1.3.1 Summary Product Characteristics (SPC)

Product information for Health Professionals

1. Name of the medicinal product

- Product name : MALACT ® tablets
- Strength : Each tablet contain Dihydroartemisimin 40mg and Piperaquine Phosphate 320mg
- Pharmaceutical form : tablet

2. Qualitative and quantitative composition

- Qualitative Declaration, The active substance should be declared by its recommended INN. Accompanied by its salt or hydrate form if relevant: Dihydroartemisimin

  Piperaquine Phosphate
- Quantitative Declaration, The quantity of the active substance must be expressed per dosage unit.

Each tablet contain Dihydroartemisimin 40mg and Piperaquine Phosphate 320mg

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Tablet.

Blue, coated and round tablet.

4. Clinical particulars

4.1 Therapeutic indications

MALACT ® Tablet is a fixed-ratio drug combination being developed to prevent and treat mixed infections of uncomplicated malaria, including plasmodium falciparum resistant to other classics antimalarial drugs, particularly in endemic area in adult, children of 6years and above.

4.2 Posology and method of administration

Tablets for oral administration.

Patient should follow doctor's instruction. The recommended dosages are in the following table.

Age(Years)	>16Years	11-15Years	6-10Years
Day 1	3 tablets	2 tablets	1 1/2 tablets
Day 2	3 tablets	2 tablets	1 1/2 tablets
Day 3	3 tablets	2 tablets	1 tablet

4.3 Contraindication

MALACT ® Tablet is contraindicated in:

• Patients with known hypersensitivity to the active substances or to any of the excipients.

• Patients with severe malaria according to WHO definition.

• patients who are taking any drug which is metabolized by the cytochrome enzyme CYP2D6 (e.g. flecainide, metoprolol, imipramine, amitryptyline, clomipramine).

• Patients with a family history of sudden death or of congenital prolongation of the QTc interval on electrocardiograms, or with any other clinical condition known to prolong the QTc interval.

• Patients taking drugs that are known to prolong the QTc interval. These drugs include:

- antiarrhythmics of classes IA and III,

- neuroleptics, antidepressive agents,

- certain antibiotics including some agents of the following classes:
macrolides, fluoroquinolones, imidazole and triazole antifungal agents,

- certain non-sedating antihistamines (terfenadine, astemizole),

- cisapride.

• Patients with a history of symptomatic cardiac arythmias or with clinically relevant bradycardia or with congestive cardiac failure accompanied by reduced left ventricle ejection fraction.

• Patients with disturbances of electrolyte balance e.g. hypokalemia or hypomagnesemia.

4.4 Special warnings and precautions for use

MALACT ® Tablet must not be used in the first trimester of pregnancy in situations where other suitable and effective antimalarials are available (see section 4.6).

MALACT ® Tablet has not been evaluated for the treatment of severe malaria, including cases of cerebral malaria or other severe manifestations such as pulmonary oedema or renal failure.

Due to limited data on safety and efficacy, MALACT ® Tablet should not be given concurrently with any other antimalarial agent (see section 4.5) unless there is no other treatment option.

If a patient deteriorates whilst taking MALACT ®Tablet, alternative treatment for malaria should be started without delay. In such cases, monitoring of the ECG is recommended and steps should be taken to correct any electrolyte disturbances.

If quinine is given after MALACT ® Tablet, close monitoring of the ECG is advised (see section 4.5).

If MALACT ® Tablet is given after mefloquine, close monitoring of food intake is advised (see section 4.5).

In patients previously treated with halofantrine, MALACT ® Tablet should not be administered earlier than one month after the last halofantrine dose.

MALACT ® Tablets is not indicated for, and has not been evaluated in, the treatment of malaria due to P. vivax, P. malariae or P. ovale, although some patients in clinical studies had co-infection with P. falciparum and P. vivax at baseline. MALACT ® Tablet is active against blood stages of Plasmodium vivax, but is not active against hypnozoites.

MALACT ® Tablet is not indicated and has not been evaluated for prophylaxis.

Like other antimalarials (e.g. halofantrine, quinine and quinidine) MALACT ® Tablet has the potential to cause QT prolongation.

Patients who remain averse to food during treatment should be closely monitored as the risk of recrudescence may be greater.

Caution is advised when administering MALACT ® Tablet to patients with severe renal, hepatic or cardiac problems (see section 4.2).

4.5 Interaction with other medical products and other forms of interaction

Interaction with other antimalarials (see section 4.4)

Interaction with CYP450 3A4 inhibitors (ketoconazole)

Both dihydroartemisinin and piperaquine are metabolised predominantly by the cytochrome enzyme CYP3A4, and do not inhibit this enzyme at therapeutic concentrations. The concurrent oral administration of ketoconazole with MALACT ® led to a modest increase (≤ 2-fold) in dihydroartemisinin, DHA, and piperaquine exposure in healthy adult subjects. This increase in exposure to the antimalarial combination was not associated with increased side effects or changes in electrocardiographic parameters. Based on this study, dose adjustment of MALACT ® is considered unnecessary in falciparum malaria patients when administered in association with ketoconazole or other potent CYP3A4 inhibitors.

Interaction with CYP450 enzymes

Studies in humans have demonstrated that artemisinins have some capacity to induce CYP3A4 and CYP2C19 and inhibit CYP2D6 and CYP1A2. Although the magnitude of the changes was generally low it is possible that these effects could alter the therapeutic response of drugs that are predominantly metabolised by these enzymes (see sections 4.4 and 5.2).

Piperaquine was found to inhibit CYP2D6 in vitro. This may be of particular clinical relevance for compounds with a low therapeutic index. Co-administration of MALACT ® with drugs that are metabolised by this iso-enzyme is contraindicated (see section 4.3 and 5.2). In vitro studies indicated that Piperaquine metabolism is inhibited by halofantrine and quinine.

Interaction with protease inhibitor anti-retroviral drugs

Due to variable patterns of inhibition, induction or competition for CYP3A4 with protease inhibitor anti-retroviral drugs, use of such drugs, especially combinations of them, concomitantly with MALACT ®, requires clinical surveillance and monitoring of clinical response/ undesirable effects.

Other interactions

Administration of MALACT ® is contra-indicated in patients taking drugs that are known to prolong the QTC interval (see section 4.3).

In patients previously treated with halofantrine, MALACT ® should be dosed at least one month after the last halofantrine dose.

Due to the limited data on safety and efficacy, MALACT ® should not be given concurrently with any other antimalarial agent.

In addition, due to the propensity of some antimalarial agents to prolong the QTC interval, caution is advised when administering MALACT ® to patients in whom there may still be detectable concentrations of these drugs in the plasma following prior treatments.

4.6 Pregnancy and lactation

Pregnancy

There is insufficient data from the use of MALACT ® in pregnant women. Based on animal data, MALACT ® 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 dihydroartemisinin have shown evidence of post-implantation losses and teratogenicity in rats and rabbits. Other artemisinin derivatives have also demonstrated teratogenic potential with an increased risk during early gestation (see section 5.3). MALACT ® treatment must not be used during the first trimester of pregnancy in situations where other suitable and effective antimalarials are available (see section 4.4). However, it should not be withheld in life-threatening situations, where no other effective antimalarials are available. During the second and third trimester, treatment should only be considered if the expected benefit to the mother outweighs the risk to the foetus.

Lactation

Animal data suggest excretion into breast milk but no data are available in humans. Women taking MALACT ® should not breast-feed during their treatment. Due to the long elimination half-life of Piperaquine, it is recommended that breast-feeding should not resume until at least one week after the last dose of MALACT ® unless potential benefits to the mother and child outweigh the risks of MALACT ® treatment.

4.7 Effects on ability to drive and use machines

Patients receiving MALACT ® should be warned that dizziness or fatigue/asthenia may occur in which case they should not drive or use machines.

4.8 Undesirable effects

Like all active ingredient, this medicine may cause side effect the side effects recording during the clinic test with this drug are less frequent and the lesser intensity more than others antimalarials.

Common side effects that may occur are caused by Piperaquine affecting the digestive tract: nausea, abdominal pain, vomiting, loss of appetite, fatigue, and general weakness. Rarely rash and itching of the skin may occur

Some of these symptoms also accompany a malaria attack; it may be difficult to distinguish whether these are malaria symptoms or the adverse effects of drug.

In case of doubt, don't hesitate to consult a Physician or a Pharmacist.

4.9 Overdose

In cases of suspected over dosage symptomatic and supportive therapy should be given as appropriate, which should include ECG and blood potassium monitoring.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antimalarials, blood schizontocide, ATC code: P01 BE52.

Pharmacodynamic effects

Treatment of Acute Uncomplicated P. falciparum Malaria

The efficacy of MALACT ® Tablets was evaluated for the treatment of acute, uncomplicated malaria (defined as symptomatic P. falciparum malaria without signs and symptoms of severe malaria or evidence of vital organ dysfunction) in 3-dose regimen studies. Baseline parasite density ranged from 500/μL - 200,000/μL (0.01% to 4% parasitemia) in the majority of patients. Studies were conducted in otherwise healthy, partially immune or non-immune adults and children (≥5kg body weight) with uncomplicated malaria in Thailand, sub-Saharan Africa, Europe, and South America.

Efficacy endpoints consisted of:

• 28-day cure rate, proportion of patients with clearance of asexual parasites within 7 days without recrudescence by day 28

• parasite clearance time (PCT), defined as time from first dose until first total and continued disappearance of asexual parasite which continues for a further 48 hours

• fever clearance time (FCT), defined as time from first dose until the first time body temperature fell below 37.5°C and remained below 37.5°C for at least a further 48 hours (only for patients with temperature >37.5°C at baseline).

5.2 Pharmacokinetic properties

Pharmacokinetic characterisation of MALACT ® is limited by the lack of an intravenous formulation, and the very high inter-and intra-subject variability of dihydroartemisinin and Piperaquine plasma concentrations and derived pharmacokinetic parameters (AUC, Cmax).

Absorption

The absorption of Dihydroartemisinin appears rapidly in the systemic circulation with peak plasma concentrations of both compounds reached about 2 hours after dosing. Mean

Cmax and AUC values of dihydroartemisinin ranged between 60.0-104 ng/mL and 146-338 ng·h/mL, respectively, in fed healthy adults after a single dose of MALACT ®. Mean Cmax and AUC values of dihydroartemisinin ranged between 49.7-104 ng/mL and 169-308 ng·h/mL, respectively. Absorption of Piperaquine, a highly lipophilic compound, starts after a lag-time of up to 2 hours, with peak plasma concentration (mean between 5.10-9.80 µg/mL) about 6-8 hours after dosing. Mean AUC values of Piperaquine ranged between 108 and 243 µg·h/mL. Food enhances the absorption of both dihydroartemisinin and Piperaquine: in healthy volunteers the relative bioavailability of dihydroartemisinin was increased more than two-fold, and that of Piperaquine sixteen-fold compared with fasted conditions when MALACT ® was taken after a high-fat meal.

Food has also been shown to increase the absorption of Piperaquine in patients with malaria, although to a lesser extent (approximately two-fold), most probably due to the lower fat content of the food ingested by acutely ill patients. The food interaction data indicate that absorption of Piperaquine under fasted conditions is very poor (assuming 100% absorption after a high-fat meal, the amount absorbed under fasted conditions would be <10% of the dose). Patients should therefore be encouraged to take the medication with a normal diet as soon as food can be tolerated.

Distribution

Dihydroartemisinin and Piperaquine are both highly bound to human serum proteins in vitro (95.4% and 99.7%, respectively). Dihydroartemisinin is also bound to human serum proteins (47-76%).

Metabolism

Dihydroartemisinin is converted to inactive metabolites.

The pharmacokinetics of Dihydroartemisinin in adults is time-dependent. During repeated administration of MALACT ®, plasma Dihydroartemisinin levels decreased significantly, the ratio of day 3/day 1 AUC was between 1.06 and 2.50. This suggests that there was induction of the enzyme responsible for the metabolism of Dihydroartemisinin. Dihydroartemisinin were reported to have a mild inducing effect on CYP3A4 activity. The clinical evidence of induction is consistent with the in vitro data described in section 4.5

Piperaquine is N-debutylated, mainly by CYP3A4, in human liver microsomes. In vivo in animals (dogs and rats), glucuronidation of Piperaquine takes place directly and after oxidative biotransformation. In humans, the exposure to Piperaquine increases with repeated administration of MALACT ® over the 3-day treatment period, consistent with the slow elimination of the compound (see section 5.2 Elimination). Systemic exposure to the metabolite desbutyl-Piperaquine, for which the in vitro antiparasitic effect is 5 to 8

fold higher than that for Piperaquine, was less than 1% of the exposure to the parent drug. Desbutyl- Piperaquine data is not available specifically for an African population. In vitro, Piperaquine significantly inhibits the activity of CYP2D6 at therapeutic plasma concentrations (see sections 4.3 and 4.5).

Elimination

Dihydroartemisinin are rapidly cleared from plasma with a terminal half-life of about 2 hours. Piperaquine is eliminated very slowly with a terminal half-life of 2-3 days in healthy volunteers and 4-6 days in patients with falciparum malaria. Demographic characteristics such as sex and weight appear to have no clinically relevant effects on the pharmacokinetics of MALACT ®.

Limited urinary excretion data are available for humans. In 16 healthy volunteers, neither Piperaquine nor Dihydroartemisinin was found in urine after administration of MALACT ®, and only traces of dihydroartemisinin.

In animals (rats and dogs), no unchanged dihydroartemisinin was detected in faeces and urine due to its rapid and extensive first-pass metabolism, but numerous metabolites (partly identified) have been detected in faeces, bile and urine. Piperaquine was excreted unchanged in faeces and with traces only in urine. Metabolites of Piperaquine were eliminated in bile/faeces.

Pharmacokinetics in special patient populations

In paediatric malaria patients, mean Cmax (CV%) of dihydroartemisinin (observed after first dose of MALACT ®) were 223 (139%), 198 (90%) and 174 ng/mL (83%) for body weight groups 5-<15, 15-<25 and 25-<35 kg, respectively, compared to 186 ng/mL (67%) in adult malaria patients. The associated mean Cmax of DHA were 54.7 (108%), 79.8 (101%) and 65.3 ng/mL (36%), respectively compared to 101 ng/mL (57%) in adult malaria patients. AUC of Piperaquine (population mean, covering the six doses of MALACT ®) were 577, 699 and 1150 µg•h/mL for paediatric malaria patients in body weight groups 5-<15, 15-<25 and 25-<35 kg, respectively, compared to a mean AUC of 758 µg•h/mL (87%) in adult malaria patients. The elimination half-lives of dihydroartemisinin and Piperaquine in children are unknown.

No specific pharmacokinetic studies have been performed either in patients with hepatic or renal insufficiency or elderly patients. Based on the pharmacokinetic data in 16 healthy subjects showing no or insignificant renal excretion of Piperaquine, and dihydroartemisinin, no dose adjustment for the use of MALACT ® in patients with renal impairment is advised.

5.3 Preclinical safety data

General toxicity

The main changes observed in repeat-dose toxicity studies were associated with the expected pharmacological action on erythrocytes, accompanied by responsive secondary haematopoiesis.

Mutagenicity

No evidence of mutagenicity was detected in in vitro or in vivo tests with an dihydroartemisinin: Piperaquine combination. In the micronucleus test myelotoxicity was seen at all dose levels (500, 1,000 and 2,000 mg/kg), but recovery was almost complete 48 hours after dosing.

Carcinogenicity

Carcinogenicity studies with the dihydroartemisinin: Piperaquine combination were not conducted.

Reproductive toxicity studies

Reproductive toxicity studies performed with the dihydroartemisinin: Piperaquine combination caused maternal toxicity and increased post-implantation loss in rats and rabbits at doses ≥50 mg/kg/day (corresponding to approximately 7 mg/kg/day dihydroartemisinin) and 175 mg/kg/day (corresponding to 25 mg/kg/day dihydroartemisinin) respectively. These effects were not observed at lower doses.

Piperaquine alone caused no sign of reproductive or development toxicity at doses up to 1,000 mg/kg/day in rats and rabbits.

Embryotoxicity has been observed in rat and rabbit reproductive toxicity studies conducted with dihydroartemisinin, a derivative of artemisinin. Artemisinins (e.g. artesunate) are known to be embryotoxic.

Dihydroartemisinin caused increases in post-implantation loss and teratogenicity (characterised as a low incidence of cardiovascular and skeletal malformations) in rats at 19.4 mg/kg, and in rabbits at 30 mg/kg. Maternal toxicity was also observed in rabbits at 30 mg/kg/day. No other adverse effects were observed at lower doses in rabbits. The no observed effect dose was 3 mg/kg/day in rats and 25 mg/kg/day in rabbits.

The embryotoxic dihydroartemisinin dose, 20 mg/kg/day in the rat, yields dihydroartemisinin and dihydroartemisinin exposures similar to those achieved in humans.

Artesunate, a structurally related compound, also caused increases in post-implantation loss and teratogenicity (low incidence of cardiovascular and skeletal malformations) in rats at 6 mg/kg and in the lowest dose tested in the rabbits, 5 mg/kg/day.

Cardiovascular Pharmacology

In toxicity studies in dogs at doses >600 mg/kg/day only, there was some evidence of prolongation of the QTC interval, at higher doses than intended for use in man. In an in vitro assay of HERG channels stably expressed in HEK293 cells, Piperaquine and the main metabolite showed some inhibitory potential in one of the currents responsible for cardiac repolarization. The potency was lower than the other antimalarial drugs tested. From the estimated IC50 values, the order of potency of HERG current block was halofantrine (IC50 = 0.04 μM) >chloroquine (2.5 μM) >mefloquine 2.6 μM) >desbutyl-Piperaquine (5.5 μM) >Piperaquine (8.1 μM). Clinical studies show, that prolongation of QTcF can occur with standard dosing of MALACT ® (see sections 4.3, 4.4 and 5.1).

6. Pharmaceutical particulars

6.1 List of excipients

Starch, Dibasic Calcium Phosphate, Colloidal Silicon Dioxide , Sodium Lauryl Sulfate ,Sodium Starch Glycollate, 15%PVP-K30(50%Alcohol*)solution, Magnesium Stearate, Purified Water, Opadry®85G68918**

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

PVC/ Aluminum foil blisters.
Packs of 9 tablets per blister, 1blister per packs.

No specific pack for the treatment of children and infants is available. The 9tablets pack should be used for this patient population and the parent or care giver should be given the necessary information (see section 6.6).

6.6 Special precautions for disposal and other handing

For the treatment of children and infants, the 9-tablets pack should be prescribed. The prescriber and pharmacist should instruct the parent or care giver on the posology for their child and that a variable number of tablets (depending on the child's body weight) will be requested for the full treatment. Therefore, the whole pack may not be used. After successful treatment the remaining tablets should be discarded or returned to the pharmacist.

7. Manufacturer

May & Baker Nig.Plc

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8. Date of revision of the text

October 29th 2020