SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

INN Name: **Artemether and Lumefantrine Powder for oral suspension**

Trade mark name : AL-BEL Powder for suspension

2. Qualitative and quantitative composition

Each 60ml contains: Artemether 240mg and Lumefantrine 1440mg

3. Pharmaceutical form

Oral suspension

4. Clinical particulars

4.1 Therapeutic indications

AL-BEL Powder for oral suspension 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

POWDER FOR ORAL SUSPENSION for oral administration.

To increase absorption, AL-BEL POWDER FOR ORAL SUSPENSION should be taken with food or a milky drink (see section 5.2). If patients are unable to tolerate food, AL-BEL POWDER FOR ORAL SUSPENSION should be administered, but the systemic exposure may be reduced. Patients who vomit within 1 hour of taking the medication should repeat the dose.

AL-BEL POWDER FOR ORAL SUSPENSION FOR CHILDREN:

Weight	Day-1		Day-2		Day-3		Total
	0 Hour	8 Hours	Morning	Night	Morning	Night	
15kg to 25kg	10ml	10ml	10ml	10ml	10ml	10ml	60ml
5 to 15kg	5ml	5ml	5ml	5ml	5ml	5ml	30ml

4.3 Contraindication

AL-BEL POWDER FOR ORAL SUSPENSION 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

AL-BEL POWDER FOR ORAL SUSPENSION must not be used in the first trimester

of pregnancy in situations where other suitable and effective antimalarials are available (see section 4.6).

AL-BEL POWDER FOR ORAL SUSPENSION 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, AL-BEL POWDER FOR ORAL SUSPENSION 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 AL-BEL POWDER FOR ORAL SUSPENSION, 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 AL-BEL POWDER FOR ORAL SUSPENSION.

If quinine is given after AL-BEL POWDER FOR ORAL SUSPENSION, close monitoring of the ECG is advised (see section 4.5).

If AL-BEL POWDER FOR ORAL SUSPENSION is given after mefloquine, close monitoring of food intake is advised (see section 4.5).

In patients previously treated with halofantrine, AL-BEL POWDER FOR ORAL SUSPENSION should not be administered earlier than one month after the last halofantrine dose.

AL-BEL POWDER FOR ORAL SUSPENSION 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. AL-BEL POWDER FOR ORAL SUSPENSION is active against blood stages of Plasmodium vivax, but is not active against hypnozoites.

AL-BEL POWDER FOR ORAL SUSPENSION is not indicated and has not been evaluated for prophylaxis.

Like other antimalarials (e.g. halofantrine, quinine and quinidine) AL-BEL POWDER

FOR ORAL SUSPENSION has the potential to cause QT prolongation.

In the adult/adolescent population included in clinical trials, 8 patients (0.8%) receiving AL-BEL POWDER FOR ORAL SUSPENSION 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 AL-BEL POWDER FOR ORAL SUSPENSION with drugs exhibiting variable patterns of inhibition, induction or competition for CYP3A4 as the therapeutic effects of some drugs could be altered (see sections 4.5 and 5.2).

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 AL-BEL POWDER FOR ORAL SUSPENSION to patients with severe renal, hepatic or cardiac problems (see section 4.2).

4.5 Interaction with other medical products and other forms of interaction

Interaction with other antimalarials (see section 4.4)

A drug interaction study with AL-BEL POWDER FOR ORAL SUSPENSION in man involved administration of a 6-dose regimen over 60 hours in healthy volunteers which was commenced at 12 hours after completion of a 3-dose regimen of mefloquine or placebo. Plasma mefloquine concentrations from the time of addition of AL-BEL POWDER FOR ORAL SUSPENSION 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 to compensate for the decrease in bioavailability.

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 AL-BEL POWDER FOR ORAL SUSPENSION (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 AL-BEL POWDER FOR ORAL SUSPENSION 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 AL-BEL POWDER FOR ORAL SUSPENSION 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 AL-BEL POWDER FOR ORAL SUSPENSION.

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 AL-BEL POWDER FOR ORAL SUSPENSION led to a modest increase ($\leqslant$ 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 AL-BEL POWDER FOR ORAL SUSPENSION is considered unnecessary in falciparum malaria patients when administered in association with ketoconazole or other potent CYP3A4 inhibitors.

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 of drugs that are predominantly metabolised by these enzymes (see sections 4.4 and 5.2).

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 AL-BEL POWDER FOR ORAL SUSPENSION with drugs that are metabolised by this iso-enzyme is contraindicated (see section 4.3 and 5.2). In vitro studies indicated that lumefantrine metabolism is inhibited by halofantrine and quinine.

Interaction with protease inhibitor anti-retroviral drugs

Due to variable patterns of inhibition, induction or competition for CYP3A4 with protease inhibitor anti-retroviral drugs, use of such drugs, especially combinations of them, concomitantly with AL-BEL POWDER FOR ORAL SUSPENSION, requires clinical surveillance and monitoring of clinical response/undesirable effects.

Other interactions

Administration of AL-BEL POWDER FOR ORAL SUSPENSION is contra-indicated in patients taking drugs that are known to prolong the QTc interval (see section 4.3).

In patients previously treated with halofantrine, AL-BEL POWDER FOR ORAL SUSPENSION should be dosed at least one month after the last halofantrine dose.

Due to the limited data on safety and efficacy, AL-BEL POWDER FOR ORAL SUSPENSION 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 AL-BEL POWDER FOR ORAL SUSPENSION to patients in whom there may still be detectable concentrations of these drugs in the plasma following prior treatments.

4.6 Pregnancy and lactation

Pregnancy

There is insufficient data from the use of artemether and lumefantrine in pregnant women. Based on animal data, AL-BEL POWDER FOR ORAL SUSPENSION is suspected to cause serious birth defects when administered during the first trimester of pregnancy (see sections 4.4 and 5.3) 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 (see section 5.3). AL-BEL POWDER FOR ORAL SUSPENSION 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.

Lactation

Animal data suggest excretion into breast milk but no data are available in humans. Women taking AL-BEL POWDER FOR ORAL SUSPENSION should not breast-feed during their treatment. Due to the long elimination half-life of lumefantrine (4 to 6 days), it is recommended that breast-feeding should not resume until at least one week after the last dose of AL-BEL POWDER FOR ORAL SUSPENSION unless potential benefits to the mother and child outweigh the risks of AL-BEL POWDER FOR ORAL SUSPENSION treatment.

4.7 Effects on ability to drive and use machines

Patients receiving AL-BEL POWDER FOR ORAL SUSPENSION 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 AL-BEL POWDER FOR ORAL SUSPENSION 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 AL-BEL POWDER FOR ORAL SUSPENSION 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	Common (1.8 %)
Electrocardiogram QT prolonged	Common	Common (5.3 %)
Nervous system disorders		
Headache	Very common	Very common (17.1 %)
Dizziness	Very common	Common (5.5 %)
Paraesthesia	Common	--
Ataxia, hypoaesthesia	Uncommon	--
Clonus, somnolence	Uncommon	Uncommon
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 %)
Skin and subcutaneous tissue disorders		
Rash	Common	Common (2.7 %)
Pruritus	Common	Uncommon
Urticaria, angioedema*	Not known	Not known
Musculoskeletal and connective tissue disorders		
Arthralgia	Very common	Common (2.1 %)

Myalgia	Very common	Common (2.2 %)
Metabolism and nutrition disorders		
Anorexia	Very common	Very common (16.8 %)
General disorders and administration site conditions		
Asthenia	Very common	Common (5.2 %)
Fatigue	Very common	Common (9.2 %)
Gait disturbance	Common	--
Immune system disorders		
Hypersensitivity	Not known	Rare
Hepatobiliary disorders		
Liver function tests increased	Uncommon	Common (4.1 %)
Psychiatric disorders		
Sleep disorders	Very common	Common (6.4 %)
Insomnia	Common	Uncommon

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

4.9 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 BE52.

Pharmacodynamic effects

AL-BEL POWDER FOR ORAL SUSPENSION 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 AL-BEL POWDER FOR ORAL SUSPENSION POWDER FOR ORAL SUSPENSION 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. 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	NA	1997-98

			22 hours [19, 44]		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 –AL-BEL POWDER FOR ORAL SUSPENSION POWDER FOR ORAL SUSPENSION administered as crushed POWDER FOR ORAL SUSPENSION

DT –AL-BEL POWDER FOR ORAL SUSPENSION Dispersible POWDER FOR ORAL SUSPENSION

AL-BEL POWDER FOR ORAL SUSPENSION is active against blood stages of Plasmodium vivax, but is not active against hypnozoites (see section 4.4).

Paediatric population

Two studies have been conducted

Study A2403 was conducted in Africa in 310 infants and children aged 2 months to 9 years, weighing 5 kg to 25 kg, with an axillary temperature ≥37.5°C. Results of 28-day cure rate (PCR-corrected), median parasite clearance time (PCT), and fever clearance time (FCT) are reported in table 3 below.

Study B2303 was conducted in Africa in 452 infants and children, aged 3 months to 12 years, weighing 5 kg to <35 kg, with fever (≥37.5°C axillary or ≥38°C rectally) or history of fever in the preceding 24 hours. This study compared crushed POWDER FOR ORAL SUSPENSION and dispersible POWDER FOR ORAL SUSPENSION. Results of 28-day cure rate (PCR-corrected), median parasite clearance time (PCT), and fever clearance time (FCT) for crushed POWDER FOR ORAL SUSPENSION are reported in table 3 below.

Table 3 Clinical efficacy by weight for pediatric studies

Study No. **Weight category**	**Median PCT[1]** **[25th, 75th percentile]**	**PCR-corrected 28-day cure rate[2]** **n/N (%) in evaluable patients**
Study A2403		
5 - <10 kg	24 hours [24, 36]	145/149 (97.3)
10 - <15 kg	35 hours [24, 36]	103/107 (96.3)
15 -25 kg	24 hours [24, 36]	41/43 (95.3)
Study B2303[CT]		
5 - <10 kg	36 hours [24, 36]	65/69 (94.2)
10 - <15 kg	35 hours [24, 36]	174/179 (97.2)
15 -<25 kg	35 hours [24, 36]	134/140 (95.7)
25-35 kg	26 hours [24, 36]	30/31 (96.8)

1 mITT population

2 Efficacy cure rate based on blood smear microscopy

CT AL-BEL POWDER FOR ORAL SUSPENSION POWDER FOR ORAL SUSPENSION administered as crushed POWDER FOR ORAL SUSPENSION

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 AL-BEL POWDER FOR ORAL SUSPENSION 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 AL-BEL POWDER FOR ORAL SUSPENSION 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 AL-BEL POWDER FOR ORAL SUSPENSION, 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 AL-BEL POWDER FOR ORAL SUSPENSION was taken after a high-fat meal.

Food has also been shown to increase the absorption of lumefantrine in patients with malaria, although to a lesser extent (approximately two-fold), most probably due to the lower fat content of the food ingested by acutely ill patients. The food interaction data indicate that absorption of lumefantrine under fasted conditions is very poor (assuming 100% absorption after a high-fat meal, the amount absorbed under fasted conditions would be <10% of the dose). Patients should therefore be encouraged to take the

medication with a normal diet as soon as food can be tolerated.

Distribution

Artemether and lumefantrine are both highly bound to human serum proteins in vitro (95.4% and 99.7%, respectively). Dihydroartemisinin is also bound to human serum proteins (47-76%).

Metabolism

Artemether is rapidly and extensively metabolised (substantial first-pass metabolism) both in vitro and in humans. Human liver microsomes metabolise artemether to the biologically active main metabolite dihydroartemisinin (demethylation), predominantly through the isoenzyme CYP3A4/5. This metabolite has also been detected in humans in vivo. .

Dihydroartemisinin is further converted to inactive metabolites.

The pharmacokinetics of artemether in adults is time-dependent. During repeated administration of AL-BEL POWDER FOR ORAL SUSPENSION, 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 AL-BEL POWDER FOR ORAL SUSPENSION over the 3-day treatment period, consistent with the slow elimination of the compound (see section 5.2 Elimination). 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 (see sections 4.3 and 4.5).

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 AL-BEL POWDER FOR ORAL SUSPENSION.

Limited urinary excretion data are available for humans. In 16 healthy volunteers, neither lumefantrine nor artemether was found in urine after administration of AL-BEL POWDER FOR ORAL SUSPENSION, 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.

Pharmacokinetics in special patient populations

In paediatric malaria patients, mean Cmax (CV%) of artemether (observed after first dose of AL-BEL POWDER FOR ORAL SUSPENSION) 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 AL-BEL POWDER FOR ORAL SUSPENSION) were 577, 699 and 1150 µg•h/mL for paediatric malaria patients in body weight groups 5-<15, 15-<25 and 25-<35 kg, respectively, compared to a mean AUC of 758 µg•h/mL (87%) in adult malaria patients. The elimination half-lives of

artemether and lumefantrine in children are unknown.

No specific pharmacokinetic studies have been performed either in patients with hepatic or renal insufficiency or elderly patients. 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 AL-BEL POWDER FOR ORAL SUSPENSION in patients with renal impairment is advised.

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.

Mutagenicity

No evidence of mutagenicity was detected in in vitro or in vivo tests with an artemether:lumefantrine combination (consisting of 1 part artemether:6 parts lumefantrine). In the micronucleus test myelotoxicity was seen at all dose levels (500, 1,000 and 2,000 mg/kg), but recovery was almost complete 48 hours after dosing.

Carcinogenicity

Carcinogenicity studies with the artemether:lumefantrine combination were not conducted.

Reproductive toxicity studies

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

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

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

known to be embryotoxic.

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

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

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

Cardiovascular Pharmacology

In toxicity studies in dogs at doses >600 mg/kg/day only, there was some evidence of prolongation of the QTc interval, at higher doses than intended for use in man. In an in vitro assay of HERG channels stably expressed in HEK293 cells, lumefrantrine and the main metabolite desbutyl-lumefantrine showed some inhibitory potential in one of the currents responsible for cardiac repolarization. The potency was lower than the other antimalarial drugs tested. From the estimated IC50 values, the order of potency of HERG current block was halofantrine (IC50 = 0.04 μM) >chloroquine (2.5 μM) >mefloquine 2.6 μM) >desbutyl-lumefantrine (5.5 μM) >lumefantrine (8.1 μM). Clinical studies show, that prolongation of QTcF can occur with standard dosing of AL-BEL POWDER FOR ORAL SUSPENSION (see sections 4.3, 4.4 and 5.1).

6. Pharmaceutical particulars

6.1 List of excipients

Sucrose
Microcrystalline Cellulose
Citric acid

Xanthan gum
Sodium benzoate
Colloidal Silicon dioxide
Encapsulate powder flavoring orange
Purified Water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 30°C.

Do not freeze.

Keep out of the sight and reach of children

6.5 Nature and contents of container

The powder for oral suspention is presented in 60ml amber PET bottle, each bottle contain 12g powder , each box contain 1 bottle with insert. Such 10 boxes are then shrink wrapped together , and 20 packed are in a carton .

Pack size: 60ml

6.6 Special precautions for disposal and other handing

For the treatment of children and infants, the AL-BEL 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 AL-BEL (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 AL-BEL should be discarded or returned to the

pharmacist.

7. Registrant

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8. Manufacturer

Manufacturer name: Front Pharmaceutical PLC

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9. Date of revision of the text

January 2017

10. DOSIMETRY (IF APPLICABLE)

N/A

11. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)

N/A