1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

Enclosed.

Summary Product Characteristics

1. **Name of the proprietary product: ZULIMAL**

   Name of the nonproprietary International Product: Artemether 80 mg + Lumefantrine 480 mg Tablets

   Route of Administration: Oral

2. **Qualitative and Quantitative composition:**

Sr. No.	Ingredients	Specification	Label Claim	Qty/ Tab in mg	Over ages	Reason for inclusion
	DRY MIXING					
1.	Artemether	IH	80.00	80.00	--	Active
2.	Lumefantrine	IH	480.00	480.00	--	Active
3.	Croscarmellose Sodium	BP	--	10.00	--	Disintegrant
4.	Polysorbate 80	BP	--	2.00	--	Surfactant
5.	Colloidal Silicon Dioxide	BP	--	5.00	--	Glidant
6.	Lactose	BP	--	20.00	--	Diluent
	FOR PASTE					
7.	H.P.M.C 5 CPS	BP	--	20.00	--	Binder
	LUBRICATION					
8.	Purified Talc	BP	--	4.00	--	Lubricant
9.	Magnesium Stearate	BP	--	8.00	--	Lubricant
10.	Colloidal Silicon Dioxide	BP	--	20.00	--	Disintegrant
11.	Croscarmellose Sodium	BP	--	25.000	--	Disintegrant
	COATING MATERIAL					
12.	Spray cell Quinoline Yellow SCMB 2210	IH	--	13.470	--	Coating Agent
13.	Isopropyl Alcohol	BP	--	q.s.	--	Solvent
14.	Methylene Dichloride	BP	--	q.s.	--	Solvent

Where, BP: British Pharmacopoeia, IH: In-House, q.s: Quantity Sufficient.
NOTE: 50 % Additional coating material taken to compensate loss during coating process

3. Pharmaceutical Form: Film Coated Tablets

4. Clinical Particulars:

4.1 Therapeutic Indications:
Treatment of malaria caused by all forms of Plasmodium including severe malaria caused by multiple drug resistant strains of P. Falciparum.

4.2 Posology and method of administration:
Posology
Artemether Lumefantrine Tablet should be taken with high fat food or drinks such as milk. Note that patients with acute malaria are frequently averse to food. Patients should be encouraged to resume normal eating as soon as food can be tolerated since this improves absorption of Artemether and Lumefantrine. In the event of vomiting within one hour of administration a repeat dose should be taken.

Weight in kg	Total Tablets	Dosage Regimen					
		Day - 1		Day – 2		Day - 3	
		8 Hrs	8 Hrs	24 Hrs	36 Hrs	48 Hrs	60 Hrs
< 10	08	Not recommended					
10-14	6	1	1	1	1	1	1
15-24	12	2	2	2	2	2	2
25-34	18	3	3	3	3	3	3
≥ 35 kg	24	4	4	4	4	4	4

4.3 Contraindications
Artemether Lumefantrine Tablet is contraindicated in individuals hypersensitive to Artemether and Lumefantrine. Therefore, there are no strict contra-indications for the use of Artemether in children. Nevertheless, no correlation has been found between QTc interval prolongation and plasma concentrations of lumefantrine caution is advised to patients who are taking drugs that are known to prolong the QT interval, such as certain antibiotics (macro/ides, fluoroquinolones, imidazole) or who are predisposed to cardiac arrhythmias.
It is advisable not to use drugs during pregnancy but in view of the high risk of malaria during pregnancy for mother and fetus, the responsible physician may consider it essential, as in the case of cerebral malaria, to treat a pregnant woman.
Artemisinin derivatives like Artemether are the fastest acting schizontocides and rapid clearance of parasites is essential. Since Artemether Lumefantrine Tablet has been designed for its use in children it is unlikely that this problem arises.

4.4 Special warnings and precautions for use
Artemether Lumefantrine Tablet should not be taken during breastfeeding. Due to the long elimination half-life of Lumefantrine, it is recommended that breastfeeding should not start until at least one week after stopping an Artemether/Lumefantrine combination Treatment

4.5 Interaction with other medicinal products and other forms of interaction
The sequential oral administration of mefloquine prior to artemether and lumefantrine combination had no effect on plasma concentrations of artemether or the artemether

dihydroartemisinin (DHA) ratio but there was a significant (around 30-40%) reduction in plasma levels (Cmax and AUC) of lumefantrine, possibly due to lower absorption secondary to a mefloquine-induced decrease In bile production. Such patients should therefore be encouraged to eat at dosing times to compensate for this decrease in bioavailability. Quinine alone caused a transient prolongation of the QTc Interval, which was consistent with its known cardio toxicity. This effect was slightly but significant greater when quinine was infused altar artemether and lumefantrine combination. Hence when artemether and lumefantrine combination is given to patients following administration of mefloquine or quinine, close monitoring of food Intake (for mefloquine) or the ECG (for quinine) should be carried out. In patients previously treated with halofantrine, Artemether Lumefantrine Tablet should be administered at least one month altar the last halofantrine dose.
Due to limited data on safety and efficacy, the combination should not be given concurrently with other antimalarials unle88 there is no other treatment option. However, if a patient deteriorates while taking the combination, alternative treatments for malaria should be commenced without delay. In such cases, monitoring of the ECG is recommended and steps should be taken to correct electrolyte disturbances.

4.6 Pregnancy and Lactation:

Pregnancy

Pregnancy Category C Artemether Lumefantrine Tablet should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Breastfeeding

It is not known whether artemether or lumefantrine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Artemether Lumefantrine Tablets are administered to a nursing woman. The benefits of breastfeeding to mother and infant should be weighed against potential risk from infant exposure to artemether and lumefantrine through breast milk.

4.7 Effects on the ability to drive and use machines

Driving and use of machinery is not recommended due to risk of dizziness and fatigue / Asthenia.

4.8 Undesirable effects:

With Artemether virtually no side effects have been seen. Laboratory abnormalities such as slight rise in transaminases and a decrease in reticulocyte count are rare and transient. A lowering of sinus frequency without causing ECG changes has been noticed. At high doses transient abdominal pain, tinnitus and diarrhea have been described but a casual relationship is unclear.
Some antimalarials such as Halofantrine and Quinine can influence the ECG pattern. Attention should be made to patient previously treated with those antimalarials. A reasonable period should be taken into account before starting treatment with Lumefantrine combinations. Sometimes rash, trouble sleeping, nausea, vomiting, diarrhea, coughing may occur. They need medical attention when persisting.

4.9 Overdose:

In cases of suspected overdosage, symptomatic and supportive therapy should be given as appropriate. ECG and blood potassium levels should be monitored.

5. Pharmacological Particulars:

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antimalarials, blood schizontocide
ATC code: P01 BF01.
Pharmacodynamic effects
Artemether is the most active derivate of the artemisinines, a new class of antimalarial drugs derived from artemisinin. The later compound is extracted from the plant Artemisia annua and Artemether is prepared semisynthetically.
Lumefantrine is a synthetic aryl amino alcohol similar to Mefloquine and Halofantrine. Both Artemether and Lumefantrine have their own action site in the malaria parasite. The presence of the endoperioxide bridge in Artemether (generating singlet oxygen and free radicals: those are very cytotoxic to the plasmodia) appears to be essential for antimalarial activity. Morphological changes of the parasitic membranes induced by Artemether have been described, being the result of free-radical action. Lumefantrine interferes more in the polymerization processes.
Other in vitro tests suggest that both cause a marked diminution of nucleic acid synthesis. Inhibition of protein synthesis as the basic mechanism of action is suggested in studies which showed morphological changes in ribosome as well as in the endoplasmic reticulum.

5.2 Pharmacokinetic properties

Orally administered Artemether is rapidly absorbed reaching therapeutic levels within 60-90 minutes. Artemether is metabolized in the liver to the demethylated derivate dihydroartemisinin (DHA). The elimination is rapid with a T½ of 2-4 hours. Dihydroartemisinin, being a potent antimalarial itself, has a T½ of about 2-4 hours. The degree of binding to plasma proteins varied markedly according to the species studied. The binding of Artemether with plasma protein in man is about 50%. Radioactivity distribution of Artemether was found to be equal between cells and plasma.
The absorption of Lumefantrine is highly influenced by lipids and food intake (from 10% in fasted to 100% at normal diet). Therefore, parents should be encouraged to give the medication with some fatty food as soon as it can be tolerated. Lumefantrine is Ndebutylated in human liver microsomes. This metabolite has 5 to 8 fold higher antiparasitic effects than Lumefantrine. Lumefantrine is found to be highly protein bound (95%).
The elimination half life in malaria treated patients will be 4 to 6 days. Lumefantrine and its metabolites are found in bile and faeces.

5.3 Pre-clinical Safety:

Not Applicable

6. Pharmaceutical Particulars:

6.1 List of Excipients:

Croscarmellose Sodium	BP
Polysorbate 80	BP
Colloidal Silicon Dioxide	BP
Lactose	BP
H.P.M.C 5 CPS	BP
Purified Talc	BP
Magnesium Stearate	BP

Spray cell Quinoline Yellow SCMB 2210	BP
Isopropyl Alcohol	IH
Methylene Dichloride	BP

6.2 Incompatibilities: None

6.3 Shelf life: 36 months

6.4 Special Precautions for storage:
Store below 30°C in a dry place. Protect from light.

6.5 Nature and contents of container:
An Alu-PVDC blister of 6 tablets packed in an inner carton, such 10 inner cartons are placed in an outer carton along with pack insert.

6.6 Special precautions for disposal and other handling
None

7. Marketing Authorization Holder: MASAN PHARM. LTD

8. Marketing Authorization Number: --

9. Date of first Authorization /renewal of the authorization: Not Applicable

10. Date of Revision of text: April 2023