1 NAME OF THE MEDICINAL PRODUCT

MALQUIT 20/120 (Artemether and Lumefantrine Tablets), 20/120 mg per Tablets, uncoatedTablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated tablet containsArtemether 20 mg
Lumefantrine 120 mg
Excipients Q.S.

Kindly refer section 6.1 for full list of Excipients.

3 PHARMACEUTICAL FORM

Uncoated tablet

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

MALQUIT is indicated for the treatment of acute uncomplicated Plasmodium falciparum malaria in adult, children and infants of 5 kg and above. Consideration should be given to official guidance regarding the appropriate use of antimalarial agents.

4.2 Posology and method of administration

Body Weight (Kg)	Age (Yrs)	Total Tablets	DOSAGE REGIMEN					
			Day 1		Day 2		Day 3	
			0hrs	8hrs	24hrs	36hrs	48hrs	60hrs
5-14	<3	6	1	1	1	1	1	1
15-24	>3- 9	12	2	2	2	2	2	2
25-34	>9-14	18	3	3	3	3	3	3
>35	>14	24	4	4	4	4	4	4

Method of administration

Route of administration is oral

4.3 Contraindications

MALQUIT is contraindicated in:

- Patients with known hypersensitivity to the active substances or to any of the excipients.
- 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 precautions for use

MALQUIT must not be used in the first trimester of pregnancy in situations where other suitable and effective antimalarials are available. MALQUIT 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, MALQUIT should not be given concurrently with any other antimalarial agent unless there is no other treatment option. If a patient deteriorates whilst taking MALQUIT, 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 MALQUIT.

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

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

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

MALQUIT 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. MALQUIT is active against blood stages of Plasmodium vivax, but is not active against hypnozoites.

MALQUIT is not indicated and has not been evaluated for prophylaxis.

Like other antimalarials (e.g. halofantrine, quinine and quinidine) MALQUIT has the potential to cause QT prolongation. In the adult/adolescent population included in clinical trials, 8 patients (0.8%) receiving MALQUIT experienced a QTcB >500 msec and 3 patients (0.4%) a QTcF >500 msec. Prolongation of QTcF interval >30 msec was observed in 36% of patients.
In the infant/children population included in clinical trials, 3 patients (0.2%) experienced a QTcB >500 msec. No patient had QTcF >500 msec. Prolongation of QTcF intervals >30 msec was observed in 34% of children weighing 5-10 kg, 31% of children weighing 10-15 kg and 24% of children weighing 15-25 kg, and 32% of children weighing 25-35 kg.
Caution is recommended when combining MALQUIT with drugs exhibiting variable patterns of inhibition, induction or competition for CYP3A4 as the therapeutic effects of some drugs could be altered. 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 MALQUIT to patients with severe renal, hepatic or cardiac problems.

4.5 Interaction with other medicinal products and other forms of interaction Contraindications of concomitant use

Interaction with drugs that are known to prolong the QTc interval

Riamet 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 Riamet 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 Riamet 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 Riamet alone. Concomitant use of strong inducers of CYP3A4 such as rifampin, carbamazepine, phenytoin, St. John's Wort is contraindicated with Riamet .
Inducers should not be administered at least one month after Riamet 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 Riamet should therefore not be given concurrently with other antimalarials unless there is no other treatment option .
If Riamet 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 Riamet. In patients previously treated with halofantrine, Riamet should not be administered earlier than one month after the last halofantrine dose.

Mefloquine

A drug interaction study with Riamet in man involved administration of a 6-dose regimen over 60 hours in healthy volunteers which was commenced at 12 hours after completion ofa 3-dose regimen of mefloquine or placebo. Plasma mefloquine concentrations from the time of addition of Riamet 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 tocompensate 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 Riamet (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 Riamet 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 Riamet 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 Riamet.

Concomitant use requiring caution Interactions affecting the use of Riamet

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 Riamet 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 Riamet is considered unnecessary in falciparum malaria patients when administered in association with ketoconazole or other potent CYP3A4 inhibitors.

Riamet 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 Riamet 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. Riamet should be usedcautiously in patients on ARTs since decreased artemether, DHA, and/or lumefantrine concentrations may result in a decrease of antimalarial efficacy of Riamet, 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 Riamet.

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 Riamet.

Interactions resulting in effects of Riamet on other drugs

Interaction with drugs metabolized by CYP450 enzymes

When Riamet 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 (see sections 4.4 and 5.2).

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 weaklyinduce, in humans, the activity of CYP2C19, CYP2B6, and CYP3A. Therefore, Riamet 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

Riamet should be taken with food or drinks rich in fat such as milk as the absorption of both artemether and lumefantrine is increased (see Section 4.2).

Grapefruit juice should be used cautiously during Riamet 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

Pregnancy Category

Safety data from an observational pregnancy study of approximately 500 pregnant women who were exposed to MALQUIT Tablets (including a third of patients who were exposed in the firrst 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 MALQUIT Tablets in the treatment of acute, uncomplicated malaria in pregnant women has not been established. MALQUIT Tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Pregnant rats dosed during the period of organogenesis at or higher than a dose of about half the highest clinical dose of 1120 mg artemether-lumefantrine per day (based on body surface area comparisons), showed increases in fetal loss, early resorptions and post implantation loss. No adverse effectswere observed in animals dosed at about one-third the highest clinical dose. Similarly, dosing in pregnant rabbits at about three times the clinical dose (based on body surface area 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 two times the clinical dose. Embryo-fetal loss is a significant reproductivetoxicity. Other artemisinins are known to be embryotoxic in animals. However, because metabolic problem in animals and humans are dissimilar, artemether exposures in animals may not be predictive of human exposures These data cannot rule out an increased risk for early pregnancy loss or foetal defects in humans.

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 MALQUIT 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.

Effects on ability to drive and use machines

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

Undesirable effects

The safety of Artemether and Lumefnatrine tablet has been evaluated in 20 clinical trials with more than 3500 patients. A total of 1810 adults and adolescents above 12 years of ageas well as 1788 infants and children of 12 years of age and below have received Riamet 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 MedDRA 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)**
Blood and lymphatic system disorders		
Delayed haemolytic anaemia[#]	Not known	Not known
Immune system disorders		
Hypersensitivity	Not known	Rare
Metabolism and nutrition disorders		
Decreased appetite	Very common	Very common (16.8 %)
Psychiatric disorders		
Sleep disorders	Very common	Common (6.4 %)
Insomnia	Common	Uncommon
Nervous system disorders		
Headache	Very common	Very common (17.1 %)
Dizziness	Very common	Common (5.5 %)
Paraesthesia	Common	--
Ataxia, hypoaesthesia	Uncommon	--
Somnolence	Uncommon	Uncommon
Clonus	Common	Uncommon
Cardiac disorders		
Palpitations	Very common	Common (1.8 %)
Electrocardiogram QT prolonged	Common	Common (5.3 %)
Respiratory, thoracic and mediastinal disorders		
Cough	Common	Very common (22.7 %)
Gastrointestinal disorders		
Vomiting	Very common	Very common (20.2 %)
Abdominal pain	Very common	Very common (12.1 %)
Nausea	Very common	Common (6.5 %)
Diarrhoea	Common	Common (8.4 %)
Hepatobiliary disorders		
Liver function tests increased	Uncommon	Common (4.1 %)
Skin and subcutaneous tissue disorders		

Rash	Common	Common (2.7 %)
Pruritus	Common	Uncommon
Urticaria	Uncommon	Uncommon
Angioedema*	Not known	Not known
Musculoskeletal and connective tissue disorders		
Arthralgia	Very common	Common (2.1 %)
Myalgia	Very common	Common (2.2 %)
General disorders and administration site conditions		
Asthenia	Very common	Common (5.2 %)
Fatigue	Very common	Common (9.2 %)
Gait disturbance	Common	--

Overdose

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

5. PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Antimalarials, blood schizonticides, ATC code: P01 BE52
Pharmacodynamic effects: MALQUIT 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 MALQUIT 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 MALQUIT 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 MALQUIT, 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 MALQUIT 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 MALQUIT and 100% for mefloquine/artesunate. In an open, multicentre clinical study conducted in Africa in 310 children weighing 5 kg to less than 25 kg and receiving a 6 dose MALQUIT according to their body weight range, the mean 28 da 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 problem was shown. In an open study (n=165) in adults the 28 day cure rate for MALQUIT 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 wer considered as treatment failures in the ITT analysis. Children of European origin were not included in clinical trials. In comparative clinical trials MALQUIT cleared gametocytes I less than one week and more rapidly than non-artemisinin antimalarials. MALQUIT is active against blood stages of Plasmodium vivax, but is not active against hypnozoites.

Pharmacokinetic properties

Pharmacokinetic characterisation of MALQUIT is limited by the lack of an intravenous formulation, and the very high inter-and intra-subject variability of artemether an 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 plasm 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 MALQUIT, 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 highl 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 MALQUIT 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 detectedin humans in vivo. Dihydroartemisinin is further converted to inactive metabolites. The pharmacokinetics of artemether in adults is time-dependent. During repeated administration of MALQUIT, 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. The clinical evidence of induction is consistent with the in vitro data described. Lumefantrine is N-debutylated, mainly by CYP3A4, in human liver microsomes. In vivo I animals (dogs and rats), glucuronidation of lumefantrine takes place directly and after oxidative biotransformation. In humans, the exposure to lumefantrine increases with repeated administration ofMALQUIT 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 fo 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 MALQUIT. 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) wereexcreted 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).

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 wereobserved 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) basedon 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 ≥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. For effects in the human.

6 PHARMACEUTICAL PARTICULARS

List of excipients

Microcrystalline cellulose phosphate, Lactose
Starch, Bronopol
Polyvinyl pyrrolidone, Magnesium stearate,
Croscarmellose sodium, Purified talc
Colloidal anhydrous silica

Incompatibilities

Not applicable

Shelf life

36 Months

Special precautions for storage

Store In cool & dry place, away from sunlight. Keep out of medicines out of reach of children.

Nature and contents of container

4 x 6 , 1 x 24 Blister pack

Special precautions for disposal and other handling

For the treatment of children and infants, the 24-tablets pack should be prescribed. The prescriber and pharmacist should instruct the parent or care giver on the posology for their child and that a variable number of tablets (depending on the child's body weight) will be requested for the full treatment. Therefore, the whole pack may not be used. After successful treatment the remaining tablets should be discarded or returned to the pharmacist.

7. APPLICANT/ MANUFACTURER

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