1. NAME OF THE MEDICINAL PRODUCT

RICNOS Artemether Lumefantrine Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated tablet contains:

Artemether 20mg

Lumefantrine 120mg

3. PHARMACEUTICAL FORM

Uncoated Tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Artemether plus Lumefantrine Tablet is indicated for the treatment of uncomplicated cases of malaria due to Plasmodium falciparum in adults, children and infants of 5 kg and above. The most recent official guidelines on the appropriate use of antimalarial agents and local information on the prevalence of resistance to antimalarial drugs must be taken into consideration for deciding on the appropriateness of therapy with Artemether plus Lumefantrine Tablet.

4.2 Posology and method of administration

Tablets for oral administration.

Number of Artemether plus Lumefantrine Tablet for treatment according to weight bands.

Weight range	**1st day of treatment**	**2nd day of treatment**	**3rd day of treatment**
≥ 5kg to < 15kg	1 tablet twice daily (2 x 20mg/120mg A/L)	1 tablet twice daily (2 x 20mg/120mg A/L)	1 tablet twice daily (2 x 20mg/120mg A/L)
15kg to <25kg	2 tablets twice daily (2 x 40mg/240mg A/L)	2 tablets twice daily (2 x 40mg/240mg A/L)	2 tablets twice daily (2 x 40mg/240mg A/L)
25kg to <35kg	3 tablets twice daily (2 x 60mg/360mg A/L)	3 tablets twice daily (2 x 60mg/360mg A/L)	3 tablets twice daily (2 x 60mg/360mg A/L))
≥ 35kg (or ≥ 12 years of age	4 tablets twice daily (2 x 80mg/480mg A/L)	4 tablets twice daily (2 x 80mg/480mg A/L)	4 tablets twice daily (2 x 80mg/480mg A/L)

Treatment should be administered at the time of initial diagnosis or at the onset of symptoms. It is preferable that the patient has a positive diagnostic test before administration. The first dose should be followed by a second dose after 8 hours. The following two days the doses of Artemether plus Lumefantrine Tablet should be given twice daily, morning and evening (i.e. 12 hours apart).

To increase absorption, Artemether plus Lumefantrine Tablet should be taken with food or a milky drink. If a patient is unable to tolerate food, Artemether plus Lumefantrine Tablet should still be administered, but the systemic exposure may be reduced. Patients who vomit within 1 hour of taking the medication should repeat the dose. The tablets can also be crushed and administered with food or a milky drink.

Renal or hepatic impairment No dose adjustments are necessary in patients with renal or hepatic impairment. However, caution is advised when administering Artemether plus Lumefantrine Tablet to patients with severe renal or hepatic problems.

Elderly No special precautions or dosage adjustments are necessary in such patients.

4.3 Contraindications

Artemether/Lumefantrine tablet is contraindicated in patients who are hypersensitive to the drug.

- Patients with severe malaria according to WHO definition.
- Patients who are taking any drug which is metabolised by the cytochrome enzyme CYP2D6 (e.g. flecainide, 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. 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.

- Patients with a history of symptomatic cardiac arythmias 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. hypokalemia or hypomagnesemia.

4.4 Special warnings and special precautions for use

1. Prolongation of the QT Interval

Some antimalarials (e.g., halofantrine, quinine, quinidine) including Artemether/Lumefantrine Tablets have been associated with prolongation of the QT interval on the electrocardiogram.

Artemether/Lumefantrine Tablets should be avoided in patients:

- With congenital prolongation of the QT interval (e.g., long QT syndrome) or any other clinical condition known to prolong the QTc interval such as patients with a history of symptomatic cardiac arrhythmias, with clinically relevant bradycardia or with severe cardiac disease.
- With a family history of congenital prolongation of the QT interval or sudden death.
- With known disturbances of electrolyte balance, e.g., hypokalemia or hypomagnesemia.
- receiving other medications that prolong the QT interval, such as class IA (quinidine, procainamide, disopyramide), or class III (amiodarone, sotalol) antiarrhythmic agents; antipsychotics (pimozide, ziprasidone); antidepressants; certain antibiotics (macrolide antibiotics, fluoroquinolone antibiotics, imidazole, and triazole antifungal agents); certain non-sedating antihistaminics (terfenadine, astemizole), or cisapride.
- Receiving medications that are metabolized by the cytochrome enzyme CYP2D6 which also have cardiac effects (e.g., flecainide, imipramine, amitriptyline, clomipramine).

2. Use of QT Prolonging Drugs and Other Antimalarials

Halofantrine and Artemether/Lumefantrine Tablets should not be administered within one month of each other due to the long elimination half-life of lumefantrine (3-6 days) and potential additive effects on the QT interval.

Antimalarials should not be given concomitantly with Artemether/Lumefantrine Tablets, unless there is no other treatment option, due to limited safety data.

Drugs that prolong the QT interval, including antimalarials such as quinine and quinidine, should be used cautiously following Artemether/Lumefantrine Tablets, due to the long elimination half-life of lumefantrine (3-6 days) and the potential for additive effects on the QT interval.

If mefloquine is administered immediately prior to Artemether/Lumefantrine Tablets there may be a decreased exposure to lumefantrine, possibly due to a mefloquine-induced decrease in bile production. Therefore, patients should be monitored for decreased efficacy and food consumption should be encouraged while taking Artemether/Lumefantrine Tablets.

3. Drug Interactions with CYP3A4

When Artemether/Lumefantrine Tablets are co-administered with substrates of CYP3A4 it may result in decreased concentrations of the substrate and potential loss of substrate efficacy. When Artemether/Lumefantrine Tablets are co-administered with an inhibitor of CYP3A4, including grapefruit juice it may result in increased concentrations of artemether and/or lumefantrine and potentiate QT prolongation. When Artemether/Lumefantrine Tablets are co-administered with inducers of CYP3A4 it may result in decreased concentrations of artemether and/or lumefantrine and loss of anti-malarial efficacy.

Drugs that have a mixed effect on CYP3A4, especially Anti-Retroviral drugs, and those that have an effect on the QT interval should be used with caution in patients taking Artemether/Lumefantrine Tablets.

Artemether/Lumefantrine Tablets 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.

4. Drug Interactions with CYP2D6

Administration of Artemether/Lumefantrine Tablets with drugs that are metabolized by CYP2D6 may significantly increase plasma concentrations of the co-administered drug and increase the risk of adverse effects. Many of the drugs metabolized by CYP2D6 can prolong the QT interval and should not be administered with Artemether/Lumefantrine Tablets due to the potential additive effect on the QT interval (e.g., fiecainide, imipramine, amitriptyline, clomipramine).

5. Recrudescence

Food enhances absorption of artemether and lumefantrine following administration of Artemether/Lumefantrine Tablets. Patients who remain averse to food during treatment should be closely monitored as the risk of recrudescence may be greater.

In the event of recrudescent *P. falciparum* infection after treatment with Artemether/Lumefantrine Tablets, patients should be treated with a different antimalarial drug.

6. Hepatic and Renal Impairment

Artemether/Lumefantrine Tablets have not been studied for efficacy and safety in patients with severe hepatic and/or renal impairment.

7. Plasmodium vivax Infection

Artemether/Lumefantrine Tablets have been shown in limited data (43 patients) to be effective in treating the erythrocytic stage of P. vivax infection. However, relapsing malaria caused by P. vivax requires additional treatment with other antimalarial agents to achieve radical cure i.e., eradicate any hypnozoites forms that may remain dormant in the liver.

8. Usage in Pregnancy — Pregnancy Category C

Safety data from an observational pregnancy study of approximately 500 pregnant women who were exposed to Artemether/Lumefantrine Tablets (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 Tablets in the treatment of acute, uncomplicated malaria in pregnant women has not been established.

Artemether/Lumefantrine Tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

9. Nursing Mothers

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 Tablets are 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.

10. Pediatric Use

The safety and effectiveness of Artemether/Lumefantrine Tablets have been established for the treatment of acute, uncomplicated malaria in studies involving pediatric patients weighing 5 kg or more. The safety and efficacy have not been established in pediatric patients who

weigh less than 5 kg. Children from non-endemic countries were not included in clinical trials.

11 .Geriatric Use

Clinical studies of Artemether/Lumefantrine Tablets did not include sufficient numbers of subjects aged 65 years and over to determine they respond differently from younger subjects. In general, the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in elderly patients should be considered when prescribing Artemether/Lumefantrine Tablets.

12. Hepatic and Renal Impairment

No specific pharmacokinetic studies have been performed in patients with either hepatic or renal impairment. Artemether/Lumefantrine Tablets have not been studied for efficacy and safety in patients with severe hepatic and/or renal impairment. No dosage adjustment is necessary in patients with mild to moderate hepatic and/or renal impairment.

4.5 Drug Interactions

Ketoconazole:

Concurrent oral administration of ketoconazole, a potent CYP3A4 inhibitor, with a single dose of Artemether/Lumefantrine Tablets resulted in a moderate increase in exposure to artemether, dihydroartemisinin (DHA, metabolite of artemether), and lumefantrine in a study of 15 healthy subjects. No dose adjustment of Artemether/Lumefantrine Tablets is necessary when administered with ketoconazole or other potent CYP3A4 inhibitors. However, due to the potential for increased concentrations of lumefantrine which could lead to QT prolongation, Artemether/Lumefantrine Tablets should be used cautiously with drugs that inhibit CYP3A4.

Prior Use of Mefloquine:

Administration of three doses of mefloquine followed 12 hours later by a 6-dose regimen of Artemether/Lumefantrine Tablets in 14 healthy volunteers demonstrated no effect of mefloquine on plasma concentrations of artemether or the artemether/DHA ratio. However, exposure to lumefantrine was reduced, possibly due to lower absorption secondary to a mefloquine-induced decrease in bile production. Patients should be monitored for decreased efficacy and food consumption should be encouraged with administration of Artemether/Lumefantrine Tablets.

CYP3A4 Metabolism: Hormonal Contraceptives and Anti-Retroviral Drugs:

Artemether induces CYP3A4 and both artemether and lumefantrine are metabolized primarily by CYP3A4.

Artemether/Lumefantrine Tablets 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.

Anti-Retroviral drugs (ARTs), such as protease inhibitors and non-nucleoside reverse transcriptase inhibitors, are known to have variable patterns of inhibition, induction or competition for CYP3A4. No formal drug-drug interaction studies between Artemether/Lumefantrine Tablets and ARTs have been performed. However, Artemether/Lumefantrine Tablets should be used cautiously in patients on ARTs as the result may be an increase in lumefantrine concentrations causing QT prolongation or a decrease in concentrations of the ART resulting in loss of efficacy, or a decrease in artemether and/or lumefantrine concentrations resulting in loss of antimalarial efficacy of Artemether/Lumefantrine Tablets.

CYP2D6 Substrates:

Lumefantrine inhibits CYP2D6 *in vitro*. Administration of Artemether/Lumefantrine Tablets with drugs that are metabolized by CYP2D6 may significantly increase plasma concentrations of the co-administered drug and increase the risk of adverse effects. Many of the drugs metabolized by CYP2D6 can prolong the QT interval and should not be administered with Artemether/Lumefantrine Tablets due to the potential additive effect on the QT interval (e.g., flecainide, imipramine, amitriptyline, clomipramine).

Sequential Use of Quinine:

A single dose of intravenous quinine (10 mg/kg bodyweight) concurrent with the final dose of a 6-dose regimen of Artemether/Lumefantrine Tablets demonstrated no effect of intravenous quinine on the systemic exposure of DHA or lumefantrine. Quinine exposure was also not altered. Exposure to artemether was decreased. This decrease in artemether exposure is not thought to be clinically significant. However, quinine and other drugs that prolong the QT interval should be used cautiously following treatment with Artemether/Lumefantrine Tablets due to the long elimination half life of lumefantrine and the potential for additive QT effects.

4.6 Pregnancy and Lactation

Pregnancy: Category C

Safety data from an observational pregnancy study of approximately 500 pregnant women who were exposed to Artemether/Lumefantrine Tablets (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 Tablets in the treatment of acute, uncomplicated malaria in pregnant women has not been established.

Artemether/Lumefantrine Tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation

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 Tablets are 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.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The safety of Artemether plus Lumefantrine Tablet has been evaluated in 20 clinical trials with more than 3500 patients. A total of 1810 adults and adolescents above 12 years of age as well as 1788 infants and children of 12 years of age and below have received Artemether plus Lumefantrine Tablet in clinical trials.

Adverse reactions reported from clinical studies and post-marketing experience are listed below according to system organ class.

Adverse reactions are ranked under headings of frequency using the frequency convention:

- Very common (≥1/10)
- Common (≥1/100 to <1/10)
- Uncommon (≥1/1,000 to <1/100)
- Rare (≥1/10,000 to <1/1,000)
- Very rare (<1/10,000)
- Not known (cannot be estimated from available data).

Table 1 Frequency of Undesirable effects

	Adults and adolescents above 12 years of age	**Infants and children of 12 years of age and below (incidence estimates*)**
Cardiac disorders		
Palpitations	Very common	Common
Electrocardiogram QT prolonged	Common	Common
Nervous system disorders		
Headache	Very common	Very common
Dizziness	Very common	Common
Paraesthesia	Common	--
Ataxia, hypoaesthesia	Uncommon	--
Clonus, somnolence	Uncommon	Uncommon
Respiratory, thoracic and mediastinal disorders		
Cough	Common	Very common
Gastrointestinal disorders		
Vomiting	Very common	Very common
Abdominal pain	Very common	Very common
Nausea	Very common	Common
Diarrhoea	Common	Common
Skin and subcutaneous tissue disorders		
Rash	Common	Common
Pruritus	Common	Uncommon
Urticaria, angioedema	Not known	Not known
Musculoskeletal and connective tissue disorders		

Arthralgia	Very common	Common
Myalgia	Very common	Common
Metabolism and nutrition disorders		
Anorexia	Very common	Very common
General disorders and administration site conditions		
Asthenia	Very common	Common
Fatigue	Very common	Common
Gait disturbance	Common	--
Immune system disorders		
Hypersensitivity	Not known	Rare
Hepatobiliary disorders		
Liver function tests increased	Uncommon	Common
Psychiatric disorders		
Sleep disorders	Very common	Common
Insomnia	Common	Uncommon

* These adverse reactions were reported during post-marketing experience. Because these spontaneously reported events are from a population of uncertain size, it is difficult to estimate their frequency.

4.9 Overdosage

There is no information on overdoses of Artemether/Lumefantrine Tablets higher than the doses recommended for treatment.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics Properties

Pharmacological Classification : 7.5 Antimalarials

ATC Code : P01BF01

Artemether plus Lumefantrine Tablet 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 nontoxic haemozoin, malaria pigment. Lumefantrine is thought to interfere with the polymerisation

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.

The antimalarial activity of the combination of lumefantrine and artemether in Artemether plus Lumefantrine Tablet is greater than that of either substance alone. In a double-blind comparative study in adults in China (n=157), the 28-day cure rate of Artemether plus Lumefantrine Tablet when given at 4 doses was 94% compared with 90% for lumefantrine and 46% for artemether based on intent-to-treat (ITT) population, when given as monotherapy. For the evaluable population, 28-day cure rates were 100% for Artemether plus Lumefantrine Tablet, compared with 92% for lumefantrine and 55% for artemether when given as monotherapy.

In areas where multi-drug-resistant strains of *P. falciparum* malaria are common and in the resident population, 28-day cure rates with the 6-dose regimen (given over 60-96 h) were 81% and 90% for Artemether plus Lumefantrine Tablet versus 94% and 96% for mefloquine/artesunate, based on the ITT population. For the evaluable population, 28--day cure rates were 97% and 95% for Artemether plus Lumefantrine Tablet and 100% for mefloquine/artesunate.

In an open, multicenter clinical study conducted in Africa in 310 children weighing 5 kg to less than 25 kg and receiving a 6-dose Artemether plus Lumefantrine Tablet according to their body weight range, the mean 28-day parasitological cure rate (PCR-corrected) was 93.9% for the ITT population and 96.7% for the evaluable population.

In non-immune patients living in regions free of malaria but with malaria acquired when travelling in endemic regions, a similar efficacy and safety profile was shown. In an open study (n=165) in adults the 28-day cure rate for Artemether plus Lumefantrine Tablet given as the 6-dose regimen was 96% (119/124) for the evaluable and 74.1% (120/162) for the ITT population. The main difference between the evaluable and ITT cure rates was owing to 38 patients who were excluded from the evaluable population for the following reasons: 33 patients were lost to follow up (19 of whom were not evaluated at day 7 and 14 of whom had had parasitic clearance at day 7 but their efficacy status at day 28 was unknown) and 5 patients took concomitant medications that were not permitted by the protocol. All these patients were considered as treatment failures in the ITT analysis.

Children of European origin were not included in clinical trials.

In comparative clinical trials Artemether plus Lumefantrine Tablet cleared gametocytes in less than one week and more rapidly than non-artemisinin antimalarials.

Artemether plus Lumefantrine Tablet is active against blood stages of *Plasmodium vivax*, but is not active against hypnozoites.

QT/QTc Prolongation:

Adults and children with malaria

Healthy adults

In a healthy adult volunteer parallel group study including a placebo and moxifloxacin control group (n=42 per group), the administration of the six dose regimen of Artemether plus Lumefantrine Tablet was associated with prolongation of QTcF. The mean changes from baseline at 68, 72, 96, and 108 hours post first dose were 7.45, 7.29, 6.12 and 6.84 msec, respectively. At 156 and 168 hours after first dose, the changes from baseline for QTcF had no difference from zero. No subject had a >30 msec increase from baseline nor an absolute increase to >500 msec. Moxifloxacin control was associated with a QTcF increase as compared to placebo for 12 hours after the single dose with a maximal change at 1 hour after dose of 14.1 msec.

5.2 Pharmacokinetic properties

Pharmacokinetic characterisation of Artemether plus Lumefantrine Tablet 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 and dihydroartemisinin, the active metabolite of artemether, appears rapidly in the systemic circulation with peak plasma concentrations of both compounds reached about 2 hours after dosing. Mean Cmax and AUC values of artemether ranged between 60.0-104 ng/mL and 146-338 ng·h/mL, respectively, in fed healthy adults after a single dose of Artemether plus Lumefantrine Tablet, 80 mg artemether/480 mg lumefantrine. Mean Cmax and AUC values of dihydroartemisinin ranged between 49.7-104 ng/mL and 169-308 ng·h/mL, respectively. Absorption of lumefantrine, a highly lipophilic compound, starts after a lag-time of up to 2 hours, with peak plasma

concentration (mean between 5.10-9.80 µg/mL) about 6-8 hours after dosing. Mean AUC values of lumefantrine ranged between 108 and 243 µg·h/mL. 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 Artemether plus Lumefantrine Tablet 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). Dihydroartemisinin 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 dihydroartemisinin (demethylation), predominantly through the isoenzyme CYP3A4/5. This metabolite has also been detected in humans *in vivo*. .

Dihydroartemisinin is further converted to inactive metabolites.

The pharmacokinetics of artemether in adults is time-dependent. During repeated administration of Artemether plus Lumefantrine Tablet, plasma artemether levels decreased significantly, while levels of the active metabolite (dihydroartemisinin) increased, although not to a statistically significant degree. The ratio of day 3/day 1 AUC for artemether was between 0.19 and 0.44, and was between 1.06 and 2.50 for dihydroartemisinin. This suggests that there was induction of the enzyme responsible for the metabolism of artemether. Artemether and dihydroartemisinin were reported to have a mild inducing effect on CYP3A4 activity.

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 exposure to lumefantrine increases with repeated administration of Artemether plus Lumefantrine Tablet over the 3-day treatment period, consistent with the slow elimination of the compound. Systemic exposure to the metabolite desbutyl-lumefantrine, for which the *in vitro* antiparasitic effect is 5 to 8 fold higher than that for 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 dihydroartemisinin are rapidly cleared from plasma with a terminal 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 plus Lumefantrine Tablet.

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 numerous metabolites (partly identified) have been detected in faeces, bile and urine. Lumefantrine is eliminated via the bile in rats and dogs, with excretion primarily in the faeces. After oral dosing to rats and dogs, metabolites (glucuronides of lumefantrine and of the desbutyl metabolite) were excreted with bile. Most of the dose was recovered in the form of the parent drug in faeces (including unabsorbed drug and drug released from glucuronide).

Pharmacokinetics in special patient populations

In paediatric malaria patients, mean Cmax (CV %) of artemether (observed after first dose of Artemether plus Lumefantrine Tablet) were 223 (139%), 198 (90%) and 174 ng/mL (83%) for body weight groups 5-<15, 15-<25 and 25-<35 kg, respectively, compared to 186 ng/mL (67%) in adult malaria patients. The associated mean Cmax of DHA were 54.7 (108%), 79.8 (101%) and 65.3 ng/mL (36%), respectively compared to 101 ng/mL (57%) in adult malaria patients. AUC of lumefantrine (population mean, covering the six doses of Artemether plus Lumefantrine Tablet) were 577, 699 and 1150 µg•h/mL for paediatric malaria patients in body weight groups 5-<15, 15-<25 and 25-<35 kg, respectively, compared to a mean AUC of 758 µg•h/mL (87%) in adult malaria patients. The elimination half-lives of artemether and lumefantrine in children are unknown.

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

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.

Carcinogenesis

Carcinogenicity studies were not conducted.

Mutagenesis

No evidence of mutagenicity was detected. The artemether: lumefantrine combination was evaluated using the Salmonella and iisc/zen'cAza/mammalian-microsome mutagenicity test, the gene mutation test with Chinese hamster cells V79, the cytogenetic test on Chinese hamster cells *in vitro*, and the rat micronucleus test, *in vivo*.

Reproductive Studies/ Impairment of Fertility

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.

Reproductive toxicity studies performed with the artemether:lumefantrine combination caused maternal toxicity and increased post-implantation loss in rats and rabbits at doses ≥ 50 mg/kg/day (corresponding to approximately 7 mg/kg/day artemether) and 175 mg/kg/day (corresponding to 25 mg/kg/day artemether) respectively. These effects were not observed at lower doses.

Lumefantrine alone caused no sign of reproductive or development toxicity at doses up to 1,000 mg/kg/day in rats and rabbits.

Embryotoxicity has been observed in rat and rabbit reproductive toxicity studies conducted with artemether, a derivative of artemisinin. Artemisinins (e.g. artesunate) are known to be embryotoxic.

Artemether caused increases in post-implantation loss and teratogenicity (characterised as a low incidence of cardiovascular and skeletal malformations) in rats at 19.4 mg/kg, and in rabbits at 30 mg/kg. Maternal toxicity was also observed in rabbits at 30 mg/kg/day. No other adverse effects were observed at lower doses in rabbits. The no observed effect dose was 3 mg/kg/day in rats and 25 mg/kg/day in rabbits.

The embryotoxic artemether dose, 20 mg/kg/day in the rat, yields artemether and dihydroartemisinin exposures similar to those achieved in humans.

Artesunate, a structurally related compound, also caused increases in post-implantation loss and teratogenicity (low incidence of cardiovascular and skeletal malformations) in rats at 6 mg/kg and in the lowest dose tested in the rabbits, 5 mg/kg/day.

Cardiovascular Pharmacology

In toxicity studies in dogs at doses $\geq$600 mg/kg/day only, there was some evidence of prolongation of the QTc interval, at higher doses than intended for use in man. In an *in vitro* assay of HERG channels stably expressed in HEK293 cells, lumefrantrine and the main metabolite desbutyl-lumefantrine showed some inhibitory potential in one of the currents responsible for cardiac repolarization. The potency was lower than the other antimalarial drugs tested. From the estimated IC_{50} values, the order of potency of HERG current block was halofantrine (IC_{50} = 0.04 μM)>chloroquine (2.5 μM)>mefloquine 2.6 μM)>desbutyl-lumefantrine (5.5 μM)>lumefantrine (8.1 μM). Clinical studies show, that prolongation of QTcF can occur with standard dosing of artemether:lumefantrine

6.0 PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Corn Starch, Colloidal silicon dioxide, Hypromellose, Methylene Chloride, Isopropyl Alcohol, Microcrystalline cellulose RQ 102, Low substituted Hydroxy propyl cellulose, Sodium Starch Glycolate, Magnesium Stearate.

6.2 Incompatibilities

None Known

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

6 Tablets are packed in a blister pack made up of Alu. Foil and clear PVC/Aclar film, such 1/2/3/4 blisters in a carton.

8 Tablets are packed in a blister pack made up of Alu. Foil and clear PVC/PE/PVdC film, such 3 blisters in a carton.

Following minimum batch details is coded on packing material

Batch No., Mfg. Date and Exp. Date.

7.1 MANUFACTURED BY:

SHANXI ZHONGBAO SHUGUANG PHARMACEUTICAL

No.1 Kangle Street, Qi County, Jinzhong, Shanxi, P.R. China.

MARKETED BY:

RICNOS PHARMACEUTICALS LIMITED

6, Lasisi Akinwale Street, Coker Orile-Iganmu, Lagos, Nigeria.