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

Registration & Regulatory Affairs (R & R) Directorate

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. NAME OF THE MEDICINAL PRODUCT

Artemether 20mg+Lumefantrine 120mg/5ml-60ml powder for oral suspension (Tamether Powder for Oral Suspension)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each bottle contains Artemether 240mg+ Lumefantrine 1440mg

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Granules, powder for oral suspension

4. Clinical particulars

4.1 Therapeutic indications

Tamether 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 falciprum or mixed infection including P. Falciprum and strains from multi drug resistant areas. Tamether 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

Body weight in kg (age in years)	Day 1 Morning Evening 0hr 8hr	Day 2 Morning Evening (24hr) (36hr)	Day 3 Morning Evening (48hr) (60hr)
5-14 (less than 3 years)	5ml 5ml	5ml 5ml	5ml 5ml
15-24 (3 to 8 years)	10ml 10ml	10ml 10ml	10ml 10ml

4.3 Contraindications

Tamether is contraindicated in:

-Patients with known hypersensitivity to either of the components

-Pregnant and lactating women

-Patients with severe malaria

4.4 Special warnings and precautions for use

Tamether is not recommended for prophylaxis

4.5 Interaction with other medicinal products and other forms of interaction

Although the likelihood of Tamether interactions with other drugs is minimal in view of its short duration of administration and wide therapeutic index, three specific pharmacokinetic and pharmacodynamic drug-drug interaction studies with ketoconazole (a patient CYP3A4 inhibitor), mefloquine and quinine have been conducted in healthy volunteers.

Interaction with antimalaria

As patients to be treated with Tamether may have recently been treated with other antimalaria, interactions with mefloquine and quinine were studied in healthy volunteers. The sequential oral administration of mefloquine prior to Tamether had no effect on plasma concentrations of artemether or the artemether/dihydroartemisinin, but there was a significant (around 30-0%) reduction in plasma levels (Cmax and AUG) of lumefantrine, possibly due to lower absorption secondary to a mefloquine-induced decrease in bile production. Based on this study, patients should be encouraged to eat at dosing times to compensate for this decrease in bioavailability.

The concurrent i.v. administration of quinine (10mg/kg BW) with Tamether had no effect on plasma concentrations of lumefantirne or quinine. Plasma concentrations of artemether and DHA appeared to be lower in this study, administration of Tamether 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 Tamether 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 ofT amether.

In a clinical trial in Thailand some patients received Tamether following treatment failures with mefloquine or quinine. One hundred and twenty-one patients received Tamether without any previous anti malaria treatment whereas 34 and 9 patients has measurable quinine or

mefloquine, respectively, at enrolment. These patients showed similar safety and pharmacokinetic profiles of Tamether to patients who had no detectable levels of other antimalarias. In the different clinical trials, a symptomatic prolongation of QTc intervals 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 Tamether. It is possible that these changes were disease-related. No correlation was found between QTc prolongation and peak plasma concentration in individual patients.

When Tamether is given sequentially to mefloquine or quinine, close monitoring of foot intake (for mefloquine) or EGG (for quinine) is necessary in addition, because data on safety and efficacy are limited. Tamether should not be given concurrently with antimalarias other than mefloquine or quinine in patients previously treated with halofantrine. Tamether should be administered at least one month after the last halofantrine dose.

If a patient deteriorates while taking Tamether, alternative treatment for malaria should be started without delay. In such cases, monitoring of the EGG is recommended and steps should be taken to correct any electrolyte disturbances.

Interaction with concomitant treatment other than antimalarias

No safety issues that could be attributed to drug interactions arose during clinical studies with Tamether in which most patients received antipyretic medication, antibiotics and fluid electrolyte replacement.

Interaction with a cyp450 3a4 inhibitor (ketoconazole)

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

Interaction with cyp450 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 enzymeCYP2C19 and perhaps also CYP3A4.

It is possible that iso-enzymeproduction could after the therapeutic effects of drugs that are

predominantly metabolized by 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 Tamether with drugs that are metabolized by this iso enzyme (e.g neuroleptics and tricylic antidepressant) is contraindicated.

4.6 Pregnancy and Lactation

4.6.1 Pregnancy

Risk Summary

Published data from clinical studies and pharmacovigilance data have not established an association with artemether/lumefantrine use during pregnancy and major birth defects, miscarriage, or adverse maternal or fetal outcomes

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Malaria during and after pregnancy increases the risk for adverse pregnancy and neonatal outcomes, including maternal anemia, severe malaria, spontaneous abortion, stillbirths, preterm delivery, low birth weight, intrauterine growth restriction, congenital malaria, and maternal and neonatal mortality.

Data

Human Data

While available studies cannot definitively establish the absence of risk, a meta-analysis of observational studies including over 500 artemether-lumefantrine exposed women in their first trimester of pregnancy, data from observational, and open label studies including more than 1200 pregnant women in their second- or third trimester exposed to artemether-lumefantrine compared to other antimalarials, and pharmacovigilance data have not demonstrated an increase in major birth defects, miscarriage, or adverse maternal or fetal outcomes. Published epidemiologic studies have important methodological limitations which hinder interpretation of data, including inability to control for confounders, such as underlying maternal disease, and maternal use of concomitant medications and missing information on the dose and duration of use.

Animal Data

Pregnant rats dosed orally during the period of organogenesis [gestational days (GD) 7 through 17] at 50 mg/kg/day artemether-lumefantrine combination (corresponding to 7 mg/kg/day artemether or higher, a dose of less than half the maximum recommended human dose (MRHD) of 1120 mg artemether-lumefantrine per day (based on body surface area (BSA) comparisons), showed increases in fetal loss, early resorptions, and postimplantation loss. No adverse effects were observed in animals dosed at 25 mg/kg/day artemether-lumefantrine (corresponding to 3.6 mg/kg/day of artemether), about one-third the MRHD (based on BSA comparison). Similarly, oral dosing in pregnant rabbits during organogenesis (GD 7 through GD 19) at 175 mg/kg/day, (corresponding to 25 mg/kg/day artemether) about 3 times the MRHD (based on BSA 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 105 mg/kg/day artemether-lumefantrine (corresponding to 15 mg/kg/day artemether), about 2 times the MRHD. Artemether and other artemisinins are associated with maternal toxicity and embryotoxicity and malformations in animals at clinically relevant exposures; however, lumefantrine doses as high as 1000 mg/kg/day, showed no evidence to suggest maternal, embryo- or fetotoxicity or teratogenicity in rats and rabbits. The relevance of the findings from the animal reproductive studies to human risk is unclear.

4.6.2 Lactation

Risk Summary

There are no data on the presence of artemether or lumefantrine in human milk, the effects on the breastfed infant or the effects on milk production. Artemether and lumefantrine are transferred into rat milk. When a drug is transferred into animal milk, it is likely that the drug will also be transferred into human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Coartem and any potential adverse effects on the breastfed infant from Coartem or from the underlying maternal condition.

4.6.3 Fertility

Contraception

Use of Coartem may reduce the efficacy of hormonal contraceptives. Advise patients using hormonal contraceptives to use an alternative non-hormonal contraceptive method or add a barrier method of contraception during treatment with Coartem.

Infertility

In animal fertility studies, administration of repeated doses of artemether-lumefantrine combination to female rats (for 2 to 4 weeks) resulted in pregnancy rates that were reduced by one half. In male rats dosed for approximately 3 months with artemether-lumefantrine combination, abnormal sperm cells, decreased sperm motility, and increased testes weight were observed.

4.7 Effects on ability to drive and use machines

4.8 Undesirable effects

The following adverse effects have been reported, dizziness and fatigue, patients receiving Tamether should not drive or use machines, anorexia, nausea, vomiting, abdominal pain, palpitations, myalgia, sleep disorders, arthragia, 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.

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Tamether 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 malaria parasite, where they are though 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 polymerization process, while artemether generates reactive metabolites as a result of the interaction between the peroxide bridge and haem iron. Both artemether and lumefantrine have a secondary action involving inhibition of nucleic acid, and protein synthesis within the malaria parasite. Data from in-vitro and in-vivo studies show that Tamether did not induce resistance.

The antimalarial activity of the combination of lumefantrine and artemether in Tamether is greater than that of either substance alone. In a double-blind comparative study in China (n=157), the 28-day cure rate of Tamether 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 Tamether versus 94% and 96% for mefloquine/artesunate (ITT). Patients of European origin were not included in trials with the six-dose regimen. However, as efficacy and safety were similar in European and Thai patients following a four-dose regimen, similar efficacy and safety profiles with the six-dose

regimen would be expected in both populations. In 319 patients in whom gamelocytes were present, the median time to gamelocyte clearance with Tamether was 96 h. Tamether was associated with more rapid gamecolyte clearance than any comparator other than mefloquine/artesunate.

Tamether 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.

5.2 Pharmacokinetic properties

Pharmacokinetics characterization of Tamether 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 (AUG, 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 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 Tamether 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.

Metabolism

Artemether is rapidly and extensively metabolized (substantial first-pass metabolism both in vitro and in humans). Human liver microsomes metabolized artemether to the biologically active main metabolite dihydroartemisinin (demethylation), predominantly through the enzyme CYP3A4/5. The pharmacokinetics of this metabolite has also been described in humans in vivo. The artemether/dihydroartemisinin AUG ratio is 12 after a single dose and 0.3 after 6 doses given over 3 days. In vivo data indicate that artemisinins have omecapacity to induce cytochrome iso enzymes CYP2C19 and CYP3A4 (see SPECIAL WARNINGS AND PRECAUTIONS FOR USE AND INTERACTIONS)

Lumefantrine is N-debutylated, mainly by CYP3M in human liver 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 attherapeutic plasma concentrations (see SPECIAL WARNINGS AND 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 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 Tamether.

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 (unidentified) 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 gods, qualitative and quantitative recovery of metabolites in bile and faeces was relatively low, most of the dole being recovered as parent drug.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Povidone K30, Aspartame, Sucrose.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in a cool and dry place below 30℃

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

HDPE Bottles for Oral Liquid preparation with caps

Size of bottles: in mm

Total height: 110.0±3.0

Mouth OD: 27.0±0.3

Body diameter: 45.0±1.5

Size of caps: in mm

Total height: 17.0±0.3

Mouth ID: 28±0.2

Body diameter: 30.0±0.3

Measuring cups for Oral Liquid preparation

Size: in mm

Total height: 33.0±0.5

Mouth Diameter: 40.0±0.8

Bottom diameter: 35±0.3

Bottle is 60ml, 1 bottle per box.

6.6 Special precautions for disposal <and other handling>

No special requirements.

7. APPLICANT/MANUFACTURER

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