Shree Life Sciences Pvt. Ltd.
09,Soham, Plot No.58, Sector-8A,
Airoli, Navi Mumbai - 400 708. India.
E-mail : info@shreelifesciences.com
Website : www.shreelifesciences.com

1.3.1 SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the Medicinal Product

ARTENORA L 80

(Artemether 80 mg + Lumefantrine 480 mg Tablets)

2. Qualitative and Quantitative Composition

Each Uncoated Tablet contains:

Artemether…….80.0 mg

Lumefantrine…….480.0 mg

Excipients…….....Q.S.

3. Pharmaceutical Form

Uncoated Tablet

4. Clinical Particulars

4.1 Therapeutic Indications

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

4.2 Posology and Method of Administration

Posology

Adults and children weighing 35 kg and above

For patients 12 years of age and above and 35 kg body weight and above, a course of treatment comprises six doses of four tablets i.e. total of 24 tablets, given over a period of 60 hours as follows: the first dose of four tablets, given at the time of initial diagnosis, should be followed by five further doses of four tablets given at 8, 24, 36, 48 and 60 hours thereafter.

Children and infants weighing 5 kg to less than 35 kg

A six-dose regimen is recommended with 1 to 3 tablets per dose, depending on bodyweight:

5 to less than 15 kg bodyweight: the first dose of one tablet, given at the time of initial diagnosis, should be followed by five further doses of one tablet given at 8, 24, 36, 48 and 60 hours thereafter.

15 to less than 25 kg bodyweight: the first dose of two tablets, given at the time of initial diagnosis, should be followed by five further doses of two tablets given at 8, 24, 36, 48 and 60 hours thereafter.

25 to less than 35 kg bodyweight: the first dose of three tablets, given at the time of initial diagnosis, should be followed by five further doses of three tablets given at 8, 24, 36, 48 and 60 hours thereafter.

Method of administration

Tablets for oral administration.

To increase absorption, ARTENORA L 80 should be taken with food or a milky drink. If patients are unable to tolerate food, ARTENORA L 80 should be administered with water, but the systemic exposure may be reduced. Patients who vomit within 1 hour of taking the medication should repeat the dose.

For administration to small children and infants, the tablet/s may be crushed.

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. flecainide, 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.
- 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.
- Patients with a history of symptomatic cardiac arythmias 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.

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4.4 Special Warnings and Precautions for use

ARTENORA L 80 must not be used in the first trimester of pregnancy in situations where other suitable and effective antimalarial are available.

ARTENORA L 80 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, ARTENORA L 80 should not be given concurrently with any other antimalarial agent unless there is no other treatment option.

If a patient deteriorates whilst taking ARTENORA L 80 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 ARTENORA L 80

If quinine is given after ARTENORA L 80 close monitoring of the ECG is advised.

If ARTENORA L 80 is given after mefloquine, close monitoring of food intake is advised

In patients previously treated with halofantrine, ARTENORA L 80 should not be administered earlier than one month after the last halofantrine dose.

ARTENORA –L- 80 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. ARTENORA L 80 is active against blood stages of Plasmodium vivax, but is not active against hypnozoites.

ARTENORA L 80 is not indicated and has not been evaluated for prophylaxis.

Like other antimalarial (e.g. halofantrine, quinine and quinidine) ARTENORA L 80 has the potential to cause QT prolongation.

In the adult/adolescent population included in clinical trials, 8 patients (0.8%) receiving ARTENORA L 80 experienced a QTcB >500 msec and 3 patients (0.4%) a QTcF >500 msec. Prolongation of QTcF interval >30 msec was observed in 36% of patients.

In the infant/children population included in clinical trials, 3 patients (0.2%) experienced a QTcB >500 msec. No patient had QTcF >500 msec. Prolongation of QTcF intervals >30 msec was observed in 34% of children weighing 5-10 kg, 31% of children weighing 10-15 kg and 24% of children weighing 15-25 kg, and 32% of children weighing 25-35 kg.

Caution is recommended when combining ARTENOR L 80 with drugs exhibiting variable patterns of inhibition, induction or competition for CYP3A4 as the therapeutic effects of some drugs could be altered.

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

Caution is advised when administering ARTENORA L 80 to patients with severe renal, hepatic or cardiac problems.

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4.5 Interactions with Other Medicinal Product and Other Form of Interaction

Artemether and Lumefantrine are substrates of CYP3A4. Administration of inducers or inhibitors of CYP3A4 may therefore lead to an increase or a reduction in exposure to Lumefantrine and Artemether.

4.6 Pregnancy and Lactation

Pregnancy

There is insufficient data from the use of Artemether and Lumefantrine in pregnant women. Based on animal data, ARTENORA L 80 is suspected to cause serious birth defects when administered during the first trimester of pregnancy .Reproductive studies with Artemether have shown evidence of post-implantation losses and teratogenicity in rats and rabbits. Other artemisinin derivatives have also demonstrated teratogenic potential with an increased risk during early gestation. ARTENORA L 80 treatment must not be used during the first trimester of pregnancy in situations where other suitable and effective antimalarial are available. However, it should not be withheld in life-threatening situations, where no other effective antimalarial 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 fetus.

Lactation

Animal data suggest excretion into breast milk but no data are available in humans. Women taking ARTENORA L 80 should not breast-feed during their treatment. Due to the long elimination half-life of Lumefantrine (4 to 6 days), it is recommended that breast-feeding should not resume until at least one week after the last dose of ARTENORA L 80 unless potential benefits to the mother and child outweigh the risks of ARTENORA L 80 treatment.

4.7 Effect on Ability to Drive and use Machine

Patients receiving ARTENORA L 80 should be warned that dizziness or fatigue/asthenia may occur in which case they should not drive or use machines.

4.8 Undesirable Effects

Headache, Dizziness, Drowsiness, Vomiting, Abdominal pain, Diarrhoea, Nausea

4.9 Overdose

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

5. Pharmacological Properties

Pharmacotherapeutic Group: Antimalarials, blood schizontocide

ATC Code: P01 BF01**.**

5.1 Pharmacodynamic Properties

Pharmacodynamics:

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 hemozoin, 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 ARTENORA L 80 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 ARTENORA L 80 also clears gametocytes more rapidly than non- artemisinin antimalarial.

5.2 Pharmacokinetic Properties

Pharmacokinetics

Pharmacokinetic characterization of ARTENORA L 80 is limited by the lack of an intravenous formulation, and the very high inter- and intra-subject variability of Artemether and Lumefantrine plasma concentrations and derived pharmacokinetic parameters (AUC, Cmax).

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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 ARTENORA L 80 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 artemisinin (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 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 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. 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 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 IC_{50} was 8.1 µM for lumefantrine and 5.5 µM for its desbutyl metabolite. Based on the available non-clinical data, a potential for QTc prolongation in the human cannot be discounted

6. Pharmaceutical Particulars

6.1 List of Excipients

1. Lactose
2. Microcrystalline cellulose powder
3. Maize starch
4. Methyl paraben sodium
5. Propyl paraben sodium
6. Isopropyl alcohol
7. P.V.P.K 30
8. Purified Talcum

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9. Magnesium Stearate

10.Croscarmellose

11. Aerosil

12. Sodium starch glycolate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years from the date of manufacturing.

Do not use the product after the expiry of the shelf life.

6.4 Special Precautions for Storage

Store in a dry place at a temperature not exceeding 25 °C.

Protect from direct sunlight.

Keep medicines out of the reach of children.

6.5 Nature and Contents of Container

1 × 6 tablets in blister packed in a carton along with leaflet.

6.6 Special Precautions for Disposal and Other Handling

No special precaution required for disposal and handling

7. Marketing Authorization Holder

SHREE LIFE SCIENCES PVT. LTD.

09, Soham, Plot No. - 58, Sector - 8A,

Airoli, Navi Mumbai - 400708, India

8. Marketing Authorization Number(S)

Not applicable

9. Date of First Authorization/Renewal of the Authorization

Not applicable

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10. Date of Revision of the Text

Not applicable