1. NAME OF THE MEDICINAL PRODUCT

FANETHA(R) Powder for Oral Suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 60ml of reconstituted suspension contains:
Artemether 180mg
Lumefantrine..... 1080mg

Excipients with known effect:

- Methyl parahydroxybenzoate
- Propyl parahydroxybenzoate
- Sugar

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

- Powder for oral suspension.
- Yellow powder
- The reconstituted suspension has a yellow colour and a taste of Orange.

4. Clinical Particulars

4.1 Therapeutic indications

It is used for the treatment of malaria in children, caused by all forms of plasmodium and multiple drug resistant strain of Plasmodium falciparum.

4.2 Posology and method of administration

- Posology

- **5-14kgs (6months-3years);** 5mls twice daily for three consecutive days.
- **15-24kgs (4-8years);** 10mls taken twice daily for three consecutive days.

- Method of administration

  Oral.

Second dose to be taken strictly after 8hours of first dose. After each dose, give your child fatty meal or something to eat or drink. If your child vomits within 1 hour of taking **FANETHA ®** oral suspension, repeat the dose immediately. Take dosage exactly as recommended, otherwise infection may return.
Direction For Reconstitution: Shake the bottle to loosen the powder, add 45ml previously boiled and

cooled water, invert the bottle and shake until all powder is dispersed, then slowly add more water up to the 60ml mark on the bottle. It is advised to shake the bottle before each use.

4.3 Contraindications

Fanetha is contraindicated in:
- patients with known hypersensitivity to the active substances or to any of the excipients listed in section 6.1
- patients who are taking any drug which is metabolised by the cytochrome enzyme CYP2D6 (e.g. 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 (proarrythmic): 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, - flecainide;
 - patients with a history of symptomatic cardiac arrythmias 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. hypokalaemia or hypomagnesemia;
- patients taking drugs that are strong inducers of CYP3A4 such as rifampin, carbamazepine, phenytoin, St. John's wort (Hypericum perforatum).

4.4 Special warnings and precaution for use

Fanetha is not recommended during the first trimester of pregnancy in situations where other suitable and effective antimalarials are available.

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

If a patient deteriorates while taking Fanetha, 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 Fanetha.

If quinine is given after Fanetha, close monitoring of the ECG is advised.

If Fanetha is given after mefloquine, close monitoring of food intake is advised.

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

Fanetha is not indicated and has not been evaluated for prophylaxis of malaria.

Fanetha should be used cautiously in patients on anti-retroviral drugs (ARTs) since decreased artemether, DHA, and/or lumefantrine concentrations may result in a decrease of antimalarial efficacy of Fanetha.

Like other antimalarials (e.g. halofantrine, quinine and quinidine) Fanetha has the potential to cause QT prolongation.

Caution is recommended when combining Fanetha with drugs exhibiting variable patterns of inhibition, moderate induction or competition for CYP3A4 as the therapeutic effects of some drugs could be altered. Drugs that have a mixed inhibitory/induction effect on CYP3A4, especially anti-retroviral drugs such as HIV

protease inhibitors and non-nucleoside reverse transcriptase inhibitors should be used with caution in patients taking Fanetha.

Caution is recommended when combining Fanetha with hormonal contraceptives. Fanetha may reduce the effectiveness of hormonal contraceptives. Therefore, patients using oral, transdermal patch, or other systemic hormonal contraceptives should be advised to use an additional non-hormonal method of birth control for about one month.

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

Renal impairment

No specific studies have been carried out in this group of patients. There is no significant renal excretion of lumefantrine, artemether and dihydroartemisinin in studies conducted in healthy volunteers and clinical experience is limited. No dose adjustment for the use of Fanetha in patients with renal impairment is recommended. Caution is advised when administering Fanetha to patients with severe renal impairment. In these patients, ECG and blood potassium monitoring is advised.

Hepatic impairment

No specific studies have been carried out in this group of patients. In patients with severe hepatic impairment, a clinically relevant increase of exposure to artemether and lumefantrine and/or their metabolites cannot be ruled out. Therefore caution should be exercised in dosing patients with severe hepatic impairment.In these patients, ECG and blood potassium monitoring is advised. No dose adjustment is recommended for patients with mild to moderate hepatic impairment.

New infections

Data for a limited number of patients in a malaria endemic area show that new infections can be treated with a second course of Fanetha. In the absence of carcinogenicity study data, and due to lack of clinical experience, more than two courses of Fanetha cannot be recommended.

4.5 Interactions with other medicinal products and other forms of interaction

Contraindications of concomitant use

Interaction with drugs that are known to prolong the QTc interval

Fanetha is contraindicated with concomitant use of drugs (they may cause prolonged QTc interval and Torsade de Pointes) 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, certain non-sedating antihistamines (terfenadine, astemizole), cisapride, flecainide.

Interaction with drugs metabolized by CYP2D6

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 Fanetha with drugs that are metabolised by this iso-enzyme is contraindicated (e.g. neuroleptics, metoprolol, and tricyclic antidepressants such as imipramine, amitriptyline, clomipramine) is contraindicated.

Interaction with strong inducers of CYP3A4 such as rifampin

Oral administration of rifampin (600 mg daily), a strong CYP3A4 inducer, with Fanetha Tablets (6-dose regimen over 3 days) in six HIV-1 and tuberculosis coinfected adults without malaria resulted in significant decreases in exposure to artemether (89%), DHA (85%) and lumefantrine (68%) when compared to exposure values after Fanetha alone. Concomitant use of strong inducers of CYP3A4 such as rifampin, carbamazepine, phenytoin, St. John's Wort is contraindicated with Fanetha.

Inducers should not be administered at least one month after Fanetha administration, unless critical to use as judged by the prescriber.

Concomitant use not recommended

Interaction with other antimalarial drugs

Data on safety and efficacy are limited, and Fanetha should therefore not be given concurrently with other antimalarials unless there is no other treatment option.

If Fanetha is given following administration of mefloquine or quinine, close monitoring of food intake (for mefloquine) or of the ECG (for quinine) is advised. The long elimination half-life of lumefantrine must be taken into account when administering quinine in patients previously treated with Fanetha. In patients previously treated with halofantrine, Fanetha should not be administered earlier than one month after the last halofantrine dose.

Mefloquine

A drug interaction study with Fanetha in man involved administration of a 6-dose regimen over 60 hours in healthy volunteers which was commenced at 12 hours after completion of a 3-dose regimen of mefloquine or placebo. Plasma mefloquine concentrations from the time of addition of Fanetha were not affected compared with a group which received mefloquine followed by placebo.

Pre-treatment with mefloquine had no effect on plasma concentrations of artemether or the artemether/dihydroartemisinin ratio but there was a significant reduction in plasma levels of lumefantrine, possibly due to lower absorption secondary to a mefloquine-induced decrease in bile production. Patients should be encouraged to eat at dosing times to compensate for the decrease in bioavailability.

Quinine

A drug interaction study in healthy male volunteers showed that the plasma concentrations of lumefantrine and quinine were not affected when i.v. quinine (10 mg/kg BW over 2 hours) was given sequentially 2 hours after the last (sixth) dose of Fanetha (so as to produce concurrent plasma peak levels of lumefantrine and quinine). Plasma concentrations of artemether and dihydroartemisinin (DHA) appeared to be lower. In this study, administration of Fanetha 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 Fanetha 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 Fanetha.

Concomitant use requiring caution

Interactions affecting the use of Fanetha

Interaction with CYP3A4 inhibitors

Both artemether and lumefantrine are metabolised predominantly by the cytochrome enzyme CYP3A4, but do not inhibit this enzyme at therapeutic concentrations.

Ketoconazole

The concurrent oral administration of ketoconazole with Fanetha led to a modest increase (≤ 2-fold) in artemether, DHA, and lumefantrine exposure in healthy adult 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 Fanetha is considered unnecessary in falciparum malaria patients when administered in association with ketoconazole or other potent CYP3A4 inhibitors.

Fanetha should be used cautiously with drugs that inhibit CYP3A4 and are contraindicated with drugs which additionally are known to prolong QTc, due to potential for increased concentrations of lumefantrine which could lead to QT prolongation.

Interaction with weak to moderate inducers of CYP3A4

When Fanetha is co-administered with moderate inducers of CYP3A4, it may result in decreased concentrations of artemether and/or lumefantrine and loss of antimalarial efficacy.

Interaction with anti-retroviral drugs such as protease inhibitors and non-nucleoside reverse transcriptase inhibitors

Both artemether and lumefantrine are metabolized by CYP3A4. ARTs, such as protease inhibitors and non-nucleoside reverse transcriptase inhibitors, are known to have variable patterns of inhibition, induction or competition for CYP3A4. Fanetha should be used cautiously in patients on ARTs since decreased artemether, DHA, and/or lumefantrine concentrations may result in a decrease of antimalarial efficacy of Fanetha, and increased lumefantrine concentrations may cause QT prolongation.

Lopinavir/ ritonavir

In a clinical study in healthy volunteers, lopinavir/ritonavir decreased the systemic exposures to artemether and DHA by approximately 40% but increased the exposure to lumefantrine by approximately 2.3- fold. Exposures to lopinavir/ritonavir were not significantly affected by concomitant use of Fanetha.

Nevirapine

In a clinical study in HIV-infected adults, nevirapine significantly reduced the median Cmax and AUC of artemether by approximately 61% and 72%, respectively and reduced the median Cmax and AUC of dihydroartemisinin by approximately 45% and 37%, respectively. Lumefantrine Cmax and AUC were non-significantly reduced by nevirapine. Artemether/lumefantrine reduced the median Cmax and AUC of nevirapine by approximately 43% and 46% respectively.

Efavirenz

Efavirenz decreased the exposures to artemether, DHA, and lumefantrine by approximately 50%, 45%, and 20%, respectively. Exposures to efavirenz were not significantly affected by concomitant use of Fanetha.

Interactions resulting in effects of Fanetha on other drugs

Interaction with drugs metabolized by CYP450 enzymes

When Fanetha is co-administered with substrates of CYP3A4 it may result in decreased concentrations of the substrate and potential loss of substrate efficacy. Studies in humans have demonstrated that artemisinins have some capacity to induce CYP3A4 and CYP2C19 and inhibit CYP2D6 and CYP1A2. Although the magnitude of the changes was generally low it is possible that these effects could alter the therapeutic response of drugs that are predominantly metabolised by these enzymes.

Interaction with 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, Fanetha 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 nonhormonal method of birth control for about one month.

Drug-food/drink interactions

Fanetha should be taken with food or drinks rich in fat such as milk as the absorption of both artemether and lumefantrine is increased.

Grapefruit juice should be used cautiously during Fanetha treatment. Administration of artemether with grapefruit juice in healthy adult subjects resulted in an approximately two fold increase in systemic exposure to the parent drug.

4.6 Pregnancy and Lactation

Women of childbearing potential

Women using oral, transdermal patch, or other systemic hormonal contraceptives should be advised to use an additional non-hormonal method of birth control for about one month.

Pregnancy

A meta-analysis of observational studies including over 500 artemether-lumefantrine exposed women in their first trimester of pregnancy assessed adverse pregnancy outcomes. The data showed that compared to quinine, artemisinin treatment, including artemether-lumefantrine, was not associated with an increased risk of miscarriage, stillbirth or congenital anomalies. However, due to the limitations of these studies, the

risk of adverse pregnancy outcomes for artemether-lumefantrine exposed women in early pregnancy cannot be excluded.

Safety data from pregnancy studies including over 1200 pregnant women who were exposed to artemether-lumefantrine during the second or third trimester did not show an increase in adverse pregnancy outcomes or teratogenic effects over background rates.

Studies in animals have shown reproductive toxicity.

Fanetha treatment is not recommended during the first trimester of pregnancy in situations where other suitable and 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 third trimester, Fanetha treatment should be considered if the expected benefit to the mother outweighs the risk to the foetus.

Breast-feeding

Animal data suggest excretion into breast milk but no data are available in humans. Women taking Fanetha should not breast-feed during their treatment. Due to the long elimination half-life of lumefantrine (2 to 6 days), it is recommended that breast-feeding should not resume until at least one week after the last dose of Fanetha unless potential benefits to the mother and child outweigh the risks of Fanetha treatment.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Asthenia, Pyrexia, Arthralgia, Myalgia, Sleep Disorders, Hepatomegaly, Palpitations, Splenomegaly, Anaemia, Nasopharyngitis, Rhinitis, Fatigue, Aspartate aminotransferase increase (Children), Eosinophilia, Tinnitus, Conjunctivitis, Constipation, Dyspepsia, Dysphagia, Peptic Ulcer, Gait disturbances, abscess, acrodermatitis, bronchitis, gastroenteritis, influenza, LRTIs, RTIs, Blood cell count decrease, White Blood cell count increase, Increased Alanine aminotransferase, decreased, Hypokalemia, Back pain, Ataxia, Clonus, Fine motor delay, Hyper-reflexia, Hypoesthesia, Nystagmus, Tremor, Agitations, Mood swings, Hematuria, Proteninuria, pharyngo-lanrygeal pain, urticaria.
Hypersensitivity reactions include Anaphylaxis, angioedema, serious skin reactions (bullous eruption) have been reported.

4.9 Overdose

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

5. Pharmacological properties:

5.1 Pharmacodynamic properties

Fanetha is an Artemether based Combination Therapy (ACT) which contains two substances active against malaria parasites. Fanetha
comprises a fixed ratio of 1:6 parts of artemether and lumefantrine, respectively. In this combination, the d rug Artemether kills the parasites very fast and potentiates the effects of the second drug Lumefantrine.
This combination therapy permits a shorter duration of treatment, thereby improving compliance. The theor etical risk for drug resistance is
significantly reduced by using combination therapy. The site of antiparasitic action of both components is th e 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 nontoxic haemozoin, 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 ha em iron. Both artemether and lumefantrine have a secondary action involving inhibition of nucleic acid- and

protein synthesis within the malarial parasite.

5.2 Pharmacokinetic properties

Absorption:

Artemether is absorbed fairly rapidly and dihydroartemisinin (DHA), the active metabolite of artemether, appears rapidly in the systemic circulation with peak plasma concentrations of both compounds 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.

Distribution

Artemether is 95.4% bound to human serum proteins in vitro. The active metabolite dihydroartemisinin (DHA) is also bound to human serum proteins (47-76%). Lumefantrine is 99.7% bound to human serum proteins in vitro.

Metabolism

Artemether is rapidly and extensively metabolised with substantial first-pass metabolism. Lumefantrine is N-debutylated, mainly by CYP3A4, in human liver microsomes.

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 of approximately 3 days. No urinary excretion data are available for humans.

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 adult 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 $\geq$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

- Citric Acid
- Xanthan Gum
- Colloidal SiliconDioxide
- Microcrystalline Cellulose
- Orange Flavour Powder
- Methyl paraben
- Propylparaben
- Sugar

6.2 Incompactibilities

- None Known.

6.3 Shelf life

36 Months

6.4 Special precautions for storage

- Store in a cool dry place below 25°C. Keep medicine away from reach of children.

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

FANETHA Oral Suspension is presented as a yellow powdered drug in 100ml PET bottle for paediatric use. Shake the bottle well before each use

6.6 Special precautions for disposal<and other handling>

Any unused product or waste material should be disposed of in accordance with local requirements.

Applicant/Manufacturer

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