UNICURE PHARMACEUTICAL LTD.

SUMMARY OF PRODUCT CHARACTERISTICS

FOR

PLUMAL TABLETS

ARTEMETHER 80mg

LUMEFANTRINE 480mg

TABLE OF CONTENT

1. Name of the medicinal product

PLUMAL DS 80 mg/480 mg tablets

2. Qualitative and quantitative composition

One tablet contains 80 mg Artemether and 480 mg Lumefantrine.

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Tablet.

Light yellow, round tablet with inscription " " on one side and " " on the other.

4. Clinical particulars

4.1 Therapeutic indications

PLUMAL DS 80/480 is indicated for the treatment of uncomplicated cases of malaria due to Plasmodium falciparum in adults and children of 35 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 PLUMAL DS 80/480.

Consideration should be given to official guidance regarding the appropriate use of antimalarial agents.

4.2 Posology and method of administration

Posology

Oral use
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.
One tablet should be taken twice a day for three days (total six doses).The first dose should be followed by a second dose after 8 hours. The following two days the doses of PLUMAL DS 80/480 should be given twice daily, morning and evening (i.e. 12 hours apart).

To increase absorption, PLUMAL DS 80/480 should be taken with food or a milky drink (see section 5.2). If a patient is unable to tolerate food, PLUMAL DS 80/480 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.
If a dose is missed, it should be taken as soon as realized and then the recommended regimen continued until the full course of treatment has been completed.
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Renal or hepatic impairment
No dose adjustments are necessary in patients with renal or hepatic impairment. However, caution is advised when administering PLUMAL DS 80/480 to patients with severe renal or hepatic problems (see section 4.4).
Paediatric patients weighing less than 35 kg:

Appropriate dose adjustments cannot be achieved with this product. Other formulations containing lower amounts of Artemether/ Lumefantrine are available for these patients.

Elderly

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

Weight in kg	Total Tablets	Dosage Regimen					
		Day-1		Day-2		Day-3	
35 kg and above		0 hour	8 hours	24 hours	36 hours	48 hours	60hours
	6	1	1	1	1	1	1

SIDE EFFECTS: Artemether Lumefantrine is well tolerated and there is no drug induced serious unwanted side effects The most common adverse experiences (>1%) in patients treated with Artemether/Lumefantrine combination are headache, dizziness, arthralgia, cough, Muglia, pruritus, rash, asthenia and fatigue. The preclinical investigations and the clinical trial programs revealed no cardiotoxicity with Artemether/Lumefantrine combination and to date there have been no reports of adverse clinical cardiac events, Recent studies comparing Artemether/Lumefantrine with halofantrine in human showed a clear distinction between the two substances and confirmed no sign of cardiotoxicity with: Artemether/Lumefantrine combination

Method of administration

Tablets for oral administration.

Patient with acute malaria is frequently averse to blood. The dose may be encouraged to resume normal eating as food can be tolerated since this improves absorption to Artemether and Lumefantrine in the event vomiting within 1 hour of administration, a repeat dose should be taken 6-dose regimen should be given over 3 days. First dose in initial diagnosis and at the 8,36,48 & 60hrs

For administration to small children and infants, the tablet/s may be crushed.

4.3 Contraindications

PLUMAL DS is contraindicated in:

• patients with known hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

• patients with severe malaria according to WHO definition*.

• 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. hypokalemia or hypomagnesemia.

• patients taking drugs that are strong inducers of CYP3A4 such as rifampin, carbamazepine, phenytoin, St. John's wort (*Hypericum perforatum*).

(*Presence of one or more of the following clinical or laboratory features:

Clinical manifestation: Prostration; impaired consciousness or unarousable coma; failure to feed; deep breathing, respiratory distress (acidotic breathing); multiple convulsions; circulatory collapse or shock; pulmonary edema (radiological); abnormal bleeding; clinical jaundice; hemoglobinuria

Laboratory test: Severe normocytic anemia; hemoglobuniuria; hypoglycemia; metabolic acidosis; renal impairment; hyperlactatemia; hyperparasitemia)

4.4 Special warnings and precautions for use

PLUMAL DS80/480 is contraindicated in:
- ✓ patients with known hypersensitivity to artemether, lumefantrine or to any of the excipients.
- ✓ patients with severe malaria according to WHO definition.
- ✓ patients with a personal or family history of congenital prolongation of the QTc interval or sudden death, or with any other clinical condition known to prolong the QTc interval, such as patients with a history of

symptomatic cardiac arrhythmias, clinically relevant bradycardia or severe cardiac diseases.
- ✓ patients taking drugs that are known to prolong QTc interval 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
- ✓ patients with known disturbances of electrolyte balance e.g. hypokalaemia or hypomagnesaemia
- ✓ patients taking any drug which is metabolized by the cytochrome enzyme CYP2D6 (e.g. lecainide, metoprolol, imipramine, amitriptyline, clomipramine
- ✓ patients taking drugs that are strong inducers of CYP3A4 such as rifampicin, carbamazepine, phenytoin, St John’s wort

PLUMAL DS is not recommended during the first trimester of pregnancy in situations where other suitable and effective antimalarials are available (see section 4.6).

PLUMAL DS 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, PLUMAL DS should not be given concurrently with any other antimalarial agent (see section 4.5) unless there is no other treatment option.

If a patient deteriorates whilst taking PLUMAL DS, 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 PLUMAL DS.

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 PLUMAL DS in patients with renal impairment is recommended. Caution is advised when administering PLUMAL DS 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 (see section 5.2). 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 PLUMAL DS. In the absence of carcinogenicity study data, and due to lack of clinical experience, more than two courses of PLUMAL DS cannot be recommended.

Excipient with known effect:

This medicine contains less than 1 mmol sodium (23 mg) per tablet, i.e. is essentially “sodium-free.”

4.5 Interaction with other medicinal products and other forms of interaction

PLUMAL DS 80/480 should not be used in patients taking drugs that are known to prolong the QTc interval , as effects may be additive and increase the risk of cardiac arrhythmia.

Interaction with other antimalarials
PLUMAL DS 80/480 should not be given concurrently with any other antimalarial agent. In addition, due to the propensity of some antimalarial agents to prolong the QTc interval, caution is advised when administering PLUMAL DS 80/480 to patients in whom there may still be detectable concentrations of these drugs in the plasma following prior treatments.
Administration of a six-dose regimen of artemether/lumefantrine (over 60 hours) starting 12 hours after completion of a three-dose regimen of mefloquine or placebo in healthy volunteers showed no effect of mefloquine on plasma concentrations of artemether or the artemether/dihydroartemisinin ratio, but a 30-40% reduction in plasma levels of lumefantrine. These are possibly due to lower absorption secondary to a mefloquine-induced decrease in bile production. Patients that have been pretreated with mefloquine should be encouraged to eat at dosing times to compensate for the decrease in bioavailability. Plasma mefloquine concentrations from the time of addition of artemether/lumefantrine were not affected compared with a group that received mefloquine followed by placebo.
In patients previously treated with halofantrine, PLUMAL DS 80/480 should be dosed at least one month after the last halofantrine dose due to the long elimination half-life of halofantrine and the potential additive/synergistic effects on the QT-interval.

Interaction with CYP450 enzymes

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 or safety profile of drugs that are predominantly metabolised 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

Interaction with CYP450 3A4 inhibitors

Ketoconazole: both artemether and lumefantrine are metabolised predominantly by the cytochrome enzyme CYP3A4, and do not inhibit this enzyme at therapeutic concentrations. The concurrent oral administration of ketoconazole with artemether/lumefantrine 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. Dose adjustment of PLUMAL DS 80/480 is not considered necessary when administered concomitantly with ketoconazole or other azole antifungals, but such combinations should be used with caution.

HIV Treatment Medications

HIV nucleoside and nucleotide reverse transcriptase inhibitors (NTRIs, e.g. abacavir, emtricitabine, lamivudine, tenofovir [TDF or TAF], zidovudine.)

Co-administration has not been studied but based on metabolism and clearance a clinically significant interaction is unlikely.

HIV non-nucleoside reverse transcriptase inhibitors (NNRTIs):

Efavirenz :Co-administration of efavirenz and artemether/lumefantrine lead to decreases in artemether exposure (51% and 79%), dihydroartemisinin exposure (46% and 75%) and lumefantrine exposure by (21% and 56%). Lumefantrine had no significant effect on efavirenz exposure in either study. Use with caution as decreased concentrations of artemether, dihydroartemisinin, or lumefantrine may result in a decrease of antimalarial efficacy.

***Nevirapine*:** Lumefantrine is metabolised predominantly by CYP3A4. Upon co-administration with artemether/lumefantrine with nevirapine decreased the AUCs of artemether and dihydroartemisinin. In a crossover study lumefantrine exposure was decreased by 20% and lumefantrine reduced nevirapine exposure by 46%. Use with caution.

***Rilpivirine*:** Co-administration has not been studied but based on metabolism and clearance a pharmacokinetic interaction is unlikely. Rilpivirine should be used with caution when co-administered with a drug that has a potential risk to prolong the QT interval.

HIV Protease Inhibitors (PIs)

***Atazanavir*:** Co-administration may increase plasma levels of artemisinins and lumefantrine. Both lumefantrine and atazanavir have been shown to prolong the QT interval.

***Darunavir*:** Co-administration may increase plasma levels of artemisinins and lumefantrine.

***Lopinavir/ritonavir*:** Data from clinical studies and population modelling suggest that co-administration of lopinavir/ritonavir and artemether decreases exposure of dihydroartemisinin (the biologically active metabolite) by ~40-60%. Lumefantrine AUC was significantly increased by 2.3-fold and there was trend towards increased Cmax (1.4-fold). The clinical meaning of these opposite effects on artemether and lumefantrine is not clear. Both lumefantrine and lopinavir have been shown to prolong the QT interval.

***Ritonavir*:** Co-administration may increase plasma levels of artemisinins and lumefantrine, as both are metabolised by CYP3A4. Caution is recommended.

HIV Integrase Strand-Transfer Inhibitors (INSTIs)

Dolutegravir, Raltegravir: Co-administration has not been studied but based on metabolism/elimination and toxicity profiles there is little potential for interaction.

Elvitegravir/cobicistat: Co-administration has not been studied. Artemether and lumefantrine are metabolized by CYP3A4. Elvitegravir/cobicistat may increase concentrations of artemisinins and lumefantrine.

Pharmacokinetic Enhancer

Cobicistat: Co-administration has not been studied. Cobicistat may increase concentrations of artemisinins and lumefantrine by inhibition of CYP3A4.

Antivirals against Hepatitis B or C Co-administration has not been studied. In many instances a clinically significant interaction appears unlikely. However, consult the summary of product characteristics of the desired medication.

Drug-food/drink interactions

PLUMAL DS 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 PLUMAL treatment. Administration of PLUMAL DS 80/480 with grapefruit juice in healthy adult subjects resulted in an approximately two fold increase in systemic exposure to the parent drug.

4.6 Fertility, 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 (see section 4.4).

Pregnancy

A moderate amount of data on pregnant women in their first trimester (more than 500 pregnancy outcomes) is available for artemether/lumefantrine. Data from a recent meta-analysis have shown that compared to quinine, artemether/lumefantrine treatment in the first trimester was not associated with an increased risk of miscarriage or stillbirth. While the data are limited, they indicate no difference in the prevalence of major congenital anomalies between treatment groups (for animal data see section 5.3). A large amount of data on pregnant women in their second and third trimester (more than 4000 documented pregnancy outcomes) is available for artemisinin derivatives including PLUMAL DS 80/480. They indicate no fetal or neonatal toxicity. PLUMAL DS 80/480 can be used during pregnancy.

PLUMAL DS treatment is not recommended during the first trimester of pregnancy in situations where other suitable and effective antimalarials are available (see section 4.4). However, it should not be withheld in life-threatening situations, where no other effective antimalarials are available. During the second and third trimester, PLUMAL DS 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 PLUMAL DS 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 PLUMAL DS unless potential benefits to the mother and child outweigh the risks of PLUMAL DS treatment.

Fertility

There is no information on the effects of PLUMAL DS on human fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Patients receiving PLUMAL DS 80/480 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 PLUMAL DS 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 PLUMAL DS 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*)**
Cardiac disorders		
Palpitations	Very common	Uncommon
Electrocardiogram QT prolonged		
Nervous system disorders		
Headache	Very common	Common
Dizziness	Very common	Common
Gait disturbance	uncommon	--
Ataxia, hypoaesthesia	uncommon	--
Clonic movements	Common	Uncommon

Somnolence	Uncommon	Uncommon
Respiratory, thoracic and mediastinal disorders		
Cough	Common	Very Common
Gastrointestinal disorders		
Vomiting	Very Common	Very Common
Abdominal pain	Very Common	Common
Nausea	Very Common	Common
Decreased appetite	Very Common	Very Common
Diarrhoea	Common	Common
Skin and subcutaneous tissue disorders		
Rash	Common	Common
Pruritus	Common	Uncommon
Urticaria	Uncommon	Uncommon
Arthralgia	Very Common	Common
Myalgia	Very Common	Common
General disorders and administration site conditions		
Asthenia	Very Common	Common
Fatigue	Very Common	Common
Immune system disorders		
Hypersensitivity	Not known	Rare
Blood and lymphatic system disorders		
Delayed haemolytic anaemia*	Not known	Not known
Hepatobiliary disorders		
Liver function tests abnormal	Uncommon	Common
Psychiatric disorders		
Sleep disorders	Very 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.

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to the marketing authorisation holder, or, if available, via the national reporting system.

4.9 Overdose

Experience of overdosage with artemether and lumefantrine is limited. In cases of suspected overdosage symptomatic and supportive therapy should be given as appropriate, which should include monitoring of ECG
and serum electrolytes.

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5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antimalarials, blood schizontocide, ATC code: P01 BF01.

Pharmacodynamic effects

PLUMAL DS comprises a fixed ratio of 1:6 parts of PLUMAL DS, 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. PLUMAL DS have a secondary action involving inhibition of nucleic acid- and protein synthesis within the malarial parasite.

Clinical efficacy

The efficacy of PLUMAL DS was evaluated for the treatment of acute, uncomplicated malaria

(defined as symptomatic P. falciparum malaria without signs and symptoms of severe malaria or evidence of vital organ dysfunction) in five 6-dose regimen studies and one study comparing the 6-dose regimen with the 4-dose regimen. Baseline parasite density ranged from 500/µL - 200,000/µL (0.01% to 4% parasitaemia) in the majority of patients.
Studies were conducted in otherwise healthy, partially immune or non-immune adults and children (≥5kg body weight) with uncomplicated malaria in Thailand, sub-Saharan Africa, Europe, and South America.

Efficacy endpoints consisted of:
• 28-day cure rate, proportion of patients with clearance of asexual parasites within 7 days without recrudescence by day 28
• parasite clearance time (PCT), defined as time from first dose until first total and continued disappearance of asexual parasite which continues for a further 48 hours
• fever clearance time (FCT), defined as time from first dose until the first time body temperature fell below 37.5°C and remained below 37.5°C for at least a further 48 hours (only for patients with temperature >37.5°C at baseline)
The modified intent to treat (mITT) population includes all patients with malaria diagnosis confirmation who received at least one dose of study drug. Evaluable patients generally are all patients who had a day 7 and a day 28 parasitological assessment or experienced treatment failure by day 28. The results are presented in the table below:

Table 2 Clinical efficacy results

Study No.	Age	Polymerase chain reaction (PCR)-corrected 28-day cure rate1 n/N (%) in evaluable patients	Median FCT2 [25th, 75th percentile]	Median PCT2 [25th, 75th percentile]	Year/ Study location
A0254	3-62 years	93/96 (96.9)	n3=59 35 hours [20, 46]	n=118 44 hours [22, 47]	1996-97 Thailand
A026	2-63 years	130/133 (97.7)	n3=87 22 hours [19, 44]	NA	1997-98 Thailand
A028	12-71 years	148/154 (96.1)	n3=76 29 hours [8, 51]	n=164 29 hours [18, 40]	1998-99 Thailand
A2401	16-66 years	119/124 (96.0)	n3=100 37 hours [18, 44]	n=162 42 hours [34, 63]	2001-05 Europe, Columbia
A2403	2 months-9 years	289/299 (96.7)	n3=309 8 hours [8, 24]	n=310 24 hours [24, 36]	2002-03 3 countries in Africa
B2303CT	3 months-12 years	403/419 (96.2)	n3=323 8 hours [8, 23]	n=452 35 hours [24, 36]	2006-07 5 countries in Africa
B2303DT	3 months-12 years	394/416 (94.7)	n3=311 8 hours [8, 24]	n=446 34 hours [24, 36]	2006-07 5 countries in Africa

1 Efficacy cure rate based on blood smear microscopy

2 mITT population

3 For patients who had a body temperature >37.5°C at baseline only

4Only the 6-dose regimen over 60 hours group data is presented

CT –PLUMAL DS tablets administered as crushed tablets

DT –PLUMAL DS Dispersible tablets

PLUMAL DS 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. In 319 adult patients in whom gametocytes were present, the median time to gametocyte clearance with PLUMAL DS was 96 hours. PLUMAL DS is active against blood stages of *Plasmodium vivax*, but is not active against hypnozoites.

Resistance
Strains of P. falciparum with a moderate decrease in susceptibility to artemether or lumefantrine alone can be
selected in vitro or in vivo, but not maintained in the case of artemether.
Alterations in some genetic regions of P. falciparum [multidrug resistant 1 (pfmdr1), chloroquine resistance

transporter (pfcrt) , and kelch 13 (K13)] based on in vitro testing and/or identification of isolates in endemic
areas where artemether/lumefantrine treatment was administered, have been reported. The clinical relevance
of these findings is not known.

QT/QTc Prolongation:

Adults and children with malaria

For information on the risk of QT/QTc prolongation in patients see section 4.4

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 PLUMAL DS 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 PLUMAL DS is limited by the lack of an intravenous formulation, and the very high inter-and intra-subject variability of PLUMAL DS 80/480 plasma concentrations and derived pharmacokinetic parameters (AUC, Cmax).

Absorption for Artemether

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. The absolute bioavailability is unknown.

Following single dose administration of 4 tablets of PLUMAL DS 80/480 in healthy volunteers, the mean (± SD) artemether Cmax value was 81 (±41) ng/ml, the corresponding value for AUC was 238 (±125) ng.h/ml, and the
mean artemether tmax value was 2.83 (± 0.94) hours. The pharmacokinetic data for dihydroartemisinin were supportive and indicated a comparable bioavailability between Test and Reference.
In healthy volunteers the relative bioavailability of artemether was increased more than two-fold when taken with food.

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%).

Metabolism
Artemether is rapidly and extensively metabolised with substantial first-pass metabolism.
Artemether is metabolised in the liver to the biologically active main metabolite DHA (demethylation), predominantly through the isoenzyme CYP3A4/5. The pharmacokinetics of artemether in adults is timedependent. During repeated administration of artemether/lumefantrine, 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. DHA is further converted to inactive metabolites, primarily by glucuronidation. In vivo data indicate that artemisinins have some capacity to induce cytochrome isoenzymes CYP2C19 and CYP3A4.

Elimination
Artemether and dihydroartemisinin are rapidly cleared from plasma with an elimination half-life of about 2 hours.
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 (unindentified) have been detected in both faeces and urine.

Absorption for Lumefantrine
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. The absolute bioavailability is unknown. Following single dose administration of 4 tablets of PLUMAL DS 80/480 in healthy volunteers, the mean (± SD) lumefantrine Cmax value was 6136 (±2880) ng/ml, the corresponding value for AUC was 99070 (±48130) ng.h/ml, and the mean lumefantrine tmax value was 5.93 (± 0.73) hours. Lumefantrine exposure from one 80 mg/480 mg tablet is equivalent to four 20 mg/120 mg tablets.
In healthy volunteers the relative bioavailability of lumefantrine, when was taken after a high-fat meal, was increased sixteen-fold compared with fasted conditions. 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. Patients should therefore be encouraged to take the medication with a normal diet as soon as food can be tolerated.

Distribution of Lumefantrine
Lumefantrine is 99.7% bound to human serum proteins in vitro.

Metabolism
Lumefantrine is N-debutylated, mainly by CYP3A4, in human liver microsomes. The systemic exposure to the metabolite desbutyl-lumefantrine, for which the in vitro antiparasitic effect is 5 to 8 fold higher than 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. In humans, the exposure to lumefantrine increases with repeated administration of PLUMAL DS 80/480 over the 3-day treatment period, consistent with the slow elimination of the compound.

Elimination
Lumefantrine is eliminated very slowly with a terminal half-life of approximately 3 days. No urinary excretion data are available for humans. Lumefantrine is eliminated via the bile in rats and dogs, with excretion primarily in the faeces. After oral dosing in rats and dogs qualitative and quantitative recovery of metabolites in bile and faeces was relatively low, most of the dose being recovered as parent drug. Pharmacokinetics in special patient populations Specific pharmacokinetic studies have not been performed in patients with hepatic or renal insufficiency. No pharmacokinetic studies are available in elderly patients.

Paediatric population
In paediatric malaria patients, mean Cmax (CV%) of artemether (observed after first dose) 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. Page 12 of 14 AUC of lumefantrine (population mean, covering the six doses of PLUMAL DS 80/480) were 577, 699 and 1150 µgh/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 PLUMAL DS 80/480 in children are unknown.

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 thePLUMAL DS 80/480 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

PLUMAL DS 80/480 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 PLUMAL DS 80/480 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 IC50 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 see sections 4.3, 4.4 and 5.1.

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6. Pharmaceutical particulars

6.1 List of excipients

Microcrystalline Cellulose

Pregelatinized starch

10% pregelatinized starch slurry

95%ethanol

Magnesium stearate

Sodium Carboxymethyl Starch

Silica

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 Months

6.4 Special precautions for storage
store below 30°C.

6.5 Nature and contents of container
PVC/PE/PVDC/aluminium blisters.

Each blister card contains 10 x 1 x 6 tablets and it is packed in a carton.

6.6 Special precautions for disposal and other handling
No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements

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7. Marketing authorisation holder

Unicure Pharmaceutical Ltd

Ikofa Village, Lagos - Benin Expressway, Ikofa

Ijebu- Ode

Email: unicurepharms@163.com

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8. Marketing authorisation number(s)

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9. Date of first authorisation/renewal of the authorisation

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10. Date of revision of the text