1. NAME OF THE MEDICINAL PRODUCT

Brand Name : ANDERMAL Artemether and Lumefantrine Tablets 20/120mg

Generic Name: Artemether and Lumefantrine Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated tablet contains

Artemether	20 mg
Lumefantrine USP	120 mg
Excipients	q.s.

3. PHARMACEUTICAL FORM

Oral tablet

4. Clinical particulars

4.1 Therapeutic indications

Artemether and Lumefantrine Tablets is indicated for the treatment of acute uncomplicated Plasmodium falciparum malaria

4.2 Posology and method of administration

Dosage

Dosage and Direction for Use:

Artemether and Lumefantrine Tablets should be taken with food. 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.

For patients who are unable to swallow the tablets such as infants and children, Artemether and Lumefantrine Tablets may be crushed and mixed with a small amount of water (1 to 2 teaspoons) in a clean container for administration immediately prior to use. The container can be rinsed with more water and the contents swallowed by the patient. The crushed tablet preparation should be followed whenever possible by food/drink (e.g., milk, formula, pudding, broth, and porridge).

In the event of vomiting within 1 to 2 hours of administration, a repeat dose should be taken. If the repeat dose is vomited, the patient should be given an alternative antimalarial for treatment.

Dosage in Adult Patients (>16 years of age)

A 3-day treatment schedule with a total of 6 doses is recommended for adult patients with a bodyweight of 35 kg and above:

Four tablets as a single initial dose, 4 tablets again after 8 hours and then 4 tablets twice-daily (morning and evening) for the following 2 days (total course of 24 tablets).

Dosage in Pediatric Patients

A 3-day treatment schedule with a total of 6 doses is recommended as below:

5 kg to less than 15 kg bodyweight: One tablet as an initial dose, 1 tablet again after 8 hours and then 1 tablet twice-daily (morning and evening) for the following 2 days (total course of 6 tablets).

15 kg to less than 25 kg bodyweight: Two tablets as an initial dose, 2 tablets again after 8 hours and then 2 tablets twice-daily (morning and evening) for the following 2 days (total course of 12 tablets).

25 kg to less than 35 kg bodyweight: Three tablets as an initial dose, 3 tablets again after 8 hours and then 3 tablets twice-daily (morning and evening) for the following 2 days (total course of 18 tablets).

35 kg bodyweight and above: Four tablets as a single initial dose, 4 tablets again after 8 hours and then 4 tablets twice-daily (morning and evening) for the following 2 days (total course of 24 tablets).

Dosage in Patients with Hepatic or Renal Impairment

No specific pharmacokinetic studies have been carried out in patients with hepatic or renal impairment. Most patients with acute malaria present with some degree of related hepatic and/or renal impairment. In clinical studies, the adverse event profile did not differ in patients with mild or moderate hepatic impairment compared to patients with normal hepatic function. No specific dose adjustments are needed for patients with mild or moderate hepatic impairment.

In clinical studies, the adverse event profile did not differ in patients with mild or moderate renal impairment compared to patients with normal renal function. There were few patients with severe renal impairment in clinical studies. There is no significant renal excretion of lumefantrine, artemether and dihydroartemisinin (DHA) in healthy volunteers and while clinical experience in this population is limited, no dose adjustment is recommended.

Caution should be exercised when administering Artemether and Lumefantrine Tablets in patients with severe hepatic or renal impairment.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients.

Severe hepatic or renal impairment.

Patients with severe malaria according to the WHO definition.

First trimester of pregnancy in situations where other suitable and effective antimalarials are available.

Patients with a family history of congenital prolongation of the QTc interval or sudden death, or with any other clinical condition known to prolong the QTc interval, such as patients with a history of symptomatic cardiac arrhythmias, clinically relevant bradycardia or severe heart disease.

Patients taking drugs that prolong the QTc interval, such as class IA and III antiarrhythmics, neuroleptics, antidepressants, certain antibiotics (including some agents in the following classes: macrolides, fluoroquinolones, imidazoles and triazoles), antifungal agents, certain non-sedating antihistamines (terfenadine, astemizole) and cisapride.

Patients with known disturbances of electrolyte balance, e.g. hypokalaemia or hypomagnesaemia.

Patients taking drugs metabolized by cytochrome CYP2D6 (e.g. flecainide, metoprolol, imipramine, amitriptyline, clomipramine).

4.4 Special warnings and precautions for use

Artemether and Lumefantrine Tablets have 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, Artemether and Lumefantrine Tablets should not be given concurrently with any other antimalarial agent unless there is no other treatment option.

Artemether and Lumefantrine Tablets should not be used concomitantly with drugs metabolized by CYP2D6. Additionally, caution is required when combining Artemether and Lumefantrine Tablets with substrates, inhibitors or inducers of CYP3A4 as the therapeutic effects of some drugs might be altered.

4.5 Interaction with other medicinal products and other forms of interaction

Rifampin

Oral administration of rifampin, a strong CYP3A4 inducer, with Artemether and Lumefantrine Tablets resulted in significant decreases in exposure to artemether, dihydroartemisinin (DHA, metabolite of artemether) and lumefantrine by 89%, 85% and 68%, respectively, when compared to exposure values after Artemether and Lumefantrine Tablets alone. Concomitant use of strong

inducers of CYP3A4 such as rifampin, carbamazepine, phenytoin, and St. John's wort is contraindicated with Artemether and Lumefantrine Tablets.

Ketoconazole

Concurrent oral administration of ketoconazole, a potent CYP3A4 inhibitor, with a single dose of Artemether and Lumefantrine Tablets resulted in a moderate increase in exposure to artemether, DHA, and lumefantrine in a study of 15 healthy subjects. No dose adjustment of Artemether and Lumefantrine Tablets is necessary when administered with ketoconazole or other potent CYP3A4 inhibitors. However, due to the potential for increased concentrations of lumefantrine which could lead to QT prolongation, Artemether and Lumefantrine Tablets should be used cautiously with drugs that inhibit CYP3A4.

Antiretroviral Drugs

Both artemether and lumefantrine are metabolized by CYP3A4. Antiretroviral drugs, such as protease inhibitors and non-nucleoside reverse transcriptase inhibitors, are known to have variable patterns of inhibition, induction or competition for CYP3A4. Therefore, the effects of antiretroviral drugs on the exposure to artemether, DHA, and lumefantrine are also variable. Artemether and Lumefantrine Tablets should be used cautiously in patients on antiretroviral drugs because decreased artemether, DHA, and/or lumefantrine concentrations may result in a decrease of antimalarial efficacy of Artemether and Lumefantrine Tablets, and increased lumefantrine concentrations may cause QT prolongation.

Prior Use of Mefloquine

Administration of 3 doses of mefloquine followed 12 hours later by a 6-dose regimen of Artemether and Lumefantrine Tablets in 14 healthy volunteers demonstrated no effect of mefloquine on plasma concentrations of artemether or the artemether/DHA ratio. However, exposure to lumefantrine was reduced, possibly due to lower absorption secondary to a mefloquine-induced decrease in bile production. Patients should be monitored for decreased efficacy and food consumption should be encouraged with administration of Artemether and Lumefantrine Tablets.

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, Artemether and Lumefantrine Tablets may potentially reduce the effectiveness of hormonal contraceptives. Patients using oral, transdermal patch, or other systemic hormonal contraceptives should be advised to use an additional non-hormonal method of birth control.

CYP2D6 Substrates

Lumefantrine inhibits CYP2D6 in vitro. Administration of Artemether and Lumefantrine Tablets with drugs that are metabolized by CYP2D6 may significantly increase plasma concentrations of the coadministered drug and increase the risk of adverse effects. Many of the drugs metabolized by CYP2D6 can prolong the QT interval and should not be administered with Artemether and Lumefantrine Tablets due to the potential additive effect on the QT interval (e.g., flecainide, imipramine, amitriptyline, clomipramine).

Sequential Use of Quinine

A single dose of intravenous quinine (10 mg/kg bodyweight) concurrent with the final dose of a 6-dose regimen of Artemether and Lumefantrine Tablets demonstrated no effect of intravenous quinine on the systemic exposure of DHA or lumefantrine. Quinine exposure was also not altered. Exposure to artemether was decreased. This decrease in artemether exposure is not thought to be clinically significant. However, quinine and other drugs that prolong the QT interval should be used cautiously following treatment with Artemether and Lumefantrine Tablets due to the long elimination half-life of lumefantrine and the potential for additive QT effects; ECG monitoring is advised if use of drugs that prolong the QT interval is medically required.

Interaction with Drugs that are known to prolong the QT Interval

Artemether and Lumefantrine Tablets are to be used with caution when coadministered with drugs that may cause prolonged QT interval 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.

4.6 Pregnancy and Lactation

Pregnancy

There have been no controlled clinical studies of the safety of Artemether and Lumefantrine

Tablets during pregnancy. Data from animal studies suggest that Artemether and Lumefantrine Tablets may cause severe birth defects when administered during the first trimester of pregnancy. In animals, reproductive toxicity studies with artemether have shown evidence of post-implantation losses and teratogenicity. Other artemisinin derivatives have in addition demonstrated teratogenic potential, with increased risk during early gestation. Artemether and Lumefantrine Tablets are contraindicated during the first trimester of pregnancy if other effective antimalarials are available. However, it should not be withheld in life-threatening situations where no other effective antimalarials are available.

During the second and the third trimesters, treatment should only be given if absolutely necessary.

Lactation

Animal data suggest that Artemether and Lumefantrine Tablets passes into the breast milk but no data are available in humans. Women who are breastfeeding should not take Artemether and Lumefantrine Tablets. Due to the long elimination half-life of lumefantrine (4 to 6 days), it is recommended that breastfeeding should not resume before day 28 unless the potential benefits to both mother and child outweigh the risks of treatment with Artemether and Lumefantrine

4.7 Effects on ability to drive and use machines

Artemether and Lumefantrine Tablets have moderate influence on the ability to drive and use machines. Patients receiving Artemether and Lumefantrine Tablets should be warned that dizziness, fatigue or asthenia may occur, in which case their ability to drive or use machines may be impaired.

4.8 Undesirable effects

Hypersensitivity Reactions.

Adverse Reactions Occurring in 3% or More of Adult Patients Treated in Clinical Trials with the 6-dose Regimen of Artemether and Lumefantrine Tablets

Musculoskeletal and connective tissue disorders	Arthralgia	219 (34)
	Myalgia	206 (32)
Gastrointestinal disorders	Nausea	169 (26)
	Vomiting	113 (17)
	Abdominal pain	112 (17)
	Diarrhea	46 (7)
Psychiatric disorders	Sleep disorder	144 (22)
	Insomnia	32 (5)
Cardiac disorders	Palpitations	115 (18)
Hepatobiliary disorders	Hepatomegaly	59 (9)
Blood and lymphatic system disorders	Splenomegaly	57 (9)
	Anemia	23 (4)
Respiratory, thoracic and mediastinal disorders	Cough	37 (6)
Skin and subcutaneous tissue disorders	Pruritus	24 (4)
	Rash	21 (3)
Ear and labyrinth disorders	Vertigo	21 (3)
Infections and infestations	Malaria	18 (3)
	Nasopharyngitis	17 (3)

* Adult patients defined as >16 years of age

Adverse Reactions Occurring in 3% or More of Pediatric Patients Treated in Clinical Trials with the 6-dose Regimen of Artemether and Lumefantrine Tablets

System Organ Class	Preferred Term	Children* N=1,332 (%)
General disorders and administration site conditions	Pyrexia	381 (29)
	Chills	72 (5)
	Asthenia	63 (5)
	Fatigue	46 (3)
Respiratory, thoracic and mediastinal disorders	Cough	302 (23)
Gastrointestinal disorders	Vomiting	242 (18)
	Abdominal pain	112 (8)
	Diarrhea	100 (8)
	Nausea	61 (5)
Infections and infestations	*Plasmodium falciparum* infection	224 (17)
	Rhinitis	51 (4)
Metabolism and nutrition disorders	Anorexia	175 (13)
Nervous system disorders	Headache	168 (13)
	Dizziness	56 (4)
Blood and lymphatic system disorders	Splenomegaly	124 (9)
	Anemia	115 (9)
Hepatobiliary disorders	Hepatomegaly	75 (6)
Investigations	Aspartate aminotransferase increased	51 (4)
Musculoskeletal and connective tissue disorders	Arthralgia	39 (3)
	Myalgia	39 (3)
Skin and subcutaneous tissue disorders	Rash	38 (3)

* Children defined as patients ≤16 years of age

Clinically significant adverse reactions reported in adults and/or children treated with the 6-dose regimen of Coartem Tablets which occurred in clinical studies at <3% regardless of causality are listed below:

Blood and lymphatic system disorders: eosinophilia

Ear and labyrinth disorders: tinnitus

Eye disorders: conjunctivitis

Gastrointestinal disorders: constipation, dyspepsia, dysphagia, peptic ulcer

General disorders: gait disturbance

Infections and infestations: abscess, acrodermatitis, bronchitis, ear infection, gastroenteritis, helminthic infection, hookworm infection, impetigo, influenza, lower respiratory tract infection, malaria, nasopharyngitis, oral herpes, pneumonia, respiratory tract infection, subcutaneous abscess, upper respiratory tract infection, urinary tract infection

Investigations: alanine aminotransferase increased, aspartate aminotransferase increased, hematocrit decreased, lymphocyte morphology abnormal, platelet count decreased, platelet count increased, white blood cell count decreased, white blood cell count increased

Metabolism and nutrition disorders: hypokalemia

Musculoskeletal and connective tissue disorders: back pain

Nervous system disorders: ataxia, clonus, fine motor delay, hyperreflexia, hypoesthesia, nystagmus, tremor

Psychiatric disorders: agitation, mood swings

Renal and urinary disorders: hematuria, proteinuria

Respiratory, thoracic and mediastinal disorders: asthma, pharyngo-laryngeal pain

Skin and subcutaneous tissue disorders: urticaria

4.9 Overdose

If overdosage is suspected, symptomatic and supportive therapy should be initiated based on the clinical picture. The ECG and electrolytes (e.g. potassium) should be monitore

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Artemether and Lumefantrine Tablets, a fixed ratio of 1:6 parts of artemether and lumefantrine, respectively, is an antimalarial agent. Artemether is rapidly metabolized into an active metabolite dihydroartemisinin (DHA). The antimalarial activity of artemether and DHA has been attributed to endoperoxide moiety. The exact mechanism by which lumefantrine exerts its antimalarial effect is not well defined. Available data suggest lumefantrine inhibits the -hematin by forming a complex with hemin. Both artemether and lumefantrine were shown toβformation and inhibit nucleic acid and protein synthesis

5.2 Pharmacokinetic properties

Absorption

Following administration of Artemether and Lumefantrine Tablets to healthy volunteers and patients with malaria, artemether is absorbed 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.

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%). Protein binding to human plasma proteins is linear.

Biotransformation

In human liver microsomes and recombinant CYP450 enzymes, the metabolism of artemether was catalyzed predominantly by CYP3A4/5. Dihydroartemisinin (DHA) is an active metabolite of artemether. The metabolism of artemether was also catalyzed to a lesser extent by CYP2B6, CYP2C9 and CYP2C19.

In human liver microsomes and in recombinant CYP450 enzymes, lumefantrine was metabolized mainly by CYP3A4 to desbutyl-lumefantrine.

Elimination

Artemether and DHA are cleared from plasma with an elimination half-life of about 2 hours. Lumefantrine is eliminated more slowly, with an elimination half-life of 3 to 6 days in healthy volunteers and in patients with falciparum malaria. Demographic characteristics such as sex and weight appear to have no clinically relevant effects on the pharmacokinetics of artemether and lumefantrine.

5.3 Preclinical safety data

Mutagenicity

No evidence of mutagenicity was detected in *in vitro* or *in vivo* tests with an artemether: lumefantrine combination (consisting of 1 part artemether: 6 parts lumefantrine). In the micronucleus test myelotoxicity was seen at all dose levels (500, 1,000 and 2,000 mg/kg), but recovery was almost complete 48 hours after dosing.

Carcinogenicity

Carcinogenicity studies with the artemether: lumefantrine combination was not conducted.

Reproductive toxicity studies

Reproductive toxicity studies performed with the artemether: lumefantrine combination caused maternal toxicity and increased post-implantation loss in rats and rabbits at doses ≥50 mg/kg/day (corresponding to approximately 7 mg/kg/day artemether) and 175 mg/kg/day (corresponding to 25 mg/kg/day artemether) respectively. These effects were not observed at lower doses.

Lumefantrine alone caused no sign of reproductive or development toxicity at doses up to 1,000 mg/kg/day in rats and rabbits.

Embryotoxicity has been observed in rat and rabbit reproductive toxicity studies conducted with artemether, a derivative of artemisinin. Artemisinins (e.g. artesunate) are known to be embryotoxic.

Artemether caused increases in post-implantation loss and teratogenicity (characterised as a low incidence of cardiovascular and skeletal malformations) in rats at 19.4 mg/kg, and in rabbits at 30 mg/kg. Maternal toxicity was also observed in rabbits at 30 mg/kg/day. No other adverse effects were observed at lower doses in rabbits. The no observed effect dose was 3 mg/kg/day in rats and 25 mg/kg/day in rabbits.

The embryotoxic artemether dose, 20 mg/kg/day in the rat, yields artemether and dihydroartemisinin exposures similar to those achieved in humans.

Artesunate, a structurally related compound, also caused increases in post-implantation loss and teratogenicity (low incidence of cardiovascular and skeletal malformations) in rats at 6 mg/kg and in the lowest dose tested in the rabbits, 5 mg/kg/day.

Cardiovascular Safety Pharmacology

In toxicity studies in dogs at doses ≥600 mg/kg/day only, 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 an *in vitro* assay of HERG channels stably expressed in HEK293 cells, lumefantrine and the main metabolite desbutyl-

lumefantrine showed some inhibitory potential in one of the currents responsible for cardiac repolarization. The potency was lower than the other antimalarial drugs tested. From the estimated IC_{50} values, the order of potency of HERG current block was halofantrine (IC_{50} = 0.04 μM) >chloroquine (2.5 μM) >mefloquine 2.6 μM) >desbutyl-lumefantrine (5.5 μM) >lumefantrine (8.1 μM).

Additional studies were performed to evaluate the in vitro effects of artemether and its active metabolite, dihydroartemisinin, on the HERG current. At concentrations that produced significant inhibition, the safety margins for artemether and dihydroartemisinin are greater than 100 if they are estimated using the total therapeutic concentration at Cmax or greater than 1000 if they are estimated using the calculated free Cmax. 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

Lactose
Microcrystalline Cellulose powder
PVP K 30
Isopropyl Alcohol
Talcum
Magnesium Sterarte
Cross povidone
Aerosil
Cross Carmalose Sodium

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

36 months from the Date of Manufacture

6.4 Special precautions for storage

Store below 30°

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

Alu PVC Blister of 24 Tablets packed in carton along with Pack Insert

6.6 Special precautions for disposal <and other handling>

No any precaution

7. <APPLICANT/MANUFACTURER>

SSM Formulations Pvt Ltd