MEFANTHER TABLET

UNIQUE PHARMACEUTICALS LTD

1.3.1

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. NAME OF THE MEDICINAL PRODUCT:

MEFANTHER TABLET (20mg/120mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

Artemether 20 mg
Lumefantrine 120 mg

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM:

Mefanther Tablet is uncoated yellow in colour, round and flat on both sides. It has "MT" and score line embossed on one side and "UNIQUE" on the other side. The score line is only to facilitate breaking of tablet for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS:

4.1. Therapeutics Indication

Mefanther Tablet is indicated for the treatment of acute, uncomplicated malaria due to Plasmodium falciparum in adults, children and infants of 5kg and above.

4.2. Posology and method of administration:

Mefanther Tablet should be taken orally with food or a milky drink to increase the absorption. If the patient is unable to tolerate food, Mefanther Tablet should still be administered, but the systemic exposure may be reduced. If the patient vomits within 1 hour of taking the medication, the dose should be repeated. As six dose regimen over three days is recommended as described in the dosage schedule below:

Dosage schedule for Mefanther Tablet (Artemether 20 mg & Lumefantrine 120 mg):

Patient Weight (Kg)	**Total tablets**	**Time**					
		Day 1		**Day 2**		**Day 3**	
		0Hour (Initial dose)	8Hours (After 1st dose)	24 Hours	36 Hours	48 Hours	60 Hours
5 – 14kg	6	1 tablet	1 tablet	1 tablet	1 tablet	1 tablet	1 tablet
15 – 24kg	12	2 tablets	2 tablets	2 tablets	2 tablets	2 tablets	2 tablets
25 – 34kg	18	3 tablets	3 tablets	3 tablets	3 tablets	3 tablets	3 tablets
Adult & Children =	24	4 tablets	4 tablets	4 tablets	4 tablets	4 tablets	4 tablets

To benefit from the full therapeutic effect, the full course of medication must be taken over the 60 hours at intervals as indicated.

4.3. Contraindications:

Mefanther Tablet is contraindicated in:

.Patients with known hypersensitivity to artemether or lumefantrine or any of the excipients.

- Patients with severe or complicated malaria.
- First trimester of pregnancy
- Patients who are taking any drug which is metabolised by the cytochrome enzyme CYP2D6 (e.g. flecainide, metoprolol, imipramine, amitriptyline, clomipramine)
- Patients who are taking any drug metabolised by strong inducers of CYP3A4 (e.g. rifampicin, carbamazepine, phenytoin, St John's wort (Hypericum perforatum) * Patients with known pre-existing prolongation of the QTc interval
- Patients with a family history of congenital prolongation of the QTc interval on electrocardiograms or of sudden death or with any other clinical condition known to prolong the QTc interval such as patients with a history of symptomatic cardiac arrhythmias, with clinically relevant bradycardia or with severe cardiac disease
- Patients taking drugs that are known to prolong the QTc interval such as: antiarrhythmics of classes IA and III, neuroleptics, 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.

4.4. Special warning and precaution for use:

Severe malaria: Mefanther Tablet is not recommended for the treatment of complicated malaria, including cases of cerebral malaria or other severe manifestations such as pulmonary oedema or renal failure. Mefanther Tablet is not indicated for, and have 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. Mefanther Tablet is active against blood stages of P. vivax, but is not active against hypnozoites. Malaria prophylaxis: Mefanther Tablet is not indicated and have not been evaluated for prophylaxis. Other antimalarials: Unless there is no other treatment option, Mefanther Tablet should not be given concurrently with any other antimalarial agent due to limited data on safety and efficacy.If a patient deteriorates while taking Mefanther Tablet, alternative treatment for malaria should be started without delay. Renal or Hepatic impairment: Caution is advised when administering Mefanther Tablet to patients with severe renal or hepatic impairment. In these patients, ECG and blood potassium monitoring is advised. Geriatric patients: There is no information suggesting that the dosage in patients over 65 years of age should be different to younger adults.

4.5. Interaction with other medicinal products and other forms of interactions:

Interactions resulting in a contraindication: Drugs that are known to prolong the QTc interval Mefanther Tablet 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 antihistamines (terfenadine, astemizole),

and cisapride . 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 Mefanther Tablet with drugs which are metabolised by this iso-enzyme is contraindicated (e.g. neuroleptics,flecainide, metoprolol, and tricyclic antidepressants such as imipramine, amitriptyline, clomipramine). Interaction with strong inducers of CYP3A4 such as rifampicin Oral administration of 600 mg rifampicin daily, a strong CYP3A4 inducer, with Mefanther Tablet 6-dose regimen over 3 days) results in significant decreases in exposure to artemether, DHA and lumefantrine when compared to exposure values after Mefanther Tablet alone. Concomitant use of strong inducers of CYP3A4 such as rifampicin, carbamazepine, phenytoin, St. John's wort is contraindicated with Mefanther Tablet. Interactions resulting in concomitant use not being recommended other antimalarials: Mefanther Tablet should not be given concurrently with other antimalarials unless there is no other treatment option. If Mefanther Tablet is given following administration of mefloquine or quinine, close monitoring of food intake (for mefloquine) or of the ECG (for quinine) is advised. The long elimination half-life of lumefantrine must be taken into account when administering quinine in patients previously treated with Mefanther Tablet. In-vitro studies indicated that lumefantrine metabolism is inhibited by halofantrine and Quinine. Due to the lack of clinical data, and due also to the propensity of some antimalarials to prolong the QTc interval, caution is advised when administering Mefanther Tablet. In particular, Mefanther Tablet must not be co-administered with halofantrine. In patients previously treated with halofantrine, Mefanther Tablet should be dosed at least one month after the last halofantrine dose. Interactions to be considered Interactions affecting the use of Mefanther Tablet

CYP450 enzymes: Both artemether and lumefantrine are metabolised by the cytochrome enzyme CYP3A4 but do not inhibit this enzyme at therapeutic concentrations. Due to the potential for increased concentrations of lumefantrine which could lead to QT prolongation, Mefanther Tablet should be used cautiously with drugs that inhibit CYP3A4. Grapefruit juice should be avoided during treatment with Mefanther.

Anti-retroviral drugs:

Due to variable patterns of inhibition, induction or competition for CYP3A4 with protease inhibitor anti-retroviral drugs, use of such drugs, especially combinations of them, concomitantly with Mefanther Tablet requires caution. Both artemether and lumefantrine are metabolized by CYP3A4. Anti-retroviral drugs, such as protease inhibitors and nonnucleoside reverse transcriptase inhibitors, are known to have variable patterns of inhibition, induction or competition for CYP3A4. Mefanther Tablet should be used cautiously in patients on antiretroviraldrugs since decreased artemether, DHA, and/or lumefantrine concentrations may result in a decrease of antimalarial efficacy of Mefanther, and increased lumefantrine concentrations may cause QT prolongation. Interaction with weak to moderate inducers of CYP3A4 When Mefanther Tabletis co-administered with weak to moderate inducers of CYP3A4 it may result in decreased concentrations of artemether and/or lumefantrine and loss of anti-malarial efficacy.

Interactions resulting in effects of Mefanther Tablet on other drugs: Interaction with drugs metabolized by CYP450 enzymes When Mefanther Tablet is co-administered with substrates of CYP3A4, it may result in decreased concentrations of the substrate and potential loss of substrate efficacy. 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 which are predominantly metabolised by these enzymes. Hormonal contraceptives: Mefanther Tablet may reduce the effectiveness of hormonal contraceptives. Patients should be advised to use an additional non -hormonal method of birth control. Drug-food/drink interactions: Mefanther Tablet should be taken with food or drinks rich in fat such as milk as the absorption of both artemether and lumefantrine is increased. Grapefruit juice should be avoided during treatment with Mefanther Tablet.

4.6 pregnancy and lactation:

There is insufficient data from the use of Arthememter and Lumefantrine in pregnant women. Artemisinins are known to be embryotoxic and teratogenic in animals, causing cardiovascular and skeletal deformities. Based on evidence from animal studies, Arthemeter is suspected to cause serious birth defects when administered during the first trimester of pregnancy. Hence treatment with Mefanther Tablet is contraindicated during the first trimester of pregnancy. During the second and the third trimester, treatment should only be considered if the expected benefit to the mother outweighs the risk to the foetus. Mefanther Tablet should not be taken by breast-feeding women as no data on excretion in milk are available. Due to the long elimination half-life of lumefantrine (4 to 6 days), it is recommended that breastfeeding should not resume until at least one week after the last dose, unless the potential benefits to the mother and child outweigh the risks of treatment.

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 Mefanther Tablet should be warned that dizziness, fatigue or asthenia may occur, in which case their ability to drive or operate machines may be impaired.

4.8 undesirable effects (SIDE EFFECTS):

The following side effects have been reported in patients treated with Artemether and Lumefantrine Tablets: The most commonly reported side effects (greater than 1 in every 10 patients treated) include headache, dizziness, feeling sick, vomiting, abdominal pain, loss of appetite, palpitations, pain in muscles and joints, fatigue and disturbed sleep. Commonly (greater than 1 in every 100 patients treated) reported side effects include alterations to the electrocardiogram (ECG), tingling in hands and feet, problems with walking, cough, diarrhoea, itching, rash and insomnia. Uncommon side effects (greater than 1 in every 1000 patients treated but less than 1 in 100): involuntary muscle jerks, coordination disturbances, altered liver function tests and drowsiness. The following side effects have been reported in patients treated with Artemether and Lumefantrine Tablets. However, frequency estimates for these effects are not available: hypersensitivity reaction, hives, rapid swelling of the face and throat (angioedema). A similar side effect profile was reported for children if any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, health care provider or pharmacist as soon as possible.

4.9 Overdose:

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

5. PHARMACOLOGICAL ACTION:

5.1. Clinical Pharmacology

Mefanther Tablet is a blood schizontocide comprising 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 non-toxic 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 synthesis and protein synthesis within the malarial parasite. The antimalarial activity of the combination of lumefantrine and artemether in MEFANTHER TABLET is greater than that of either substance alone.

5.2. Pharmacokinetics 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 concentrations 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 between 2 to 3-fold, and that of lumefantrine 16-fold when taken after a high-fat meal as compared with administration under fasted conditions. Distribution: Artemether and lumefantrine are both highly bound to human serum proteins in vitro (95.4% and 99.7%, respectively). Dihydroartemisinin is also bound to human serum proteins (47% to 76%).

5.3. Metabolism:

Artemether is rapidly and extensively metabolized (substantial first-pass metabolism) both in vitro and in humans. Human liver microsomes metabolise arthemether to biologically active main metabolite dihydroartemisinin (demethylation), predominantly through the isoenzyme CYP3A4/5. This metabolite has also been detected in humans in vivo. Dihydroartemisinin (DHA) is further converted to inactive metabolites. During repeated administration of Arthemether/Lumefantrine Tablets, systemic exposure of artemether decreased significantly, while concentrations of DHA increased, although not to a statistically significant degree. The artemether/DHAAUC ratio is 1.2 after a single dose and 0.3 after 6 doses given over 3 days. This suggests that there was induction of enzymes responsible for the metabolism of artemether. Lumefantrine was metabolized mainly by CYP3A4 to desbutyl-lumefantrine. The systemic exposure to the metabolite desbutyl-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.

5.4. **Elimination:** Artemether and DHA are rapidly cleared from plasma with an elimination half-life of about 2 hours. Lumefantrine is eliminated more 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. Limited urinary excretion data are available for humans. In 16 healthy volunteers, neither lumefantrine nor artemether was found in the urine after oral

administration of the tablet, and urinary excretion of DHA amounted to less than 0.01% of the artemether dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients also contains:

S.No	Excipients	Reference
1.	Hypromellose	BP
2.	Microcrystalline cellulose	BP
3.	Magnesium stearate	BP
4.	Colloidal silicon dioxide	BP
5.	Sodium starch glycolate	BP
6.	Polysorbate 80	BP

6.2. Incompatibilities:

None known or Not Applicable. (Decide on which of afore mentioned)

6.3. Shelf life:

24 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:

Mefanther tablets container closure system is composed of inner carton containing 1 blister strip of 24 tablets each with a pack insert.

6.6 Presentation:

Mefanther Tablet Tablets: Blister of 1 x 24 tablets in a carton along with pack insert

6.7 Special precautions for disposal and other handling:

After use, dispose the packaging materials and unused medicines properly. Do not throw into wastewater or household waste but dispose properly to protect the environment.

7. APPLICANT/MANUFACTURER:

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