1. NAME OF THE MEDICINAL PRODUCT

GOL ARTEMETHER AND LUMEFANTRINE TABLETS 80mg/480mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:
Artemether 80mg Lumefantrine
480mg.

3. PHARMACEUTICAL FORM

Yellow colored, capsule shaped, biconvex, uncoated tablet with a score on one side and "GOL" debossed on the other side.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS

4.1 : **Therapeutic indications**

GOL ARTEMETHER 80/ LUMEFANTRINE 480MG TABLETS is an antimalarial agent indicated for the treatment of acute uncomplicated malaria due to Plasmodium falciparum in adults and children of 5 kg and above.

4.2 **Posology and method of administration;** Oral use

Treatment should be administered at the time of initial diagnosis or at the onset of symptoms.

Adults and children weighing 35 kg and above

For patients 12 years of age and above and 35 kg body weight and above, a course of treatment comprises six doses of four tablets i.e. total of 24 tablets, given over a period of 60 hours as follows: the first dose of four tablets, given at the time of initial diagnosis or onset of symptoms, should be followed by five further doses of four tablets given at 8, 24, 36, 48 and 60 hours thereafter.

Children and infants weighing 5 kg to less than 35 kg

A six-dose regimen is recommended with 1 to 3 tablets per dose, depending on bodyweight:
5 to less than 15 kg bodyweight: the first dose of one tablet, given at the time of initial diagnosis, should be followed by five further doses of one tablet given at 8, 24, 36, 48 and 60 hours thereafter.
15 to less than 25 kg bodyweight: the first dose of two tablets, given at the time of initial diagnosis, should be followed by five further doses of two tablets given at 8, 24, 36, 48 and 60 hours thereafter.
25 to less than 35 kg bodyweight: the first dose of three tablets, given at the time of initial diagnosis, should be followed by five further doses of three tablets given at 8, 24, 36, 48 and 60 hours thereafter.

Infants weighing less than 5 kg

The safety and efficacy of GOL ARTEMETHER 80 / LUMEFANTRINE 480MG TABLETS have not been established in infants weighing less than 5 kg and no dosing recommendations can be made. Currently available data are described in section 5.1 and 5.2.

Older people

There is no information suggesting that the dosage in patients over 65 years of age should be different than in younger adults.

Renal or hepatic impairment

No dose adjustments are necessary in patients with renal or hepatic impairment. However, caution is advised when administering GOL ARTEMETHER / LUMEFANTRINE TABLETS 80/480MG to patients
with severe renal or hepatic problems

Elderly:

No special precautions or dosage adjustments are necessary in such patients.

4.3 Contraindications

GOL ARTEMETHER / LUMEFANTRINE TABLETS 80/480MG is contraindicated in:

- patients with known hypersensitivity to artemether, lumefantrine or to any of the excipients.
- patients with severe malaria according to WHO definition.
- patients with a personal or 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, clinically relevant bradycardia or severe cardiac diseases.
- patients taking drugs that are known to prolong 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 antihistamines (terfenadine, artemizole)
  - cisapride
  - patients with known disturbances of electrolyte balance e.g. hypokalemia or hypomagnesaemia
  - patients taking any drug which is metabolized by the cytochrom e 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*).

(*Presence of one or more of the following clinical or laboratory features:
Clinical manifestation: Prostration; impaired consciousness or unarousable coma; failure to feed; deep breathing, respiratory distress (acidotic breathing); multiple convulsions; circulatory collapse or shock; pulmonary edema (radiological); abnormal bleeding; clinical jaundice; hemoglobinuria
Laboratory test: Severe normocytic anemia; hemoglobuniuria; hypoglycemia; metabolic acidosis; renal impairment; hyperlactatemia; hyperparasitemia)

4.4 Special warnings and precautions for use

GOL A/L is not recommended during the first trimester of pregnancy in situations where other suitable and effective antimalarials are available (see section 4.6).

GOL A/L 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, GOL A/L 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 GOL A/L, 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 GOL A/L. If quinine is given after GOL A/L, close monitoring of the ECG is advised (see section 4.5).

If GOL A/L is given after mefloquine, close monitoring of food intake is advised (see section 4.5).

In patients previously treated with halofantrine, GOL A/L should not be administered earlier than one month after the last halofantrine dose.

GOL A/L is not indicated and has not been evaluated for prophylaxis of malaria.

GOL A/L should be used cautiously in patients on anti-retroviral drugs (ARTs) since decreased artemether, DHA, and/or lumefantrine concentrations may result in a decrease of antimalarial efficacy of GOL A/L, (see section 4.5).

Like other antimalarials (e.g. halofantrine, quinine and quinidine) GOL A/L has the potential to cause QT prolongation (see section 5.1).

Caution is recommended when combining GOL A/L with drugs exhibiting variable patterns of inhibition, moderate induction or competition for CYP3A4 as the therapeutic effects of some drugs could be altered. Drugs that have a mixed inhibitory/induction effect on CYP3A4, especially anti-retroviral drugs such as HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors should be used with caution in patients taking GOL A/L (see sections 4.5 and 5.2).

Caution is recommended when combining GOL A/L with hormonal contraceptives. GOL A/L may reduce the effectiveness of hormonal contraceptives. Therefore, patients using oral, transdermal patch, or other systemic hormonal contraceptives should be advised to use an additional non-hormonal method of birth control for about one month (see sections 4.5).

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

Renal impairment

No specific studies have been carried out in this group of patients. There is no significant renal excretion of lumefantrine, artemether and dihydroartemisinin in studies conducted in healthy volunteers and clinical experience is limited. No dose adjustment for the use of GOL A/L in patients with renal impairment is recommended. Caution is advised when administering GOL A/L to patients with severe renal impairment. In these patients, ECG and blood potassium monitoring is advised.

Hepatic impairment

No specific studies have been carried out in this group of patients. In patients with severe hepatic impairment, a clinically relevant increase of exposure to artemether and lumefantrine and/or their metabolites cannot be ruled out. Therefore caution should be exercised in dosing patients with severe hepatic impairment (see section 5.2). In these patients, ECG and blood potassium monitoring is advised. No dose adjustment is recommended for patients with mild to moderate hepatic impairment.

New infections

Data for a limited number of patients in a malaria endemic area show that new infections can be treated with a second course of GOL A/L. In the absence of carcinogenicity study data, and due to lack of clinical experience, more than two courses of GOL A/L cannot be recommended.

4.5 Interaction with other medicinal products and other forms of interaction

Contraindications of concomitant use

Interaction with drugs that are known to prolong the QTc interval

GOL A/L is contraindicated with concomitant use of drugs (they may cause prolonged QTc interval and Torsade de Pointes) 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 antihistamines (terfenadine, astemizole), cisapride, flecainide (see section 4.3)

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 GOL A/L 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 (see sections 4.3 and 5.2).

Interaction with strong inducers of CYP3A4 such as rifampin

Oral administration of rifampin (600 mg daily), a strong CYP3A4 inducer, with GOL A/L 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 GOL A/L alone. Concomitant use of strong inducers of CYP3A4 such as rifampin, carbamazepine, phenytoin, St. John's Wort is contraindicated with GOL A/L (see section 4.3).

Inducers should not be administered at least one month after GOL A/L administration, unless critical to use as judged by the prescriber.

Concomitant use not recommended

Interaction with other antimalarial drugs (see section 4.4)

Data on safety and efficacy are limited, and GOL A/L should therefore not be given concurrently with other antimalarials unless there is no other treatment option (see section 4.4).

If GOL A/L 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 GOL A/L. In patients previously treated with halofantrine, GOL A/L should not be administered earlier than one month after the last halofantrine dose (see section 4.4).

Mefloquine

A drug interaction study with GOL A/L 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 GOL A/L 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 theartemether/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 GOL A/L (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 GOL A/L 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 GOL A/L 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 GOL A/L.

Concomitant use requiring caution

Interactions affecting the use of GOL A/L**.**

Interaction with CYP3A4 inhibitors

Both artemether and lumefantrine are metabolised predominantly by the cytochrome enzyme CYP3A4, but do not inhibit this enzyme at therapeutic concentrations.

Ketoconazole

The concurrent oral administration of ketoconazole with GOL A/L led to a modest increase (≤ 2-fold) in artemether, DHA, and lumefantrine 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 GOL A/L is considered unnecessary in falciparum malaria patients when administered in association with ketoconazole or other potent CYP3A4 inhibitors.

GOL A/L should be used cautiously with drugs that inhibit CYP3A4 and are contraindicated with drugs which additionally are known to prolong QTc (see Section 4.3 Contraindications), due to potential for increased concentrations of lumefantrine which could lead to QT prolongation.

Interaction with weak to moderate inducers of CYP3A4

When GOL A/L is co-administered with moderate inducers of CYP3A4, it may result in decreased concentrations of artemether and/or lumefantrine and loss of antimalarial efficacy (see section 4.4).

Interaction with anti-retroviral drugs such as protease inhibitors and non-nucleoside reverse transcriptase inhibitors

Both artemether and lumefantrine are metabolized by CYP3A4. ARTs, such as protease inhibitors and non-nucleoside reverse transcriptase inhibitors, are known to have variable patterns of inhibition, induction or competition for CYP3A4. GOL A/L should be used cautiously in patients on ARTs since decreased artemether, DHA, and/or lumefantrine concentrations may result in a decrease of antimalarial efficacy of GOL A/L, and increased lumefantrine concentrations may cause QT prolongation (see Section 4.4).

Lopinavir/ ritonavir

In a clinical study in healthy volunteers, lopinavir/ritonavir decreased the systemic exposures to artemether and DHA by approximately 40% but increased the exposure to lumefantrine by approximately 2.3- fold. Exposures to lopinavir/ritonavir were not significantly affected by concomitant use of GOL A/L.

Nevirapine

In a clinical study in HIV-infected adults, nevirapine significantly reduced the median Cmax and AUC of artemether by approximately 61% and 72%, respectively and reduced the median Cmax and AUC of dihydroartemisinin by approximately 45% and 37%, respectively. Lumefantrine Cmax and AUC were non-significantly reduced by nevirapine. Artemether/lumefantrine reduced the median Cmax and AUC of nevirapine by approximately 43% and 46% respectively.

Efavirenz

Efavirenz decreased the exposures to artemether, DHA, and lumefantrine by approximately 50%, 45%,and 20%, respectively. Exposures to efavirenz were not significantly affected by concomitant use of GOL A/L.

Interactions resulting in effects of GOL A/L on other drugs

Interaction with drugs metabolized by CYP450 enzymes

When GOL A/L is co-administered with substrates of CYP3A4 it may result in decreased concentrations of the substrate and potential loss of substrate efficacy. 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).

Interaction with hormonal contraceptives

In vitro, the metabolism of ethinyl estradiol and levonorgestrel was not induced by artemether, DHA, or lumefantrine. However, artemether has been reported to weakly induce, in humans, the activity of CYP2C19, CYP2B6, and CYP3A. Therefore, GOL A/L may potentially reduce the effectiveness of hormonal contraceptives. Patients using oral, transdermal patch, or other systemic hormonal contraceptives should be advised to use an additional nonhormonal method of birth control for about one month (see sections 4.4 and 4.6).

Drug-food/drink interactions

GOL A/L should be taken with food or drinks rich in fat such as milk as the absorption of both artemether and lumefantrine is increased (see Section 4.2).

Grapefruit juice should be used cautiously during GOL A/L treatment. Administration of artemether with grapefruit juice in healthy adult subjects resulted in an approximately two fold increase in systemic exposure to the parent drug.

4.6 Fertility, Pregnancy and Lactation

Women of childbearing potential

Women using oral, transdermal patch, or other systemic hormonal contraceptives should be advised to use an additional non-hormonal method of birth control for about one month (see section 4.4).

Pregnancy

A meta-analysis of observational studies including over 500 artemether-lumefantrine exposed women in their first trimester of pregnancy assessed adverse pregnancy outcomes. The data showed that compared to quinine, artemisinin treatment, including artemether-lumefantrine, was not associated with an increased risk of miscarriage, stillbirth or congenital anomalies. However, due to the limitations of these studies, the risk of adverse pregnancy outcomes for artemether-lumefantrine exposed women in early pregnancy cannot be excluded.

Safety data from pregnancy studies including over 1200 pregnant women who were exposed to artemether-lumefantrine during the second or third trimester did not show an increase in adverse pregnancy outcomes or teratogenic effects over background rates.

Studies in animals have shown reproductive toxicity (see section 5.3).

GOL A/L treatment is not recommended 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, GOL A/L treatment should be considered if the expected benefit to the mother outweighs the risk to the foetus.

Breast-feeding

Animal data suggest excretion into breast milk but no data are available in humans. Women taking GOL A/L should not breast-feed during their treatment. Due to the long elimination half-life of lumefantrine (2 to 6 days), it is recommended that breast-feeding should not resume until at least one week after the last dose of GOL A/L unless potential benefits to the mother and child outweigh the risks of GOL A/L treatment.

Fertility

There is no information on the effects of GOL A/L on human fertility (see section 5.3).

4.7. Effects on ability to drive and use machines: Patients receiving GOL ARTEMETHER 80 / LUMEFANTRINE 480MG TABLETS 20/120 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 Undesirable effects:

The safety of artemether/lumefantrine has been evaluated in clinical trials with more than 3500 patients. A total of 1810 adults and adolescents above 12 years of age as well as 1788 infants and children of 12 years of age and below have received artemether/lumefantrine in clinical trials.

Adverse reactions reported from clinical studies and post-marketing experience are listed below according to system organ class.

Adverse reactions are ranked under headings of frequency using the MedDRA frequency 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 available data).

Table 2: Frequency of undesirable effects

	Adults and adolescents above 12 years of age	**Infants and children of 12 years of age and below (incidence estimates*)**
Cardiac disorders		
Palpitations	Very common	Common
Electrocardiogram QT prolonged	Common	Common
Nervous system disorders		
Headache	Very common	Very common
Dizziness	Very common	Common
Paraesthesia	Common	--
Gait disturbance	Common	--

Ataxia, hypoaesthesia	Uncommon	--
Clonic movements, somnolence	Uncommon	Uncommon
Respiratory, thoracic and mediastinal disorders		
Cough	Common	Very common
Gastrointestinal disorders		
Vomiting	Very common	Very common
Abdominal pain	Very common	Very common
Nausea	Very common	Common
Anorexia	Very common	Very common
Diarrhoea	Common	Common
Skin and subcutaneous tissue disorders		
Rash	Common	Common
Pruritus	Common	Uncommon
Urticaria, angioedema*	Not known	Not known
Arthralgia	Very common	Common
Myalgia	Very common	Common
General disorders and administration site conditions		
Asthenia	Very common	Common
Fatigue	Very common	Common
Gait disturbance	Common	
Immune system disorders		
Hypersensitivity	Not known	Rare
Hepatobiliary disorders		
Liver function tests increased	Uncommon	Common
Psychiatric disorders		
Sleep disorders	Very common	Common
Insomnia	Common	Uncommon

* These adverse reactions were reported during post-marketing experience. Because these spontaneously reported events are from a population of uncertain size, it is difficult to estimate their frequency.

Has been reported up to a few weeks after treatment has been stopped.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 **Overdose:**

There is no information on overdoses of GOL ARTEMETHER 80/ LUMEFANTRINE 480MG TABLETS. In cases of suspected overdosage symptomatic and supportive therapy should be given as appropriate, which should include monitoring of ECG and serum electrolytes.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

a Pharmacotherapeutic group: Antimalarials, Artemisinin-based combination,
ATC code: P01BF01

b Pharmacodynamic effects:

GOL A/L Tablet 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.

GOL A/L has been reported to have potent activity in terms of clearing gametocytes.

By 2015, resistance to artemisinins emerged in Southeast Asia. Studies with GOL A/L in this region showed delayed parasite clearance (manifested as a higher proportion of patients with parasitemia on Day 3 after initiation of treatment), although overall efficacy as measured by cure rates after 28 days, remained high (WHO 2014). In Africa, only isolated reports on delayed parasite clearance are available and a clear trend towards resistance development was not observed.

Treatment of Acute Uncomplicated P. falciparum Malaria

The efficacy of GOL A/L 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 five 6-dose regimen studies and one study comparing the 6-dose regimen with the 4-dose regimen. Baseline parasite density ranged from 500/µ l - 200,000/µ l (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)

The modified intent to treat (mITT) population includes all patients with malaria diagnosis confirmation who received at least one dose of study drug. Evaluable patients generally are all patients who had a day 7 and a day 28 parasitological assessment or experienced treatment failure by day 28. The results are presented in the table below:

Table 2 Clinical efficacy results

Study No.	Age	Polymerase chain reaction (PCR)-corrected 28-day cure	Median FCT[2] [25th, 75th percentile]	Median PCT[2] [25th, 75th percentile]	Year/ Study location

		rate[1] n/N (%) in evaluable patients			
A025[4]	3-62 years	93/96 (96.9)	n[3]=59 35 hours [20, 46]	n=118 44 hours [22, 47]	1996-97 Thailand
A026	2-63 years	130/133 (97.7)	n[3]=87 22 hours [19, 44]	NA	1997-98 Thailand
A028	12-71 years	148/154 (96.1)	n[3]=76 29 hours [8, 51]	n=164 29 hours [18, 40]	1998-99 Thailand
A2401	16-66 years	119/124 (96.0)	n[3]=100 37 hours [18, 44]	n=162 42 hours [34, 63]	2001-05 Europe, Columbia
A2403	2 months-9 years	289/299 (96.7)	n[3]=309 8 hours [8, 24]	n=310 24 hours [24, 36]	2002-03 3 countries in Africa
B2303[CT]	3 months-12 years	403/419 (96.2)	n[3]=323 8 hours [8, 23]	n=452 35 hours [24, 36]	2006-07 5 countries in Africa
B2303[DT]	3 months-12 years	394/416 (94.7)	n[3]=311 8 hours [8, 24]	n=446 34 hours [24, 36]	2006-07 5 countries in Africa

[1] Efficacy cure rate based on blood smear microscopy
[2] mITT population
[3] For patients who had a body temperature >37.5° C at baseline only
[4]Only the 6-dose regimen over 60 hours group data is presented
[CT] – GOL A/L tablets administered as crushed tablets
[DT] – GOL A/L Dispersible tablets
GOL A/L 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. In 319 adult patients in whom gametocytes were present, the median time to gametocyte clearance with GOL A/L was 96 hours. GOL A/L is active against blood stages of *Plasmodium vivax*, but is not active against hypnozoites.

Paediatric population
Three studies have been conducted
Study A2403 was conducted in Africa in 310 infants and children aged 2 months to 9 years, weighing 5 kg to 25 kg, with an axillary temperature ≥ 37.5° C. Results of 28-day cure rate (PCR-corrected), median parasite clearance time (PCT), and fever clearance time (FCT) are reported in table 3 below.
Study B2303 was conducted in Africa in 452 infants and children, aged 3 months to 12 years, weighing 5 kg to <35 kg, with fever (≥ 37.5° C axillary or ≥ 38° C rectally) or history of fever in the preceding 24 hours. This study compared crushed tablets and dispersible tablets. Results of 28-day cure rate (PCR-corrected), median parasite clearance time (PCT), and fever clearance time (FCT) for crushed tablets are reported in table 3 below:

Table 3 Clinical efficacy by weight for pediatric studies

Study No. **Weight category**	**Median PCT[1]** **[25th, 75th percentile]**	**PCR-corrected 28-day cure rate[2] n/N (%) in evaluable patients**
Study A2403 5 - <10 kg 10 - <15 kg 15 -25 kg	24 hours [24, 36] 35 hours [24, 36] 24 hours [24, 36]	145/149 (97.3) 103/107 (96.3) 41/43 (95.3)
Study B2303[CT] 5 - <10 kg	36 hours [24, 36] 35 hours [24, 36]	65/69 (94.2) 174/179 (97.2)

10 - <15 kg 15 -<25 kg 25-35 kg	35 hours [24, 36] 26 hours [24, 36]	134/140 (95.7) 30/31 (96.8)

[1] mITT population
[2] Efficacy cure rate based on blood smear microscopy
[CT] GOL A/L tablets administered as crushed tablets
Study B2306, was a multi-centre, open-label, single-arm study conducted in 20 infants in Africa, Benin and Burkina Faso to evaluate the efficacy, safety and pharmacokinetics of dispersible tablets in infants aged >28 days and <5 kg of body weight, who were treated with one dispersible tablet (20 mg artemether/120 mg lumefantrine) given twice-daily for three days and followed up for six weeks (core follow-up) and at the age of 12 months (long-term follow-up).
Dispersible tablets were well tolerated with reported adverse events of mild to moderate severity. In the per protocol population, PCR-corrected cure rate at days 28 and 42 was 100% (95% CI: 79.4, 100). For important exposure results, see section 5.2. Although neurotoxicity was not observed in the patients in Study B2306, artemether has been associated with neurotoxicity in studies in rats and dogs, see section 5.3.

QT/QTc Prolongation:
Adults and children with malaria
For information on the risk of QT/QTc prolongation in patients see section 4.4
Healthy adults
In a healthy adult volunteer parallel group study including a placebo and moxifloxacin control group (n=42 per group), the administration of the six dose regimen of GOLA/L was associated with prolongation of QTcF. The mean changes from baseline at 68, 72, 96, and 108 hours post first dose were 7.45, 7.29, 6.12 and 6.84 msec, respectively. At 156 and 168 hours after first dose, the changes from baseline for QTcF had no difference from zero. No subject had a >30 msec increase from baseline nor an absolute increase to >500 msec. Moxifloxacin control was associated with a QTcF increase as compared to placebo for 12 hours after the single dose with a maximal change at 1 hour after dose of 14.1 msec.
In the adult/adolescent population included in clinical trials, 8 patients (0.8%) receiving GOL A/L experienced a QTcB >500 msec and 3 patients (0.4%) a QTcF >500 msec. Prolongation of QTcF interval >30 msec was observed in 36% of patients.
In clinical trials conducted in children with the 6-dose regimen, no patient had post-baseline QTcF >500 msec whereas 29.4% had QTcF increase from baseline >30 msec and 5.1% >60 msec. In clinical trials conducted in adults and adolescents with the 6-dose regimen, post-baseline QTcF prolongation of >500 msec was reported in 0.2% of patients, whereas QTcF increase from baseline >30 msec was reported in 33.9% and >60 msec in 6.2% of patients.
In the infant/children population included in clinical trials, 3 patients (0.2%) experienced a QTcB >500 msec. No patient had QTcF >500 msec. Prolongation of QTcF intervals >30 msec was observed in 34% of children weighing 5-10 kg, 31% of children weighing 10-15 kg and 24% of children weighing 15-25 kg, and 32% of children weighing 25-35 kg.

5.2 Pharmacokinetic properties

No pharmacokinetic data are available for GOL ARTEMETHER 80/ LUMEFANTRINE 480MG TABLETS A bioequivalence study was conducted with Coartem 80/480mg, which is proportionally similar to GOL ARTEMETHER 80/ LUMEFANTRINE 480MG TABLETS in
composition.

Artemether Absorption: Artemether is absorbed fairly rapidly and dihydro-artemisinin (DHA), the active metabolite of artemether, appears rapidly in the systemic circulation with peak plasma concentrations of both compounds reached about 2 hours after dosing. The absolute bioavailability is unknown. Following single dose administration of 4 tablets of GOL ARTEMETHER 80/ LUMEFANTRINE 480MG

TABLETS in healthy volunteers, the mean (± SD) artemether Cmax value was 81 (±41) ng/ml, the corresponding value for AUC was 238 (±125) ng.h/ml, and the mean artemether tmax value was 2.83 (± 0.94) hours. The pharmacokinetic data for dihydro-artemisinin were supportive and indicated a comparable bioavailability between Test and Reference.

In healthy volunteers the relative bioavailability of artemether was increased more than two-fold when taken with food.

Artemether Distribution: Artemether is 95.4% bound to human serum proteins in vitro. The active metabolite dihydro-artemisinin (DHA) is also bound to human serum proteins (47-76%).

Metabolism:

Artemether is rapidly and extensively metabolized with substantial first-pass metabolism. Artemether is metabolized in the liver to the biologically active main metabolite DHA (demethylation), predominantly through the isoenzyme CYP3A4/5. The pharmacokinetics of artemether in adults is time dependent. During repeated administration of artemether/lumefantrine, plasma artemether levels decreased significantly, while levels of the active metabolite (dihydro-artemisinin) 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 dihydro-artemisinin. This suggests that there was induction of the enzyme responsible for the metabolism of artemether. DHA is further converted to inactive metabolites, primarily by glucuronidation. In vivo data indicate that artemisinins have some capacity to induce cytochrome isoenzymes CYP2C19 and CYP3A4.

Artemether Elimination: Artemether and dihydro-artemisinin are rapidly cleared from plasma with an elimination half-life of about 2 hours. No urinary excretion data are available for humans. In rats and dogs unchanged artemether has not been detected in feces and urine due to its rapid and high-first-pass metabolism, but several metabolites (un- identified) have been detected in both faeces and urine.

Lumefantrine Absorption: Absorption of lumefantrine, a highly lipophilic compound, starts after a lag-time of up to 2 hours, with peak plasma concentration about 6-8 hours after dosing. The absolute bioavailability is unknown. Following single dose administration of 4 tablets of GOL ARTEMETHER 80/ LUMEFANTRINE 480MG TABLETS in healthy volunteers, the mean (± SD) lumefantrine Cmax value was 6136 (±2880) ng/ml, the corresponding value for AUC was 99070 (±48130)

ng.h/ml, and the mean lumefantrine tmax value was 5.93 (± 0.73) hours. Lumefantrine exposure from one 80 mg/480 mg tablet is equivalent to four 20 mg/120 mg tablets. In healthy volunteers the relative bioavailability of lumefantrine, when taken after a high-fat meal, was increased sixteenfold compared with fasted conditions. Food has also been shown to increase the absorption of lumefantrine 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 lumefantrine under fasted conditions is very poor. Patients should therefore be encouraged to take the medication with a normal diet as soon as food can be tolerated.

Distribution: Lumefantrine is 99.7% bound to human serum proteins in vitro.

Metabolism: Lumefantrine is N-debutylated, mainly by CYP3A4, in human liver microsomes. The systemic exposure to the metabolite desbutyl-lumefantrine, for which the in vitro antiparasitic effect is 5 to 8-fold higher than 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. In humans, the exposure to lumefantrine increases with repeated administration of artemether/lumefantrine over the 3-day treatment period, consistent with the slow elimination of the compound. Elimination
Lumefantrine is eliminated very slowly with a terminal half-life of approximately 3 days. No urinary excretion data are available for humans. Lumefantrine is eliminated via the bile in rats and dogs, with excretion primarily in the faeces. After oral dosing in rats and dogs qualitative and quantitative recovery of metabolites in bile and faeces was relatively low, most of the dose being recovered as parent drug.

Pharmacokinetics in Special Patient Populations:
Specific pharmacokinetic studies have not been performed in patients with hepatic or renal insufficiency. No pharmacokinetic studies are available in elderly patients.

Pediatric population:
In pediatric malaria patients, mean Cmax (CV%) of artemether (observed after first dose) 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 lumefantrine (population mean, covering the six doses of artemether/lumefantrine) were 577, 699 and 1150 µgh/ml for pediatric 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 artemether and lumefantrine in children are unknown.

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 hematopoiesis.

Mutagenicity: No evidence of mutagenicity was detected in in vitro or in vivo tests with an artemether: lumefantrine combination (consisting of 1-part artemether: 6 parts lumefantrine). 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 artemether/lumefantrine combination were not conducted.

Reproductive toxicity studies: Reproductive toxicity studies performed with the artemether/lumefantrine 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 artemether) and 175 mg/kg/day (corresponding to 25 mg/kg/day artemether) respectively. These effects were not observed at lower doses. Lumefantrine 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 artemether, a derivative of artemisinin. Artemisinins (e.g. artesunate) are known to be embryotoxic in animals. Artemether caused increases in post- implantation loss and teratogenicity (characterized 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 artemether dose, 20 mg/kg/day in the rat, yields artemether and dihydro-artemisinin 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 (see section 4.6 for data in humans).

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, lumefantrine and the main metabolite desbutyllumefantrine showed some inhibitory potential in one of the currents responsible for cardiac repolarization. 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) > desbutyllumefantrine (5.5 μM) > lumefantrine (8.1 μM). Clinical studies show, that prolongation of QTcF can occur with standard dosing of artemether/lumefantrine

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose anhydrous BP, croscarmellose sodium BP, polysorbate 80 BP, sodium methylparaben BP, sodium propylparaben BP, quinoline yellow supra, HPMC 5cps BP, aerosil BP, avicel pH 102/101 BP, sodium starch glycolate BP, magnesium stearate BP

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

The shelf life of GOL ARTEMETHER 80/ LUMEFANTRINE 480MG TABLETS is 36 months from the date of manufacture

6.4 Special Precautions for Storage

GOL ARTEMETHER 80/ LUMEFANTRINE 480MG TABLETS should be stored in a cool dry place. Do not store above 30°C

6.5. Nature and Content of Container

The 24-tablets pack is contained in a blister of PVC and aluminium foil. The blister is packaged in a monocarton which is then packed into a corrugated cardboard box.

6.6 Special Precautions for Disposal

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

7.0 Applicant/Manufacturer

GLOBAL ORGANICS LTD,
PLOT NO 868, KM 34
AJEGUNLE BUS-STOP,
LAGOS ABEOKUTA EXPRESSWAY,
LAGOS STATE.