1.3 PRODUCT INFORMATION

1.3.1 Summary of Product Characteristics (SmPC)

1.3.1.1 Name of the medicinal product

Artemether 80mg + Lumefantrine 480mg Tablets

1.3.1.2. Qualitative and quantitative composition

Each tablet contains: Artemether 80mg;
Lumefantrine 480mg

1.3.1.3. Pharmaceutical form

Yellow Tablet .

1.3.1.4. Clinical particulars

1.3.1.4.1 Therapeutic indications

This drug is a combination of artemether and lumefantrine which acts as blood schizontocides.

It is indicated for the treatment of adults and children with acute, uncomplicated infections due to Plasmodium falciparum or mixed infection including P.Falciparum and strains from multi drug resistant areas.

This drug is recommended for use as a standby emergency treatment for travelers to areawhere the parasite is resistant to other drugs.

1.3.1.4.2 Posology and method of administration

Route of administration: Oral

Dosage in Adults:

Weight in kg	Total tablets						
		Day-1		Day-2		Day-3	
		O Hour	8 Hours	24 Hours	36 Hours	48 Hours	60 Hours
Adult	6	1	1	1	1	1	1

1.3.1.4.3 Contraindications

This drug is contraindicated in :

- Patients with known hypersensitivity to either of the components.
- Pregnant and lactation women.
- Patients with severe malaria.

1.3.1.4.4 Special warnings and precautions for use

This drug is not recommended for prophylaxis.

1.3.1.4.5 Interaction with other medicinal products and other forms of interaction

Although the likelihood of this drug interations with other drugs is minimal in view of its short duration of administration and wide therapeutic index, three specific pharmacodynamic drug-drug interaction studies with ketoconazole (a potent CYP3A4 inhibitor), mefloquine, and have been conducted in healthy voluteers.

Interaction with antimalarials:

As patients to be treated with This drug may have recently been treated with other antimalarials with mefloquine and quinine were studied in healthy volunteers. The sequential oral administration of mefloquine prior to This drug had no effect on plasma concentrations of artemether or the artemether/dihy-droartemisinin ratio but these was a significant (around 30-40%) reduction in plasma levels (Cmax and AUC) of lumefantrine possibly due to lower absorption secondary to a mefloquine-induced decrease in bioavailability. The current i.v. Administration of quinine (10mg/kg BW) with this drug had no effects on the plasma concentrations of lumefantrine or quinine. Plasma concentrations of artemether and DHA appeared to be lower in this study, administration of This drug to 14 subjects had no effect on QTc interval infusion of quinine alone in 14 other subjects caused a transient prolongation of QTc interval, which was consistent with the known cardiotoxicity of quinine. This effect was slightly but significantly, greater when quinine was infused after this drug in 14 additional subjects. It would thus appear that the inherent risk of QTc prolongation associated with i.v. Quinine was enhanced by prior administration of This drug. In a clinical trial in Thailand some patients received This drug following treatment failures with mefloquine or quinine. One hundred and twenty-one patients received This drug following without any previous antimalatial treatment 34 and 9 patients had measurable quinine, respectively, at enrollment . This patients showed similar safety and pharmacokinetic prolongation of QTc interval by >30ms, with an actual QTc > 450ms in males and > 470ms in females, was observed in approxiamately 5% of patients treated with various dose regiments of This drug. It is possible that these changes were disease-related. No correction was found between QTc. Prolongation and peak plasma concentration in individual patients. When This drug is given sequentially to mefloquine or quinine, close monitoring of food intake (for mefloquine) or ECG (for quinine) is necessary in addition, because data on safety and efficacy are limited. This drug should not be given concurrently with antimalarials other than mefloquine or quinine in patients previously treated with halofantrine, This drug should be monitoring of the ECGs is recommended and steps should be taken to correct any electrolyte disturbances.

Interaction with concomitant treatment other drugs

No safety issues that could be atributed to drug interactions.

Arose during clinical studies with This drug, in which most patients receive antipyretic medication, antibiotics and fluid electrolyte disturbances.

Interaction with a CYP450 3A4 inhibitor (Ketoconazole)
The concurrent oral administration of ketoconazole with This drug led to a modest increase (<2-fold) in artemether, DHA, and lumefantrine exposure in healthy subjects. This increase in exposure to the antimalarial combination was not associated with increased side effects or changes in electrocardiographic parameters. Based on this study, dose adjustment of This drug is considered unnecessary in falciparum malaria patients when administered in association with ketoconazole or other potent CYP3A4 inhibitors.

Interaction with CYP 450 enzymes
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 production should alter the therapeutic effects of drugs that are predomlnantly metabolized 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 this drug with drugs that are metabolized by this iso-enzyme (e.g. Neuroleptics and tricyclic antidepressants) is contraindicated.

1.3.1.4.6 Pregnancy and lactation
The drug shall not be used in pregnant and lactation women.

1.3.1.4.7 Effects on ability to drive and use machines
Should not drive or use machines after treatment of this drug.

1.3.1.4.8 Adverse effects
The following adverse effects have been reported dizziness and fatique, patients receiving this drug should not drive or use machines, anorexiz, nausea, vomiting, abdominal pain palpitations, myalgia, sleep disorders, arthralgia, headache and rash. In children and adults treated with this combinations the frequency and degree of QTC prolongations was lower compared with other antimalarials. Stiches show no indication of cardiotoxicity.

1.3.1.5 Pharmacological properties
1.3.1.5.1 Pharmacodynamic properties

This drug comprises a fixed ratio of 1:6 parts of artemether and lumefantrine, respectiviely. The site of antiparasitic action of both compo nents is the food vacuole of the malarial parasite, where they are thought to interfere with the conversion of heam, a toxc intermediate produced during haemoglobin breakdown, to the non-toxic haezmozoin, malaria pigment. Lumefantrine is though to interfer with the polymerisation process, while artemether generates reactive metabolites as a result often interaction between its peroxide bridge and haem iron. Both artemether and

lumefantrine have a second action involving inhibition of nucleic acid. and protein synthesis within the malaria parasite. Date from in-vitro and in-vivo studies show that this drug did not induce resisteance.
The antimalarial activity of the combination of lumefantrine and artemether in this drug is greater than that of either substance alone. In a double-blind comparative study in China (n=157), the 28-day cure rate of this drug when given as 4 doses was 94%, compared with 90% for lumefantrine and 46% for artemether when given as monotherapy (intention to treat analysis, ITT). In areas where multi-drug-resistant strains of falciparum malaria are common and in the resident population, 28-day cure rates with the 6-dose regiment (given over 60-96 h) were 87% and 90% for This drug versus 94% and 96% for mefloquine/artesubate(ITT). Patients of European origin were not included in trains with the six-dose regiment, similar efficacy and safety profiles with the six-dose regimen would be expected in both populations. In 319 patients in whom gametocytes were present, the median time to gametocyte clearance with This drug as 96 h. Temether was associated with more rapid gametocyle clearance than any comparator other than mefloquine/artesunate.
This drug is active against blood stages of Plasmodium vivax, but is not active against bypnozoites. Therefore, sequential treatment with primaquine should be used to achieve hypnoite eradication (see section SPECIAL WARNINGS ANDPRECAUTIONS FOR USE).

1.3.1.5.2 Pharmacokinetic properties

Pharmacokinetic characterization of this drug is limited by the lack of an intravenous formulation, and the very high inter-and intrasubject variability of artemether and lumefantrine plasma concentrations and derved pharmacokinetic parameters (AUC, Cmax).

Absorption

Artemether is absorbed fairly rapidly with peak plasma concentrations reached about 2 hours after dosing. Absorption of lumefantrin, a high lipophilic compound, starts after a lag-time of up to 2 hours , with peak plasma concentration about 2 hours after dosing. Food enhances the absorption of both artemether and lumefantrin: in healthy volunteers the relative bioavailability f artemether was increased more than two-fold, and that of lumefantrin sixteen-fold compared with fasted conditions while this drug was taken after a high-fat meal. Food has also been shown to increase the absorption of lumefantrine in patients with malaria, although to lesser extent (approximately two-fold), most probaly 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 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). Dihydroartemisinin is also bound to human serum protein (47%-76%) protein binding to human plasma protein is linear.

Metabolism

Artemether is rapaidly and extensively metabollsed (substantial first-pass metabolism both in vitro and in humans. Human liver microsomes metabolised artemether to the biologicallu active main metabolite has also been described to human in vivo. The artemether/dihydroartememisinin AUC ratio is 12 after a single dose and 0.3 after 6 doses given over 3 days. In-vivo data indicate that artemisinins have some capacity to induce cytochrome iso enzymes CYP2C19 and CYP3A4 lumefantrine takes place directly by CYP3M, in human live microsomes in-vivo in animals (dogs and rats), glucuronidation of lumefantrine takes place directly and after oxidative biotrans formation.

In-vitro lumefantrine significantly inhibits the activity of CYP2D6 at therapeutic plasma concentrations (see PRECAUTIONS FOR USE AND INTERACTIONS).

Elimination

Artemether and dihydroertemisinin are rapidly cleared from plasma with an elimination half-life of about 2 hours. Lumefantrine is eliminated very slowly with a terminal half-life 2-3 days in healthy volunteers and 4-6 days in patients with falcipurum malaria. Demographic characteristics of This drug.

No urinary excretion data are available for humans. In rats and dogs unchanged artemether has not be detected in both feaces ans urine due to its rapid and high-first-pass metabolism, but several metabolites (unidentified) have been detected in both feaces and urine. Lumefantrine is eliminated via the bile in rats and dogs, with excretiion primary 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 drug being recovered as parent drug.

1.3.1.6. Pharmaceutical particulars

1.3.1.6.1 Shelf life

Three years

1.3.1.6.2Special precautions for storage

Store below30°C. Keep out of reach and sight of children.

1.3.1.6.3 Nature and contents of container

1*6 Tablets per Blister.

1.3.1.6.4 Special precautions for disposal and other handling

Not applicable.