1.3.1 Summary of product characteristics

1. NAME OF THE MEDICINAL PRODUCT

1.1 Product Name : Lingomal tablets 80/480

1.2 Generic Name : Artemether 80mg & Lumefantrine 480mg Tablets

1.3 Pharmaceutical Form : Uncoated Tablets

1.4 Packaging :1 blister of 6 tablets packed in an inner carton. Such 10 inner cartons packed in an outer carton.

2. QUALITY AND QUANTITATIVE COMPOSITION

Batch size: 150000 Tablets

Sr. No.	Ingredients	Reference	Qty./tab (mg)	O.A (%)	Actual qty.	Function
ACTIVE INGREDIENT						
1.	*Artemether	PHI	80.000	-	80.000	Active
2.	*Lumefantrine	PHI	480.000		480.000	Active
3.	@Microcrystalline Cellulose	BP	226.000		226.000	Diluent
4.	Cross carmellose Sodium	USPNF	20.000		20.000	Disintegrant
BINDER PREPARATION						
5.	Hypromellose (HPMC 5cps)	USP	35.000		35.000	Binder
6.	Polysorbate 80	BP	1.000		1.000	Surfactant
7.	Purified Water	BP	q.s.		q.s.	Solvent
LUBRICATION						
8.	Cross carmellose Sodium	USPNF	60.000		60.000	Disintegrant
9.	Colloidal Anhydrous Silica	BP	20.000		20.000	Glidant
10.	Sodium Lauryl Sulphate	BP	20.000		20.000	Lubricant
11.	Magnesium Stearate	BP	18.000		18.000	Lubricant

*Quantity of Artemether IH & Lumefantrine USP to be dispensed on 100% assay on as is basis.

@Extra quantity of Artemether IH & Lumefantrine USP should be compensated with Microcrystalline Cellulose BP.

Theoretical compression weight per weight per tablet = 960 mg

Note: If assay found above 100% calculated on as is basis then there is no need of calculation.

Legend:

BP = British Pharmacopoeia

IH = In-house

USPNF = United States Pharmacopoeia and the National Formulary

USP = United States Pharmacopoeia

3. PHARMACEUTICAL FORM VISUAL DESCRIPTION:

Yellow colored caplet shaped uncoated tablets with breakline on one side and plain on other side.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS:

Treatment of acute uncomplicated malaria caused by Plasmodium falciparum in adults, children and infants of more than 5 kg. Should take into account the recommendations for appropriate use of antimalarial treatments.

4.2 Posology and method of administration

One tablet to be taken at the initial diagnosis, again after 8 hours, then 1 tablet twice daily (morning and evening) on each of the following two days. (Total course comprises 6 tablets)

Weight in kgs	Age in yrs	Dosage Regimen					
		DAY 1		DAY 2		DAY 3	
		0 hr	8 hr	24 hr	36 hr	48 hr	60 hr
> 34	>14	1 tab	1 tab	1 tab	1 tab	1 tab	1 tab

4.3 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).

(*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

Lingomal 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, Lingomal should not be given concurrently with any other antimalarial agent unless there is no other treatment option.
If a patient deteriorates whilst taking Lingomal, 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 Lingomal.
In the case of administration of quinine after Lingomal, a close monitoring of the ECG is advised.
If Lingomal is administered after taking mefloquine, food intake must be closely monitored.
In patients previously treated by halofantrine, it is recommended to follow a period of at least one month after the last halofantrine prior to administration of Lingomal.
Lingomal should be used with caution in patients treated with antiretroviral (ARV) drugs

because the decline in concentrations of artemether, dihydroartemisinin (DHA) and lumefantrine can lead to lower efficiency Lingomal antimalarial.

Caution is recommended when combining Lingomal 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 Lingomal.

Caution is recommended when combining Lingomal with hormonal contraceptives. Meritem Forte 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.

If food intolerance persists during treatment, close monitoring is recommended because of the higher risk of treatment failure.

Renal impairment

Caution is advised when administering Lingomal to patients with severe renal impairment. In these patients, ECG and blood potassium monitoring is advised.

Hepatic impairment

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.

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 Lingomal. In the absence of carcinogenicity study data, and due to lack of clinical experience, more than two courses of Lingomal cannot be recommended.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction with the drugs known to lengthen the interval Qtc

Lingomal 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 antihistaminics (terfenadine, astemizole), cisapride, flecainide.

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 Lingomal 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.

Interaction with the powerful inducers of CYP3A4 such as rifampicin

Concomitant use of strong inducers of CYP3A4 such as rifampin, carbamazepine, phenytoin, St. John's Wort is contraindicated with Lingomal.

Concomitant use not recommended

Interaction with other antimalarials

If Lingomal is given as a result of administration of mefloquine and quinine, a close monitoring of the ingestion of food (mefloquine) or ECG (quinine) is recommended. In patients previously treated by halofantrine, Lingomal should not be given earlier than one month after the last dose of halofantrine.

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.

Interaction with the anti-retroviral drugs

Both artemether and lumefantrine are metabolized by CYP3A4. Lingomal should be used with caution in patients on anti-retrovirals because a reduction of artemether, DHA, and/or concentrations of lumefantrine can cause a decrease in antimalarials efficacy of Lingomal, and increased the lumefantrine concentrations can lead to a lengthening of the QT.

Interaction with weak to moderate inducers of CYP3A4

When Arthefantrine is co-administered with low to moderate inducers of CYP3A4, it may result in decreased concentrations of artemether and/or lumefantrine and loss of antimalarial efficacy.

Interactions resulting from the effects of the Arthefantrine on other drugs

Interaction with drugs metabolized by cytochrome P450 enzymes

When Lingomal 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.

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, Lingomal may potentially reduce the effectiveness of hormonal contraceptives.

Food/drink interactions

Lingomal should be taken with food or beverages high in fat such as milk that absorption of artemether and lumefantrine is increased. Grapefruit juice should be avoided during treatment.

4.6 Fertility, pregnancy and lactation

Pregnancy

Lingomal should not be used during the first trimester of pregnancy in situations where some other appropriate and effective antimalarial drugs are available. However, the treatment should not be delayed in situations where the prognosis is engaged if some other effective antimalarials are not available. During the second and third quarters of the pregnancy, the treatment will be considered unless the benefit intended for the mother is greater than the potential risk to the fetus.

Breastfeeding

Women treated by Lingomal should not breastfeed during their treatment. Because of the long half-life of elimination of lumefantrine (2 to 6 days), it is recommended a delay of at least a week after the last taken of Lingomal before resuming breastfeeding, unless the potential benefits for the mother and the child outweigh the risks of the treatment by Lingomal.

4.7 Effects on ability to drive and use machines

Patients consuming artemether and lumefantrine should be warned that dizziness or fatigue/asthenia may occur in which case they should not drive or use machines.

4.8 Undesirable effects

Adverse reactions reported during clinical studies and post-marketing experience are listed below according to classes of organ systems.

Most of the side effects are mild to moderate and generally disappear after a few days to a few weeks after treatment. Some side effects are more commonly reported in children and others are more commonly reported in adults. In cases where there is a difference, the frequency listed below is the more common one.

Some side effects could be serious and need immediate medical attention. Rare (may affect up to 1 in 1,000 people)

If you get a rash, swelling of the face, lips, tongue or throat with difficulty in swallowing or breathing, tell your doctor straight away. These are signs of an allergic reaction.

Other side effects are:

Very common (may affect more than 1 in 10 people)

Fast heart beat, headache, dizziness, cough, being sick (vomiting), stomach pain, feeling sick (nausea), joints or muscles aching, loss of appetite, general weakness, tiredness, trouble with sleeping.

Common (may affect up to 1 in 10 people)

Involuntary muscle contractions (sometimes in rapid spasms), heart rhythm disturbances (called QTc prolongation), Symptoms such as unexplained persistent nausea, stomach problems, loss of appetite or unusual tiredness or weakness (signs of liver problems),diarrhoea, abnormal walking*)), tingling or numbness of the hands and feet*)), a rash or itching on the skin, insomnia.

Uncommon (may affect up to 1 in 100 patients)

inability to coordinate movements*), decreased skin sensitivity*), sleepiness, itching rash.

*) These side effects have been reported in adults and adolescents above 12 years of age.

4.9 Overdose

A suspected overdose: symptomatic treatment, electrocardiographic monitoring and supervision of the kaliemia.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Class pharmacotherapeutic: antimalarial. Blood Schizonticide, code ATC: P01BF01

Pharmacodynamic effects

Lingomal is a fixed combination of artemether and lumefantrine in proportion respective of 1 to 6. Each of the active principles operates at the level of the digestive vacuole of the parasite where they seem to affect the transformation of the heme, product of degradation of hemoglobin that is toxic to the parasite, no toxic, pigment hemozoin from Plasmodium. The lumefantrine seems to interfere with the intraparasitaire polymerization. Artemether is through toxic free radicals produced as a result of the cleavage of endoperoxide binding catalyzed by intraparasitaire iron of the heme. Artemether and lumefantrine then block the synthesis of nucleic acids and protein intraparasitaires.

5.2 Pharmacokinetic properties

Absorption

Artemether is absorbed quickly enough and the dihydroartemisinin, the active metabolite of artemether appears quickly in the systemic circulation with, for each of them, a peak plasma concentration reached about 2 hours after oral administration.

The absorption of the lumefantrine, composed highly lipophilic, starts in 2 hours after oral administration, peak plasma concentration is achieved approximately 6-8 hours (average value between 5, 10-9, 80 µg/mL). Average AUC of lumefantrine values the ties between 108 and 243 µg•h/mL.

Food intake increases the absorption of the lumefantrine and artemether. In healthy volunteers, when Lingomal was taken after a high fat meal, the related biodisponibilites the lumefantrine and artemether increased respectively by a factor 2 and factor 16 compared to a plug on an empty stomach.

Distribution

In vitro, binding of artemether and lumefantrine in human plasma proteins is important (respectively 95.4% and 99.7%). The dihydroartemisinin binds to human serum as (47-76%).

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 Lingomal.

5.3 Preclinical safety data

None known

6. Pharmaceutical particulars

6.1 List of excipients

Microcrystalline cellulose BP
Cross carmellose Sodium USPNF
Hypromellose (HPMC 5cps) USP
Polysorbate 80 BP
Colloidal Anhydrous Silica USPNF
Sodium Lauryl Sulphate BP
Magnesium Stearate BP

6.2 Incompatibilities

None reported

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at a temperature not exceeding 30°C in a dry place. Protect from light.

6.5 Nature and contents of container

1 blister of 6 tablets packed in an inner carton. Such 10 inner cartons packed in an outer carton.

6.6 Special precautions for disposal and other handling

No special requirements

7.0 MANUFACTURER

WINTECH PHARMACEUTICALS LTD.
Address: Office No. 2 & 3, 3rd floor, Broadway Shopping Centre, Dr. Ambedkar Road, Dadar T.T. Mumbai- 400014, India Tel: (+ 9122) 42123456 (100 lines)

8.0 DISTRIBUTED BY:

PATRICK LINGO PHARMACEUTICALS LTD

113, Obainwu Street, Onitsha, Nigeria