disorders | | QTc prolonged<br>Tachycardia | Cardiac conduction disorders<br>Sinus arrhythmias<br>Bradycardia |
| Respiratory, thoracic and mediastinal disorders | | | Cough |
| Gastrointestinal disorders | | | Vomiting<br>Abdominal pain<br>Diarrhoea<br>Nausea |
| Hepatobiliary disorders | | | Hepatitis<br>Hepatomegaly<br>Abnormal liver function tests |
| Skin and subcutaneous Tissue disorders | | | Pruritis |
| Musculoskeletal and connective tissue | | | Arthralgia<br>Myalgia |

| | | | |
|---|---|---|---|
| disorders | | | |
| General disorders and administration site conditions | | Asthenia<br>Pyrexia | |

*Description of selected adverse reactions*
The ADRs noted for Dihydroartemisin/Piperaquine phosphate were generally mild in severity, and the majority were non-serious. Reactions such as cough, pyrexia, headache, P. falciparum infection, anaemia, asthenia, anorexia and the observed changes in blood cell parameters are consistent with those expected in patients with acute malaria. The effect on prolongation of the QTc interval was observed on Day 2, and had resolved by Day 7 (the next time point at which ECGs were performed).

*Paediatric population*
A tabular overview of the frequency of the ADRs in paediatric patients is given below. The majority of paediatric experience is derived from African children aged 6 months to 5 years.
Frequency of ADRs in paediatric patients participating in clinical studies with Dihydroartemisin/Piperaquine phosphate tablets:

| SOC | Very Common | Common | Uncommon |
|---|---|---|---|
| Infections and infestations | Influenza<br>P. falciparum infection | Respiratory tract infection<br>Ear infection | |
| Blood and lymphatic system disorders | | Anaemia<br>Leuckocytoses NEC<br>Leukopenias/neutropenia<br>Thrombocytopenia | Hypochromasia<br>Lymphadenopathy<br>Splenomegaly<br>Thrombocythaemia |
| Metabolism and nutrition disorders | | Anorexia | |
| Nervous system disorders | | | Convulsion<br>Headache |
| Eye disorders | | Conjunctivitis | |
| Cardiac disorders | | Heart rate irregular<br>QT/QTc prolonged | Cardiac murmur<br>Cardiac conduction disorders |
| Respiratory, thoracic and mediastinal disorders | Cough | | Epistaxis<br>Rhinorrhoea |
| Gastrointestinal disorders | | Abdominal pain<br>Vomiting<br>Diarrhoea | Nausea<br>Stomatitis |
| Hepatobiliary disorders | | | Hepatitis<br>Hepatomegaly<br>Jaundice<br>Abnormal liver function tests |
| Skin and subcutaneous Tissue disorders | | Dermatitis<br>Rash | Pruritis<br>Acanthosis |
| Musculoskeletal and connective tissue disorders | | | Arthralgia |
| General disorders and administration site conditions | Pyrexia | Asthenia | |

### 4.9 Overdose

In clinical trials, nine patients received double the cumulative intended dose of Dihydroartemisin/Piperaquine phosphate. The safety profile of these patients did not differ from that of patients receiving the recommended dose, with no patient reporting SAEs.

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 (see section 4.4)

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiprotozoals, antimalarials, Artemisinin and derivatives, combinations, ATC code: P01BF05

*Pharmacodynamic effects*
DHA is able to reach high concentrations within the parasitized erythrocytes. Its endoperoxide bridge is thought to be essential for its antimalarial activity, causing free-radical damage to parasite membrane systems including:
• Inhibition of falciparum sarcoplasmic-endoplasmic reticulum calcium ATPase,
• Interference with mitochondrial electron transport
• Interference with parasite transport proteins
• Disruption of parasite mitochondrial function

The exact mechanism of action of piperaquine is unknown, but it likely mirrors that of chloroquine, a close structural analogue. Chloroquine binds to toxic haeme (derived from the patient's haemoglobin) within the malaria parasite, preventing its detoxification via a polymerisation step.

Piperaquine is a bisquinoline, and this class has shown good antimalarial activity against chloroquine-resistant Plasmodium strains in vitro. The bulky bisquinolone structure may be important for activity against chloroquine- resistant strains, and may act through the following mechanisms:
• Inhibition of the transporters that efflux chloroquine from the parasite food vacuole
• Inhibition of haem-digestion pathway in the parasite food vacuole.

Resistance to piperaquine (when used as monotherapy) has been reported.
The efficacy and safety of Dihydroartemisinin/Piperaquine phosphate have been assessed in two large randomised, open-label clinical trials:

### 5.2 Pharmacokinetic properties

Pharmacokinetic profiles of DHA and piperaquine have been investigated in animal models and in different human populations (healthy volunteers, adult patients and paediatric patients).

*Absorption*
DHA is very rapidly absorbed, Tmax being approximately 1-2 hrs after single and multiple dosing. In patients, mean Cmax (CV %) and AUCINF of DHA (observed after the first dose) were 752 (47 %) ng/ml and 2,002 (45 %) ng/ml*h, respectively.

DHA bioavailability appears to be higher in malaria patients than in healthy volunteers, possibly because malaria per sehas an effect on DHA disposition. This may reflect malaria-associated impairment of hepatic function, causing an increase in DHA bioavailability (reduction of first hepatic effect) without affecting its apparent elimination half-life, which is absorption rate limited. In healthy

male volunteers under fasting conditions, mean Cmax and AUCINF of DHA ranged between 180-252 ng/ml and 516-684 ng/ml*h, respectively.

The systemic exposure to DHA was slightly lower following the last dose of Dihydroartemisinin/Piperaquine phosphate (lower than after the first dose by up to 15 %). DHA pharmacokinetic parameters were found to be similar in healthy volunteers of Asian and Caucasian origin. DHA systemic exposure on the last day of treatment was higher in females than in males, the difference being within 30 %.

In healthy volunteers, DHA exposure was increased by 43 % when administered with a high fat/high calorie meal.

Piperaquine, a highly lipophilic compound, is slowly absorbed. In humans, piperaquine has a Tmax of approximately 5 hours following a single and repeated dose. In patients mean (CV %) Cmax and AUC0-24 (observed after the first dose) were 179 (62 %) ng/ml and 1,679 (47 %) ng/ml*h, respectively. Due to its slow elimination, piperaquine accumulates in plasma after multiple doses with an accumulation factor of approximately 3. Piperaquine pharmacokinetic parameters were found to be similar in healthy volunteers of Asian and Caucasian origin. On the other hand, on the last day of Eurtartesim treatment, the piperaquine maximum plasma concentration was higher in female than in male healthy volunteers, the difference being in the order of 30 to 50 %.

In healthy volunteers, piperaquine exposure is increased approximately 3-fold when administered with a high fat/high calorie meal. This pharmacokinetic effect is accompanied by an increased effect on prolongation of the QT interval. Accordingly, Dihydroartemisinin/Piperaquine phosphate should be administered with water no less than 3 hours after the last food intake, and no food should be taken within 3 hours after each dose (see section 4.2).

*Distribution*
Both piperaquine and DHA are highly bound to human plasma proteins: the protein binding observed in in vitro studies was 44-93 % for DHA and >99 % for piperaquine. Moreover, from in vitro and in vivo data in animals, piperaquine and DHA tend to accumulate in RBC.

DHA was observed to have a small volume of distribution in humans (0.8 l/kg; CV 35.5 %). Pharmacokinetic parameters observed for piperaquine in humans indicate that this active substance has a large volume of distribution (730 l/kg; CV % 37.5 %).

*Biotransformation*
DHA is principally converted to α-DHA-β-glucuronide (α-DHA-G). Studies in human liver microsomes showed that DHA was metabolised by the UDP-glucuronosyltransferase (UGT1A9 and UGT2B7) to α-DHA-G with no cytochrome P450-mediated metabolism. In vitro drug-drug interaction studies revealed that DHA is an inhibitor of CYP1A2; therefore, there is the potential for DHA to increase plasma concentrations of CYP1A2 substrates (see section 4.5).

The metabolism of piperaquine in humans has not been studied in vivo. In vitro metabolism studies demonstrated that piperaquine is metabolised by human hepatocytes (approximately 85 % of piperaquine remained after 2 hours incubation at 37°C). Piperaquine was mainly metabolised by CYP3A4 and to a lesser extent by CYP2C9 and CYP2C19. Piperaquine was found to be an inhibitor of CYP3A4 (also in a time-dependent way) and to a lesser extent of CYP2C19, while it stimulated the activity of CYP2E1. As a consequence, there is the potential for increasing plasma concentrations of CYP3A4 substrates, and also for the increase of piperaquine plasma concentrations when D-ARTEPP is concomitantly administered with CYP3A4 substrates, and CYP3A4 inhibitors, respectively (see section 4.5).

No effect on the metabolite profile of piperaquine in human hepatocytes was observed when piperaquine was co-incubated with DHA. The piperaquine major metabolites were a carboxyl acid cleavage product, and a mono-N-oxidated product.

*Elimination*
The elimination half-life of DHA is approximately 1 hour. The mean oral clearance for adult patients with malaria was 1.34 l/h/kg. The mean oral clearance was slightly higher for paediatric patients, however the differences were minor in magnitude (<20 %). DHA is eliminated by metabolism (mainly glucuroconjugation). Its clearance was found to be slightly lower in female than in male healthy volunteers. Data regarding DHA excretion in humans are scarce. However, it is reported in the literature that the excretion of unchanged active substance in human urine and faeces is negligible for artemisinin derivatives.

The elimination half-life of piperaquine is around 22 days for adult patients and around 20 days for paediatric patients. The mean oral clearance for adult patients with malaria was 2.09 l/h/kg, while in paediatric patients was 2.43 l/h/kg. Due to its long elimination half-life, piperaquine accumulates after multiple dosing.

Animal studies showed that radiolabelled piperaquine is excreted by the biliary route, while urinary excretion is negligible.

*Pharmacokinetics in special patient populations*
No specific pharmacokinetic studies have been performed in patients with hepatic or renal insufficiency, or in elderly patients.

In a paediatric pharmacokinetic study, and based on very limited sampling, minor differences were observed for DHA pharmacokinetics between the paediatric and adult populations. The mean clearance (1.45 l/h/kg) was slightly faster in the paediatric patients than in the adult patients (1.34 l/h/kg), while the mean volume of distribution in the paediatric patients (0.705 l/kg) was lower than in the adults (0.801 l/kg).

The same comparison showed that piperaquine absorption rate constant and terminal half-life in children were predominantly similar to those seen in adults. However, the apparent clearance was faster (1.30 versus 1.14 l/h/kg) and the apparent total volume of distribution was lower in the paediatric population (623 versus 730 l/kg).

## 5.3 Preclinical safety data

*General toxicity*
Literature data concerning chronic toxicity of piperaquine in dogs and monkeys indicate some hepatotoxicity and mild reversible depression of total white cell and neutrophil counts.
The most important nonclinical safety findings after repeated dosing were the infiltration of macrophages with intracytoplasmic basophilic granular material consistent with phospholipidosis and degenerative lesions in numerous organs and tissues. These adverse reactions were seen in animals at exposure levels similar to clinical exposure levels, and with possible relevance to clinical use. It is not known whether these toxic effects are reversible.
DHA and piperaquine were not genotoxic/clastogenic based on in vitro and in vivo testing.
No carcinogenicity studies have been performed.

DHA causes embryolethality and teratogenicity in rats and rabbits.

Piperaquine did not induce malformation in rats and rabbits. In a perinatal and postnatal development study (segment III) in female rats treated with 80 mg/kg, some animals had a delay of delivery

inducing mortality of the neonates. In females delivering normally the development, behaviour and growth of the surviving progeny was normal following exposure in utero or via milk.
No reproduction toxicity studies have been performed with the combination of DHA and piperaquine.

*Central nervous system (CNS) toxicity*
There is potential for neurotoxicity of artemisinin derivatives in man and animals, which is strongly related to the dose, route and formulations of the different DHA pro-drugs. In humans, the potential neurotoxicity of orally administered DHA can be considered highly unlikely, given the rapid clearance of DHA, and its short exposure (3 days of treatment for malaria patients). There was no evidence of DHA-induced lesions in the specific nuclei in rats or dogs, even at lethal dose.

*Cardiovascular toxicity*
Effects on blood pressure and on PR and QRS duration were observed at high piperaquine doses. The most important potential cardiac effect was related to cardiac conduction.
In the hERG test, the IC50 was 0.15 µmol for piperaquine and 7.7 µmol for DHA. The association of DHA and piperaquine does not produce hERG inhibition greater than that of the single compounds.

*Phototoxicity*
There are no phototoxicity concerns with DHA, as it does not absorb in the range of 290-700 nm. Piperaquine has an absorption maximum at 352 nm. Since piperaquine is present in the skin (about 9% in the non-pigmented rat and only 3% in the pigmented rat), slight phototoxic reactions (swelling and erythema) were observed 24 hours after oral treatment in mice exposed to UV radiation.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

*Tablet core*
Pregelatinized starch,
Microcrystalline cellulose
Dextrin
Hypromellose
Croscarmellose sodique
Magnesium stearate
Sweetener.

### 6.2 Incompatibilities

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

### 6.3 Shelf life

24 months

### 6.4 Special precautions for storage

Stored in tightly closed containers, protected from light, not above 30℃

### 6.5 Nature and contents of container

Packaged in box, 2 blister @ 3 dispersible tablets

### 6.6 Special precautions for disposal

Dihydroartemisinin/Piperaquine Phosphate (20/160mg) dispersible tablets
Guilin Pharmaceutical Co., Ltd.

No special requirements.

## 7. MANUFACTURER

Guilin Pharmaceutical Co., Ltd.
No 43, Qilidian Road,
Guilin, Guangxi China
Postcode: 541004
Tel.: 86-773-3841973
Fax: 86-773-3841973

## 8. REGISTERED BY

PT. Pharma Laboratories, Indonesia

## 9. IMPORTED AND DISTRIBUTED BY

PT. Bhineka Usada Raya, Indonesia

## 10. REGISTRATION NUMBER

DKI

**HARUS DENGAN RESEP DOKTER**

**Informasi Produk Untuk Pasien**
**D-Artepp® Dispersible**
**Dihydroartemisinin / Piperaquine phosphate**
**Tablet Dispersible 20 mg – 160 mg**

**Baca leaflet ini dengan teliti sebelum anda menggunakan obat ini**
Simpan leaflet ini. Anda mungkin membutuhkan untuk membacanya kembali. Bila anda mempunyai pertanyaan lebih lanjut, tanyakan dokter atau apoteker anda. Obat ini telah diresepkan untuk anak-anak. Jangan memberikan obat ini pada orang lain karena mungkin dapat membahayakan mereka, bahkan bila gejala-gejalanya sama dengan anda. Bila ada efek samping serius, atau bila anda mengalami efek samping yang tidak ada dalam daftar pada leaflet ini, beritahu dokter atau apoteker anda.

**Pada leflet ini**:


**1. Apa D-ARTEPP Dispersible dan untuk apa digunakan**
D-Artepp Dispersible mengandung komposisi Dihydroartemisinin dan Piperaquin Phosphate.
D-Artepp Dispersible digunakan untuk pengobatan malaria tanpa komplikasi yang disebabkan oleh *Plasmodium falciparum*, pada anak usia diatas 6 bulan dengan berat badan 5 kilogram atau lebih.

**2. Sebelum anak anda meminum D-ARTEPP Dispersible**
**Jangan menggunakan D-ARTEPP Dispersible** :
- Bila anak anda alergi (hipersensitif) terhadap zat aktif (piperaquine phosphate atau dihydroartemisinin, atau terhadap bahan-bahan lain dari D-ARTEPP Dispersible (lihat bagian 6 untuk daftarnya)
- Bila anak anda mempunyai infeksi malaria berat yang sudah mempengaruhi bagian tubuh seperti otak, paru-paru dan ginjal
- Bila anak anda memiliki gangguan jantung, seperti perubahan irama atau kecepatan dari denyut jantung atau penyakit jantung
- Bila anda mengetahui bahwa anggota keluarga anda (orang tua, kakek, saudara laki-laki atau perempuan) meninggal tiba-tiba karena masalah jantung atau dilahirkan dengan masalah jantung
- Bila anda menemukan perubahan pada kadar garam pada tubuh anak Anda (ketidakseimbangan elektrolit);
- Bila anak anda sedang meminum obat-obatan lain yang dapat memberikan efek pada ritme jantung, seperti: - kuinidine, disopyramide, procainamide, amiodarone, dofetilide, ibutilide, hidroquinidine atau sotalol;
  - obat-obatan yang digunakan untuk mengobati depresi;
  - obat-obat yang digunakan untuk mengobati masalah kesehatan mental seperti phenothiazines, sertindole, sultopride, chlorpromazine, haloperidol, mesoridazine, pimozide, atau thioridazine;

- obat-obatan yang digunakan untuk mengobati infeksi, termasuk beberapa jenis obat-obatan yang digunakan untuk mengobati infeksi bakteri (macrolides {seperti erythromycin atau clarithromycin} dan fluoroquinolones [seperti moxifloxacin dan sparfloxacin]) atau infeksi jamur (termasuk fluconazole dan imidazole) pentamidine (digunakan untuk mengobati jenis pneumonia yang spesifik) dan saquinavir (untuk pengobatan HIV);
- antihistamin digunakan untuk mengobati alergi atau inflamasi seperti terfenadine, astemizole atau mizolastine;
- obat-obat tertentu yang digunakan untuk mengobati masalah lambung seperti cisapride, domperidone atau droperidol;
- obat-obat lain seperti alkaloid vinca dan arsenic trioxide (digunakan untuk mengobati kanker tertentu), bepridil (digunakan untuk mengobati angina), diphemanil (digunakan untuk mengobati gangguan lambung), levomethadyl dan methadone (digunakan untuk mengobati adiksi obat), dan probucol (digunakan untuk mengobati kolesterol tinggi dalam darah).

- Bila anak anda akhir-akhir ini (sebagai contoh dalam waktu kira-kira satu bulan) diobati dengan obat-obat tertentu atau meminum obat-obat tertentu untuk mencegah malaria. Obat-obat ini termasuk: mefloquine, halofantrine, lumefantrine, chloroquine atau quinine. Bila ada dari salah satu obat-obat diatas digunakan untuk anak Anda atau bila anda tidak yakin, tanyakan dokter atau apoteker Anda sebelum meminum atau memberikan D-ARTEPP Dispersible.

**Perawatan khusus dengan D-ARTEPP Dispersible**

Beritahukan kepada dokter atau apoteker anda sebelum menggunakan obat ini apabila anak anda memiliki:

- gangguan hati atau ginjal;
- infeksi malaria disebabkan oleh parasit lain selain *Plasmodium falciparum*;
- meminum obat-obat lain untuk pengobatan malaria (selain dari yang disebutkan diatas)
- kehamilan atau menyusui (lihat di bawah ini);
- meminum obat-obat lain yang dapat menyebabkan kemungkinan interaksi metabolik. Contoh obat tersebut terdapat pada bagian “Meminum obat lain”.
- Bila anda tidak yakin tentang semua yang disebutkan diatas , silakan tanyakan pada dokter atau apoteker anda sebelum memberikan anak anda D-ARTEPP Dispersible.

**Penggunaan pada anak-anak**

Jangan memberikan obat ini untuk bayi dibawah 6 bulan atau berat badan dibawah 5 kg.

**Meminum obat lain**

Silakan beritahukan pada dokter atau apoteker anda bila anak anda sedang meminum atau baru-baru ini meminum obat lain, termasuk obat yang diperoleh tanpa resep dokter. Beberapa obat dapat mempengaruhi mekanisme kerja D-ARTEPP Dispersible dan dokter anda mungkin memutuskan bahwa D-ARTEPP Dispersible tidak cocok untuk anak anda atau pemeriksaan tambahan diperlukan ketika anak anda sedang meminum obat yang dapat menyebabkan interaksi obat. Contoh obat tersebut antara lain:

- beberapa obat yang digunakan untuk mengobati kolesterol tinggi dalam darah (seperti atorvastatin, lovastatin, simvastatin);
- obat-obat yang digunakan untuk mengobati hipertensi dan masalah jantung (seperti diltiazem, nifedipine, nitrendipine, verapamil, felodipine, amlodipine);

- obat yang digunakan untuk mengobati HIV (obat-obat antiretroviral): penghambat protease (seperti amprenavir, atazanavir, indinavir, nelfinavir, ritonavir), penghambat non-nucleoside reverse transcriptase (such as efavirenz, nevirapine);
- obat yang digunakan untuk mengobati infeksi mikroba (seperti telithromycin, rifampicin, dapsone);
- obat yang digunakan untuk membantu anak Anda tidur : benzodiazepine (seperti midazolam, triazolam, diazepam, alprazolam), zaleplon, zolpidem;
- obat yang digunakan untuk mencegah/mengobati serangan epilepsi: barbiturate (seperti phenobarbital), carbamazepine atau phenytoin;
- obat yang digunakan setelah transplantasi organ dan pada penyakit autoimun (seperti cyclosporin, tacrolimus);
- hormon, termasuk yang berisi kontrasepsi hormon (seperti gestodene, progesterone, estradiol), testosterone;
- glukokortikoid (hydrocortisone, dexamethasone);
- omeprazole (digunakan untuk mengobati penyakit berhubungan dengan produksi asam lambung);
- paracetamol (digunakan untuk mengobati nyeri dan demam);
- theophylline (digunakan untuk memperbaiki aliran udara paru-paru);
- nefazodone (digunakan untuk mengobati depresi);
- aprepitant (digunakan untuk mengobati mual);
- beberapa gas (seperti enflurane, halothane dan isoflurane) digunakan untuk memberikan anastesi umum.

**Meminum D-ARTEPP dispersible tanpa makanan dan minuman**
Anak anda harus meminum D-ARTEPP dispersible tablet hanya dengan air.
Anak anda harus meminum obat ini dalam perut kosong. Anak anda harus meminum setiap dosis tidak kurang dari 3 jam setelah makan terakhir, dan tidak ada makanan dalam waktu 3 jam setelah minum D-ARTEPP dispersible.
Anak anda dapat meminum air kapan saja. Anak anda seharusnya tidak meminum D-ARTEPP dispersible dengan jus jeruk (*grapefruit*) karena dapat menyebabkan interaksi.

**Kehamilan dan menyusui**
Beritahu dokter anda bila anak perempuan anda hamil, atau bila anak perempuan anda menyusui. D-ARTEPP Dispersible tidak boleh digunakan pada kehamilan bila dokter anda dapat memberikan obat alternatif. Bila anak perempuan anda menerima D-ARTEPP Dispersible ketika hamil, mohon daftarkan kehamilan tersebut di tempat untuk mengamati hasil kehamilan. Anak perempuan anda tidak boleh menyusui ketika meminum obat ini. Bila anak perempuan meminum suplemen folat untuk mencegah cacat lahir, anda dapat melanjutkan meminumnya pada saat bersamaan dengan D-ARTEPP Dispersible. Tanyakan kepada dokter atau apoteker untuk memberikan saran sebelum memberikan anak perempuan anda obat-obatan lain selama kehamilan dan menyusui.

**Mengendarai dan menggunakan mesin**
Mengendarai dan menggunakan mesin memungkinkan saat minum D-ARTEPP Dispersible.

**3. Bagaimana meminum D-ARTEPP DISPERSIBLE**
Pasien harus mengikuti instruksi dokter. Dosis rekomendasi sebagai berikut :

| Berat Badan | Dosis | | Kekuatan Tablet dan Jumlah tablet per dosis |
|---|---|---|---|
| (kg) | DHA | PQP | |
| 5 to < 8 | 20 | 160 | 1 X 20/160 mg tablet |
| 8 to < 11 | 30 | 240 | 1 ½ X 20/160 mg tablet |
| 11 to <17 | 40 | 320 | 2 X 20/160 mg tablet |
| 17 to <25 | 60 | 480 | 1 ½ x 40/320 mg tablet |
| 25 to<36 | 80 | 640 | 2 X 40/320 mg tablet |

**Aturan penggunaan**

D-ARTEPP Dispersible tablet harus diminum dengan sedikit air (Kira-kira 10 mL per tablet) dalam cangkir. Biarkan tablet larut dan aduk perlahan sebelum memberikan larutan ke pasien untuk diminum segera. Kemudian, segera bilas cangkir dengan menambahkan sedikit air (kira-kira 10 mL) dan berikan ke pasien untuk minum semuanya. Setiap dosis harus di minum tidak kurang dari 3 jam setelah makan, dan tidak makan dalam waktu 3 jam setelah minum obat.

**Mual ketika meminum obat ini**

Bila ini terjadi dalam :

1. 30 menit setelah minum D-ARTEPP Dispersible, seluruh dosis harus diminum lagi.
2. 31-60 menit, setengah dosis harus diminum lagi.

Pemberian kembali D-ARTEPP dispersible tidak boleh lebih dari sebelumnya. Bila anak anda mual setelah dosis kedua, jangan memberikan anak anda dosis selanjutnya. Hubungi dokter anda segera untuk memperoleh obat alternatif lain untuk malaria

**Minum obat ini, bila infeksi malaria kembali**

- Bila anda dan anak anda mendapat serangan malaria lagi, Anda mendapatkan pengobatan kedua menggunakan D-ARTEPP Dispersible dalam satu tahun bila dokter Anda berpikir ini adalah pengobatan yang cocok. Anak Anda tidak boleh menggunakan lebih dari dua kali pengobatan dalam 1 tahun. Bila ini terjadi, bicarakan dengan dokter Anda. Anak anda tidak harus meminum rangkaian pengobatan kedua D-ARTEPP Dispersible dalam 2 bulan dari pengobatan pertama.
- Bila anak anda terinfeksi lebih dari 2 kali dalam setahun, dokter anda akan meresepkan pengobatan alternatif

**Bila anak Anda meminum lebih D-ARTEPP Dispersible tablet**

Bila anda memberikan anak anda dosis lebih dari yang direkomendasikan, segera hubungi dokter anda. Dokter anda mugkin menyarankan pengawasan khusus untuk anda karena pemberian dosis yang lebih tinggi dari rekomendasi dosis mungkin dapat menyebabkan efek samping berat dan tidak diinginkan pada jantung. (Lihat juga pada bagian 4)

**Bila anak Anda lupa minum D-ARTEPP Dispersible**

Bila anda lupa memberi anak anda dosis kedua D-ARTEPP Dispersible pada saat yang tepat, minum segera setelah ingat. Lalu berikan dosis ketiga (terakhir) kira-kira 24 jam setelah dosis kedua. Bila anda lupa untuk memberikan anak anda dosis ketiga (terakhir) pada saat yang tepat, minum segera setelah ingat. Jangan pernah minum lebih dari satu dosis pada hari yang sama untuk mengejar dosis

yang lewat. Periksa dengan dokter atau apoteker sebelum anda memberikan anak anda D-ARTEPP Dispersible.

**Bila anak anda berhenti minum D-ARTEPP Dispersible**
Untuk obat bekerja lebih efektif, anda harus memberikan anak anda obat sesuai yang diinstruksikan dan harus menyelesaikan dalam 3 hari pengobatan. Bila anda tidak dapat melakukan ini, konsultasikan dengan dokter atau apoteker. Bila anda memiliki pertanyaan lebih lanjut dalam penggunaan obat ini, tanyakan dokter atau apoteker anda.

**4. Kemungkinan efek samping**
Seperti semua obat-obatan, D-ARTEPP Dispersible dapat menyebabkan efek samping, meskipun tidak setiap orang mendapatkannya. Kebanyakan efek samping tidak berat dan dapat hilang dalam beberapa hari atau minggu setelah pengobatan.
Bila anak anda mengalami ruam, bengkak pada wajah, bibir, lidah atau tenggorokan dengan kesulitan menelan atau bernapas, ini mungkin menunjukan tanda reaksi alergi. Beritahu dokter anda segera, atau pergi segera ke unit gawat darurat rumah sakit terdekat, bawa leaflet ini bersama anda.
Masalah jantung, yang dinamakan QT prolongation, dapat terjadi ketika memberikan D-ARTEPP Dispersible untuk anak anda dan selama beberapa hari setelah mendapat dosis terakhir. Hal ini dapat menyebabkan irama jantung yang tidak normal dan mengancam jiwa.
**Dokter anda dapat mengambil catatan elektrik pada jantung anak anda (*electrocardiogram*/EKG), ketika anak anda diobati dan setelah dosis diberikan. Dokter akan memberitahu anda ketika melakukannya.**
**Bila anda mencatat sesuatu yang berbeda terkait irama jantung anak Anda atau mempunyai gejala (seperti palpitasi atau denyut jantung tidak teratur), Anda harus menghubungi dokter Anda segera mungkin sebelum meminum dosis berikutnya.**
**Efek samping pada anak-anak**
Sangat umum (terjadi lebih dari 1 dalam 10 pasien)
Influenza, batuk, demam.
Umum (terjadi kurang dari 1 dalam 10 pasien tetapi lebih dari 1 dalam 100)
Infeksi saluran napas, infeksi telinga, anemia, ketidaknormalan dalam beberapa tipe sel darah (sel darah putih dan platelet), nafsu makan rendah atau hilang nafsu makan, infeksi mata, gangguan ritme jantung (berubah seperti dewasa, perubahan EKG ), nyeri perut, mual, bengkak, ruam, lemas.
Tidak umum (berakibat pada kurang dari 1 dari 100 pasien tetapi lebih dari 1 dalam 1000)
Ketidaknormalan sel darah merah, jumlah platelet yang berlebih,pembesaran beberapa organ (seperti hati dan limpa), pembengkakan kelenjar limfe, kajang (sawan), sakit kepala, ketidaknormalan suara jantung (didengarkan oleh dokter dengan stetoskop),pendarahan hidung, hidung berair, muntah, pembengkakan di mulut, peradangan atau pembesaran dari hati, penyakit kuning, ketidaknormalan test fungsi hati, test darah, gatal-gatal dan pembengkakan pada kulit, nyeri pada sendi.
Bila efek samping menjadi serius, atau bila terjadi efek samping tidak ada pada leaflet ini, silakan beritahu dokter atau apoteker.

**5. Bagaimana untuk menyimpan D-ARTEPP DISPERSIBLE**
Simpan D-ARTEPP Dispersible tablet jauh dari jangkauan atau penglihatan anak-anak.
Jangan meminum D-ARTEPP Dispersible setelah kadaluarsa dimana dinyatakan pada kemasan sebagai ‘EXP’. Tanggal kadaluarsa menunjukkan hari terakhir pada bulan tersebut.
Simpan dalam wadah tertutup rapat, terlindung dari cahaya, jangan simpan pada suhu diatas 30°C.
Jangan gunakan D-ARTEPP Dispersible bila anda menemukan kemasan blister terbuka.
Obat tidak boleh dibuang lewat air limbah atau limbah rumah tangga.

Tanyakan apoteker bagaimana untuk membuang obat-obat yang tidak diperlukan. Hal tersebut akan membantu untuk menjaga lingkungan.

**6. INFORMASI lebih lanjut apa isi D-ARTEPP Dispersible**
Setiap tablet mengandung dihydroartemisinin 20 mg dan piperaquine phosphate 160 mg.
Seperti Apa isi **D-ARTEPP Dispersible dalam kemasan**
D-ARTEPP Dispersible merupakan tablet bulat, berwarna hampir putih atau kuning pucat, satu sisi ada tulisan "D" dan satu sisi lagi angka.

Kemasan : Dus, 2 Blister @ 3 tablet dispersible

**Golongan Obat Keras**
Harus dengan resep dokter.

**Produsen**
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