1. NAME OF THE MEDICINAL PRODUCT

ARTEFEX QS (SOFTGELS OF ARTEMETHER AND LUMEFANTRINE)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Soft Gelatin Capsule Contains:
Artemether Ph.Int 80 mg
Lumefantrine Ph.Int 480 mg
Excipients q.s.

Sr.no	Name of Raw Material	Specification	Wt.per Cap. (Mg)	O.A. % Per Capsules	Qty .per Cap. With O.A. % (Mg)
A	**Active Ingredients**				
1	Artemether	Ph.Int	80	10 %	88
2	Lumefantrine	Ph.Int	480	10 %	528
B	**Excipients**				
1	Refined Corn Oil	USP	78.7	-	78.7
2	Hydrogenated Vegetable oil	BP	150	-	150
3	White Bees Wax	BP	150	-	150
4	Soya Lecithin	USP	5	-	5
5	Butylated Hydroxy Anisole	BP	0.1	-	0.1
6	Butylated Hydroxy Toluene	BP	0.05	-	0.05
7	Methyl Paraben	BP	0.1	-	0.1
8	Propyl Paraben	BP	0.01	-	0.01

3. PHARMACEUTICAL FORM

Soft Gelatin Capsules

4. Clinical particulars

Therapeutic indications Riamet 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.

4.1 Posology and method of administration

Posology

This medication is usually taken twice a day for 3 days (6 doses) or as directed by your doctor. On your first day of treatment, take your first dose, followed by your second dose 8 hours later. Then each day for the next 2 days, take one dose in the morning and one dose in the evening.

Method of administration: Oral Route

4.2 Contraindications

ARTEFEX QS (SOFTGELS OF ARTEMETHER AND LUMEFANTRINE) are contraindicated in the following conditions: In those with hypersensitivity to the active substances or any of the excipients. In cases of severe malaria. In the first trimester of pregnancy. 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 are not indicated for prophylaxis, or for treating severe malaria, including cerebral malaria, or malaria with pulmonary oedema or renal failure. Use with caution in patients with severe hepatic or renal insufficiency and patients refusing food intake. Patients who remain averse to food during treatment should be closely monitored as the risk of recrudescence may be greater.

4.3 Special warnings and precautions for use

Not be given to children except under medical advice. Keep the product out of reach children.

Artefex is not recommended during the first trimester of pregnancy in situations where other suitable and effective antimalarials are available.
Due to limited data on safety and efficacy, Artefex should not be given concurrently with any other antimalarial agent (see section 4.5) unless there is no other treatment options.
The long elimination half-life of lumefantrine must be taken into account when administering quinine in patients previously treated with Riamet.
If quinine is given after Artefex, close monitoring of the ECG is advised (see section 4.5).
If Artefex is given after mefloquine, close monitoring of food intake is advised (see section 4.5).
In patients previously treated with halofantrine, Artefex should not be administered earlier than one month after the last halofantrine dose.
It is not indicated and has not been evaluated for prophylaxis of malaria.
Artefex 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 Artefex, (see section 4.5).
Like other antimalarials (e.g. halofantrine, quinine and quinidine) Artefex has the potential to cause QT prolongation (see section 5.1).
Caution is recommended when combining Artefex 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 Artefex (see sections 4.5 and 5.2).

Caution is recommended when combining artefex with hormonal contraceptives. Artefex 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 (see sections 4.5).
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 Artefex in patients with renal impairment is recommended. Caution is advised when administering Artefex 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 Artefex. In the absence of carcinogenicity study data, and due to lack of clinical experience, more than two courses of Artefex cannot be recommended.

4.4 Interaction with other medicinal products and other forms of interaction

ARTEFEX QS (SOFTGELS OF ARTEMETHER AND LUMEFANTRINE) combination is well tolerated by children and adults, with most adverse events being of mild to moderate severity and duration. Many of the reported events are likely to be related to the underlying malaria and/or to an unsatisfactory response to treatment rather than to the combination. Common adverse events reported with artemether and lumefantrine combination included headache, dizziness, sleep disorder, abdominal pain, anorexia, diarrhoea, vomiting, nausea, palpitation, cough, arthralgia, myalgia, pruritus, rash, asthenia and fatigue. Somnolence, involuntary muscle contractions, paraesthesia, hypoaesthesia, abnormal gait, ataxia were other adverse effects reported with artemether and lumefantrine combination. Rare adverse event included hypersensitivity. Unspecified personality disorders have also been reported in children <5 years treated with artemether and lumefantrine combination

4.5 Pregnancy and Lactation

ARTEFEX QS (SOFTGELS OF ARTEMETHER AND LUMEFANTRINE) cannot be taken during pregnancy and nursing with doctor's advice.

4.6 Effects on ability to drive and use machines

Intake of ARTEFEX QS (SOFTGELS OF ARTEMETHER AND LUMEFANTRINE) does not affect the ability to drive and operate machines.

4.7 Undesirable effects

Common adverse events reported with artemether and lumefantrine combination included headache, dizziness, sleep disorder, abdominal pain, anorexia, diarrhea, vomiting, nausea, palpitation, cough, arthralgia, myalgia, pruritus, rash, asthenia and fatigue. Somnolence, involuntary muscle contractions, paraesthesia, hypoesthesia, abnormal gait, ataxia were other adverse effects reported with artemether and lumefantrine combination. Rare adverse event included hypersensitivity.

4.8 Overdose

Experience with overdosage is limited. In cases of suspected overdosage, symptomatic and supportive therapy should be given as appropriate. ECG and blood potassium levels should be monitored

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: antimalarials,

ATC code: P01BF01

Mechanism of action:

Artemether: A semi-synthetic derivative of artemisinin, artemether mechanism of action includes:

Binding to heme: Artemether peroxide group binds to heme, a by-product of haemoglobin degradation, to release toxic free radicals.

Disrupting cellular functions: The free radicals disrupt the parasite's Ca2+ transport and other cellular functions.

Rapid onset: Artemether has a rapid onset of action and is quickly cleared from the body.

Lumefantrine: A synthetic fluorone derivative, lumefantrine mechanism of action includes:

Binding to hemin: Lumefantrine binds to hemin, preventing it from being detoxified into hemozoin, a crystalline malaria pigment.

Slow onset: Lumefantrine has a slower onset of action than artemether, which allows it to clear any remaining parasites.

Pharmacodynamic effects:

ARTEFEX QS 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 hemoglobin breakdown, to the nontoxic haemozoin, malaria pigment. Lumefantrine is thought to interfere with the polymerization 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. ARTEFEX QS has been reported to have potent activity in terms of clearing gametocytes. By 2015, resistance to artemisinin emerged in Southeast Asia. Studies with ARTEFEX QS in this region showed delayed parasite clearance (manifested as a higher proportion of patients with parasitemia on Day 3 after initiation of treatment), although overall efficacy as measured by cure rates after 28 days, remained high (WHO 2014). In Africa, only isolated reports on delayed parasite clearance are available and a clear trend towards resistance development was not observed. Treatment of Acute Uncomplicated P. falciparum Malaria. The efficacy of ARTEFEX QS 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. Page 7 of 12 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)

5.2 Pharmacokinetic properties

Pharmacokinetic characterization of artemether and lumefantrine 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 with peak plasma concentrations reached about 2 hours after dosing. Absorption of lumefantrine, a highly lipophilic compound, starts after a lag-time of up to 2 hours, with peak plasma concentration about 6-8 hours after dosing. 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 Artefex 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). Lumefantrine 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 Lumefantrine (demethylation), predominantly through the isoenzyme CYP3A4/5. This metabolite has also been detected in humans in vivo. The artemether/ Lumefantrine AUC ratio is 1.2 after a single dose and 0.3 after 6 doses given over 3 days. In vivo data indicate that artemether have some capacity to induce cytochrome isoenzyme CYP2C19 and CYP3A4. Lumefantrine is further converted to inactive metabolites. Following repeated administration of Artefex (alone or in combination with

mefloquine), serum artemether levels decreased significantly, while levels of the metabolite Lumefantrine is increased, although not to a statistically significant degree. This indicates that there was induction of the enzyme responsible for the metabolism of artemether. 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 systemic exposure to the metabolite desbutyl-lumefantrine, for which the in vitro antiparasitic effect is 5 to 8 fold higher than lumefantrine, was less than 1% of the exposure to the parent drug. Desbutyl-lumefantrine data is not available specifically for an African population. In vitro, lumefantrine significantly inhibits the activity of CYP2D6 at therapeutic plasma concentrations. Elimination Artemether and Lumefantrine is are rapidly cleared from plasma with an elimination 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 artemether and lumefantrine. No urinary excretion data are available for humans. In rats and dogs unchanged artemether has not been detected in faeces and urine due to its rapid and high-first-pass metabolism, but several metabolites (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. After oral dosing in rats and dogs qualitative and quantitative recovery of metabolites in bile and faeces was relatively low, most of the dose being recovered as parent drug.

5.3 Preclinical safety data

General toxicity

The main changes observed in repeat-dose toxicity studies were associated with the expected pharmacological action on erythrocytes, accompanied by responsive secondary haematopoiesis.

Neurotoxicity

Studies in dogs and rats have shown that intramuscular injections of artemether resulted in brain lesions. Changes observed mainly in brainstem nuclei included chromatolysis, eosinophilic cytoplasmic granulation, spheroids, apoptosis and dark neurons. Lesions were observed in rats dosed for at least 7 days and dogs for at least 8 days, but lesions were not observed after shorter intramuscular treatment courses or after oral dosing. The estimated artemether 24 h AUC after 7 days of dosing at the no observed effect level is approximately 7-fold greater or more than the estimated artemether 24 h AUC in adult humans. The hearing threshold was affected at 20 dB by oral artemether administration to dogs at a dose of about 29 times the highest artemether clinical dose (160 mg/day) based on body surface area comparisons. Most nervous system disorder adverse events in the studies of the 6-dose regimen were mild in intensity and resolved by the end of the study.

Mutagenicity

Artemether and lumefantrine were not genotoxic/clastogenic based on *in vitro* and *in vivo* testing.

Carcinogenicity

Carcinogenicity studies were not conducted.

Reproductive toxicity studies

Embryotoxicity was observed in rat and rabbit reproductive toxicity studies conducted with artemether, a derivative of artemisinin. Artemisinins are known to be embryotoxic. Lumefantrine alone caused no sign of reproductive or development toxicity at doses up to 1,000 mg/kg/day in rats and rabbits, doses which are at least 10 times higher than the daily human dose based on body surface area comparisons.

Reproductive toxicity studies performed with the artemether-lumefantrine combination caused maternal toxicity and increased post-implantation loss in rats and rabbits.

Artemether caused increases in post-implantation loss and teratogenicity (characterised as a low incidence of cardiovascular and skeletal malformations) in rats and rabbits. The embryotoxic artemether dose in the rat yields artemether and dihydroartemisinin exposures similar to those achieved in humans based on AUC.

Fertility

Artemether-lumefantrine administration yielded altered sperm motility, abnormal sperm, reduced epididymal sperm count, increased testes weight, and embryotoxicity; other reproductive effects (decreased implants and viable embryos, increased preimplantation loss) were also observed. The no adverse effect level for fertility was 300 mg/kg/day. The relevance to this finding in humans is unknown.

Juvenile toxicity studies

A study investigated the neurotoxicity of oral artemether in juvenile rats. Mortality, clinical signs and reductions in body weight parameters occurred most notably in younger rats. Despite the systemic toxicity noted, there were no effects of artemether on any of the functional tests performed and there was no evidence of a direct neurotoxic effect in juvenile rats.

Very young animals are more sensitive to the toxic effect of artemether than adult animals. There is no difference in sensitivity in slightly older animals compared to adult animals. Clinical studies have established the safety of artemether and lumefantrine administration in patients weighing 5 kg and above.

Cardiovascular Safety Pharmacology

In toxicity studies in dogs at doses >600 mg/kg/day, there was some evidence of prolongation of the QTc interval (safety margin of 1.3-fold to 2.2-fold for artemether using calculated free Cmax), at higher doses than intended for use in man. In vitro hERG assays showed a safety margin of >100 for artemether and dihydroartemisinin. The hERG IC_{50} was 8.1 μ M for lumefantrine and 5.5 μ M for its desbutyl metabolite.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

1. Refined Corn Oil.....USP
2. Hydrogenated Vegetable Oil ..... BP
3. White Bees Wax.....BP
4. Butylated Hydroxy Anisole..... BP
5. Butylated Hydroxy Toluene..... BP
6. Soya lecithin .....USP
7. Methyl Paraben ..... BP
8. Propyl Paraben..... BP

6.2 Incompatibilities

None known.

6.3 Shelf life

24 months from the date of manufacturing.

6.4 Special precautions for storage

Store below 30°C in a cool & dry place,
Protect from direct light, heat & moisture.

Keep out of reach of children.

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

6 Capsules packed in Alu-PVC Blister Pack, 1 Blisters packed in mono carton along with package insert and 10 Mono Cartons are packed in 1 Outer Carton.

6.6 Special precautions for disposal <and other handling>

Not applicable

7. <APPLICANT/MANUFACTURER>

ASOJ SOFT CAPS PVT. LTD.
Asoj, Baroda – Halol Highway,
Dist. Baroda – 391 510. Gujarat.