SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Co-fan QS

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Artemether 80 mg

Lumefantrine 480 mg

3. PHARMACEUTICAL FORM

Tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Co-fan QS is a fixed combination of Artemether and Lumefantrine which acts as blood schizontocide. Co-fan QS is indicated for:

- The treatment of acute uncomplicated malaria caused by Plasmodium falciparum, including cases are sensitive to Plasmodium falciparum or resistant to other antimalarials.

- Stand-by emergency treatment: most tourists and business travellers, considerable to be non-immune, will able to obtain prompt medical attention if malaria is suspected. However, a minority at risk of infection may be unable to obtain such care within 24 hours of the onset of symptoms, particularly if they are in an isolated location far from medical services. In such cases, prescribers are advised to issue Co-fan QS to be carried by the traveller for self-administration ("stand-by emergency treatment").

- Co-fan QS is only used for the treatment of acute uncomplicated malaria infections caused by a parasite called "Plasmodium flaciparum". This parasite is a tiny organism made up of one cell that is found inside red blood cells

4.2. Posology and method of administration

Co-fan QS is in form of tablet and should be taken orally with meals.

Co-fan QS is indicated for children over 35kg and adults. A treatment regimen of 6 dosages in 3 days is recommended as follow:

Dosing schedule for Co-fan QS:

Body weight	Age	**Day 1**		**Day 2**		**Day 3**	
		0 hour	8 hours	Morning	Evening	Morning	Evening
Children over 35kg and adults	>14	1 tablet	1 tablet	1 tablet	1 tablet	1 tablet	1 tablet

For adults and children over 35kg a standard three days treatment schedule with a total of six-doses is recommended as follow: one tablet as a single dose at the time of initial diagnosis, again one tablets after eight hours and then one tablets twice daily (morning and evening) on each of the following two days (total comprises 6 tablets).

Adjustment of dosing in old people or renal failure patients is not necessary.

It is advisable to take Co-fan QS with fatty food or milk, especially in day 1 and Day 2. Patients who have severe malaria usually lose appetite, so it is necessary to advise them return to the normal diet, because the absorbtion of medicine is enhanced by food. Vomiting within one hour requires repeating the dose.

4.3. Contraindications

Co-fan DS tablets are contraindicated:

- In those with hypersensitivity to the active substances or any of the excipients.
- In cases of severe malaria, including cerebral malaria, pulmonary edema or renal failure.
- In the first trimester of pregnancy.
- Small children (under 14 years or under 35kg of weight)
- Patients with a 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, patients with clinically relevant bradycardia or with severe cardiac disease, family history of sudden death, disturbances of electrolyte balance, e.g. hypokalaemia or hypomagnesaemia.
- Concomitant use of drugs that are known to be metabolised by cytochrome enzyme CYP2D6 (e.g. flecainide, metoprolol, imipramine, amitriptyline, clomipramine).
- Patients taking drugs that are known to prolong the QTc interval such as antiarrhythmics of classes IA and III, neuroleptics, antidepressant agents, certain antibiotics including some agents of the following classes: macrolides, fluoroquinolones, imidazole, and triazole antifungal agents, certain non-sedating antihistaminics (terfenadine, astemizole), cisapride.
- Artemether and lumefantrine tablets are not indicated for prophylaxis, or for treating severe malaria, including cerebral malaria, or malaria with pulmonary oedema or renal failure. It is also not indicated for and has not been evaluated in, the treatment of malaria due to P. vivax, P. malariae or P. ovale.

4.4. Special warnings and precautions for use

Co-fan QS is not recommended during the first trimester of pregnancy in situations where other suitable and effective antimalarials are available.

Co-fan QS 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, Co-fan QS 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 Co-fan QS, 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 Co-fan QS.

If quinine is given after Co-fan QS, close monitoring of the ECG is advised

If Co-fan QS is given after mefloquine, close monitoring of food intake is advised.

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

Co-fan QS is not indicated and has not been evaluated for prophylaxis of malaria.

Co-fan QS 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 Co-fan QS.

Like other antimalarials (e.g. halofantrine, quinine and quinidine) Co-fan QS has the potential to cause QT prolongation.

Caution is recommended when combining Co-fan QS 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 Co-fan QS.

Caution is recommended when combining Co-fan QS with hormonal contraceptives. Co-fan QS 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 Co-fan QS in patients with renal impairment is recommended. Caution is advised when administering Co-fan QS 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 Co-fan QS. In the absence of carcinogenicity study data, and due to lack of clinical experience, more than two courses of Co-fan QS 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

Interaction with drugs that are known to prolong the QTc interval

Co-fan QS is contraindicated with concomitant use of drugs (they may cause prolonged QTc interval and Torsade de Pointes) such as: antiarrhythmics of classes IA and III, neuroleptics and antidepressant agents, certain antibiotics including some agents of the following classes: macrolides, fluoroquinolones, imidazole, and triazole antifungal agents, certain non-sedating antihistaminics (terfenadine, astemizole), cisapride, flecainide.

Interaction with drugs metabolized by CYP2D6

Lumefantrine was found to inhibit CYP2D6 in vitro. This may be of particular clinical relevance for compounds with a low therapeutic index. Co-administration of Co-fan QS with drugs that are metabolised by this iso-enzyme is contraindicated (e.g. neuroleptics, metoprolol, and tricyclic antidepressants such as imipramine, amitriptyline, clomipramine) is contraindicated

Interaction with strong inducers of CYP3A4 such as rifampin

Oral administration of rifampin (600 mg daily), a strong CYP3A4 inducer, with Co-fan QS Tablets (6-dose regimen over 3 days) in six HIV-1 and tuberculosis coinfected adults without malaria resulted in significant decreases in exposure to artemether (89%), DHA (85%) and lumefantrine (68%) when compared to exposure values after Co-fan QS alone. Concomitant use of strong inducers of CYP3A4 such as rifampin, carbamazepine, phenytoin, St. John's Wort is contraindicated with Co-fan QS

Inducers should not be administered at least one month after Co-fan QS administration, unless critical to use as judged by the prescriber.

Interaction with other antimalarial drugs (see section 4.4)

Data on safety and efficacy are limited, and Co-fan QS should therefore not be given concurrently with other antimalarials unless there is no other treatment option (see section 4.4).

If Co-fan QS is given following administration of mefloquine or quinine, close monitoring of food intake (for mefloquine) or of the ECG (for quinine) is advised. The long elimination half-life of lumefantrine must be taken into account when administering quinine in patients previously treated with Co-fan QS. In patients previously treated with halofantrine, Co-fan QS should not be administered earlier than one month after the last halofantrine dose.

Mefloquine

A drug interaction study with Co-fan QS 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 Co-fan QS 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.

Quinine

A drug interaction study in healthy male volunteers showed that the plasma concentrations of lumefantrine and quinine were not affected when i.v. quinine (10 mg/kg BW over 2 hours) was given sequentially 2 hours after the last (sixth) dose of Co-fan QS (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 Co-fan QS 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 Co-fan QS 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 Co-fan QS.

Interaction with CYP3A4 inhibitors

Both artemether and lumefantrine are metabolised predominantly by the cytochrome enzyme CYP3A4, but do not inhibit this enzyme at therapeutic concentrations.

Ketoconazole

The concurrent oral administration of ketoconazole with Co-fan QS led to a modest increase (≤ 2-fold) in artemether, DHA, and lumefantrine exposure in healthy adult subjects. This increase in exposure to the antimalarial combination was not associated with increased side effects or changes in electrocardiographic parameters. Based on this study, dose adjustment of Co-fan QS is considered unnecessary in falciparum malaria patients when administered in association with ketoconazole or other potent CYP3A4 inhibitors.

Co-fan QS should be used cautiously with drugs that inhibit CYP3A4 and are contraindicated with drugs which additionally are known to prolong QTc, due to potential for increased concentrations of lumefantrine which could lead to QT prolongation.

Interaction with weak to moderate inducers of CYP3A4

When Co-fan QS is co-administered with moderate inducers of CYP3A4, it may result in decreased concentrations of artemether and/or lumefantrine and loss of antimalarial efficacy.

Interaction with anti-retroviral drugs such as protease inhibitors and non-nucleoside reverse transcriptase inhibitors

Both artemether and lumefantrine are metabolized by CYP3A4. ARTs, such as protease inhibitors and non-nucleoside reverse transcriptase inhibitors, are known to have variable patterns of inhibition, induction or competition for CYP3A4. Co-fan QS should be used cautiously in patients on ARTs since decreased artemether, DHA, and/or lumefantrine concentrations may result in a decrease of antimalarial efficacy of Co-fan QS, and increased lumefantrine concentrations may cause QT prolongation.

Lopinavir/ritonavir

In a clinical study in healthy volunteers, lopinavir/ritonavir decreased the systemic exposures to artemether and DHA by approximately 40% but increased the exposure to lumefantrine by approximately 2.3- fold. Exposures to lopinavir/ritonavir were not significantly affected by concomitant use of Co-fan QS.

Nevirapine

In a clinical study in HIV-infected adults, nevirapine significantly reduced the median Cmax and AUC of artemether by approximately 61% and 72%, respectively and reduced the median Cmax and AUC of dihydroartemisinin by approximately 45% and 37%, respectively. Lumefantrine Cmax and AUC were

non-significantly reduced by nevirapine. Artemether/lumefantrine reduced the median Cmax and AUC of nevirapine by approximately 43% and 46% respectively.

Efavirenz

Efavirenz decreased the exposures to artemether, DHA, and lumefantrine by approximately 50%, 45%, and 20%, respectively. Exposures to efavirenz were not significantly affected by concomitant use of Co-fan QS.

Interactions resulting in effects of Co-fan QS on other drugs

Interaction with drugs metabolized by CYP450 enzymes

When Co-fan QS is co-administered with substrates of CYP3A4 it may result in decreased concentrations of the substrate and potential loss of substrate efficacy. Studies in humans have demonstrated that artemisinins have some capacity to induce CYP3A4 and CYP2C19 and inhibit CYP2D6 and CYP1A2. Although the magnitude of the changes was generally low it is possible that these effects could alter the therapeutic response of drugs that are predominantly metabolised by these enzymes.

Interaction with hormonal contraceptives

In vitro, the metabolism of ethinyl estradiol and levonorgestrel was not induced by artemether, DHA, or lumefantrine. However, artemether has been reported to weakly induce, in humans, the activity of CYP2C19, CYP2B6, and CYP3A. Therefore, Co-fan QS may potentially reduce the effectiveness of hormonal contraceptives. Patients using oral, transdermal patch, or other systemic hormonal contraceptives should be advised to use an additional nonhormonal method of birth control for about one month.

Drug-food/drink interactions

Co-fan QS should be taken with food or drinks rich in fat such as milk as the absorption of both artemether and lumefantrine is increased.

Grapefruit juice should be used cautiously during Co-fan QS treatment. Administration of artemether with grapefruit juice in healthy adult subjects resulted in an approximately two fold increase in systemic exposure to the parent drug.

4.6. 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

A meta-analysis of observational studies including over 500 artemether-lumefantrine exposed women in their first trimester of pregnancy assessed adverse pregnancy outcomes. The data showed that compared to quinine, artemisinin treatment, including artemether-lumefantrine, was not associated with an increased risk of miscarriage, stillbirth or congenital anomalies. However, due to the limitations of these studies, the risk of adverse pregnancy outcomes for artemether-lumefantrine exposed women in early pregnancy cannot be excluded.

Safety data from pregnancy studies including over 1200 pregnant women who were exposed to artemether-lumefantrine during the second or third trimester did not show an increase in adverse pregnancy outcomes or teratogenic effects over background rates.

Studies in animals have shown reproductive toxicity.

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

Fertility

There is no information on the effects of Co-fan QS on human fertility

4.7. Effects on ability to drive and use machines

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

4.8. Undesirable effects

	Adults and adolescents above 12 years of age	Infants and children of 12 years of age and below (incidence estimates)
Blood and lymphatic system disorders		
Delayed haemolytic anaemia[#]	Not Known	Not Known
Immune system disorders		
Hypersensitivity	Not known	Rare
Metabolism and nutrition disorders		
Decreased appetite	Very common	Very common (16.8 %)
Psychiatric disorders		
Sleep disorders	Very common	Common (6.4 %)
Insomnia	Common	Uncommon
Nervous system disorders		
Headache	Very common	Very common (17.1 %)
Dizziness	Very common	Common (5.5 %)
Paraesthesia	Common	--
Ataxia, hypoaesthesia	Uncommon	--
Somnolence	Uncommon	Uncommon
Clonus	Common	Uncommon
Cardiac disorders		
Palpitations	Very common	Common (1.8 %)
Electrocardiogram QT prolonged	Common	Common (5.3 %)
Respiratory, thoracic and mediastinal disorders		
Cough	Common	Very common (22.7 %)
Gastrointestinal disorders		
Vomiting	Very common	Very common (20.2 %)
Abdominal pain	Very common	Very common (12.1 %)
Nausea	Very common	Common (6.5 %)
Diarrhoea	Common	Common (8.4 %)
Hepatobiliary disorders		
Liver function tests increased	Uncommon	Common (4.1 %)
Skin and subcutaneous tissue disorders		
Rash	Common	Common (2.7 %)
Pruritus	Common	Uncommon
Urticaria	Uncommon	Uncommon
Angioedema*	Not known	Not known
Musculoskeletal and connective tissue disorders		
Arthralgia	Very common	Common (2.1 %)

Myalgia	Very common	Common (2.2 %)
General disorders and administration site conditions		
Asthenia	Very common	Common (5.2 %)
Fatigue	Very common	Common (9.2 %)
Gait disturbance	Common	--

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

Both compounds, artemether and lumefantrine, have their own action site in the malarial parasite

Both artemether and lumefantrine act as blood schizontocides.

The site of antiparasitic action of both components of the combination 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 non-toxic haemozoin, malaria pigment.

Parasites in the infected erythrocytes ingest and degrade haemoglobin and concentrate the iron in a food vacuole in the form of toxic haem. Normally, the haem is then made harmless by conversion into haemozoin.

The presence of the endoperoxide bridge in artemether, generating singlet oxygen and free radicals which are very cytotoxic to the plasmodia, appears to be essential for antimalarial activity. Artemether is concentrated in the food vacuole. It then splits its endoperoxide bridge as it interacts with haem, blocking conversion to haemozoin, destroying existing haemozoin and releasing haem and a cluster of free radicals into the parasite.

Lumefantrine is thought to interfere with the haem polymerisation process, a critical detoxifying pathway for the malaria parasite.

Both artemether and lumefantrine have a secondary action involving inhibition of nucleic acid and protein synthesis within the malarial parasite. Inhibition of protein synthesis as the basic mechanism of action is suggested in studies which showed morphological changes in ribosomes as well as in the endoplasmic reticulum

Artemether and lumefantrine combination is active against the blood stages of P. vivax, but is not active against hypnozoites. Therefore, an 8- amino-quinoline derivative such as primaquine should be given sequentially after the combination in cases of mixed infections of P. falciparum and P. vivax to achieve hypnozoites eradication.

The combination is also associated with rapid gametocyte clearance.

5.2. Pharmacokinetic properties

Artemether is absorbed fairly rapidly with peak plasma concentrations reached about 2 hours after dosing. Absorption of lumefantrine, a highly lipophilic compound, starts after a lag period of up to 2 hours, with peak plasma concentration about 6-8 hours after dosing.

Food enhances the absorption of both artemether and lumefantrine. The relative bioavailability of artemether was increased more than two fold and that of lumefantrine sixteen fold compared with fasted conditions when artemether and lumefantrine tablets were taken after a high fat meal. Likewise, in patients with malaria, food increases the absorption of lumefantrine, although to a lesser extent (approximately two-fold), most probably due to the lower fat content of the food eaten by acutely ill patients. Acutely ill patients are reluctant to eat and tend to avoid high-fat foods. In order to improve bioavailability, patients should be encouraged to take the drug with a normal diet as soon as food can be tolerated.

Artemether and lumefantrine are both highly bound to human serum proteins in vitro (95.4% and 99.7%, respectively). The artemisinin metabolite dihydroartemisinin is also bound to human serum proteins (47%-76%). Radioacivity distribution of artemether was found to be equal between cells and plasma.

Artemether is rapidly and extensively metabolised by human liver microsomes (mostly through the enzyme CYP3A4/5) in vitro and in vivo, with a substantial first pass metabolism. The main active metabolite is dihydroartemisinin

Lumefantrine is N-debutylated in human liver microsomes. Lumefantrine is metabolised predominantly by the enzyme CYP3A4 in human liver microsomes. At therapeutic plasma concentrations, lumefantrine significantly inhibits the enzyme CYP2D6 in vitro. Lumefantrine and his metabolites are found in bile and faeces

Artemether and dihydroartemisinin are rapidly cleared from plasma with an elimination half-life of approximately 2-3 hours. Conversely, lumefantrine is eliminated very slowly with a terminal half-life of 2-3 days in healthy volunteers and 4-6 days in patients with falciparummalaria.

No urinary excretion data are available for humans. In animal studies, unchanged artemether has not been detected in both faeces and urine due to its rapid and high first-pass metabolism, but several metabolites (unidentified) have been detected in both faeces and urine. Lumefantrine is eliminated via the bile in rats and dogs with excretion primarily in the faeces

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipient

Avicel 101

Polyvinyl pyrrolidone (PVP) K30

Eragel

Talcum

Aerosil

Crosscarmellose sodium

Tween 80

Dicalci phosphate

Ethanol 96%

Magnesium stearate

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 months

6.4. Special precautions for storage

Store below 30ºC.

Keep the container tightly closed in order to protect from moisture

6.5. Nature and contents of container

Box of 1 blister x 6 tablets.

6.6. Special precautions for disposal

No special requirements for disposal.