Member of TGI Group of Companies

1.3.1 SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

PRODUCT NAME : Artemether 20 mg + Lumefantrine 120 mg Tablets

BRAND NAME : CO-MAL Tablets

DESCRIPTION :

Yellow colour, round uncoated tablet packaged in an ALU-PVC blister pack.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PRODUCT NAME: Artemether 20 mg + Lumefantnine 120 mg Tablets

Each uncoated tablet contains:
Artemether 20 mg
Lumefantrine 120 mg
Excipients….....q.s.

For complete list of excipients refer section 6.1.

3. PHARMACEUTICAL FORM:

Uncoated Tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic Indication:

CO-MAL is a fixed-dose combination of Artemether and Lumefantrine, which acts as a blood schizontocide. It is indicated for: Treatment, including stand-by emergency treatment of adults, children and infants (weighing 5 kg or more) with acute, uncomplicated infections due to Plasmodium falciparum or mixed infections including P. falciparum. Because CO-MAL is effective against both drug-sensitive and drug-resistant P. falciparum it is also recommended for malaria infections acquired in areas where the parasites may be resistant to other antimalarial.

4.2 Posology and method of administration:

To increase absorption , tablet should be taken with food or a milky drink. if patient unable to tolerate food , tablet should be administrated but the systemic exposure may be reduced .patient who vomits within one hour of taking the medication should be repeat the dose .For administration to small children and infants , the tablet mat be crushed.

- **For patient 12 years of age and above and 35 kg body weight and above**
- Four tablets of 20 mg/120 mg as a single dose at the time of initial diagnosis, again 4 tablets after 8 hours and then 4 tablets twice daily (morning and evening) on each of the following two days (total course comprises 24 tablets of 20 mg/120 mg tablets).

- **Dosage in infants and children**

- 5 to <15 kg bodyweight: One tablet of 20 mg/120 mg at the time of initial diagnosis, 1 tablet again after 8 hours and then 1 tablet twice daily (morning and evening) on each of the following two days (total course comprises 6 tablets of 20 mg/120 mg).

- 15 to <25 kg bodyweight: Two tablets of 20 mg/120 mg as a single dose at the time of initial diagnosis, 2 tablets again after 8 hours and then 2 tablets twice daily (morning and evening) on each of the following two days (total course comprises 12 tablets of 20 mg/120 mg).

- 25 to 35 kg bodyweight: Three tablets of 20 mg/120 mg as a single dose at the time of initial diagnosis, 3 tablets again after 8 hours and then 3 tablets twice daily (morning and evening) on each of the following two days (total course comprises 18 tablets of 20 mg/120 mg).

- The of 20 mg/120 mg tablet/s may be crushed for administration to infants and children.

4.3 Contraindications:

CO-MAL is contraindicated in:Known hypersensitivity to artemether, lumefantrine or to any of the excipients of CO-MAL .

- Patients with severe malaria according to WHO definition*.
- First trimester of pregnancy in situations where other suitable and effective anti-malarials are available (see section WOMEN OF CHILD-BEARING POTENTIAL, PREGNANCY, BREAST-FEEDING AND FERTILITY).
- Patients with a family history of congenital prolongation of the QTc interval or sudden death or with any other clinical condition known to prolong the QTc interval such as patients with a history of symptomatic cardiac arrhythmias, with clinically relevant bradycardia or with severe cardiac disease.
- Patients taking drugs that are known to prolong the QTc interval such as:
  - antiarrhythmics of classes IA and III,
  - neuroleptics and antidepressant agents,
  - certain antibiotics including some agents of the following classes: macrolides, fluoroquinolones, imidazole, and triazole antifungal agents,
  - certain non-sedating antihistaminics (terfenadine, astemizole),
  - cisapride.
- Patients with known disturbances of electrolyte balance e.g. hypokalemia or hypomagnesaemia.
- Patients taking any drug which is metabolized by the cytochrome enzyme CYP2D6 (e.g. flecainide, metoprolol, imipramine, amitriptyline, clomipramine).
- Patients taking drugs that are strong inducers of CYP3A4 such as rifampicin,

carbamazepine, phenytoin, St. John’s wort (Hypericum perforatum).

4.4 Special warning and precautions for use

Artemether 20 mg and Lumefantrine 120 mg Tablets must not be used in the first trimester of pregnancy in situations where other suitable and effective antimalarial are available. Artemether 20 mg and Lumefantrine 120 mg Tablets 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. If a patient deteriorates whilst taking Artemether 20 mg and Lumefantrine 120 mg Tablets, 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.

The long elimination half-life of lumefantrine must be taken into account when administering quinine in patients previously treated with Artemether 20 mg and Lumefantrine 120 mg Tablets. If quinine is given after Artemether 20 mg and Lumefantrine 120 mg Tablets, close monitoring of the ECG is advised. If Artemether 20 mg and Lumefantrine 120 mg Tablets is given after mefloquine, close monitoring of food intake is advised.

In patients previously treated with halofantrine, Artemether 20 mg and Lumefantrine 120 mg Tablets should not be administered earlier than one month after the last halofantrine dose. Like other antimalarials (e.g. halofantrine, quinine and quinidine Artemether 20 mg and Lumefantrine 120 mg Tablets has the potential to cause QT prolongation.

Caution is recommended when combining Artemether 20 mg and Lumefantrine 120 mg Tablets with drugs exhibiting variable patterns of inhibition, induction or competition for CYP3A4 as the therapeutic effects of some drugs could be altered. 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 Artemether 20 mg and Lumefantrine 120 mg Tablets to patients with severe renal, hepatic or cardiac problems.

4.5 Drug Interactions

Artemether and lumefantrine is contraindicated with concomitant use of drugs (they may cause prolonged QTc interval and Torsade de Pointes) such as: antiarrhythmic of classes IA and III, neuroleptics and antidepressant agents, certain antibiotics including some agents of the following
classes: macrolides, fluoroquinolones, imidazole, and triazole antifungal agents, certain no sedating antihistaminic (terfenadine, astemizole), cisapride, flecainide.

b) Interaction with drugs metabolized by CYP2D6:

Lumefantrine was found to inhibit CYP2D6 in vitro. This may be of particular clinical relevance for compounds with a low therapeutic index. Co-administration of Artemether and Lumefentrine with drugs that are metabolised by this iso-enzyme is contraindicated (e.g. neuroleptics, metoprolol, and tricyclic antidepressants such as imipramine, amitriptyline, clomipramine) is contraindicated .

c) Interaction with strong inducers of CYP3A4 such as rifampin:

Oral administration of rifampin (600 mg daily), a strong CYP3A4 inducer, with Artemether and Lumefentrine Tablets (6-dose regimen over 3 days) in six HIV-1 and tuberculosis coinfected adults without malaria resulted in significant decreases in exposure to Artemether (89%), DHA (85%) and lumefantrine (68%) when compared to exposure values after Artemether and Lumefentrine alone. Concomitant use of strong inducers of CYP3A4 such as rifampin, carbamazepine, phenytoin, St. John's Wort is contraindicated with Artemether and Lumefentrine
Inducers should not be administered at least one month after Artemether and Lumefentrine administration, unless critical to use as judged by the prescriber.

d) Interaction with other antimalarial drugs:
Data on safety and efficacy are limited, Artemether and Lumefentrine should therefore not be given concurrently with other antimalarials unless there is no other treatment option. If Artemether and Lumefentrine is given following administration of mefloquine or quinine, close monitoring of food intake (for mefloquine) or of the ECG (for quinine) is advised. The long elimination half-life of lumefantrine must be taken into account when administering quinine in patients previously treated with Artemether and Lumefentrine. In patients previously treated with halofantrine. Artemether and Lumefentrine should not be administered earlier than one month after the last halofantrine dose

Mefloquine:
A drug interaction study with Artemether and Lumefentrine in man involved administration of a 6-
dose regimen over 60 hours in healthy volunteers which was commenced at 12 hours after completion of a 3-dose regimen of mefloquine or placebo. Plasma mefloquine concentrations from
the time of addition of Artemether and Lumefentrine were not affected compared with a group which received mefloquine followed by placebo.

Pre-treatment with mefloquine had no effect on plasma concentrations of artemether or the artemether/dihydroartemisinin ratio but there was a significant reduction in plasma levels of lumefantrine, possibly due to lower absorption secondary to a mefloquine-induced decrease in bile production. Patients should be encouraged to eat at dosing times to compensate for the decrease in bioavailability.

Quinine:
A drug interaction study in healthy male volunteers showed that the plasma concentrations of lumefantrine and quinine were not affected when i.v. quinine (10 mg/kg BW over 2 hours) was given sequentially 2 hours after the last (sixth) dose of Artemether and Lumefentrine (so as to produce concurrent plasma peak levels of lumefantrine and quinine). Plasma concentrations of artemether and dihydroartemisinin (DHA) appeared to be lower. In this study, administration of Artemether and Lumefentrine to 14 subjects had no effect on QTc interval. Infusion of quinine alone in 14 other subjects caused a transient prolongation of QTc interval, which was consistent with the known cardiotoxicity of quinine. This effect was slightly, but significantly, greater when quinine was infused after Artemether and Lumefentrine in 14 additional subjects. It would thus appear that the inherent risk of QTc prolongation associated with i.v. quinine was enhanced by prior administration of Artemether and Lumefentrine.

4.6 Pregnancy & Lactation

Pregnancy
There is insufficient data from the use of artemether and lumefantrine in pregnant women. In animal studies Artemether 80 mg and Lumefantrine 480 mg Tablets, as well as other artemisinin derivates, have been shown to cause post-implantation losses and serious birth defects when administered during the first trimester of pregnancy. Therefore, Artemether 80 mg and Lumefantrine 480 mg Tablets should not be used during the first trimester of pregnancy in situations where other suitable and effective anti-malarials are available. Nonetheless, it may be used when it is the only treatment immediately available.

Lactation
The amounts of artemether, dihydroartemisinin and lumefantrine in breast milk are small. Therefore, lactating women can receive artemisinin-based combination therapies for malaria treatment.

4.7 Effects on ability to drive and use machines:

No studies on the effects on the ability to drive and use machines have been performed. Patients receiving Artemether 20 mg and Lumefantrine 120 mg Tablets should be warned that dizziness, fatigue or asthenia may occur, in which case their ability to drive or operate machines may be impaired.

4.8 Adverse Effects

Cardiac disorders : Palpitations, Electrocardiogram QT prolonged
Nervous system disorders: Headache, Dizziness, Paraesthesia.
Respiratory, thoracic and mediastinal disorders: Cough.
Gastrointestinal disorders: Vomiting, Abdominal pain, Nausea, Diarrhoea.
Skin and subcutaneoustissue disorders: Rash, Pruritus, Myalgia.
Immune system disorders: Hypersensitivity.
Psychiatric disorders: Sleep disorders, Insomnia.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties

Mechanism of action
Artemether 20 mg and Lumefantrine 120 mg Tablets comprises a fixed ratio of 1:6 parts of artemether and lumefantrine, respectively. The site of antiparasitic action of both components is the food vacuole of the malarial parasite, where they are thought to interfere with the conversion of haem, a toxic intermediate produced during haemoglobin breakdown, to the nontoxic haemozoin, malaria pigment. Lumefantrine is thought to interfere with the polymerisation process, while artemether generates reactive metabolites

as a result of the interaction between its peroxide bridge and haem iron. Both artemether and lumefantrine have a secondary action involving inhibition of nucleic acid- and protein synthesis within the malarial parasite.

5.2 Pharmacokinetic properties

Pharmacokinetic characterization of Artemether and lumefantrine is limited by the lack of an intravenous formulation, and the very high inter-and intra-subject variability of artemether and lumefantrine plasma concentrations and derived pharmacokinetic parameters (AUC, Cmax).

i) Absorption:
During acute P. falciparum malaria infection, there is marked intra- and inter-patient variability with regard to Lumefantrine absorption, probably because of differences in food intake. Food enhances the absorption of both artemether and lumefantrine. In healthy volunteers when it was taken after a high-fat meal the relative bioavailability of artemether was more than doubled, and that of lumefantrine increased sixteen-fold compared with fasted conditions. Likewise, in patients with malaria, food increases the absorption of lumefantrine, although to a lesser extent (approximately two-fold), most probably due to the lower fat content of the food eaten by acutely ill patients. Acutely ill patients are reluctant to eat and tend to avoid high-fat foods. In order to improve bioavailability, patients should be encouraged to take it with a normal diet as soon as food can be tolerated.

ii) Distribution:
Artemether and lumefantrine 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

Artemether is rapidly and extensively metabolised (substantial first-pass metabolism) both *in vitro* and in humans. Human liver microsomes metabolise artemether to the biologically active main metabolite dihydroartemisinin (demethylation), predominantly through the isoenzyme CYP3A4/5. This metabolite has also been detected in humans *in vivo*.
Dihydroartemisinin is further converted to inactive metabolites. The pharmacokinetics of artemether in adults is time-dependent. During repeated administration of artemether plasma levels decreased significantly, while levels of the active metabolite (dihydroartemisinin) increased, although not to a statistically significant degree. The ratio of day 3/day 1 AUC for artemether was between 0.19 and 0.44, and was between 1.06 and 2.50 for dihydroartemisinin. This suggests that there was induction of the enzyme responsible for the metabolism of artemether. Artemether and
dihydroartemisinin were reported to have a mild inducing effect on CYP3A4 activity. The clinical evidence of induction is consistent with the *in vitro* data. Lumefantrine is N-debutylated, mainly by CYP3A4, in human liver microsomes. *In vivo* in animals (dogs and rats), glucuronidation of lumefantrine takes place directly and after oxidative biotransformation. In humans, the exposure to lumefantrine increases with repeated administration of Lumefantrine 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-lumefantrine, for which the *in vitro* antiparasitic effect is 5 to 8 fold higher than that for lumefantrine, was less than 1% of the exposure to the parent drug. Desbutyl-lumefantrine data is not available specifically for an African population. *In vitro,* lumefantrine significantly inhibits the activity of CYP2D6 at therapeutic plasma concentrations

Elimination

Artemether and dihydroartemisinin are rapidly cleared from plasma with a terminal half-life of about 2 hours. Lumefantrine is eliminated very slowly with an elimination half-life of 2 to 6 days.Demographic characteristics such as sex and weight appear to have no clinically relevant effects on the pharmacokinetics of Artemether and Lumefentrine .

Limited urinary excretion data are available for humans. In 16 healthy volunteers, neither lumefantrine nor artemether was found in urine after administration of Artemether and Lumefentrine , and only traces of dihydroartemisinin were detected (urinary excretion of dihydroartemisinin amounted to less than 0.01% of the artemether dose).

In animals (rats and dogs), no unchanged artemether 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. Lumefantrine was excreted unchanged in faeces and with traces only in urine. Metabolites of lumefantrine were eliminated in bile/faeces.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Artemether 20 mg and Lumefantrine 120 mg Tablets

List of Excipients:

- Micro crystalline cellulose powder 101
- Cross Carmellos Sodium
- Sodium benzoate
- PVPK 30
- Lactose

- Iso Propyl Alcohol
- Talcum
- Sodium Starch Glycolate
- Aerosil
- Magnesium Stearate

6.2 Incompatibilities

Not Applicable

6.3 Shelf Life

36 Months.

6.4 Special precautions for storage:

Do not store above 30°C. Protect from light.
Keep the medicine out of reach of children.

6.5 Nature and contents of container

24 tablets packed in an ALU-PVC Blister pack along with leaflet .

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements

7. *APPLICANT*

Manufactured for:
CHI PHARMACEUTICAL LTD
14 CHIVITA AVENUE, AJAO ESTATE,
ISOLO, LAGOS

Manufactured on contract by:

SAGAR VITACEUTICALS NIGERIA LIMITED.
COMMERCIAL DISTRICT B BLOCK,
PLOT 6, NEW MAKUN CITYKM 53/55,
LAGOS-IBADAN EXPRESSWAY.SAGAMU,
OGUN STATE NIGERIA.