Prescription only medicine

Malarshin® Forte

Artemether 80mg + Lumefantrine 480mg

COMPOSITION
Each Film Coated tablet contains:
Artemether 80 mg
Lumefantrine 480 mg
Excipients Q.S.

PHARMACOLOGY
Pharmacodynamics
Pharmacotherapeutic group: antimalarials, blood schizontocide, ATC code: P01BF01.
Pharmacodynamic effects
Artemether and Lumefantrine 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.

Pharmacokinetics
Pharmacokinetic characterisation of Artemether and Lumefantrine Tablets 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).
Absorption
Artemether is absorbed fairly rapidly and dihydroartemisinin, the active metabolite of artemether, 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 artemether ranged between 60.0-104 ng/mL and 146-338 ng·h/ml, respectively, in fed healthy adults after a single dose of Artemether and Lumefantrine Tablets, 80 mg artemether/480 mg lumefantrine. Mean Cmax and AUG values of dihydroartemisinin - ranged between 49.7-104 ng/mL and 169-308 ng·h/mL, respectively. Absorption of lumefantrine, a highly lipophilic compound, starts after a lag-time of up to 2 hours, with peak plasma concentration (mean between 5.10-9.80 g/mL) about 6-8 hours after dosing. Mean AUC values of lumefantrine ranged between 108 and 243 µgh/ml. Food enhances the absorption of both artemether and lumefantrine: in healthy volunteers the relative bioavailability of artemether was increased more than two-fold, and that of lumefantrine sixteen-fold compared with fasted conditions when Artemether and Lumefantrine Tablets was taken after a high-fat meal. 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 (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
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 and Lumefantrine Tablets, plasma artemether 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 described in section 4.5.
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 Artemether and Lumefantrine Tablets over the 3-day treatment period, consistent with the slow elimination of the compound. 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 Lumefantrine Tablets.
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 Lumefantrine Tablets, 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.

INDICATIONS
Artemether and Lumefantrine Tablets is indicated for the treatment of acute uncomplicated Plasmodium falciparum malaria in adult. Consideration should be given to official guidance regarding the appropriate use of antimalarial agents.

DOSAGE AND ADMINISTRATION
Adults: The adult dosage for patients with bodyweight of 35 kg and above is 1 tablet per dose for a total of 6 doses.

Body weight (in kg)	No. of tablets per dose
5 to < 15 kg	1
15 to <25 kg	2
25 to <35 kg	3
35 kg and over	4

Tablets for oral administration.
To increase absorption, Artemether and Lumefantrine Tablets should be taken with food or a milky drink. If patients are unable to tolerate food, Artemether and Lumefantrine Tablets should be administered, but the systemic exposure may be reduced. Patients who vomit within 1 hour of taking the medication should repeat the dose. For administration to small children and infants, the tablet/s may be crushed.

CONTRAINDICATIONS
- 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 metabolised by the cytochrome enzyme CYP2D6 (e.g. 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 (proarrythmic). 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.
  - flecainide
- patients with a history of symptomatic cardiac arrythmias 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.
- patients taking drugs that are strong inducers of CYP3A4 such as rifampin, carbamazepine, phenytoin, St. John's wort (Hypericum perforatum).

WARNINGS AND PRECAUTIONS
Artemether and Lumefantrine Tablets must not be used in the first trimester of pregnancy in situations where other suitable and effective antimalarials are available.
Artemether and Lumefantrine 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.
Due to limited data on safety and efficacy, Artemether and Lumefantrine Tablets should not be given concurrently with any other antimalarial agent unless there is no other treatment option. If a patient deteriorates whilst taking Artemether and Lumefantrine 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 and Lumefantrine Tablets.
If quinine is given after Artemether and Lumefantrine Tablets, close monitoring of the ECG is advised.
If Artemether and Lumefantrine Tablets is given after mefloquine, close monitoring of food intake is advised.
In patients previously treated with halofantrine, Artemether and Lumefantrine Tablets should not be administered earlier than one month after the last halofantrine dose.
Artemether and Lumefantrine Tablets is not indicated and has not been evaluated for prophylaxis.
Artemether and Lumefantrine Tablets 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 Artemether and Lumefantrine Tablets.
Like other antimalarials (e.g. halofantrine, quinine and quinidine) Artemether and Lumefantrine Tablets has the potential to cause QT prolongation.

Caution is recommended when combining Artemether and Lumefantrine Tablets 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 Artemether and Lumefantrine Tablets. Caution is recommended when combining Artemether and Lumefantrine Tablets with hormonal contraceptives. Artemether and Lumefantrine Tablets 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.
Patients who remain averse to food during treatment should be closely monitored as the risk of recrudescence may be greater. 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.

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 Artemether and Lumefantrine Tablets in patients with renal impairment is recommended. Caution is advised when administering Artemether and Lumefantrine Tablets 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. No dose adjustment is recommended for patients with mild to moderate hepatic impairment. Caution is advised when administering Artemether and Lumefantrine Tablets to patients with severe hepatic impairment. In these patients, ECG and blood potassium monitoring is advised.
Elderly
There is no information suggesting that the dosage in patients over 65 years of age should be different than in younger adults.
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 Artemether and Lumefantrine Tablets. In the absence of carcinogenicity study data, and due to lack of clinical experience, more than two courses of Artemether and Lumefantrine Tablets cannot be recommended.

SIDE EFFECTS
Artemether and Lumefantrine Tablets does not prevent malaria. Common side effects of Artemether and Lumefantrine Tablets include headache, dizziness, loss of appetite, weakness, fever, chills, tiredness, muscle or joint pain, nausea, vomiting, abdominal pain, cough, and trouble sleeping (insomnia).

PREGNANCY & LACTATION
Pregnancy: There is insufficient data from the use of artemether and lumefantrine in pregnant women. Based on animal data, Artemether and Lumefantrine Tablets is suspected to cause serious birth defects when administered during the first trimester of pregnancy Reproductive studies with artemether 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.
Safety data from an observational pregnancy study of approximately 500 pregnant women who were exposed to Artemether and Lumefantrine Tablets (including a third of patients who were exposed in the first trimester), and published data of another over 500 pregnant women who were exposed to artemether lumefantrine (including over 50 patients who were exposed in the first trimester), as well as published data of over 1,000 pregnant women who were exposed to artemisinin derivatives, did not show an increase in adverse pregnancy outcomes or teratogenic effects over background rates. Artemether and Lumefantrine Tablets treatment must not be used during the first trimester of pregnancy in situations where other suitable and effective antimalarials are available. 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. Breastfeeding: Animal data suggest excretion into breast milk but no data are available in humans. Women taking Artemether and Lumefantrine Tablets 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 Artemether and Lumefantrine Tablets unless potential benefits to the mother and child outweigh the risks of Artemether and Lumefantrine Tablets treatment.
Fertility: There is no information on the effects of Artemether and Lumefantrine Tablets on human fertility.

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

SHELF-LIFE
36 months

STORAGE AND HANDLING INSTRUCTIONS
Store in a dark, dry place, Not exceeding 30°C temp.
Keep all medicines out of reach of children.

PACKAGING INFORMATION
10 x 1 x 6 Tablets Blister Pack

NAFDAC Reg. No.:
Mfg. Lic. No. : G/25/2489

Product License Holder:
Shinfield Pharmaceuticals Ltd, 400 Thames
Valley Park, RG6 1PT, Reading, United Kingdom
Email: products@shinfield-pharma.com
Tel: +44 (0) 1189 653845

Mktd by:

SHINFIELD PHARMACEUTICALS NIG LTD,
22/23 God's Gift Plaza, Opp Uga Boys High, Aguata, Anambra, Nigeria
Contact: Email: products-ng@shinfield-pharma.com Tel: +234 (0) 8033572403

Manufactured by:
Uniza™ LIFECARE PVT. LTD.
Sr. No. 919/7, (Old Sr. No. 404), Kadi-Detroj Road, Balasar, Tal. Kadi, Dist. Mehsana, Gujarat-382715. INDIA.
A Division of PASHUPATI

PRODUCT
COUNTRY: NIGERIA
LANGUAGE: ENGLISH
PARTY/DIV.: UNIZA

INSERT
SIZE: 5.5X8.5 INCH
60 GSM MAPLITHO
FRONT/BACK
FOLD WITH BRAND ON FRONT
COLOR: ONE