1.3 PRODUCT INFORMATION

1.3.1 SUMMARY OF PRODUCT CHARACTERISTICS (SMPC)

1. Name of drug product

CEVLAR

1.1 (Trade) name of product

Artemether and Lumefantrine Tablets

1.2 Strength

Each uncoated tablet contains:
Artemether……..80 mg
Lumefantrine……..……....480 mg
Excipients……q.s.

1.3 Pharmaceutical Dosage Form

Uncoated tablets for oral use.

2. QUALITATIVE & QUANTITATIVE COMPOSITION

2.1 Qualitative Declaration

Each uncoated tablet contains:
Artemether……..80 mg
Lumefantrine……...480 mg
Excipients……q.s.

2.2 Quantitative Declaration

Batch size: 1, 00,000 Tablet/ 63.000 kg

Sr. No	Name of Raw Material	Spec	Label claim / tab	Qty per tablet (mg)	Qty per Batch	Use
Dry Mixing						
1	Artemether	IH	80	80	8.000	Active
2	PVPK-30	BP		1.5	0.150	Disintegrant
3	Isopropyl Alcohol	BP	---	---	---	Solvent
Binding						
4	Lumefantrine	USP	480	480	48.00	Active
5	Microcrystalline Cellulose	BP	---	10.00	1.00	Disintegrant
6	Croscarmellose Sodium	BP	---	10	1.00	Disintegrant
7	Sodium Starch Glycolate	BP	---	1.5	0.15	Disintegrant
8	Starch	BP	---	5.0	0.5	Binder
9	PVPK-30	BP	---	15.00	1.5	Binder
10	Isopropyl Alcohol	BP	---	---	---	Solvent
Lubrication						
11	Sodium Lauryl Sulfate	BP	---	2.0	0.200	Lubricant
12	Croscarmellose Sodium	BP	---	4.00	0.4	Lubricant
13	Talc	BP	---	13.00	1.3	Lubricant
14	Colloidal Anhydrous Silica	BP	---	2.00	0.2	Lubricant
15	Magnesium Stearate	BP	---	6.00	0.6	Lubricant
Total (Uncoated Tablet average Weight)			---	630.00	63.00	

3. PHARMACEUTICAL DOSAGE FORM

Uncoated tablets for oral use

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Cevlar is indicated for the treatment of acute uncomplicated Plasmodium falciparum malaria in adults, 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

Posology

Adults and children weighing 35 kg and above

For patients 12 years of age and above and 35 kg body weight and above, a course of treatment comprises six doses of four tablets i.e. total of 24 tablets, given over a period of 60 hours as follows: the first dose of four tablets, given at the time of initial diagnosis, should be followed by five further doses of four tablets given at 8, 24, 36, 48 and 60 hours thereafter.

Children and infants weighing 5 kg to less than 35 kg

A six-dose regimen is recommended with 1 to 3 tablets per dose, depending on bodyweight:

5 to less than 15 kg bodyweight: the first dose of one tablet, given at the time of initial diagnosis, should be followed by five further doses of one tablet given at 8, 24, 36, 48 and 60 hours thereafter.

15 to less than 25 kg bodyweight: the first dose of two tablets, given at the time of initial diagnosis, should be followed by five further doses of two tablets given at 8, 24, 36, 48 and 60 hours thereafter.

25 to less than 35 kg bodyweight: the first dose of three tablets, given at the time of initial diagnosis, should be followed by five further doses of three tablets given at 8, 24, 36, 48 and 60 hours thereafter.

Method of administration

Tablets for oral administration.

4.3 Contraindications

Cevlar 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. 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 (Hypericumperforatum).
(*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

Cevlar (Artemether and Lumefantrine Tablets) must not be used in the first trimester of pregnancy in situations where other suitable and effective antimalarial are available. Cevlar (Artemether and Lumefantrine Tablets) 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, Cevlar (Artemether and Lumefantrine Tablets) should not be given concurrently with any other antimalarial agent unless there is no other treatment option.

If a patient deteriorates whilst taking Cevlar (Artemether and Lumefantrine Tablets), 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 Cevlar (Artemether and Lumefantrine Tablets). If quinine is given after Cevlar (Artemether and Lumefantrine Tablets), close monitoring of the ECG is advised. If Cevlar (Artemether and Lumefantrine Tablets) is given after mefloquine, close monitoring of food intake is advised.

In patients previously treated with halofantrine, Cevlar (Artemether and Lumefantrine Tablets) should not be administered earlier than one month after the last halofantrine dose.

Cevlar (Artemether and Lumefantrine Tablets) is not indicated and has not been evaluated for prophylaxis of malaria.

Cevlar (Artemether and Lumefantrine Tablets) should be used cautiously in patients on anti-retroviral drugs (ARTs) since decreased artemether, DHA, and/or lumefantrine concentrations may result in a decrease of antimalarial efficacy of Cevlar (Artemether and Lumefantrine Tablets) Like other antimalarials (e.g. halofantrine, quinine and quinidine) Cevlar (Artemether and Lumefantrine Tablets) has the potential to cause QT prolongation

Caution is recommended when combining Cevlar (Artemether and Lumefantrine Tablets) with drugs exhibiting variable patterns of inhibition, moderate induction or competition for CYP3A4 as the therapeutic effects of some drugs could be altered. Drugs that have a mixed inhibitory/induction effect on CYP3A4, especially anti-retroviral drugs such as HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors should be used with caution in patients taking Cevlar (Artemether and Lumefantrine Tablets).

Caution is recommended when combining Cevlar (Artemether and Lumefantrine Tablets) with hormonal contraceptives. Cevlar (Artemether and 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 for about one month.

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

Renal impairment

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

Hepatic impairment

No specific studies have been carried out in this group of patients. In patients with severe hepatic impairment, a clinically relevant increase of exposure to artemether and lumefantrine and/or their

metabolites cannot be ruled out. Therefore caution should be exercised in dosing patients with severe hepatic impairment. In these patients, ECG and blood potassium monitoring is advised. No dose adjustment is recommended for patients with mild to moderate hepatic impairment.

Older people

There is no information suggesting that the dosage in patients over 65 years of age should be different than in younger adults.

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 Cevlar (Artemether and Lumefantrine Tablets). In the absence of carcinogenicity study data, and due to lack of clinical experience, more than two courses of Cevlar (Artemether and Lumefantrine Tablets) cannot be recommended.

4.5 Interaction with Other Drugs, Other Forms of Interactions

Other NSAIDs including cyclooxygenase-2 selective inhibitors and corticosteroids: Co-administration of diclofenac with other systemic NSAIDs or corticosteroids may increase the risk of gastrointestinal bleeding or ulceration. Avoid concomitant use of two or more NSAIDs.

Diuretics and antihypertensive agents: Like other NSAIDs, concomitant use of diclofenac with diuretics and antihypertensive agents (e.g. beta-blockers, angiotensin converting enzyme (ACE) inhibitors may cause a decrease in their antihypertensive effect via inhibition of vasodilatory prostaglandin synthesis.

Therefore, the combination should be administered with caution and patients, especially the elderly, should have their blood pressure periodically monitored. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy periodically thereafter, particularly for diuretics and ACE inhibitors due to the increased risk of nephrotoxicity

Cardiac glycosides: NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels.

Lithium: If used concomitantly, diclofenac may increase plasma concentrations of lithium Monitoring of the serum lithium level is recommended.

Methotrexate: Diclofenac can inhibit the tubular renal clearance of methotrexate hereby increasing methotrexate levels. Caution is recommended when NSAIDs, including diclofenac, are administered less than 24 hours before treatment with methotrexate, since blood concentrations of methotrexate may rise and the toxicity of this substance be increase. Cases of serious toxicity have been reported when methotrexate and NSAIDs including diclofenac are given within 24 hours of each other. This interaction is mediated through accumulation of methotrexate resulting from impairment of renal excretion in the presence of the NSAID.

Ciclosporin: Diclofenac, like other NSAIDs, may increase the nephrotoxicity of ciclosporin due to the effect on renal prostaglandins. Therefore, it should be given at doses lower than those that would be used in patients not receiving ciclosporin.

Mifepristone: NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.

Anti-coagulants and anti-platelet agents: Caution is recommended since concomitant administration could increase the risk of bleeding. Although clinical investigations do not appear to indicate that diclofenac has an influence on the effect of anticoagulants, there are reports of an increased risk of haemorrhage in patients receiving diclofenac and anticoagulant concomitantly. Therefore, to be certain that no change in anticoagulant dosage is required, close monitoring of such patients is required. As with other nonsteroidal anti-inflammatory agents, diclofenac in a high dose can reversibly inhibit platelet aggregation. NSAID

Digoxin: If used concomitantly, diclofenac may raise plasma concentrations of digoxin. Monitoring of the serum digoxin level is recommended.

Selective serotonin reuptake inhibitors (SSRls): lncreased risk of gastrointestinal bleeding .

Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus. This might be mediated through renal antiprostagladin effects of both NSAID and calcineurin inhibitor.

Quinolone antibacterials: Convulsions may occur due to an interaction between quinolones and NSAIDs. This may occur in patients with or without a previous history of epilepsy or convulsions. Therefore, caution should be exercised when considering the use of a quinolone in patients who are already receiving an NSAID.

Phenytoin: When using phenytoin concomitantly with diclofenac, monitoring of phenytoin plasma concentrations is recommended due to an expected increase in exposure to phenytoin.

Colestipol and cholestyramine: These agents can induce a delay or decrease in absorption of diclofenac.

Therefore, it is recommended to administer diclofenac at least one hour before or 4 to 6 hours after administration of colestipol/ cholestyramine.

Zidovudine: lncreased risk of haematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HIV (+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

Antidiabetic agents: Clinical studies have shown that Diclofenac Potassium tablets can be given together with oral antidiabetic agents without influencing their clinical effect. However there have been isolated reports of hypoglycaemic and hyperglycaemic effects which have required adjustment to the dosage of hypoglycaemic agents. For this reason, monitoring of the blood glucose level is recommended as a precautionary measure during concomitant therapy.

Drugs known to cause hyperkalemia: Concomitant treatment with potassium-sparing diuretics, ciclosporin, tacrolimus or trimethoprim may be associated with increased serum potassium levels, which should therefore be monitored frequently.

Potent CYP2C9 inhibitors: Caution is recommended when co-prescribing diclofenac with potent CYP2C9 inhibitors (such as voriconazole), which could result in a significant increase in peak plasma concentrations and exposure to diclofenac due to inhibition of diclofenac metabolism.

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.

Pregnancy

Based on animal data, Cevlar (Artemether and Lumefantrine Tablets) is suspected to cause serious birth defects when administered during the first trimester of pregnancy. Reproductive studies with artemether have shown evidence of post-implantation losses and teratogenicity in rats and rabbits.

Other artemisinin derivatives have also demonstrated teratogenic potential with an increased risk during early gestation.

Safety data from an observational pregnancy study of approximately 500 pregnant women who were exposed to Cevlar (Artemether and Lumefantrine Tablets) (including a third of patients who were exposed in the first trimester), and published data of another over 500 pregnant women who were exposed to artemether- lumefantrine (including over 50 patients who were exposed in the first trimester), as well as published data of over 1,000 pregnant women who were exposed to artemisinin derivatives, did not show an increase in adverse pregnancy outcomes or teratogenic effects over background rates.

Cevlar (Artemether and Lumefantrine Tablets) treatment must not be used 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, treatment should only 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 Cevlar (Artemether and Lumefantrine Tablets) 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 Cevlar (Artemether and Lumefantrine Tablets) unless potential benefits to the mother and child outweigh the risks of Cevlar (Artemether and Lumefantrine Tablets) treatment.

Fertility

There is no information on the effects of Cevlar (Artemether and Lumefantrine Tablets) on human fertility

4.7 Effects on ability to drive and operate machine

Undesirable effects such as dizziness, drowsiness, fatigue and visual disturbances are possible after taking NSAIDs. If affected, patients should not drive or operate machinery.

4.8 Undesirable effects

Adverse reactions are ranked under the heading of frequency, the most frequent first, using the following convention:

very common: (>1/10); common (≥ 1/100, <1/10); uncommon (≥ 1/1,000, <1/100); rare (≥1/10,000, <1/1000); very rare (<1/10,000); Unknown: cannot be estimated from available data.

The following undesirable effects include those reported with other short-term or long-term use .**Blood and lymphatic system disorders**	
Very rare	Thrombocytopenia, leucopoenia, anaemia (including haemolytic and aplastic anaemia), agranulocytosis.
Unknown	Neutropenia
Immune system disorders	
Rare	Hypersensitivity, anaphylactic and anaphylactoid reactions (including hypotension and shock).
Very rare	Angioneurotic oedema (including face oedema).
Psychiatric disorders	
Very rare	Disorientation, depression, insomnia, nightmare, irritability, psychotic disorder.
Nervous system disorders	
Common	Headache, dizziness.
Rare	Somnolence, tiredness.
Very rare	Paraesthesia, memory impairment, convulsion, anxiety, tremor, aseptic meningitis*, taste disturbances, cerebrovascular accident.
Unknown	Confusion, hallucinations, disturbances of sensation malaise
Eye disorders	
Very rare	Visual disturbance, vision blurred, diplopia.
Unknown	Optic neuritis.
Ear and labyrinth disorders	

Common	Vertigo.
Very rare	Tinnitus, hearing impaired.
Cardiac disorders	
Very rare	Palpitations, chest pain, cardiac failure, myocardial infarction.
Vascular disorders	
Very rare	Hypertension, hypotension, vasculitis.
Respiratory, thoracic and mediastinal disorders	
Rare	Asthma (including dyspnoea).
Very rare	Pneumonitis.
Gastrointestinal disorders	
Common	Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, flatulence, anorexia.
Rare	Gastritis, gastrointestinal haemorrhage, haematemesis, diarrhoea haemorrhagic, melaena, gastrointestinal ulcer with or without bleeding or perforation (sometimes fatal particularly in the elderly).
Very rare	Colitis (including haemorrhagic colitis and exacerbation of ulcerative colitis or Crohn's disease), constipation, stomatitis (including ulcerative stomatitis), glossitis, oesophageal disorder, diaphragm-like intestinal strictures, pancreatitis.
Unknown	Ischaemic colitis
Hepatobiliary disorders	
Common	Transaminases increased.
Rare	Hepatitis, jaundice, liver disorder.

Very rare	Fulminant hepatitis, hepatic necrosis, hepatic failure.
Skin and subcutaneous tissue disorders	
Common	Rash.
Rare	Urticaria.
Very rare	Bullous eruptions, eczema, erythema, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), dermatitis exfoliative, loss of hair, photosensitivity reaction, purpura, allergic purpura, pruritus.
Renal and urinary disorders	
Very rare	Acute renal failure, haematuria, proteinuria, nephrotic syndrome, interstitial nephritis, renal papillary necrosis.
General disorders and administration site conditions	
Rare	Oedema
Reproductive system and breast disorders	
Very rare	Impotence

* especially in patients with existing autoimmune disorders, such as systemic lupus erythematosus, mixed connective tissue disease, with symptoms such as stiff neck, headache, nausea, vomiting, fever or disorientation.

Clinical trial and epidemiological data consistently point towards an increased risk of arterial thrombotic events (for example myocardial infarction or stroke) associated with the use of diclofenac, particularly at high dose (150mg daily) and in long term treatment.

4.9 Overdose

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

5. Pharmacological properties

5.1 Pharmacodynamic properties

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

Pharmacodynamic effects

Cevlar (Artemether and Lumefantrine Tablets) 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.

Treatment of Acute Uncomplicated P. falciparum Malaria The efficacy of Cevlar (Artemether and Lumefantrine Tablets) 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% parasitemia) 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.

Cevlar (Artemether and Lumefantrine Tablets) 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. Cevlar (Artemether and Lumefantrine Tablets) is active against blood stages of Plasmodium vivax, but is not active against hypnozoites.

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 Cevlar (Artemether and Lumefantrine Tablets) 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.

In the adult/adolescent population included in clinical trials, 8 patients (0.8%) receiving Cevlar (Artemether and Lumefantrine Tablets) 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 clinical trials conducted in children with the 6-dose regimen, no patient had post-baseline QTcF>500 msec whereas 29.4% had QTcF increase from baseline >30 msec and 5.1% >60 msec. In clinical trials conducted in adults and adolescents with the 6-dose regimen, post-baseline QTcF prolongation of >500 msec was reported in 0.2% of patients, whereas QTcF increase from baseline >30 msec was reported in 33.9% and >60 msec in 6.2% 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.

5.2 Pharmacokinetic properties

Pharmacokinetic characterisation of Cevlar (Artemether and Lumefantrine tablets) 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 Cevlar (Artemether and Lumefantrine tablets), 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 Cevlar (Artemether and Lumefantrine tablets) 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%).

Biotransformation

Artemether is rapidly and extensively metabolised (substantial first-pass metabolism) both in vitro and in humans. Human liver microsomesmetaboliseartemether 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 Cevlar (Artemether and Lumefantrine tablets), 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 in section 4.5

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 Cevlar (Artemether and Lumefantrine tablets) 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 an elimination half-life of 2 to 6 days. Demographic characteristics such as sex and weight appear to have no clinically relevant effects on the pharmacokinetics of Cevlar (Artemether and Lumefantrine tablets),

Limited urinary excretion data are available for humans. In 16 healthy volunteers, neither lumefantrine nor artemether was found in urine after administration of Cevlar (Artemether and Lumefantrine tablets), and only traces of dihydroartemisinin were detected (urinary excretion of dihydroartemisinin amounted to less than 0.01% of the artemether dose).

In animals (rats and dogs), no unchanged artemether was detected in faeces and urine due to its rapid and extensive first-pass metabolism, but numerous metabolites (partly identified) have been detected

in faeces, bile and urine. Lumefantrine was excreted unchanged in faeces and with traces only in urine. Metabolites of lumefantrine were eliminated in bile/faeces.

Dose proportionality

No specific dose proportionality studies were performed. Limited data suggest a dose-proportional increase of systemic exposure to lumefantrine when doubling Cevlar (Artemether and Lumefantrine tablets), dose. No conclusive data is available for Artemether.

Bioavailability/bioequivalence studies

Systemic exposure to lumefantrine, artemether and dihydroartemisinin was similar following administration of Cevlar (Artemether and Lumefantrine tablets), as dispersible tablets and crushed tablets in healthy adults.

Systemic exposure to lumefantrine was similar following administration of Cevlar (Artemether and Lumefantrine tablets), dispersible tablets and intact tablets in healthy adults. However, exposure to artemether and dihydroartemisinin was significantly lower (by 20-35%) for the dispersible than for the intact tablet. These findings are not considered to be clinically relevant for the use of the dispersible tablets in the paediatric population since adequate efficacy of Cevlar (Artemether and Lumefantrine tablets), dispersible tablets was demonstrated in this population. The dispersible tablet is not recommended for use in adults.

Older people

No specific pharmacokinetic studies have been performed in elderly patients. However, there is no information suggesting that the dosage in patients over 65 years of age should be different than in younger adults.

Paediatric population

In paediatric malaria patients, mean Cmax (CV%) of artemether (observed after first dose of Cevlar (Artemether and Lumefantrine tablets), 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 Cevlar (Artemether and Lumefantrine tablets), 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.

Hepatic and Renal impairment

No specific pharmacokinetic studies have been performed either in patients with hepatic or renal insufficiency or elderly patients. The primary clearance mechanism of both artemether and lumefantrine may be affected in patients with hepatic impairment. In patients with severe hepatic impairment, a clinically significant 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. Based on the pharmacokinetic data in 16 healthy subjects showing no or insignificant renal excretion of lumefantrine, artemether and dihydroartemisinin, no dose adjustment for the use of Cevlar (Artemether and Lumefantrine tablets), in patients with renal impairment is advised.

5.3 Pre-clinical safety data

None stated.

6. Pharmaceutical particulars

6.1 List of excipients

- PVPK-30 BP
- Isopropyl Alcohol BP
- Microcrystalline Cellulose BP
- Croscarmellose Sodium BP
- Sodium Starch Glycolate BP
- Maize Starch BP
- Sodium Lauryl Sulfate BP
- Purified Talc BP
- Colloidal Anhydrous Silica BP
- Magnesium Stearate BP

6.2 Incompatibilities

Not Applicable

6.3 Shelf-Life

36 months from the date of manufacture.

6.3 Special Precautions for Storage

Store at a temperature not exceeding 30°C. Protect from light and moisture.

Keep medicine out of reach of children.

6.4 Nature and Contents of Container

6 tablets to be packed in an Alu Pvc Blister. Such 1 blister to be packed in a mono carton along with pack insert. Such 10 monocartons to be packed in an outer carton.

7. Marketing authorisation holder

HALEWOOD LABORATORIES PVT.LTD.

Plot No. 319, Phase – II, G.I.D.C.,

Vatva, Ahmedabad – 382445.

8. Marketing authorisation number(s)

Not Applicable

9. Date of first authorisation/renewal of the authorisation

Not Applicable

10. Date of revision of the text

Not Applicable