1.3 Product Information

1.3.1 Summary of product characteristics (SmPC)

1. 3.1.1 Name of the medicinal product:

ZEXIT TABLETS
(Artemether 20 mg and Lumefantrine 120 mg Tablets)

1.3.1.2 Qualitative and quantitative composition:
Each Uncoated Tablet Contains:
Artemether 20 mg
Lumefantrine USP 120 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	20.000	NA	20.00	Medicament
2.	Lumefantrine	USP	120.000	NA	120.00	Medicament
3.	Maize starch	BP	NA	NA	45.58	Diluent
4.	Microcrystalline cellulose	BP	NA	NA	16.25	Diluent
5.	Tartrazine	IH	NA	NA	0.10	Colour
b)	**Binder Preparation**					
6.	Maize Starch	BP	NA	NA	6.25	Binder
7.	Gelatin (Gelling grade)	BP	NA	NA	1.25	Solubilizing agent
8.	Povidone (K-30)	BP	NA	NA	1.25	Binder
9.	Methyl Hydroxybenzoate	BP	NA	NA	0.25	Preservative
10.	Propyl Hydroxybenzoate	BP	NA	NA	0.025	Preservative
11.	Polysorbate 80	BP	NA	NA	1.30	Wetting agent
12.	Purified Water	BP	NA	NA	-----	Vehicle
c)	**Lubrication**					
13.	Purified Talc	BP	NA	NA	4.25	Glidant
14.	Magnesium Stearate	BP	NA	NA	2.50	Lubricant
15.	Crospovidone (Type A)	BP	NA	NA	4.50	Disintegrant
16.	Colloidal Anhydrous Silica	BP	NA	NA	1.50	Glidant
	Average Weight of Uncoated Tablet (In mg)				**225.00 mg**	

1.3.1.3 Pharmaceutical form: Uncoated Tablets

Description: Yellow coloured, round shaped, biconvex, uncoated tablet, breakline on one side and plain on other side.

1.3.1.4 Clinical Particulars

1.3.1.4.1 Therapeutic indications

ZEXIT TABLETS (Artemether 20 mg and Lumefantrine 120 mg Tablets) are indicated for the treatment of acute uncomplicated Plasmodium falciparum malaria in adults, children and infants of 5 kg and above. Consideration should be given to official guidance regarding the appropriate use of antimalarial agents.

1.3.1.4.2 Posology and method of administration

Method of Administration

A standard 3 days treatment schedule with a total of 6 doses is recommended as follows:

Weight in Kg	**Total tablets**	**DOSAGE REGIMEN**					
		Day 1		**Day 2**		**Day 3**	
		0 Hr	**8 Hr**	**24 Hr**	**36 Hr**	**48 Hr**	**60 Hr**
Adults (35kg & Above)	24	4	4	4	4	4	4
25kg - 34kg (8-12years)	18	3	3	3	3	3	3
15kg - 24kg (3-8years)	12	2	2	2	2	2	2
5kg - 14kg (< 3years)	6	1	1	1	1	1	1

Second dose to be taken after 8 hours of first dose.
Better taken with food especially fatty meal.

1.3.1.4.3 Contraindications

1.3.1.4.3 Contraindications

Hypersensitivity

Known hypersensitivity to artemether, lumefantrine, or to any of the excipients of **ZEXIT TABLETS** (Artemether 20 mg and Lumefantrine 120 mg Tablets)

Strong CYP3A4 Inducers

Coadministration of strong inducers of CYP3A4 such as rifampin, carbamazepine, phenytoin, and St. John's wort with **ZEXIT TABLETS** (Artemether 20 mg and Lumefantrine 120 mg Tablets) can result in decreased concentrations of artemether and/or lumefantrine and loss of antimalarial efficacy

1.3.1.4.4 Special warnings and precautions for use

ZEXIT TABLETS (Artemether 20 mg and Lumefantrine 120 mg Tablets) has not been evaluated for prophylaxis and for the treatment of cerebral malaria or other severe manifestations of severe malaria including pulmonary edema or renal failure.

ZEXIT TABLETS (Artemether 20 mg and Lumefantrine 120 mg Tablets) is not indicated for, and has not been evaluated in, the treatment of malaria due to P.vivax, P. malariae or P. ovale, although some patients in clinical studies had co-infection with P. falciparum and P. vivax at baseline. **ZEXIT TABLETS** (Artemether 20 mg and Lumefantrine 120 mg Tablets) are active against blood stages of Plasmodium vivax, but are not active against hypnozoites.

Like other antimalarials (e.g. halofantrine, quinine, quinidine), **ZEXIT TABLETS** (Artemether 20 mg and Lumefantrine 120 mg Tablets) has the potential to cause QTc.

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

If a patient deteriorates whilst taking **ZEXIT TABLETS** (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 **ZEXIT TABLETS** (Artemether 20 mg and Lumefantrine 120 mg Tablets).

1.3.1.4.5 Interaction with other medicinal products and other forms of interaction

With other antimalarials: Data on safety and efficacy are limited, and **ZEXIT TABLETS** (Artemether 20 mg and Lumefantrine 120 mg Tablets) should therefore not be given concurrently with other antimalarials unless there is no other treatment option. The long elimination half-life of lumefantrine must be taken into account when administering quinine in patients previously treated with **ZEXIT TABLETS** (Artemether 20 mg and Lumefantrine 120 mg Tablets)

Patients previously treated with other antimalarials: If **ZEXIT TABLETS** (Artemether 20 mg and Lumefantrine 120 mg Tablets) is given following administration of mefloquine or quinine, close monitoring of food intake (for mefloquine) or of the ECG (for quinine) 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.

With other drugs: Caution is recommended when combining **ZEXIT TABLETS** (Artemether 20 mg and Lumefantrine 120 mg Tablets) with substrates, inhibitors or weak to moderate inducers of 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 TABLETS** (Artemether 20 mg and Lumefantrine 120 mg Tablets)

With hormonal contraceptives: ZEXIT TABLETS (Artemether 20 mg and Lumefantrine 120 mg Tablets) may reduce the effectiveness of hormonal contraceptives. Therefore, patients should be advised to use an additional non-hormonal method of birth control.

1.3.1.4.6 Pregnancy and Lactation:

Pregnancy:

Artemether-lumefantrine 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.

Lactation

Animal data suggest excretion into breast milk but no data are available in humans. Women taking Artemether-lumefantrine 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-lumefantrine unless potential benefits to the mother and child outweigh the risks of Artemether-lumefantrine treatment.

1.3.1.4.7 Effects on the ability to drive and use machines

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

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 Overdoses

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

1.3.1.5 Pharmacological properties

1.3.1.5.1 Pharmacodynamic properties

ZEXIT TABLETS (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.

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.
Neurotoxicity
Studies in dogs and rats have shown that intramuscular injections of artemether resulted in brain lesions mainly in brainstem nuclei. Changes observed mainly in brainstem nuclei included chromatolysis, eosinophilic cytoplasmic granulation, spheroids, apoptosis and dark neurons. Lesions were observed in rats dosed for at least 7 days and dogs for at least 8 days, but lesions were not observed after shorter intramuscular treatment courses or after oral dosing. The estimated artemether 24 h AUC after 7 days of dosing at the no observed effect level is approximately 7-fold greater or more than the estimated artemether 24 h AUC in adult humans. The hearing threshold was affected at 20 dB by oral artemether administration to dogs at a dose of about 29 times the highest artemether clinical dose (160 mg/day) based on body surface area comparisons. Most nervous system disorder adverse events in the studies of the 6-dose regimen were mild in intensity and resolved by the end of the study.
Mutagenicity
Artemether and lumefantrine were not genotoxic/clastogenic based on in vitro and in vivo testing.
Carcinogenicity
Carcinogenicity studies were not conducted.
Reproductive toxicity studies
Embryotoxicity was observed in rat and rabbit reproductive toxicity studies conducted with artemether, a derivative of artemisinin. Artemisinins are known to be embryotoxic. Lumefantrine alone caused no sign of reproductive or development toxicity at doses up to 1,000 mg/kg/day in rats and rabbits, doses which are at least 10 times higher than the daily human dose based on body surface area comparisons.
Reproductive toxicity studies performed with the artemether-lumefantrine combination caused maternal toxicity and increased post-implantation loss in rats and rabbits.
Artemether caused increases in post-implantation loss and teratogenicity (characterised as a low incidence of cardiovascular and skeletal malformations) in rats and rabbits. The embryotoxic artemether dose in the rat yields artemether and dihydroartemisinin exposures similar to those achieved in humans based on AUC.

Fertility
Artemether-lumefantrine administration yielded altered sperm motility, abnormal sperm, reduced epididymal sperm count, increased testes weight, and embryotoxicity; other reproductive effects (decreased implants and viable embryos, increased preimplantation loss) were also observed. The no adverse effect level for fertility was 300 mg/kg/day. The relevance to this finding in humans is unknown.

Juvenile toxicity studies
A study investigated the neurotoxicity of oral artemether in juvenile rats. Mortality, clinical signs and reductions in body weight parameters occurred most notably in younger rats. Despite the systemic toxicity noted, there were no effects of artemether on any of the functional tests performed and there was no evidence of a direct neurotoxic effect in juvenile rats.
Very young animals are more sensitive to the toxic effect of artemether than adult animals. There is no difference in sensitivity in slightly older animals compared to adult animals. Clinical studies have established the safety of artemether and lumefantrine administration in patients weighing 5 kg and above.

Cardiovascular Safety Pharmacology
In toxicity studies in dogs at doses >600 mg/kg/day, there was some evidence of prolongation of the QTc interval (safety margin of 1.3-fold to 2.2-fold for artemether using calculated free Cmax), at higher doses than intended for use in man. In vitro hERG assays showed a safety margin of >100 for artemether and dihydroartemisinin. The hERG IC50 was 8.1 μM for lumefantrine and 5.5 μM for its desbutyl metabolite.

1.3.1.6 Pharmaceutical particulars

1.3.1.6.1 List of excipients
Microcrystalline cellulose, Maize Starch, Gelatin (Gelling grade), Povidone K-30, Methyl Hydroxybenzoate, Propyl Hydroxybenzoate, Polysorbate 80, Purified water, Purified Talc, Magnesium Stearate, Crospovidone (Type A), Colloidal Anhydrous Silica, Tartrazine.

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: 24 Tablets in an ALU-PVC blister.
Secondary packing: 1 blister packed in inner carton along with leaflet.
Tertiary packing: 10 inner cartons are packed in an outer carton. Shrink individual outer carton. Such 36 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
Not applicable

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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