BRAND NAME:	**FANMET CAPSULES**
GENERIC NAME:	**Dihydroartemisinin & Piperaquine Phosphate Capsules**

1.3 PRODUCT INFORMATION

1.3.1 SUMMARY OF PRODUCT CHARACTERISTICS (SMPC)

Enclosed

BRAND NAME:	**FANMET CAPSULES**
GENERIC NAME:	**Dihydroartemisinin & Piperaquine Phosphate Capsules**

1. Name of drug product

FANMET CAPSULES

1.1 (Trade) name of product

Dihydroartemisinin & Piperaquine Phosphate Capsules

1.2 Strength

Dihydroartemisinin 40 mg

Piperaquine Phosphate 320 mg

1.3 Pharmaceutical Dosage Form

Oral dosage form **(**Capsules)

2. QUALITATIVE & QUANTITATIVE COMPOSITION

2.1 Qualitative Declaration

Each Hard Gelatin Capsules Contains:

Dihydroartemisinin……..40 mg

Piperaquine Phosphate…….320 mg

Excipients ……..…….q.s.

Capsules Shaped contains approved color

BRAND NAME:	**FANMET CAPSULES**
GENERIC NAME:	**Dihydroartemisinin & Piperaquine Phosphate Capsules**

Batch Formula:

Batch Size: 1,00,000 Capsules

Sr. No.	Ingredients	Spec.	Unit Formula (mg)	Batch Formula (kg)
DRY MIXING				
1	Dihydroartemisinin	IH	40.000*	4.000
2	Piperaquine Phosphate	IH	320.00*	32.000
3	Maize starch	BP	20.000*	2.200
4	Crosspovidone (polyplasdone XL)	USP	2.000	0.200
BINDER				
5	PVPK-30	USP	20.000	2.000
6	Isopropyl alcohol	BP	q.s	25.000
LUBRICATION				
7	Purified Talc	BP	8.000	0.800
8	Colloidal anhydrous silica	BP	1.500	0.150
9	Maize Starch	BP	17.000	1.700
10	Magnesium Stearate	BP	1.500	0.150
Weigh of Compressed Tablet			**430.00mg**	**43.00 Kg**
COATING				
11	E. H.G. Capsule size “0” Blue Opaque Cap / Light blue Opaque Body unprinted	IH	95.000	1,02,000 NOS.***
Weigh of Coated Tablet			**525.00mg**	**52.50 kg**

Remark:

*Quantity of Dihydroartemisinin & Piperaquine phosphate is taken after calculation based on assay.

**Maize starch quantity change according to change in quantity of Dihydroartemisinin and Piperaquine phosphate and 10% extra maize starch to be added in dry mixing stage to compensate loss during drying process.

*** 2.0% extra empty capsule to be issued for compensates the loss during filling.

BRAND NAME:	**FANMET CAPSULES**
GENERIC NAME:	**Dihydroartemisinin & Piperaquine Phosphate Capsules**

3. PHARMACEUTICAL DOSAGE FORM

Capsules

E.H.G. Capsules size ‘’0’’ blue opaque cap/ light blue opague body unprinted filled with white to off white colour powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

FANMET CAPSULES is indicated for the treatment of uncomplicated Plasmodium falciparum malaria, P. Vivax & P. malariae in adults, children and infants 6 months and over and weighing 7 kg or more.

4.2 Posology and method of administration

As directed by the Physician OR as stated below:

Posology

FANMET CAPSULES should be administered over three consecutive days for a total of three doses taken at the same time each day.

1st Day	2nd Day	3rd day
3 Capsules	3 Capsules	3 Capsules

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

- 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.

4.4 Special warnings and precautions for use

It 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 FANMET CAPSULES 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 FANMET CAPSULES 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 FANMET CAPSULES.

FANMET CAPSULES 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 FANMET CAPSULES should be given in a 12-month period.

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.

This medicine should not be taken in patients who have a history of arrhythmia or bradycardia (heart rhythm abnormality); congestive heart failure with reduced ventricular ejection. (Less blood is pumped by the heart)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 FANMET CAPSULES.

Hepatic and renal impairment

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

FANMET CAPSULES 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 FANMET CAPSULES 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 FANMET CAPSULES on co-administered medicinal products

Piperaquine is metabolised by, and is an inhibitor of, CYP3A4. The concurrent administration of oral FANMET CAPSULES 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 FANMET CAPSULES. 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 FANMET CAPSULES.

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 FANMET CAPSULES 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 FANMET CAPSULES

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 FANMET CAPSULES 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 (see section 4.4). Therefore, particular caution is required if FANMET CAPSULES 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. The interactions documented above for adults and the warnings in section 4.4 should be considered for the paediatric population.

Food interaction

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

4.6 Fertility, pregnancy and lactation

Pregnancy: In pregnant women, this medication is reserved for cases where its use is essential.

Breast-feeding: The available data do not make it possible to know whether this medication passes into breast milk. Women receiving this medication should not breastfeed for the duration of treatment.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Most side effects do not require any medical attention and disappear as your body adjusts to the medicine. Consult your doctor if they persist or if you're worried about them

Common side effects is

Palpitations

Atrial arrhythmias (altered heart rate)

Cough

Breathlessness

Nausea

Vomiting

Weakness

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.

5.0 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-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.

Pharmacokinetic properties

A) Dihydroartemisinin:

Absorption:

The reported oral bioavailability of Artenimol was reported to be 45% in healthy adults. The observed Tmax was 1-2 h. This is known to increase in malaria infected patients which could be attributed to reduced metabolism by the liver or the drug's collection in infected erythrocytes. Artenimol was obeserved to have flip-flop kinetics with an overall absorption half-life of 1.04 h. When administered with food the AUC for Artenimol increases by 144%. Cmax was observed to increase by 129% but was not found to be statistically significant. Food was observed to delay Tmax by 1 h.

Volume of Distribution: Artenimol was observed to have a mean apparent volume of distribution of 0.801 L/kg in adult patients and 0.705 L/kg in pediatric patients wit P. falciparum malaria.

Protein Binding: Artenimol has been reported to be 44-93% bound to plasma proteins. The identity of these proteins has not been reported.

Metabolism: The primary metabolite of Artenimol is the glucuronide conjugate, α-artenimol-β-glucuronide Label. It is largely metabolized by UGT1A9 with some contribution by UGT2B7.

Elimination: Artenimol is eliminated via metabolism to glucuronide conjugates Label. There is little data on elimination of Artenimol but elimination of unchanged artemisinin compounds in feces and urine has been reported to be negligible.

B) Piperaquine Phosphate:

Absorption:

Piperaquine is slowly absorbed and exhibits multiple peaks in its plasma concentration curve suggestive of enterohepatic recycling occurring alongside the absorption process. Due to this complication there is no discreet value for bioavailability but piperaquine is highly absorbed into systemic circulation. When taken with food, Cmax increases by 217% and mean exposure increases by 177%. Tmax is not affected by food and remains around 5 h. Piperaquine has been observed to accumulate more in females to a degree of 30-50% more than males. It also collects in red blood cells similar to Artenimol.

Volume of Distribution: Piperaquine is thought to distribute into a central compartment with an apparent volume of 26.7 L/kg, and two peripheral compartments with apparent volumes of 76.8 L/kg and 617 L/kg. These combine for a total volume of distribution of 720.5 L/kg.

Protein Binding: Piperaquine's binding to plasma proteins is considered to be virtually complete. It has been measured to be >99% in humans, rats, and dogs.

Metabolism: Piperaquine undergoes N-dealkylation, separating its aliphatic bridge from one of the nitrogen-containing rings 3. The resulting aldehyde is then oxidized to a carboxylic acid to form metabolite 1 (M1). The same nitrogen-containing rings can also undergo hydroxylation at one of two sites to form M3 or M4. M2 is formed via N-oxidation of one of the nitrogens in the quinoline groups at either side of the molecule. M5 results when both of these nitrogens are oxidized. M1 and M2 are the major metabolism products. Each of these metabolites were observed in the urine.

Elimination: Piperaquine is mainly excreted in the feces with a negligible amount in the urine.

5.3 Preclinical safety data

Non-clinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction and development.

BRAND NAME:	**FANMET CAPSULES**
GENERIC NAME:	**Dihydroartemisinin & Piperaquine Phosphate Capsules**

6. Pharmaceutical Particulars

6.1. List of excipients

Maize Starch

Crosspovidone

PVP K-30

Isopropyl alcohol

Purified Talc

Colloidal Anhydrous Silica

Magnesium Stearate

E. H.G. Capsule size "0" Blue Opaque Cap / Light blue Opaque Body unprinted

6.2. Incompatibilities

None

6.3. Shelf life

36 Months.

6.4. Special precautions for storage

Store below above 30^0 C. Protect from light.

6.5. Nature and contents of container

1 X 9 Capsules packed in Alu-PVC Blister.

6.6. Instruction for use and handling

No special requirement

7. Marketing Authorization Holder

MAXHEAL LABORATORIES PVT LTD

PLOT NO. - 2-7/80-85, SURSEZ,

G.I.D.C SACHIN, SURAT GUJARAT-

394230. INDIA

8. Marketing Authorization Number

Not Applicable.

9. Date of First Authorization /Renewal of the Authorization

Not Applicable.

10. Date of Revision of the

Not Applicable.

MAYDON PHARMACEUTICALS LTD.
15, Wilmer Street,
Off Town Planning Way,
Ilupeju Lagos.
Phone: 08074150577,
09037655687
e mail: maydonpharma@yahoo.com

6th December, 2023

The Deputy Director
Drug R&R
NAFDAC
Isolo,
Lagos.

Dear sir/ma,

SUBMISSION OF LAB SAMPLES

We hereby submit the samples of our products below for laboratory analysis.

- **CLONEX A CREAM**
- **DIADON CAPSULES**
- **WORMTAC**
- **DIFLAZON 50MG**
- **FANMET CAPSULES**
- **TENZELTOL 200MG TABLET**

Please find attached all the necessary supporting documents for your perusal

Yours faithfully

Pharm Ayobambo f
Managing Director