1.3 Product Information

1.3.1 Summary of product characteristics (SmPC)

1. 3.1.1 Name of the medicinal product:

ZEXIT FORTE TABLETS
(Artemether 80 mg and Lumefantrine 480 mg Tablets)

1.3.1.2 Qualitative and quantitative composition:

Each Uncoated Tablet Contains:
Artemether.....80 mg
Lumefantrine USP.....480 mg
Approved Colour Used.
Excipients.....QS

Sr. No.	Ingredients	Specifi-cation	Label Claim / Tablet (In mg)	Over-ages added (In %)	Qty. / Tablet (In mg)	Reason For Function
a)	**Dry Mixing**					
1.	Artemether	IH	80.000	NA	80.000	Medicament
2.	Lumefantrine	USP	480.000	NA	480.000	Medicament
3.	Maize Starch	BP	NA	NA	182.730	Diluent
4.	Microcrystalline Cellulose	BP	NA	NA	65.000	Diluent
b)	**Binder Preparation**					
5.	Maize Starch	BP	NA	NA	25.000	Binder
6.	Gelatin (Gelling grade)	BP	NA	NA	5.000	Binder
7.	Povidone K-30	BP	NA	NA	5.000	Binder
8.	Methyl Hydroxybenzoate	BP	NA	NA	1.000	Preservative
9.	Propyl Hydroxybenzoate	BP	NA	NA	0.100	Preservative
10.	Polysorbate-80	BP	NA	NA	5.170	Wetting Agent
11.	Purified Water	BP	NA	NA	--	Vehicle
c)	**Lubrication**					
12.	Purified Talc	BP	NA	NA	17.000	Glidant
13.	Magnesium Stearate	BP	NA	NA	10.000	Lubricant
14.	Crospovidone (Type A)	BP	NA	NA	18.000	Disintegrant
15.	Colloidal Anhydrous Silica	BP	NA	NA	6.000	Glidant
	Average Weight of Uncoated Tablet (In mg)				**900.000**	

1.3.1.3 Pharmaceutical form: Uncoated Tablets

Description: Yellow coloured, round shaped, biconvex, uncoated tablet, plain on both sides.

1.3.1.4 Clinical Particulars

1.3.1.4.1 Therapeutic indications

ZEXIT FORTE TABLETS (Artemether 80 mg and Lumefantrine 480 mg Tablets) are indicated for the treatment of uncomplicated cases of malaria due to *Plasmodium falciparum* in adults and children of 35 kg and above.

The most recent official guidelines on the appropriate use of antimalarial agents and local information on the prevalence of resistance to antimalarial drugs must be taken into consideration for deciding on the appropriateness of therapy with **ZEXIT FORTE TABLETS** (Artemether 80 mg and Lumefantrine 480 mg Tablets)

1.3.1.4.2 Posology and method of administration

Route: Oral

Method of Administration:

Recommended Dose						
Artemether + Lumefantrine						
Body Weight	**Day 1**		**Day 2**		**Day 3**	
	0 Hr	**8 Hrs**	**24 Hrs**	**36 Hrs**	**48 Hrs**	**60 Hrs**
35 kg & above	1 Tablet	1 Tablet	1 Tablet	1 Tablet	1 Tablet	1 Tablet

Second dose to be taken after 8 hours of first dose.

Better taken with food especially fatty meal.

1.3.1.4.3 Contraindications

ZEXIT FORTE TABLETS (Artemether 80 mg and Lumefantrine 480 mg Tablets) are contraindicated in:

- 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, astemizole)
- cisapride
- patients with known disturbances of electrolyte balance e.g. hypokalaemia 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

1.3.1.4.4 Special warnings and precautions for use

ZEXIT FORTE TABLETS (Artemether 80 mg and Lumefantrine 480 mg Tablets) must not be used in the first trimester of pregnancy in situations where other suitable and effective antimalarials are available.

ZEXIT FORTE TABLETS (Artemether 80 mg and Lumefantrine 480 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.

Due to limited data on safety and efficacy, **ZEXIT FORTE TABLETS** (Artemether 80 mg and Lumefantrine 480 mg Tablets) should not be given concurrently with any other antimalarial agent unless there is no other treatment option.

If a patient deteriorates whilst taking **ZEXIT FORTE TABLETS** (Artemether 80 mg and Lumefantrine 480 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 and Lumefantrine Tablets.

If quinine is given after **ZEXIT FORTE TABLETS** (Artemether 80 mg and Lumefantrine 480 mg Tablets), close monitoring of the ECG is advised.

If **ZEXIT FORTE TABLETS** (Artemether 80 mg and Lumefantrine 480 mg Tablets) is given after mefloquine, close monitoring of food intake is advised.

In patients previously treated with halofantrine, **ZEXIT FORTE TABLETS** (Artemether 80 mg and Lumefantrine 480 mg Tablets) should not be administered earlier than one month after the last halofantrine dose.

ZEXIT FORTE TABLETS (Artemether 80 mg and Lumefantrine 480 mg Tablets) is not indicated and has not been evaluated for prophylaxis of malaria.

ZEXIT FORTE TABLETS (Artemether 80 mg and Lumefantrine 480 mg Tablets) 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 **ZEXIT FORTE TABLETS** (Artemether 80 mg and Lumefantrine 480 mg Tablets).

Like other antimalarials (e.g. halofantrine, quinine and quinidine) **ZEXIT FORTE TABLETS** (Artemether 80 mg and Lumefantrine 480 mg Tablets) has the potential to cause QT prolongation. Caution is recommended when combining **ZEXIT FORTE TABLETS** (Artemether 80 mg and Lumefantrine 480 mg 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 **ZEXIT FORTE TABLETS** (Artemether 80 mg and Lumefantrine 480 mg Tablets).

Caution is recommended when combining **ZEXIT FORTE TABLETS** (Artemether 80 mg and Lumefantrine 480 mg Tablets) with hormonal contraceptives. **ZEXIT FORTE TABLETS** (Artemether 80 mg and Lumefantrine 480 mg 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.

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. 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. In these patients, ECG and blood potassium monitoring is advised. No dose adjustment is recommended for patients with mild to moderate hepatic impairment.

Older people

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.

1.3.1.4.5 Interaction with other medicinal products and other forms of interaction

Both artemether and lumefantrine are CYP450 3A4 substrates. Inhibitors and inducers of CYP3A4 may affect artemether's and lumefantrine's serum concentrations. Artemether may induce CYP3A4/5. CYP2D6 may be inhibited.

Aurothioglucose: Increased risk of blood dyscrasias. Avoid aurothioglucose co-administration.

Halofantrine: may increase risk of QTc prolongation. Avoid halofantrine co-administration.

Manufacturer recommends against the co-administration of artemether/lumefantrine with the following drugs that may prolong QTc: antiarrhythmics, such as amiodarone, disopyramide, flecainide, procainamide, sotalol, and quinidine; antibacterials, such as macrolides and quinolones; antidepressants (imipramine, amitriptyline, clomipramine); antifungals such as imidazoles and triazoles; terfenadine; other antimalarials; antipsychotic drugs (droperidol, pimozide and ziprasidone); . However, there is no evidence that co-administration with these drugs would be harmful.

Rifampicin, efavirenz, nevirapine, phenobarbital, phenytoin, and carbamazepine, may decrease artemether and lumefantrine serum concentrations. Monitor closely for anti-malarial activity with co-administration.

HIV-protease inhibitors may increase artemether and lumefantrine serum concentrations. Consider EKG monitoring for QTc prolongation.

Grapefruit juice: may increase artemether and lumefantrine serum concentrations.

Oral contraceptive: may reduce the effectiveness of hormonal contraceptives. Use an additional barrier form of contraception.

1.3.1.4.6 Pregnancy and Lactation

Pregnancy

A moderate amount of data on pregnant women in their first trimester (more than 500 pregnancy outcomes) is available for artemether/lumefantrine. Data from a recent meta-analysis have shown that compared to quinine, artemether/lumefantrine treatment in the first trimester was not associated with an increased risk of miscarriage or stillbirth. While the data are limited, they indicate no difference in the prevalence of major congenital anomalies between treatment groups.

A large amount of data on pregnant women in their second and third trimester (more than 4000 documented pregnancy outcomes) is available for artemisinin derivatives including artemether/lumefantrine. They indicate no fetal or neonatal toxicity.

ZEXIT FORTE TABLETS (Artemether 80 mg and Lumefantrine 480 mg Tablets) can be used during pregnancy.

Lactation
The amounts of artemether, dihydroartemisinin and lumefantrine in breast milk are small. Therefore, breastfeeding women can receive artemisinin-based combination therapies (including **ZEXIT FORTE TABLETS** (Artemether 80 mg and Lumefantrine 480 mg Tablets) for malaria treatment.

1.3.1.4.7 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 **ZEXIT FORTE TABLETS** (Artemether 80 mg and Lumefantrine 480 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.

1.3.1.4.8 Undesirable effects
The most common side effects in adults are: headache, feeling dizzy, feeling weak, loss of appetite, muscle and joint pain or stiffness, feeling tired, chills, fever.
The most common side effects in children are: fever, cough, vomiting, headache, loss of appetite.

1.3.1.4.9 Overdose
Experience of overdosage with artemether and lumefantrine is limited. In cases of suspected overdosage symptomatic and supportive therapy should be given as appropriate, which should include monitoring of ECG and serum electrolytes.

1.3.1.5 Pharmacological properties
1.3.1.5.1 Pharmacodynamic properties
ZEXIT FORTE TABLETS (Artemether 80 mg and Lumefantrine 480 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.
The antimalarial activity of the combination of lumefantrine and artemether is greater than that of either substance alone. In a double-blind comparative study in adults in China (n=157), the 28-day cure rate of artemether/ lumefantrine when given at four doses was 94% compared with 90% for lumefantrine and 46% for artemether based on intent-to-treat (ITT) population, when given as monotherapy.

1.3.1.5.2 Pharmacokinetic properties
Absorption
Artemether is absorbed fairly rapidly with peak plasma concentrations reached about 2 hours after dosing. Absorption of lumefantrine, a highly lipophilic compound, starts after a lag-time of up to 2 hours, with peak plasma concentration about 6 to 8 hours after administration. 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 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 (DHA) is also bound to human serum proteins (47% to 76%). Protein binding to human plasma protein is linear.

Metabolism

Artemether is rapidly and extensively metabolised (substantial first-pass metabolism). Human liver microsomes metabolise artemether to the biologically active main metabolite dihydroartemisinin (demethylation), predominantly through the enzyme CYP3A4/5. The pharmacokinetics of this metabolite has also been described in humans *in vivo*. The artemether/dihydroartemisinin AUC ratio is 1.2 after a single dose and 0.3 after 6 doses given over 3 days. Artemether and DHA were reported to have a mild inducing effect on CYP3A4 activity, which is not expected to present a problem in the general patient population.

During repeated administration of Artemether and lumefantrine, plasma artemether levels decreased significantly, while levels of the active metabolite (dihydroartemisinin) increased, although not to a statistically significant degree. This confirms that there was induction of the enzyme responsible for the metabolism of artemether.

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 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 compound.

In vitro lumefantrine significantly inhibits the activity of CYP2D6 at therapeutic plasma concentrations.

Elimination

Artemether and dihydroartemisinin are rapidly cleared from plasma with an elimination half-life of about 2 hours, while 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.

In healthy volunteers, neither lumefantrine nor artemether was found in urine after administration of artemether and lumefantrine, and urinary excretion of DHA 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. Lumefantrine was excreted unchanged in faeces and with traces only in urine. Metabolites of both drug components were eliminated in bile/faeces and urine.

1.3.1.5.3 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 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 (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 artemether dose, 20 mg/kg/day in the rat, yields artemether 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, lumefantrine and the main metabolite desbutyl-lumefantrine 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) > desbutyl-lumefantrine (5.5 μM) > lumefantrine (8.1 μM). Clinical studies show, that prolongation of QTcF can occur with standard dosing of artemether/lumefantrine.

1.3.1.6 Pharmaceutical particulars

1.3.1.6.1 List of excipients

Maize Starch, Microcrystalline Cellulose, Gelatin (Gelling grade), Povidone K-30, Methyl Hydroxybenzoate, Propyl Hydroxybenzoate, Polysorbate-80, Purified Water, Purified Talc, Magnesium Stearate, Crospovidone (Type A), Colloidal Anhydrous Silica

1.3.1.6.2 Incompatibilities

Not applicable

1.3.1.6.3 Shelf life

36 months

1.3.1.6.4 Special precautions for storage

Store below 30°C in a dry and dark place.
Keep all medicines out of reach of children.

1.3.1.6.5 Nature and contents of container
Primary packing: 6 Tablets in an ALU-PVC blister.
Secondary packing: 1 Blister is packed in an inner carton along with leaflet.
Tertiary packing: Such 10 inner cartons are packed in an outer carton. Shrink individual outer carton. Such 30 Shrinks are packed in a 5 Ply corrugated box sealed with BOPP tape & strap with strapping roll.

1.3.1.6.6 Special precautions for disposal and other handling
None

1.3.1.7 Applicant / Manufacturer
Applicant

Applicant name and address	**M/s. SYNERMED NIG. LTD.** 3, Abike Jokogbola Street, Solebo Estate, Aga, Ikorodu, Lagos, Nigeria
Contact person's phone number	
Contact person's email	

Manufacturer

Manufacturer name and address	**M/s. IMPULSE PHARMA PVT. LTD.** J-201, J-202/1 , MIDC Tarapur, Boisar, Dist. Palghar - 401506, Maharashtra State, India.
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