

MALAFENTRINE DS (Artemether 80 mg + Lumefantrine 480 mg Tablets)	
Summary of Product Characteristics	

1. Name of the product: MALAFENTRINE DS

2. Qualitative and Quantitative formula:

Sr. No.	Ingredients	Specification	Label Qty/ Tablet (mg)
Dry mixing		--	--
1.	Artemether	IHS	80.00
2.	Lumefantrine	IHS	480.00
3.	Crospovidone	IP	2.500
4.	Colloidal silicon dioxide	IP	5.00
BINDER			
5.	Maize Starch	IP	36.250
6.	Polyvinylpyrrolidone K- 30	IP	4.500
7.	Purified water	IP	q.s.
Lubrication			
8.	Colloidal silicon dioxide	IP	15.250
9.	Sodium starch glycollate	IP	6.500
10.	Magnesium Stearate	IP	10.000
Average Weight			640 mg

3. a) Pharmaceutical Form: Uncoated Tablet.

b) Presentation: Yellow coloured round shaped biconvex uncoated tablet plain on both sides.

c) Dosage

Artemether and lumefantrine tablets 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 1 hour of administration a repeat dose should be taken.

Dosage Schedule:

Body Weight	Day 1		Day 2		Day 3	
	0 Hrs	8 Hrs after	24 Hrs	36 Hrs	48 Hrs	60 Hrs
Adults	1 tablet	1 tablet	1 tablet	1 tablet	1 tablet	1 tablet

4. Clinical Data:

4.1. Therapeutic Indications:

Malafentrine DS is a fixed combination of artemether and lumefantrine which acts as a blood schizontocide. It is indicated for:

1. Treatment of adults and children with infections due to *P. falciparum* or mixed infections including *P. falciparum*, It is effective against both drug-sensitive and drug-resistant *P. falciparum*.
2. It is also recommended for malaria infections acquired in areas where the parasites may be resistant to other antimalarials, well as "stand-by emergency treatment" for non-immune tourists and business travelers, will be able to obtain prompt medical attention if malaria is suspected.

MALAFENTRINE DS (Artemether 80 mg + Lumefantrine 480 mg Tablets)					
Summary of Product Characteristics					

4.2. Dosage and Instructions:

Artemether and lumefantrine tablets 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 1 hour of administration a repeat dose should be taken.

Dosage Schedule:

Body Weight	Day 1		Day 2		Day 3	
	0 Hrs	8 Hrs after	24 Hrs	36 Hrs	48 Hrs	60 Hrs
Adults	1 tablet	1 tablet	1 tablet	1 tablet	1 tablet	1 tablet

4.3. Contraindications:

Artemether and lumefantrine tablets are contraindicated:

- In those with hypersensitivity to the active substances or any of the excipients.
- In cases of severe malaria.
- In the first trimester of pregnancy.

4.4. Warning & Special Precautions for administration:

- Use with caution in patients with severe hepatic or renal insufficiency and patients refusing food intake.
- Patients who remain averse to food during treatment should be closely monitored as the risk of recrudescence may be greater.
- Avoid use in patients with known QT prolongation, those with hypokalemia or hypomagnesemia, and those taking other drugs that prolong the QT interval.
- Antimalarials should not be given concomitantly, unless there is no other treatment option, due to limited safety data.
- QT prolonging drugs, including quinine and quinidine, should be used cautiously following Malafentrine DS Tablets.
- Substrates, inhibitors, or inducers of CYP3A4, including antiretroviral medications, should be used cautiously with Malafentrine DS Tablets, due to a potential loss of efficacy of the concomitant drug or additive QT prolongation.

MALAFENTRINE DS (Artemether 80 mg + Lumefantrine 480 mg Tablets)	
Summary of Product Characteristics	

4.5. Drug Interactions:

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 (C_{max} 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 cardiotoxicity. This effect was slightly but significantly greater when quinine was infused after artemether and lumefantrine combination. Thus, prior administration of artemether and lumefantrine combination appears to enhance the inherent risk of QTc-prolongation from IV quinine.

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 and lumefantrine tablets should be administered at least one month after the last halofantrine dose.

Due to limited data on safety and efficacy, the combination should not be given concurrently with other antimalarials unless 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.

Whereas in vitro studies with artemether at therapeutic concentrations revealed no significant interactions with cytochrome P450 enzymes, the artemisinins have some capacity to induce the production of the cytochrome enzyme CYP2C19 and perhaps also CYP3A4. It is possible that iso-enzyme induction could alter the therapeutic effects of drugs that are predominantly metabolized by these enzymes.

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 artemether and lumefantrine tablets with drugs that are metabolized by this iso-enzyme (e.g. neuroleptics and tricyclic antidepressants) is contraindicated.

4.6. Pregnancy & Breastfeeding:

Reproductive toxicity studies in rats and rabbits have shown no evidence of teratogenicity for the combination or for the individual components, lumefantrine and artemether. Malafentrine DS treatment should only be considered if the expected benefit to the mother outweighs the risk to the fetus.

No data are available on the excretion of either of the two components in breast milk.

4.7. Side – Effects:

Headache, dizziness, loss of appetite, weakness, fever, chills, tiredness, muscle/joint pain, nausea, vomiting, abdominal pain, cough, and trouble sleeping may occur.

4.8 Overdosage:

In cases of suspected overdosage, symptomatic and supportive therapy should be given as appropriate.

MALAFENTRINE DS (Artemether 80 mg + Lumefantrine 480 mg Tablets)	
Summary of Product Characteristics	

5. Pharmacological characteristics:

5.1. Pharmacodynamic characteristics:

Blood schizontocide agent, 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 non-toxic haemozoin, malaria pigment. Lumefantrine is thought to interfere with the polymerization 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, Data from in-vitro and in-vivo studies show that Malafentrine DS does not induce resistance.

The independent antimalarial activity of both lumefantrine and artemether is enhanced by their combination which has been shown to potentiate the blood schizontocidal effects. It is also effective against drug-resistant strains of *P. falciparum* malaria. Comprehensive in-vitro studies using laboratory-maintained and fresh-field parasite isolates from different malaria endemic areas have shown marked synergy of the two components.

Results of comparative clinical trials indicate that Malafentrine DS also clears gametocytes more rapidly than non-artemisinin antimalarials.

5.2. Pharmacokinetics characteristics:

Absorption

Artemether is absorbed 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 6-8 hours after dosing. 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 Malafentrine DS was taken after a high-fat meal. 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 (97.9% and 99.9%, respectively). Distribution has not been further investigated in humans, but in rats artemether is well distributed throughout the body, with some affinity for the brown fat and adrenal glands, while lumefantrine has an affinity for adipose and glandular tissue and to some extent for the lungs, spleen (due to slow elimination from lymphoid tissue) and bone marrow.

Metabolism

Artemether is rapidly and extensively metabolized (substantial first-pass metabolism) both in vitro and in humans. Human liver microsomes metabolize artemether to the biologically active main metabolite dihydroartemisinin (demethylation), predominantly through the enzyme CYP3A4/5. This metabolite has also been detected in humans in vivo. Lumefantrine is N-debutylated, mainly by CYP3A4, in human liver microsomes. In vivo in dogs and rats, glucuronidation of lumefantrine takes place directly and after oxidative biotransformation. In vitro lumefantrine significantly inhibits the activity of CYP2D6 at therapeutic plasma concentrations.

Elimination

Artemether is rapidly cleared from plasma with an elimination half-life of about 2 hours. Lumefantrine is eliminated very slowly with a terminal half-life of 2-3 days in healthy volunteers and 4-6 days in patients with *falciparum* malaria.

No urinary excretion data are available for humans. In rats and dogs unchanged artemether has not been detected in feces and urine due to its rapid and high-first-pass metabolism, but several metabolites (unidentified) have been detected in both feces and urine. Lumefantrine is eliminated

MALAFENTRINE DS (Artemether 80 mg + Lumefantrine 480 mg Tablets)	
Summary of Product Characteristics	

via the bile in rats and dogs, with excretion primarily in the feces. After oral dosing in rats and dogs qualitative and quantitative recovery of metabolites in bile and feces was relatively low, most of the dose being recovered as parent drug.

5.3. Pre – Clinical Safety Data:

Not available.

6. Pharmaceutical Data:

6.1. List of excipients

Sr. No.	Ingredients	Specification
1	Crospovidone	IP
2.	Colloidal silicon dioxide	IP
3	Maize Starch	IP
4.	Polyvinylpyrrolidone K- 30	IP
5.	Purified water	IP
6.	Colloidal silicon dioxide	IP
7	Sodium starch glycollate	IP
8.	Magnesium Stearate	IP

6.2. Incompatibilities: Not Applicable

6.3. Duration of Storage: 36 Months (3 years)

6.4. Special precautions for Storage:

Store in a cool & dry place below 30°C.

Keep all medicines away from the reach of children.

6.5. Nature and content of the external packaging:

One Alu- Pvc blister of 6 tablets packed in a carton along with insert.

6.6 Instructions for use and handling and disposal

No special requirements.

7. Marketing authorisation holder

SOCOMED PHARMA PVT. LTD.

No.3, Maruti Paradies/Plot 93-95, Sector 15,

CBD Belapur/ Navi Mumbai- 400 614.

Tel: +91 22 2758 3001/3.

8. Number(s) in the national register of finished pharmaceutical products

Mfg. Lic. No. In India: MH/104554A

9. Renewal of the Authorization : 31/05/2014

10. Date Of Revision of The Text: 30/05/2019