National Agency for Food & Drug Administration & Control (NAFDAC)

Registration & Regulatory Affairs (R & R) Directorate

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. NAME OF THE DRUG PRODUCT :

AMATEM SOFTGEL (Artemether and Lumefantrine Capsules)

Pharmaceutical Dosage Form: Soft Gelatin Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITIONS:

2.1 Qualitative Declaration :

The active ingredient shall be declared by its recommended INN, accompanied by its salt or hydrate form if relevant.

Each Soft Gelatin Capsule Contains:

Artemether Ph. Int.	20 mg
Lumefantrine Ph. Int.	120 mg
Excipients	q.s.

2.2 Quantitative Declaration

Quantity of active ingredient must be expressed per dosage unit (for metered dose inhalation product, per puff), per unit volume or per unit of weight.

Each Soft Gelatin Capsule Contains:

Artemether Ph. Int.	20 mg
Lumefantrine Ph. Int.	120 mg
Excipients	q.s.

For full list of Excipients, see section 6.1

3. PHARMACEUTICAL FORM :

AMATEM SOFTGEL Capsules are available in Soft Gelatin Capsules Dosage Form for Oral Use.

4. CLINICAL PARTICULARS:

4.1 Therapeutically indications:

AMATEM SOFTGEL Capsules (Artemether and Lumefantrine Capsules) are indicated for the treatment of P. falciparum malaria cases resistant to both chloroquine and sulphadoxine pyrimethamine combination. The combination is not recommended for first line treatment of malaria.

4.2 Posology and method of administration:

AMATEM SOFTGEL Capsules are administered by Oral Route.

Posology

Dosage and Administration

Artemether and Lumefantrine Capsule 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.

For adults and children weighing 35 kg and above a standard three days treatment schedule with a total of 8 doses is recommended as follows: four capsules as a single dose at the time of initial diagnosis, again four capsules after eight hours and then four capsules twice daily (morning and evening) on each of the following two days.

For Adults and children weighing 25 to less than 35 kg, a six-dose regimen is recommended with three capsules as a single dose at the time of initial diagnosis, again three capsules after eight hours and then three capsules twice daily (morning and evening) on each of the following two days.

For Adults and children weighing 15 to less than 25 kg, a four-dose regimen is recommended with two capsules as a single dose at the time of initial diagnosis, again two capsules after eight hours and then two capsules twice daily (morning and evening) on each of the following two days.

Dosage in elderly patients

Although no studies have been carried out in the elderly, no special precautions or dosage adjustments are considered necessary in such patients.

Dosage in patients with renal or hepatic impairment

No specific studies have been carried out in these groups of patients and no specific dose adjustment recommendations can be made for these patients. Most patients with acute malaria present with some degree of related hepatic impairment. The adverse event profile did not differ in patients with and those without hepatic impairment. Moreover, baseline abnormalities in liver function tests improved in nearly all patients after treatment with artemether and lumefantrine combination.

New and recrudescent infections in adults, children and infants

Data for a limited number of patients show that new and recrudescent infections can be treated with a second course of artemether and lumefantrine combination.

4.3 Contra-indications:

Artemether and Lumefantrine are contraindicated in the following conditions:

- In those with hypersensitivity to the active substances or any of the excipients.
- In cases of severe malaria.
- In the first trimester of pregnancy.
- 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, patients with clinically relevant bradycardia or with severe cardiac disease, family history of sudden death, disturbances of electrolyte balance, e.g. hypokalaemia or hypomagnesaemia.
- Concomitant use of drugs that are known to be metabolised by cytochrome enzyme CYP2D6 (e.g. flecainide, metoprolol, imipramine, amitriptyline, clomipramine).
- 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 antihistaminics (terfenadine, astemizole), cisapride.
- Artemether and lumefantrine are not indicated for prophylaxis, or for treating severe malaria, including cerebral malaria, or malaria with pulmonary oedema or renal failure. It is also not

indicated for and has not been evaluated in, the treatment of malaria due to *P. vivax, P. malariae* or *P. ovale*.

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.

Side-Effects:

Artemether and lumefantrine combination is well tolerated by children and adults, with most adverse events being of mild to moderate severity and duration. Many of the reported events are likely to be related to the underlying malaria and/or to an unsatisfactory response to treatment rather than to the combination.

Common adverse events reported with artemether and lumefantrine combination included headache, dizziness, sleep disorder, abdominal pain, anorexia, diarrhoea, vomiting, nausea, palpitation, cough, arthralgia, myalgia, pruritus, rash, asthenia and fatigue. Somnolence, involuntary muscle contractions, paraesthesia, hypoaesthesia, abnormal gait, ataxia were other adverse effects reported with artemether and lumefantrine combination. Rare adverse event included hypersensitivity.

Unspecified personality disorders have also been reported in children <5 years treated with artemether and lumefantrine combination

4.4 Special Warning and Precautions for use :

Not be given to children except under medical advice. Keep the product out of reach children.

4.5 Interaction with other drugs, other forms of interactions :

Artemether and lumefantrine combination is well tolerated by children and adults, with most adverse events being of mild to moderate severity and duration. Many of the reported events are

likely to be related to the underlying malaria and/or to an unsatisfactory response to treatment rather than to the combination.

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Unspecified personality disorders have also been reported in children <5 years treated with artemether and lumefantrine combination

4.6 Use in pregnancy and lactation :

AMATEM SOFTGEL capsules cannot be taken during pregnancy and nursing with doctor's advice.

4.7 Effects on ability to drive and use machines:

Intake of AMATEM SOFTGEL Capsules does not affect the ability to drive and operate machines.

4.8 Undesirable effects :

Common adverse events reported with artemether and lumefantrine combination included headache, dizziness, sleep disorder, abdominal pain, anorexia, diarrhea, vomiting, nausea, palpitation, cough, arthralgia, myalgia, pruritus, rash, asthenia and fatigue. Somnolence, involuntary muscle contractions, paranesthesia, hypoesthesia, abnormal gait, ataxia were other adverse effects reported with artemether and lumefantrine combination. Rare adverse event included hypersensitivity.

4.9 Overdoses :

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

5. PHARMACEUTICAL PROPERTIES:

Pharmacotherapeutic group: antimalarials, blood schizontocide, ATC code: P01BF01.

5.1 Pharmacodynamic effects

Amatem comprises 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 hemoglobin breakdown, to the nontoxic 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. Amatem has been reported to have potent activity in terms of clearing gametocytes.

By 2015, resistance to artemisinin emerged in Southeast Asia. Studies with Amatem in this region showed delayed parasite clearance (manifested as a higher proportion of patients with parasitemia on Day 3 after initiation of treatment), although overall efficacy as measured by cure rates after 28 days, remained high (WHO 2014). In Africa, only isolated reports on delayed parasite clearance are available and a clear trend towards resistance development was not observed. Treatment of Acute Uncomplicated P. falciparum Malaria.

The efficacy of Amatem was evaluated for the treatment of acute, uncomplicatedmalaria (defined as symptomatic P. falciparum malaria without signs and symptoms of severe malaria or evidence of vital organ dysfunction) in five 6-dose regimen studies and one study comparing the 6-dose regimen with the 4-dose regimen. Baseline parasite density ranged from 500/µL - 200,000/µL (0.01% to 4% parasitemia) in the majority of patients. Studies were conducted in otherwise healthy, partially immune or non-immune adults and children (≥5kg body weight) with uncomplicated malaria in Thailand, sub-Saharan Africa, Europe, and South America.

Efficacy endpoints consisted of:

• 28-day cure rate, proportion of patients with clearance of asexual parasites within 7 days without recrudescence by day 28

• parasite clearance time (PCT), defined as time from first dose until first total and continued disappearance of asexual parasite which continues for a further 48 hours

• fever clearance time (FCT), defined as time from first dose until the first time body temperature fell below 37.5°C and remained below 37.5°C for at least a further 48 hours (only for patients with temperature >37.5°C at baseline)

5.2 Pharmaco-kinetic properties:

BIOAVAILABILITY/BIOEQUIVALENCE:

Pharmacokinetic characterization of artemether and lumefantrine 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).

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 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 Riamet was taken after a high-fat meal.

Food has also been shown to increase the absorption of lumefantrine in patients with malaria, although to a lesser extent (approximately two-fold), most probably due to the lower fat content of the food ingested by acutely ill patients. The food interaction data indicate that absorption of lumefantrine under fasted conditions is very poor (assuming 100 % absorption after a high-fat meal, the amount absorbed under fasted conditions would be < 10 % of the dose). 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 (95.4% and 99.7%, respectively). Lumefantrine is also bound to human serum proteins (47-76%).

Metabolism

Artemether is rapidly and extensively metabolised (substantial first-pass metabolism) both in vitro and in humans. Human liver microsomes metabolise artemether to the biologically active main metabolite Lumefantrine (demethylation), predominantly through the isoenzyme CYP3A4/5.

This metabolite has also been detected in humans in vivo. The artemether/ Lumefantrine AUC ratio is 1.2 after a single dose and 0.3 after 6 doses given over 3 days. In vivo data indicate that artemether have some capacity to induce cytochrome isoenzymes CYP2C19 and CYP3A4. Lumefantrine is further converted to inactive metabolites.

Following repeated administration of Riamet (alone or in combination with mefloquine), serum artemether levels decreased significantly, while levels of the metabolite Lumefantrine is increased, although not to a statistically significant degree. This indicates that there was induction of the enzyme responsible for the metabolism of artemether.

Lumefantrine is N-debutylated, mainly by CYP3A4, in human liver microsomes. In vivo in animals (dogs and rats), glucuronidation of lumefantrine takes place directly and after oxidative biotransformation. In humans, the systemic exposure to the metabolite desbutyl-lumefantrine, for which the in vitro antiparasitic effect is 5 to 8 fold higher than lumefantrine, was less than 1% of the exposure to the parent drug. Desbutyl-lumefantrine data is not available specifically for an African population. In vitro, lumefantrine significantly inhibits the activity of CYP2D6 at therapeutic plasma concentrations.

Elimination

Artemether and Lumefantrine is are 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. Demographic characteristics such as sex and weight appear to have no clinically relevant effects on the pharmacokinetics of artemether and lumefantrine.

No urinary excretion data are available for humans. In rats and dogs unchanged artemether has not been detected in faeces and urine due to its rapid and high-first-pass metabolism, but several metabolites (unindentified) have been detected in both faeces and urine. Lumefantrine is eliminated via the bile in rats and dogs, with excretion primarily in the faeces. After oral dosing in rats and dogs qualitative and quantitative recovery of metabolites in bile and faeces was relatively low, most of the dose being recovered as parent drug.

Pharmacokinetics in special patient populations

No specific pharmacokinetic studies have been performed either in patients with hepatic or renal insufficiency, or in children or elderly patients.

5.3 Pre-clinical safety data :

Pregnancy rates were reduced by about one half in female rats dosed for 2 to 4 weeks with the artemether-lumefantrine combination at 1000 mg/kg (about 9 times the clinical dose based on body surface area comparisons). Male rats dosed for 70 days showed increases in abnormal sperm (87 % abnormal) and increased testes weights at 30 mg/kg doses (about one third the clinical dose). Higher doses (about 9 times the clinical dose) resulted in decreased sperm motility and 100 % abnormal sperm cells.

Safety data from an observational pregnancy study of approximately 500 pregnant women who were exposed to the artemether-lumefantrine combination (including a third of patients who were exposed in the first trimester), and published data of over 1000 pregnant patients who were exposed to artemisinin derivatives, did not show an increase in adverse pregnancy outcomes or teratogenic effects over background rate.

The efficacy of artemether-lumefantrine combination in the treatment of acute, uncomplicated malaria in pregnant women has not been established.

Artemether-lumefantrine combination should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Pregnant rats dosed during the period of organogenesis at or higher than a dose of about half the highest clinical dose of 1120 mg artemether-lumefantrine per day (based on body surface area comparisons), showed increases in fetal loss, early resorptions and post implantation loss. No adverse effects were observed in animals dosed at about one-third the highest clinical dose. Similarly, dosing in pregnant rabbits at about three times the clinical dose (based on body surface area comparisons) resulted in abortions, preimplantation loss, post implantation loss and decreases in the number of live fetuses. No adverse reproductive effects were detected in rabbits at two times the clinical dose. Embryo-fetal loss is a significant reproductive toxicity. Other Artemether are known to be embryotoxic in animals. However, because metabolic profiles in animals and humans

are dissimilar, artemether exposures in animals may not be predictive of human exposures. These data cannot rule out an increased risk for early pregnancy loss or fetal defects in humans.

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 combination is administered to a nursing woman. Animal data suggest both artemether and lumefantrine are excreted into breast milk. The benefits of breastfeeding to mother and infant should be weighed against potential risk from infant exposure to artemether and lumefantrine through breast milk.

6. PHARMACEUTICAL PARTICULARS :

6.1 List of Excipients: (For Fill Material)

Refined Soya Oil U.S.P.
Hydrogenated Vegetable Oil N.F.
Bees Wax B.P.
Soyalecithin U.S.P.
Butylated Hydroxy Anisole B.P.
Butylated Hydroxu Toluene B.P.

Shell Excipients : (For Encapsulation)

Gelatin B.P.
Glycerin B.P.
Methyl Paraben B.P.
Propyl Paraben B.P.
Titanium Dioxide B.P.
Purified Water B.P.

6.2 Incompatibilities :

None Reported.

6.3 Shelf life :

Shelf-life of drug product as claimed on the package for sale. Shelf-life after dilution or reconstitution according to directions. Shelf-life after first opening of container.

The Shelf-Life is 30 months from the date of manufacture.

6.4 Special precaution for storage:

Store in a dry place, below 30ºC. Keep out of reach of children.

6.5 Nature and contents of container:

AMATEM soft gelatin capsules are available in a blister strip containing 12 capsules each. 1 such strips are packed in a printed mono carton, along with a pack insert.

7. MARKETING AUTHORIZATION HOLDER :

OLIVE HEALTHCARE
197/2, Athiyawad,
Dabhel Village, Daman
India.

8. MARKETING AUTHORIZATION NUMBER :

NIL

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF AUTHORIZATION :

NIL

10. DATE OF REVISION OF THE TEXT :

NIL