

SHANDONG XIER KANGTAI PHARMACEUTICAL CO., LTD.

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1. NAME OF THE MEDICINAL PRODUCT

ARTERINE FORTE

Artemether 80mg + Lumefantrine 480mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains: Artemether 80mg;

Lumefantrine 480mg

Excipients:

Lactose	58mg
Dextrin	28mg
Hydroxypropylcellulose	1mg
Sodium Bicarbonate	14mg
Sodium Lauryl Sulphate	7mg
Starch	30mg

3. PHARMACEUTICAL FORM

Oral Tablet.

4. CLINICAL PARTICULARS

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 area where the parasite is resistant to other drugs.

4.2 Posology and method of administration

Dosage and Administration

Route of administration: Oral

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

Dosage in Adults:

For tablets as a single dose at the time of initial diagnosis again after 8 hours, then 1 tablet twice

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daily on each of the following two days (total course comprises 6tablets) .

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.

4.4 Special warnings and precautions for use

This drug is not recommended for prophylaxis.

4.5 Interaction with other medicinal products and other forms of interaction

Although the likelihood of this drug interactions 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 volunteers.

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/dihydroartemisinin ratio but there was a significant (around 30-40%) reduction in plasma levels (C_{max} 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 antimalarial 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 approximately 5% of patients treated with various dose regimens 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

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electrolyte disturbances.

Interaction with concomitant treatment other drugs

No safety issues that could be attributed 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 artemisinin 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 predominantly 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.

4.6 Pregnancy and Lactation

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

4.7 Effects on ability to drive and use machines

Should not drive or use machines after treatment of this drug.

4.8 Undesirable effects

With Artemether virtually no side effects have been seen. Laboratory abnormalities such as slight rise in transaminases and a decrease in reticulocyte count are rare and transient. A lowering of sinus frequency without causing ECG change has been noticed. At high doses transient abdominal pain, tinnitus and diarrhea have been described but a causal relationship is unclear. Some antimalarials halofantrine and quinine can influence the ECG pattern. Attention should be made to patients previously treated with those antimalarials. A reasonable period should be taken in account before starting a treatment with Lumefantrine combinations. For those patients physicians will prescribed Artemisinin derivatives in mono therapy in case of severe paludism. Sometimes it could be possible that the following common side effect occur, rash, check this with your doctor. Other common side effects may occur as difficulty in sleeping, nausea, vomiting, diarrhea, coughing. They need attention when persistent.

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4.9 Overdose

In case of overdose, emergency symptomatic treatment in a specialised facility is required, which should include ECG and kaliemia monitoring.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

This drug 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 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 an 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. Data from in-vitro and in-vivo studies show that this drug did not induce resistance.

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 regimen (given over 60-96 h) were 87% and 90% for This drug versus 94% and 96% for mefloquine/artesunate (ITT). Patients of European origin were not included in trials with the six-dose regimen, 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 was 96 h. Artemether was associated with more rapid gametocyte clearance than any comparator other than mefloquine/artesunate.

This drug is active against blood stages of Plasmodium vivax, but is not active against hypnozoites. Therefore, sequential treatment with primaquine should be used to achieve hypnozoite eradication (see section SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

5.2 Pharmacokinetic properties

Pharmacokinetic characterization of this drug is limited by the lack of an intravenous formulation, and the very high inter- and intraindividual variability of artemether and lumefantrine plasma concentrations and derived pharmacokinetic parameters (AUC, C_{max}).

Absorption

Artemether is absorbed fairly rapidly with peak plasma concentrations reached about 2 hours after dosing. Absorption of lumefantrine, 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 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 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 a lesser extent (approximately two-fold), most

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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 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 rapidly and extensively metabolised (substantial first-pass metabolism both in vitro and in humans. Human liver microsomes metabolised artemether to the biologically active main metabolite has also been described to human in vivo. The artemether/dihydroartemisinin 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 biotransformation.

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

Elimination

Artemether and dihydroartemisinin 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 falciparum 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 faeces and urine due to its rapid and high-first-pass metabolism, but several metabolites (unidentified) have been detected in both faeces and urine. Lumefantrine is eliminated via the bile in rats and dogs, with excretion 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.

5.3 Preclinical safety data

Toxicology

In accordance with the international guidelines, requirements and GLP standards, Novartis has evaluated

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the safety of coartemether and its individual components in the full range of toxicity studies from acute to subchronic treatment in the appropriate laboratory animal species, using various routes of administration. The preclinical profile of coartemether and its components was found to be satisfactory. Adverse effects predominantly reflected the pharmacological action of the drug (e.g. targeting red blood cells). No evidence of teratogenicity, mutagenicity, phototoxicity, neurotoxicity or cardiotoxicity was found.

Coartemether has not been evaluated for the treatment of complicated malaria, including cases of cerebral malaria or other severe manifestations such as pulmonary oedema or renal failure.

Coartemether 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. coartemether is active against blood stages of *Plasmodium vivax*, but is not active against hypnozoites. Therefore, sequential treatment with primaquine may be used to achieve hypnozoite eradication. Coartemether is not indicated and has not been evaluated for prophylaxis.

Halofantrine, quinine and quinidine are known to cause QT interval prolongation. Asymptomatic prolongation of QTc intervals by >30 ms, with an actual QTc >450 ms in males and >470 ms in females, was observed in approximately 5% of patients treated with various dose regimens of Coartemether in clinical trials. It is possible that these changes were disease related.

Concurrent administration of Coartemether and other antimalarials, should be avoided.

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 coartemether to patients with severe renal, hepatic or cardiac problems.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

1	Lactose
2	Dextrin
3	Hydroxypropylcellulose
4	Sodium Bicarbonate
5	Sodium Lauryl Sulphate
6	Starch

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store in a cool & dry place. Keep all medicine out of the reach of children.

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6.5 Nature and contents of container

6 Tablets/Blister/Box, 10 boxes/middle box.

6.6 Special precautions for disposal

Not applicable.

7. APPLICANT/MANUFACTURER

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