1.3.1 Summary of Product Characteristics (SmPC)

1.3.1.1 Name of the Medicinal Product

International Non– Proprietary Name (INN): Dihydroartemisinin +Piperaquine tablet

1.3.1.2 ATC and Forensic Classification

ATC Classification: Antimalarial.

1.3.1.3. Qualitative and quantitative composition

Each tablet contains: Dihydroartemisinin 40mg + Piperaquine 320mg

1.3.1.4. Pharmaceutical form

Oral Tablet

A film-coated tablet , remove the coat, the color of core is almost white to slight yellow.

1.3.1.5. Clinical particulars

1.3.1.5.1 Therapeutic indications

ARTEPIP Tablet (Dihydroartemisinin 40mg +Piperaquine 320mg) is indicated for the treatment of uncomplicated Plasmodium falciparum malaria in adults, 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.

1.3.1.5.2 Posology and method of administration

ARTEPIP should be taken orally with water and after food.

For patients unable to swallow the tablets, such as infants and young children, ARTEPIP may be crushed and mixed with water. The mixture should be used immediately after preparation.

1.3.1.5.3 Contraindications

- Hypersensitivity to any of the active substances or to any of the excipients.
- 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.

1.3.1.5.4 Special warnings and precautions for use

ARTEPIP should not be used to treat severe falciparum malaria 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 antimalarial agent is started due to treatment failure or a new malaria infection.

ARTEPIP should not be used during pregnancy in situations where other suitable and effective antimalarials are available.

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 coadministered with other CYP3A4 substrates (due to competition) and, especially, with CYP3A4 inhibitors, resulting in an exacerbation of the effect on QTc prolongation. Therefore, particular caution is required if

ARTEPIP is administered to patients taking such medicinal products, and ECG monitoring is advised due to the risk of higher plasma concentrations of piperaquine.
Caution is advised if ARTEPIP is administered to patients with jaundice and/or with moderate or severe renal or hepatic insufficiency, and ECG and blood potassium monitoring are advised.

1.3.1.5.5 Interaction with other medicinal products and other forms of interaction

ARTEPIP is contraindicated in patients already taking other 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 ARTEPIP is commenced (e.g. mefloquine, halofantrine, lumefantrine, chloroquine, quinine and other antimalarial agents) taking into account their elimination half-life.

Absorption of piperaquine is increased in the presence of fatty food which may increase its effect on QTc interval. Therefore, ARTEPIP should be taken with water only. ARTEPIP should not be taken with grapefruit juice as it is likely to lead to increased piperaquine plasma concentrations.

1.3.1.5.6 Pregnancy and lactation

Pregnancy
There are insufficient data on the use of DHA and piperaquine in pregnant women. Based on animal data, ARTEPIP (Dihydroartemisinin +Piperaquine) is suspected to cause serious birth defects when administered during the first trimester of pregnancy. Reproductive studies with artemisinin derivatives have demonstrated teratogenic potential with an increased risk during early gestation. 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.

ARTEPIP should not be used during pregnancy in situations where other suitable and effective anti- malarials are available.

Nursing Mothers
Animal data suggest excretion of piperaquine into breast milk but no data are available in humans. Women taking ARTEPIP Tablet should not breast-feed during their treatment.

1.3.1.5.7 Effects on ability to drive and use machines

Adverse effects on the ability to drive and operate machinery have not been observed.

1.3.1.5.8 Undesirable effects
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 **ARTEPIP**:
(Dihydroartemisinin 40mg +Piperaquine 320mg) Tablet:

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

Description of selected adverse reactions

The ADRs noted for **ARTEPIP** (Dihydroartemisinin +Piperaquine) 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 ARTEPIP:

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

1.3.1.5.9 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.

1.3.1.6 Pharmacological properties

1.3.2.6.1 Pharmacodynamic properties

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

Pharmacodynamic effects

Artenimol 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 Eurartesim have been assessed in two large randomised, open-label clinical trials:

Study DM040010 was conducted in Asian adult and paediatric patients with uncomplicated *P. falciparum* malaria. Eurartesim treatment was compared with Artesunate + Mefloquine (AS + MQ). The primary end-point was the PCR-corrected cure rate at Day 63.

Study DM040011 was conducted in African paediatric patients with uncomplicated *P. falciparum* malaria. Eurartesim treatment was compared with Artemether + Lumefantrine (A + L). The primary end-point was PCR-corrected cure rate at Day 28.

The results for the primary endpoint in the modified intent to treat (m-ITT) populations (defined as all randomised patients who received at least one dose of the study treatment, with the exclusion of those patients lost to follow up for unknown reasons) were as follows:

Study	PCR-corrected cure rate (m-ITT)			
	Eurartesim	**AS + MQ**	**A + L**	**95 % two-sided CI on the treatment difference (Eurartesim - Comparator); p-value**
DM040010 (n=1087)	97.0%	95.3%	-	(-0.84, 4.19)%; p=0.161
DM040011 (n=1524)	92.7%	-	94.8%	(-4.59, 0.45)%; p=0.128

In each case the results confirmed that Eurartesim was not inferior to the comparator medicinal product. In both studies, the true treatment failure rate was below the 5% efficacy threshold set by WHO.

The age-specific PCR-corrected cure rates in the m-ITT populations are tabulated below for the Asian and African studies, respectively:

Study	PCR-corrected cure rate (m-ITT)			
	Eurartesim	**AS + MQ**	**A + L**	**95% two-sided CI on the treatment difference (Eurartesim - Comparator); p-value**
DM04010 (n=1087)				
≤5years	100.0%	100.0%	-	-
>5 to ≤12years	98.2%	96.5%	-	(-3.67, 7.09)%; 0.605
>12 to ≤18 years	97.3%	100.0%	-	(-6.40, 0.99)%; 1.000
>18 to ≤64 years	96.6%	94.4%	-	(-0.98, 5.30)%; 0.146
DM04011 (n=1524)				
≤1 year	91.5%	-	98.5%	(-12.66, -1.32)%(1); 0.064
>1 to ≤ 2 years	92.6%	-	94.6%	(-6.76, 2.63)%; 0.413
>2 to ≤5 years	93.0%	-	94.0%	(-4.41, 2.47)%; 0.590

(1) This CI is asymptotic because the exact CI could not be computed

1.3.1.6.2 Pharmacokinetic properties

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

Absorption

Artenimol (Dihydroartemisinin) is very rapidly absorbed, T_{max} being approximately 1-2 hrs after single and multiple dosing. In patients, mean C_{max}(CV%) and AUC_{INF} of artenimol (observed after the first dose of Eurartesim) were 752 (47%) ng/ml and 2,002 (45 %) ng/ml*h, respectively.

Artenimol bioavailability appears to be higher in malaria patients than in healthy volunteers, possibly because malaria *per se* has an effect on artenimol disposition. This may reflect malaria-associated impairment of hepatic function, causing an increase in artenimol 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 C_{max} and AUC_{INF} of artenimol ranged between 180-252 ng/ml and 516-684 ng/ml*h, respectively.

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

In healthy volunteers, artenimol 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 T_{max} of approximately 5 hours following a single and repeated dose. In patients mean (CV%) C_{max} and AUC_{0-24} (observed after the first dose of Eurartesim) 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, Eurartesim 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 artenimol are highly bound to human plasma proteins: the protein binding observed in *in vitro* studies was 44-93% for artenimol and >99% for piperaquine. Moreover, from *in vitro* and *in vivo* data in animals, piperaquine and artenimol tend to accumulate in RBC.

Artenimol 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

Artenimol is principally converted to α- artenimol-β-glucuronide (α- artenimol-G). Studies in human liver microsomes showed that artenimol was metabolised by the UDP-glucuronosyltransferase (UGT1A9 and UGT2B7) to α- artenimol-G with no cytochrome P450-mediated metabolism.

In vitro drug-drug interaction studies revealed that artenimol is an inhibitor of CYP1A2; therefore, there is the potential for artenimol to increase plasma concentrations of CYP1A2 substrates (see section 4.5).

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.

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

In human studies, piperaquine was found to be a mild inhibitor of CYP3A4 enzyme while potent inhibitors of CYP3A4 activity caused mild inhibition of piperaquine metabolism (see section 4.5).

Elimination

The elimination half-life of artenimol 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%). Artenimol is eliminated by metabolism (mainly glucuroconjugation). Its clearance was found to be slightly lower in female than in male healthy volunteers. Data regarding artenimol 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 people.

In a paediatric pharmacokinetic study, and based on very limited sampling, minor differences were observed for artenimol 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).

1.3.1.6.3 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.

Artenimol and piperaquine were not genotoxic/clastogenic based on *in vitro* and *in vivo* testing.

No carcinogenicity studies have been performed.

Artenimol 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 artenimol 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 artenimol pro-drugs. In humans, the potential neurotoxicity of orally administered artenimol can be considered highly unlikely, given the rapid clearance ofartenimol, and its short exposure (3 days of treatment for malaria patients). There was no evidence of artenimol-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 IC_{50} was 0.15 µmol for piperaquine and 7.7 µmol forartenimol. The association of artenimol and piperaquine does not produce hERG inhibition greater than that of the single compounds.

Phototoxicity

There are no phototoxicity concerns withartenimol, 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.

1.3.1.7 Pharmaceutical Particulars

1.3.1.7.1 Incompatibilities

Not applicable.

1.3.1.7 2 Shelf life:

36 Months

1.3.1.7.3 Special precautions for storage :

Store below 30°C. Protect from light.

1.3.1.7.4 Nature and contents of container

Tablets are packaged in PVC/ aluminum blisters containing 3, 6, 9 or 12 tablets.

1.3.1.7.5 Special precautions for disposal

No special requirements.

1.3.1.8. Marketing authorisation holder

Ningbo Voice Biochemic Co., Ltd.
298 West Zhonghsan Road, Ningbo . P.R. China