1.3.1 Summary of Product Characteristics (SmPC)

1. Name of the medicinal product:

NOMEPRAMAL TABLETS

1.1 Name of the medicinal product:

1.2 Strength:

Each film coated tablet contains:
Dihydroartemisinin: 40 mg
Piperaquine Phosphate: 320 mg
Excipients: q.s.
Colour: Indigo Carmine

1.3 Pharmaceutical form:

Tablet

2. Qualitative and quantitative composition

NOMEPRAMAL TABLETS (Dihydroartemisinin and Piperaquine Phosphate Tablets)

Each film coated tablet contains:
Dihydroartemisinin: 40 mg
Piperaquine Phosphate: 320 mg
Excipients: q.s.
Colour: Indigo Carmine

3. Pharmaceutical form

Tablet

4. Clinical particulars:

4.1 Therapeutic indications:

Dihydroartemisinin and Piperaquine Phosphate Tablets is indicated for the treatment of uncomplicated malaria in adults, children and infants. Dihydroartemisinin and Piperaquine Phosphate Tablets is active against all Plasmodium parasites that cause malaria in humans.

4.2 Posology and method of administration

Posology

Dihydroartemisinin and Piperaquine Phosphate Tablets should be administered over three consecutive days for a total of three doses taken at the same time each day.

Dosing should be based on body weight as shown in the following table:

Body weight	Number of tablets	Daily dose	
		Piperaquine	Dihydroartemisinin
25 kg to less than 36 kg	2 tablets per day for 3 days	640 mg	80 mg
36 kg to less than 60 kg	3 tablets per day for 3 days	960 mg	120 mg
60 kg to less than 80 kg	4 tablets per day for 3 days	1280 mg	160 mg
80 kg or more	5 tablets per day for 3 days	1600 mg	200 mg

For patients weighing less than 25 kg, a lower strength tablet is available and should be used if required.

If a patient vomits within 30 minutes of taking Dihydroartemisinin and Piperaquine Phosphate Tablets, 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 Dihydroartemisinin and Piperaquine Phosphate Tablets should not be attempted more than once. If the second dose is vomited, alternative antimalarial therapy should be started.

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.

There are no data on a second course of treatment.

No more than two courses of Dihydroartemisinin and Piperaquine Phosphate Tablets may be given within a 12-month period.

A second course of Dihydroartemisinin and Piperaquine Phosphate Tablets should not be given within 2 months after the first course due to the long elimination half-life of piperaquine.

Special populations

Elderly

Clinical studies of Dihydroartemisinin and Piperaquine Phosphate Tablets did not include patients aged 65 years and over, therefore no dosing recommendation can be made. Considering the possibility of age-associated decrease in hepatic and renal function, as well as a potential for heart disorders caution should be exercised when administering the product to the elderly.

Hepatic and renal impairment

Dihydroartemisinin and Piperaquine Phosphate Tablets has not been evaluated in subjects with moderate or severe renal or hepatic insufficiency. Therefore, caution is advised when administering Dihydroartemisinin and Piperaquine Phosphate Tablets to these patients.

Method of administration

Dihydroartemisinin and Piperaquine Phosphate Tablets should be taken orally with water and without food.

- Each dose should be taken no less than three hours after the last food intake.
- No food should be taken within 3 hours after each dose.

Fill a cup (Approximately 10ml per tablet) with water. Place the tablet (or half tablet) in the liquid. As soon as the tablet has dispersed completely swallow all the mixture. Afterwards, immediately rinse the cup with as additional small amount of water (approximately 10ml) and drink the water completely.

As directed by Physician.

Method of administration: Oral

4.3 Contraindications

- Hypersensitivity to 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 QTcinterval 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), antidepressivemedicinal products.
- Certain antimicrobialmedicinal products, including medicinal products of the following classes:
  − macrolides (e.g. erythromycin, clarithromycin),

− fluoroquinolones (e.g. moxifloxacin, sparfloxacin),
− imidazole and triazole antifungal medicinal products,
− 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 Eurartesim is started (e.g. mefloquine, halofantrine, lumefantrine, chloroquine, quinine and other antimalarialmedicinal products) taking intoaccount their elimination half-life.

4.4 Special warnings and precautions for use

Dihydroartemisinin and Piperaquine Phosphate Tablets should not be used to treat complicated malaria.

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.

Piperaquine is a mild inhibitor of CYP3A4. Caution is recommended when co-administering Dihydroartemisinin and Piperaquine Phosphate Tablets with medicinal products exhibiting variable patterns of inhibition, induction or competition for CYP3A4 as the therapeutic and/or toxic effects of some coadministered medicinal products could be altered.

Piperaquine is also a substrate of CYP3A4. A moderate increase of piperaquine plasma concentrations (<2-fold) was observed when co-administered with strong CYP3A4 inhibitors, resulting in a potential exacerbation of the effect on QTc prolongation.

Exposure to piperaquine may also be increased when co-administered with mild or moderate CYP3A4-inhibitors (e.g. oral contraceptives). Therefore, caution should be applied when coadministering Dihydroartemisinin and Piperaquine Phosphate Tablets with any CYP3A4-inhibitor and ECG monitoring should be considered.

Due to the lack of multiple dose PK data for piperaquine, administration of any strong CYP3A4-inhibitors should be discouraged after initiation (i.e. the first dose) of Dihydroartemisinin and Piperaquine Phosphate Tablets.

Dihydroartemisinin and Piperaquine Phosphate Tablets should not be used during pregnancy in situations where other suitable and effective antimalarials are available.

In the absence of carcinogenicity study data, and due to lack of clinical experience with repeated courses of treatment in humans, no more than two courses of Dihydroartemisinin and Piperaquine Phosphate Tablets should be given in a 12-month period.

Effects on cardiac repolarization

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

The WHO guidelines no longer recommend performing an ECG before prescribing piperaquine/dihydroartemisinin. However, piperaquine/dihydroartemisinin should not be used in patients with known congenital long QT interval syndromes or those who have a clinical condition or are taking a medication that prolongs the QT interval.

There has been no evidence of piperaquine-related cardiotoxicity in large randomized trials or in extensive deployment in the field.

Delayed Haemolytic Anaemia

Delayed haemolytic anaemia has been observed up to one month following use of IV artesunate and oral artemisinin-based combination treatment (ACT) including reports involving piperaquine/dihydroartemisinin. Risk factors may include young age (children under 5 years old) and previous treatment with IV artesunate.
Patients and caregivers should be advised to be vigilant for signs and symptoms of post-treatment haemolysis such as pallor, jaundice, dark-coloured urine, fever, fatigue, shortness of breath, dizziness and confusion.

Paediatric population

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 Dihydroartemisinin and Piperaquine Phosphate Tablets.

Hepatic and renal impairment

Piperaquine/dihydroartemisinin has not been evaluated in patients with moderate or severe renal or hepatic insufficiency. Due to the potential for higher plasma concentrations of piperaquine to occur, caution is advised if Dihydroartemisinin and Piperaquine Phosphate Tablets 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

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.

A limited number of drug-drug pharmacokinetic interaction studies with Dihydroartemisinin and Piperaquine Phosphate Tablets have been performed in healthy adult subjects. The assessment of the potential for drug-drug interactions to occur is therefore based on either in vivo or in vitro studies.

Effect of Dihydroartemisinin and Piperaquine Phosphate Tablets on co-administered medicinal products

Piperaquine is metabolised by, and is an inhibitor of, CYP3A4. The concurrent administration of oral Dihydroartemisinin and Piperaquine Phosphate Tablets with 7.5 mg oral midazolam, a CYP3A4 probe substrate, led to a modest increase (≤2 fold) in midazolam and its metabolites exposure in healthy adult subjects. This inhibitory effect was no longer evident one week after last administration of Dihydroartemisinin and Piperaquine Phosphate Tablets. Therefore, 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 Dihydroartemisinin and Piperaquine Phosphate Tablets.

From in vitro data, 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.

Dihydroartemisinin administration may result in a slight decrease in CYP1A2 activity. Caution is therefore, advised when Dihydroartemisinin and Piperaquine Phosphate Tablets 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 dihydroartemisinin.

Effect of co-administered medicinal products on Dihydroartemisinin and Piperaquine Phosphate Tablets

Piperaquine is metabolised by CYP3A4 in vitro. The concurrent administration of a single dose of oral clarithromycin, (a strong CYP3A4 inhibitor probe) with a single dose of oral Dihydroartemisinin and Piperaquine Phosphate Tablets led to a modest increase (≤2-fold) in piperaquine exposure in healthy adult subjects. This increase in exposure to the antimalarial combination may result in an exacerbation of the effect on QTc. Therefore, particular caution is required if Dihydroartemisinin and Piperaquine Phosphate Tablets is administered to patients taking potent CYP3A4 inhibitors (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.

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

Paediatric population

Drug-drug interaction studies have only been performed in adults. The extent of interactions in the paediatric population is not known.

Oral contraceptives

When co-administered to healthy women, Dihydroartemisinin and Piperaquine Phosphate Tablets exerted only a minimum effect on an estrogen/progestinic combination oral contraceptive treatment, increasing the ethynilestradiol rate of absorption (expressed by geometric mean Cmax) by about 28% but not significantly changing the exposure to ethynilestradiol and levonorgestrel and not influencing contraception activity as demonstrated by the similar plasma concentrations of follicle stimulating hormone (FSH), luteinizing hormone (LH) and progesterone observed after oral contraceptive treatment with or without concomitant Dihydroartemisinin and Piperaquine Phosphate Tablets administration.

Food interaction

Absorption of piperaquine is increased in the presence of fatty food which may increase its effect on QTc interval. Therefore, Dihydroartemisinin and Piperaquine Phosphate Tablets should be taken with water only, Dihydroartemisinin and Piperaquine Phosphate Tablets should

not be taken with grapefruit juice as it is likely to lead to increased piperaquine plasma concentrations.

4.6 Fertility, pregnancy and breastfeeding

Pregnancy

There are insufficient data on the use of dihydroartemisinin and piperaquine in pregnant women. Based on animal data, piperaquine/dihydroartemisinin 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.

Dihydroartemisinin and Piperaquine Phosphate Tablets should not be used during pregnancy in situations where other suitable and effective antimalarials are available.

Breast-feeding

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.

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 dihydroartemisinin in both females and males.

4.7 Effects on ability to drive and use machines:

Adverse event data collected in clinical trials suggest that It 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 piperaquine/dihydroartemisinin 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 piperaquine/dihydroartemisinin.

In a randomized trial in which 767 adults and children with uncomplicated P. falciparum malaria were exposed to piperaquine/dihydroartemisinin, 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 QTcprolonged (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 piperaquine/dihydroartemisinin 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. Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness, 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

SOC	Very common	Common	Uncommon
Infections and infestations		P. falciparum infection	Respiratory tract infection; influenza
Blood and lymphatic system disorders		Anaemia	
Metabolism and nutrition disorders			Anorexia
Nervous system disorders		Headache	Convulsion; dizziness
Cardiac disorders		QTc interval prolongation; tachycardia	Cardiac conduction disorders; sinus arrhythmia; bradycardia
Respiratory, thoracic and mediastinal disorders			Cough
Gastrointestinal			Vomiting; diarrhoea;

disorders			nausea; abdominal pain
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 piperaquine/dihydroartemisinin 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 acutemalaria. 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 majorityof paediatric experience is derived from African children aged 6 months to 5 years.

Frequency of ADRs in paediatric patients participating in clinical studies with Dihydroartemisinin and Piperaquine Phosphate Tablets

SOC	Very common	Common	Uncommon
Infections and infestations	Influenza; P. falciparum infection	Respiratory tract infection; ear infection	
Blood and lymphatic system disorders		Thrombocytopenia; leukopenia/neutropenia; leukocytosis; anaemia	Thrombocytosis; splenomegaly; lymphadenopathy; hypochromasia
Metabolism and nutrition disorders		Anorexia	

Nervous system disorders			Convulsion; headache
Eye disorders		Conjunctivitis	
Cardiac disorders		QTc interval prolongation; heart rate irregular	Cardiac conduction, disorders; cardiac murmur
Respiratory, thoracic and mediastinal disorders	Cough		Rhinorrhoea; epistaxis
Gastrointestinal disorders		Vomiting; diarrhoea; abdominal pain	Stomatitis; nausea
Hepatobiliary disorders			Hepatitis; hepatomegaly; abnormal liver function tests; jaundice
Skin and subcutaneous tissue disorders		Dermatitis; rash	Acanthosis; pruritis
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 piperaquine/dihydroartemisinin. 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

5. Pharmacological properties:

5.1 Pharmacodynamics properties:

Pharmacotherapeutic group: Antiprotozoals, antimalarials, artemisinin and derivatives, combinations,

ATC code: P01BF05

Pharmacodynamic effects

Dihydroartemisinin 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, aclose structural analogue. Chloroquine binds to toxic haem (derived from the patient's haemoglobin) within the malaria parasite, preventing its detoxification via a polymerisation step.

Piperaquine is a bisquinolone, and this class has shown good antimalarial activity against chloroquine-resistantPlasmodium strains in vitro. The bulky bisquinolone structure may be important for activityagainst 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.

5.2 Pharmacokinetic Properties

The absorption characteristics of Dihydroartemisinin and Piperaquine Phosphate Tablets have been determined after administration of Dihydroartemisinin/Piperaquine Tetraphosphate 40/320 mg FDC chewable tablets in healthy volunteers in the fasting state as follows:

Pharmacokinetic variable'	**Mean value ± standard deviation (*)**	
	Dihydroartemisinin	Piperaquine
Maximum concentration (Cmax) ng/ml	107 ± 54 (93)	28 ± 12 (25)
Area under the curve (AUC0–∞), a measure of the extent of absorptionng. hour/ml	236 ± 122	1474 ± 912
Time to attain maximum concentration (tmax) hour	1.27 ± 0.58	3.65 ± 1.97

	Dihydroartemisinin	Piperaquine
General		
	Bioavailability is higher in patients with malaria compared to healthy volunteers.	
Absorption		
Absolute bioavailability	NA	NA
Oral Bioavailability	NA	NA
Food effect	Exposure increased by 43% with a high fat/high calorie meal	Exposure increased approximately 3-fold with a high fat/high calorie meal
Distribution		
Volume of distribution (mean)	0.8 L/kg	730 L/kg
Plasma protein binding in vitro	44–93%	> 99%
Tissue distribution	Accumulates in red blood cells	Accumulates in red blood cells
Metabolism		
	Hepatic glucuronidation to α-artenimol-β-glucuronide	Hepatic: major metabolites are a carboxyl acid cleavage product and a mono-N-oxidated product
Elimination		
Mean elimination half-life	1 hour	22 days
Mean oral clearance	1.34 L/h/kg	2.1 L/h/kg
% of dose excreted in urine	Negligible as intact drug	NA
% of dose excreted in faeces	Negligible as intact drug	NA
Pharmacokinetic linearity	NA	NA
Drug interactions (in vitro)	NA	NA
Transporters		

Metabolising enzymes	UGT1A9 and UGT2B7	CYP3A4 (mainly), CYP2C9 and CYP2C19
	Inhibitor of CYP1A2	Mild inhibitor of CYP3A4 and CYP2C19 Inducer of CYP2E1
Special populations		
Renal impairment	NA	NA
Hepatic impairment	NA	NA
Elderly patients	NA	NA

Patients with hepatic or renal insufficiency

No specific pharmacokinetic studies have been performed in patients with hepatic or renalinsufficiency, or in elderly people.

Paediatrics

In a paediatric pharmacokinetic study, and based on very limited sampling, minor differences wereobserved for dihydroartemisinin pharmacokinetics between the paediatric and adult populations. The meanclearance (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 lowerthan in the adults (0.801 L/kg). The same comparison showed that piperaquine absorption rate constant and terminal half-life inchildren were predominantly similar to those seen in adults. However, the apparent clearance wasfaster (1.30 versus1.14 L/h/kg) and the apparent total volume of distribution was lower in thepaediatric 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.

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

Dihydroartemisinin 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 dihydroartemisinin 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 dihydroartemisinin pro-drugs. In humans, the potential neurotoxicity of orally administered dihydroartemisinin can be considered highly unlikely, given the rapid clearance of dihydroartemisinin, and its short exposure (3 days of treatment for malaria patients). There was no evidence of dihydroartemisinin-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 fordihydroartemisinin. The associationof dihydroartemisinin and piperaquine does not produce hERG inhibition greater than that of the single compounds.

Phototoxicity

There are no phototoxicity concerns with dihydroartemisinin, 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 anderythema) were observed 24 hours after oral treatment in mice exposed to UV radiation.

6. Pharmaceutical particulars

6.1 List of excipients

Sr. No	Ingredients	SPEC
1	Dihydroartemisinin	IH
2	Piperaquine Phosphate	IH
3	Lactose	BP
4	Starch	BP
5	Crosspovidone	BP
6	Microcrystalline Cellulose	BP
7	Starch	BP
8	Sodium Methyl Paraben	BP
9	Sodium Propyl Paraben	BP
10	Sodium Benzoate	BP
11	Sodium Starch Glycolate	BP
12	Purified Talc	BP
13	Magnesium Stearate	BP
14	Starch	BP
15	Microcrystalline Cellulose	BP
16	Starch (Compensate)	BP

6.2 Incompatibilities

None

6.3 Shelf life

36 Months (3 Years) from date of manufacturing

6.4 Special precautions for storage

Store below 30°C in a dry place. |Protect from light. Keep medicines out of reach of children.

6.5 Nature and contents of container

NOMEPRAMAL TABLETS (Dihydroartemisinin and Piperaquine Phosphate Tablets) is Alu-Alu blister of 9 tablet such 10 Blister packed in a carton along with pack insert.

6.6 Special precautions for disposal:

None

7. Registrant:

M/s NOMEDI PHARMACEUTICALS LTD
387, Agege Motor Road, Mushin,

P. O. Box 11623, Ikeja, Lagos, Nigeria.

8. MANUFACTURER

CORAL LABORATORIES LTD.

Plot No. 27-28, Pharmacity, Selaqui, Dehradun,

Uttarakhand, India

Phone: 0135-2698422/466

Fax: 0135-2699121

E-mail: doon@corallab.com

9. Date of revision of the text: NA

2.16.2 PATIENT INFORMATION LEAFLET

Enclosed

NOMEPRAMAL TABLETS

Dihydroartemisinin and Piperaquine Phosphate Tablets

COMPOSITION:
Each film coated tablet contains:
Dihydroartemisinin ..... 40 mg
Piperaquine Phosphate ... 320 mg
Excipients ..... q.s.
Colour: Indigo Carmine

THERAPEUTIC CLASS:
Antimalarial

PHARMACOLOGY:
Dihydroartemisinin: Dihydroartemisinin mainly interferes with the membrane structures of trophozoites (erythrocytic asexual forms), i.e. whorled food vacuole membrane, distended mitochondria, swollen nuclear 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.

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.

INDICATIONS:
NOMEPRAMAL TABLET is indicated for the treatment of uncomplicated Plasmodium falciparum malaria.

DOSAGE:

Weight (Age group)	5 - 9.9 kg (6 months-1 Year)	10 – 19.9 kg (≥ 2-9 Years)	20 – 39.9 kg (≥ 10-14 Years)	≥ 40 kg (≥ 15 Years)
Day 1	0.5 Tablet	1 Tablet	2 Tablets	3 Tablets
Day 2	0.5 Tablet	1 Tablet	2 Tablets	3 Tablets
Day 3	0.5 Tablet	1 Tablet	2 Tablets	3 Tablets
Total	1.5 Tablets	3 Tablets	6 Tablets	9 Tablets

METHOD OF ADMINISTRATION:
NOMEPRAMAL TABLETS should be taken orally with water 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.

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

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.

WARNINGS & PRECAUTIONS:
NOMEPRAMAL TABLETS 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 anti- malarial agent is started due to treatment failure or a new malaria infection.

Piperaquine is an inhibitor of CYP3A4. Caution is recommended when co-administering NOMEPRAMAL TABLETS 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.

NOMEPRAMAL TABLETS should not be used during pregnancy in situations where other suitable and effective antimalarials are available. Women taking NOMEPRAMAL TABLETS should not breast-feed during their treatment.

In the absence of carcinogenicity study data, and due to lack of clinical experience with repeated courses of treatment in humans, no more than two courses of NOMEPRAMAL TABLETS should be given in a 12- month period.

SIDE EFFECTS:
Most common side effects observed: Headache, prolonged QTc, P falciparum infection, Anaemia, Tachycardia, Asthenia, Pyrexia.

OVERDOSAGE:
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.

STORAGE CONDITION:
Store below 30°C, in a dry place. Protect from Light.
Keep medicine out of reach of children.

PRESENTATION:
Blister Pack of 9 Tablets.

NAFDAC Reg. No.:

Manufactured by:
Coral Laboratories Ltd.
Plot No. 27/28, Pharmacity, Selaqui,
Dehradun - 248 011, Uttarakhand, INDIA.
Email: exports@corallab.com
Website : www.corallab.com

Manufactured for:
Nomedi Pharmaceuticals Limited.
RC: 871751 *An Oculus PharmaCare Ltd. Company.*
387, Agege Motor Road, Mushin, P. O. Box 11623,
Ikeja, Lagos - Nigeria.
Tel: 0813 336 8311
Email: info@nomedipharma-ng.com
Website: www.nomedipharma-ng.com

90 (W) x 150 (H) mm

PANTONE 160 C

PATIENT INFORMATION LEAFLET: INFORMATION FOR THE USER

NOMEPRAMAL TABLETS

(Dihydroartemisinin and Piperaquine Phosphate Tablets)

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

• Keep this leaflet. You may need to read it again.

• If you have any further questions, ask your doctor, health care provider or pharmacist.

• This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.

• If you get any side effects, talk to your doctor, health care provider or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet

1. WHAT NOMEPRAMAL TABLETS IS AND WHAT IT IS USED FOR

NOMEPRAMAL TABLETS is indicated for the treatment of uncomplicated malaria in adults, children and infants NOMEPRAMAL TABLETS is active against all Plasmodium parasites that cause malaria in humans.

Consideration should be given to official guidance on the appropriate use of antimalarial medicinal products.

For complete cure it is important that you complete the prescribed dose as advised by your doctor, pharmacist or health care provider.

2. WHAT YOU NEED TO KNOW BEFORE YOU TAKE NOMEPRAMAL TABLETS

Do not take NOMEPRAMAL TABLETS

NOMEPRAMAL TABLETS should not be used in patients with known congenital long QT interval syndromes or those who have a clinical condition or are taking a medication that prolongs the QT interval.

Warnings and precautions

Dihydroartemisinin and Piperaquine Phosphate Tablets should not be used to treat complicated malaria.

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.

Piperaquine is a mild inhibitor of CYP3A4. Caution is recommended when co-administering Dihydroartemisinin and Piperaquine Phosphate Tablets with medicinal products exhibiting variable patterns of inhibition, induction or competition for CYP3A4 as the therapeutic and/or toxic effects of some coadministered medicinal products could be altered.

Piperaquine is also a substrate of CYP3A4. A moderate increase of piperaquine plasma concentrations (<2-fold) was observed when co-administered with strong CYP3A4 inhibitors, resulting in a potential exacerbation of the effect on QTc prolongation.

Exposure to piperaquine may also be increased when co-administered with mild or moderate CYP3A4-inhibitors (e.g. oral contraceptives). Therefore, caution should be applied when coadministering Dihydroartemisinin and Piperaquine Phosphate Tablets with any CYP3A4-inhibitor and ECG monitoring should be considered.

Due to the lack of multiple dose PK data for piperaquine, administration of any strong CYP3A4-inhibitors should be discouraged after initiation (i.e. the first dose) of Dihydroartemisinin and Piperaquine Phosphate Tablets.

Dihydroartemisinin and Piperaquine Phosphate Tablets should not be used during pregnancy in situations where other suitable and effective antimalarials are available.

In the absence of carcinogenicity study data, and due to lack of clinical experience with repeated courses of treatment in humans, no more than two courses of Dihydroartemisinin and Piperaquine Phosphate Tablets should be given in a 12-month period.

<u>Effects on cardiac repolarization</u>

In clinical trials with piperaquine/dihydroartemisinin limited ECGs were obtained during treatment. These showed that QTc prolongation occurred more frequently and to a larger extent

in association with piperaquine/dihydroartemisinin therapy than with the comparators for details of the comparators). Analysis of cardiac adverse events in clinical trials showed that these were reported more frequently in piperaquine/dihydroartemisinin-treated patients than in those treated with comparator antimalarial. Before the third dose of piperaquine/dihydroartemisinin, in one of the two Phase III studies 3/767 patients (0.4%) were reported to have a QTcF value of >500 milliseconds (ms) versus none in the comparator group.

The WHO guidelines no longer recommend performing an ECG before prescribing piperaquine/dihydroartemisinin. However, piperaquine/dihydroartemisinin should not be used in patients with known congenital long QT interval syndromes or those who have a clinical condition or are taking a medication that prolongs the QT interval.

There has been no evidence of piperaquine-related cardiotoxicity in large randomized trials or in extensive deployment in the field.

Delayed Haemolytic Anaemia

Delayed haemolytic anaemia has been observed up to one month following use of IV artesunate and oral artemisinin-based combination treatment (ACT) including reports involving piperaquine/dihydroartemisinin. Risk factors may include young age (children under 5 years old) and previous treatment with IV artesunate.
Patients and caregivers should be advised to be vigilant for signs and symptoms of post-treatment haemolysis such as pallor, jaundice, dark-coloured urine, fever, fatigue, shortness of breath, dizziness and confusion.

Paediatric population

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 Dihydroartemisinin and Piperaquine Phosphate Tablets.

Hepatic and renal impairment

Piperaquine/dihydroartemisinin has not been evaluated in patients with moderate or severe renal or hepatic insufficiency. Due to the potential for higher plasma concentrations of piperaquine to occur, caution is advised if Dihydroartemisinin and Piperaquine Phosphate Tablets is administered to patients with jaundice and/or with moderate or severe renal or hepatic insufficiency, and ECG and blood potassium monitoring are advised.

Pregnancy and breast-feeding

Pregnancy

There are insufficient data on the use of dihydroartemisinin and piperaquine in pregnant women. Based on animal data, piperaquine/dihydroartemisinin 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.

Dihydroartemisinin and Piperaquine Phosphate Tablets should not be used during pregnancy in situations where other suitable and effective antimalarials are available.

Breast-feeding

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.

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 dihydroartemisinin in both females and males.

Driving and using machines

Adverse event data collected in clinical trials suggest that **NOMEPRAMAL TABLETS** has no influence on the ability to drive and operate machines once the patient has recovered from the acute infection.

3. HOW TO TAKE NOMEPRAMAL TABLETS

Always take **NOMEPRAMAL TABLETS** exactly as your doctor has told you. You should check with your doctor, pharmacist or health care provider if you are not sure.

If you take more NOMEPRAMAL TABLETS than you should

If you accidentally take a lot more tablets than the doctor prescribed, contact a doctor or the nearest hospital emergency department immediately, or make sure that someone else contacts them for you. If any of these symptoms occur, **stop the treatment and consult a doctor immediately.**

If you forget to take NOMEPRAMAL TABLETS

Try to make sure that you do not miss any dose. However, if you do forget a dose, take the missed dose as soon as you realise that you have forgotten it. Then take the next dose after the prescribed interval. **Do not take a double dose to make up for a forgotten tablet.**

If you stop taking NOMEPRAMAL TABLETS

To be effective the medicine must be taken regularly at the dose prescribed and for as long as your doctor has advised. The disappearance of fever or any other symptoms does not mean that you are completely cured. Any sensations of fatigue, nausea, vomiting might not be due to the drug but to the infection itself. Reducing or suspending your treatment would have no effect on these sensations or symptoms and would only delay your recovery.

If you have any further questions on the use of this product, ask your doctor, pharmacist or health care provider.

4. POSSIBLE SIDE EFFECTS

The reported adverse effects of this drug are generally tolerable and temporary and they include dizziness, headache, cough, nausea, vomiting, anorexia, asthenia, abdominal pain, diarrhea, fever, as well as changes in biochemical and blood indices.

5. HOW TO STORE NOMEPRAMAL TABLETS (Dihydroartemisinin and Piperaquine Phosphate Tablets)

Keep this medicine out of the sight and reach of children.

Store below 30°C. Do not use **NOMEPRAMAL TABLETS (Dihydroartemisinin and Piperaquine Phosphate Tablets)** after the expiry date which is stated on the blister and the outer packaging after EXP. The expiry date refers to the last day of that month. Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. CONTENTS OF THE PACK AND OTHER INFORMATION

What **NOMEPRAMAL TABLETS (Dihydroartemisinin and Piperaquine Phosphate Tablets)** contains

The active ingredients are Dihydroartemisinin 40mg and Piperaquine Phosphate 320mg.

The other ingredients are:

Lactose BP, Starch BP, Crosspovidone BP, Microcrystalline Cellulose BP, Sodium Methyl Paraben BP, Sodium Propyl Paraben BP, Sodium Benzoate BP, Sodium Starch Glycolate BP, Purified Talc BP, Magnesium Stearate BP, Microcrystalline Cellulose BP.

What NOMEPRAMAL TABLETS (Dihydroartemisinin and Piperaquine Phosphate Tablets) looks like and contents of the pack

NOMEPRAMAL TABLETS (Dihydroartemisinin and Piperaquine Phosphate Tablets) description;

Blue coloured, round, biconvex, film coated tablets.

Carton containing;

NOMEPRAMAL TABLETS (Dihydroartemisinin and Piperaquine Phosphate Tablets) is Alu-Alu blister of 9 tablet such 10 Blister packed in a carton along with pack insert.