SUMMARY OF PRODUCT CHARACTERISTICS

SYNRIAM™ 150+750 mg
(Arterolane Maleate and Piperaquine Phosphate Tablet)

1. NAME OF THE MEDICINAL PRODUCT

SYNRIAM™ 150+750 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains
Arterolane maleate equivalent to
Arterolane……..… 150 mg
Piperaquine phosphate…….. 750 mg

For the list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated Tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

SYNRIAM™ 150+750 mg (arterolane 150 mg and piperaquine phosphate 750 mg tablet) is indicated for the treatment of:

- acute uncomplicated *Plasmodium falciparum* malaria infection

It has been shown to be effective in geographical regions where resistance to chloroquine has been reported.

Limitations of Use
SYNRIAM™ 150+750 mg is not indicated for patients with severe or complicated *P. falciparum* malaria.

SYNRIAM™ 150+750 mg is not indicated for prevention of malaria.

4.2 Posology and method of administration

Administration Instructions
SYNRIAM™ 150+750 mg may be taken with or without food. Patients with acute malaria are frequently averse to food. Patients should be encouraged to resume normal

eating as soon as food can be tolerated. Administration with food has been shown to improve absorption of arterolane and piperaquine (see **section 5.2**).

SYNRIAM™ 150+750 mg should be administered over 3 consecutive days for a total of 3 doses taken at the same time each day.

In the event of vomiting within 30 minutes of administration, a repeat dose should be taken. If the repeat dose is also vomited within 30 minutes of administration, the patient should be given an alternative antimalarial for treatment.

Adults and Children more than 12 years
SYNRIAM™ 150+750 mg is recommended for adults and children more than 12 years.

Day of treatment	Dose
Day 1	1 tablet
Day 2	1 tablet
Day 3	1 tablet

Children 6 months to 12 years
SYNRIAM™ Dispersible Tablet 37.5 + 187.5 mg (arterolane 37.5 mg and piperaquine phosphate 187.5 mg tablet) is recommended for children aged 6 months to 12 years of age. For more information, please refer prescribing information of **SYNRIAM™ Dispersible Tablet 37.5 + 187.5 mg**.

Dosage in Patients with Renal or Hepatic Impairment
No specific pharmacokinetic studies have been carried out in patients with hepatic or renal impairment. Most patients with acute malaria present with some degree of hepatic and/or renal impairment.

The data available on the metabolism of arterolane maleate and piperaquine phosphate indicates that very little drug is excreted unchanged in urine.

Caution should be exercised when administering **SYNRIAM™** in patients with moderate to severe hepatic or renal impairment.

Instruct the patients to follow the below directions:
- take the tablets as instructed and complete the 3 days course of treatment
- if you forget to take the second dose at the right time, take it as soon as you remember. Then take the third (last) dose approximately 24 hours after the second dose
- if you forget to take the third (last) dose at the right time, take it as soon as you remember

- never take more than one dose on the same day to make up for a missed dose.

4.3 Contraindications

Patients hypersensitive to any of the active or inactive ingredients of this product.

Presently, any other specific contraindications are unknown.

4.4 Special warnings and precautions for use

Prolongation of QT Interval

Adults and children more than 12 years
QTc was normal in subjects who were treated with arterolane maleate and piperaquine phosphate alone.

In a trial conducted on the combination product of arterolane maleate and piperaquine phosphate (AM-PQP) in patients with acute uncomplicated *P. falciparum* malaria, no case of *Torsade de Pointes*, sudden death, ventricular tachycardia, ventricular fibrillation and flutter, syncope or seizure has been reported which could be identified as a direct outcome of significant prolongation of QTc interval. No patient was discontinued for any significant prolongation.

The mean ± SD QTc after Fridericia's correction was 389.0 ± 25.67 msec on Day 0 and 410.7 ± 26.71 msec on Day 2 after arterolane and piperaquine treatment.

In patients on arterolane maleate and piperaquine phosphate, 0.6% (4 out of 714) had QTcF > 500 msec and 6.9% (49 out of 714) had change in QTcF interval > 60 msec from baseline. All the 4 patients with QTcF prolongation > 500 msec had uneventful recovery and completed the study of 42 days duration.

In another trial conducted in patients with acute uncomplicated *P. vivax* malaria, there was no QTc prolongation of > 500 msec in patients treated with FDC of arterolane and piperaquine phosphate. However, the proportion of patients with QTc prolongation of > 60 msec from baseline were 1.9% in patients treated with FDC of arterolane and piperaquine phosphate whereas in 3.2% of patients in chloroquine group.

SYNRIAM™ should be avoided in patients:
- with congenital prolongation of the QT interval (e.g., long QT syndrome) or any other clinical condition known to prolong the QTc interval such as patients with a history of symptomatic cardiac arrhythmias, with clinically relevant bradycardia or with severe cardiac disease.
- with a family history of congenital prolongation of the QT interval or sudden death.

- with known disturbances of electrolyte balance, e.g., hypokalaemia or hypomagnesaemia.
- receiving other medications that prolong the QT interval, such as class IA (quinidine, procainamide, disopyramide), or class III (amiodarone, sotalol) antiarrhythmic agents; antipsychotics (pimozide, ziprasidone); antidepressants; certain antibiotics (macrolide antibiotics, fluoroquinolone antibiotics, imidazole, and triazole antifungal agents); or certain non-sedating antihistaminics (terfenadine, astemizole).

Use of QT Prolonging Drugs and Other Antimalarials
Halofantrine and **SYNRIAM™** should not be administered within three months of each other due to the long elimination half-life of piperaquine phosphate and potential additive effects on the QT interval.

Other antimalarials should not be given concomitantly with **SYNRIAM™**.

Drugs that prolong the QT interval, including antimalarials such as quinine and quinidine, should be used cautiously following **SYNRIAM™**, due to the long elimination half-life of piperaquine and potential additive effects on the QT interval.

Drug Interactions with CYP3A4
In vitro metabolism studies conducted in human liver microsomes have indicated that CYP3A4 is the primary isozyme responsible for metabolism of arterolane and piperaquine.

The pharmacokinetic parameters obtained for intravenous arterolane following pre-treatment with oral ketoconazole to rats were similar to those obtained in studies in the absence of ketoconazole. Hence, hepatic CYP3A4 is unlikely to play a major role in the systemic clearance of arterolane. Oral bioavailability of arterolane in rats increased ~ 20 fold with pretreatment of ketoconazole at the 3.5 mg/kg dose level, but was unaffected at the 35 mg/kg dose. These data most likely indicate an involvement of intestinal CYP3A and/ or P-glycoprotein in the dose dependent bioavailability of arterolane in the rat.

Drugs that have a mixed effect on CYP3A4, especially anti-retroviral drugs, and those that have an effect on the QT interval should be used with caution in patients taking **SYNRIAM™**.

Drug Interactions with CYP2D6
In vitro studies did not indicate either arterolane maleate or piperaquine phosphate was metabolized by CYP2D6.

Recrudescence
In the event of recrudescent *P. falciparum* infection after treatment with arterolane maleate and piperaquine phosphate, patients should be treated with a different antimalarial drug.

Hepatic and Renal Impairment
No specific pharmacokinetic studies have been performed in patients with hepatic or renal impairment (see **section 4.2**).

Elderly
Clinical studies of **SYNRIAM™** have included elderly patients up to 77 years of age. In general, greater frequency of decreased hepatic, renal, or cardiac function, and of presence of concomitant disease or other drug therapy in elderly patients should be considered when prescribing **SYNRIAM™**. The systemic exposure of arterolane maleate in healthy elderly male subjects has been found to be similar to that in healthy young male subjects (see **section 5.2**).

4.5 Interaction with other medicinal products and other forms of interaction

No clinical drug interaction studies of **SYNRIAM™** have been performed with other drugs.

Anti-Retroviral drugs (ARTs), such as protease inhibitors and non-nucleoside reverse transcriptase inhibitors, are known to have variable patterns of inhibition, induction or competition for CYP3A4. No formal drug-drug interaction studies of arterolane maleate and piperaquine phosphate with ARTs have been performed. However, **SYNRIAM™** should be used cautiously in patients on ARTs. The result may be an increase in piperaquine concentrations causing QT prolongation or a decrease in concentrations of the ART resulting in loss of efficacy, or a decrease in arterolane and/or piperaquine concentrations resulting in loss of antimalarial efficacy of arterolane maleate and piperaquine phosphate.

Quinine and other drugs that prolong the QT interval, should be used cautiously following **SYNRIAM™**, due to the long elimination half-life of piperaquine phosphate and potential additive effects on the QT interval.

4.6 Pregnancy and lactation

Pregnancy
The efficacy of **SYNRIAM™** in the treatment of acute uncomplicated malaria in pregnant women has not been established. Pregnant women were not included in the clinical studies conducted with this combination.

However, during the conduct of a phase III, double-blind, randomised, multicenter trial comparing the safety and efficacy of fixed dose combination tablets of arterolane maleate and piperaquine phosphate with artemether-lumefantrine tablets in patients with acute uncomplicated *Plasmodium falciparum* malaria, 6 patients were found to be pregnant during study follow-up. Out of six patients, five had received arterolane maleate and piperaquine phosphate while one patient had received artemether and lumefantrine. Out of five patients who were administered arterolane maleate and piperaquine phosphate**,** four patients had normal delivery while one patient had spontaneous abortion. One patient in artemether and lumefantrine group had premature rupture of membranes on 27th week of twin pregnancy consecutive to urinary infection resulting in premature delivery. Both the neonates could not survive. Both these serious adverse events were considered not related to the study medication.

Arterolane maleate in rabbits did not show any teratogenic findings and the No Observed Effect Level (NOEL) for foetal organisms was 30 mg/kg, higher than that of maternal NOEL (10 mg/kg). However, in rats at similar highest dose (90 mg/kg), there was increased post-implantation loss, reduced body weight gain, reduced foetal weights and an increased incidence of interventricular septal defect, dilated aortic arch, reduced spleen size, ductus arteriosus and/or pulmonary trunk narrowing. An isolated incidence of interventricular septal defect was also noticed in a single foetus (1/135 foetuses) at 10 mg/kg. Hence, 10 mg/kg was considered as NOEL for foetal organisms and 30 mg/kg for maternal organisms and reproductive parameters in this study (see **section 5.3**).

There are no published data relating to the safety of piperaquine in pregnancy. Although extensive experience with other closely related aminoquinoline drugs such as chloroquine in these patient groups suggests that piperaquine is likely to be safe, use of piperaquine during pregnancy cannot be recommended at this time.

SYNRIAM^{TM} should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the foetus.

Fertility
There is no information on the effects of **SYNRIAM^{TM}** on human fertility.

Fertility, early embryonic and pre-weaning development in rats were least affected with arterolane alone and the No Observed Effect Level (NOEL) was 25 mg/kg body weight. However, in toxicity study of combination of arterolane and piperaquine, the estrous cyclicity of rats was affected leading to increased pre-coital duration. These effects have been attributed to piperaquine phosphate as such findings have also been observed in repeated dose toxicity study in rats with piperaquine phosphate. In mice, NOAEL for reproduction toxicity was 20 + 4 mg/kg (see **section 5.3**).

Lactation

Lactating women were not included in the clinical studies conducted with **SYNRIAM™**.

In excretion and mass balance experiments with ^{14}C arterolane maleate, low levels of radioactivity were detected in foetal tissues from pregnant rats, as well as in milk from lactating rats. The highest mean concentration of total radioactivity in milk was noticed at 8h post dose, less than that measured in plasma (plasma: milk ratio of 1:1 at 8 h and 0.6 at all other times). No significant radioactivity remains in the milk by 48h post dose. Considering the lipophilicity of piperaquine, it is expected to be excreted in human milk.

There are no published data relating to the safety of piperaquine phosphate in lactation. Although extensive experience with other closely related aminoquinoline drugs such as chloroquine in these patient groups suggests that piperaquine is likely to be safely used, use of piperaquine phosphate during lactation cannot be recommended at this time.

The benefits of breastfeeding to mother and infant should be weighed against potential risk from infant exposure to **SYNRIAM™** through breast milk.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, when driving vehicles or operating machines it should be taken into account that occasionally dizziness may occur.

4.8 Undesirable effects

Summary of the safety profile

The safety of **SYNRIAM™ 150+750 mg** has been evaluated in two phase III randomized trials in 873 adults and children more than 12 years. In comparative trials, the adverse reaction profile of **SYNRIAM™ 150+750 mg** appeared similar to that of another antimalarial regimen.

In a randomized, double blind, multicenter trial 714 patients of *P. falciparum* malaria were exposed to **SYNRIAM™ 150+750 mg**. Majority of the adverse reactions were related to deranged laboratory parameters in the study. Most adverse reactions were mild to moderate in severity. The most commonly reported adverse reactions were neutropenia, aspartate aminotransferase increased, eosinophil count increased, haematocrit decreased, haemoglobin decreased, lymphocyte count increased, monocyte count increased, neutrophil count decreased, reticulocyte count increased

and white blood cell count decreased. No death was reported in the trial. Discontinuation of **SYNRIAM™ 150+750 mg** due to adverse drug reactions occurred in 2.8% patients. A total of 4 (0.6%) patients had serious adverse events in the study which were not related to study medication.

In another randomized, open label, multicenter trial 159 patients of *P. vivax* malaria were exposed to **SYNRIAM™ 150+750 mg**. Majority of the adverse reactions were related to deranged laboratory parameters in the study. The most commonly reported adverse drug reactions were eosinophil count increased, haematocrit decreased, haemoglobin decreased and reticulocyte count increased. Most of the adverse reactions were mild or moderate in severity. No death was reported in the trial. A total of 4 (2.5%) patients had serious adverse events in the study; 3 (1.9%) were not related to study medication.

Tabulated list of adverse reactions

In the tables below, adverse drug reactions (ADRs) are listed under system organ class (SOC), and ranked by headings of frequency, using the following 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 the available data).

Description of selected adverse reactions

The ADRs noted for **SYNRIAM™** were generally mild in severity, and the majority were non-serious. Reactions such as anaemia, cough, pyrexia, headache, asthenia, anorexia and the observed changes in blood cell parameters are consistent with those expected in patients with acute malaria.

Table: Frequency of ADRs in Adults and Children more than 12 years Participated in Clinical Trials with SYNRIAM™ 150+750 mg

SOC	Very Common	Common	Uncommon
Blood and lymphatic system disorders	Eosinophilia, Neutropenia	Anaemia, Leukocytosis, Leukopenia, Lymphocytosis, Reticulocytosis, Thrombocytopenia	Lymphopenia, Monocytosis, Neutrophilia, Thrombocythaemia
Cardiac disorders		Bradycardia	Arrhythmia, Bradyarrhythmia, Bundle branch block right, Sinus arrhythmia, Sinus bradycardia, Tachycardia
Ear and labyrinth disorders			Tinnitus

SOC	Very Common	Common	Uncommon
Gastrointestinal disorders		Abdominal pain, Abdominal pain upper, Diarrhoea, Nausea, Vomiting	Abdominal distension, Abdominal pain lower, Constipation, Epigastric discomfort, Salivary hypersecretion, Tongue ulceration
General disorders and administration site conditions		Asthenia	Chills, Pyrexia, Fatigue, Hyperthermia, Hypertrophy, Inflammation, Pain
Hepatobiliary disorders		Hyperbilirubinaemia	Jaundice
Infections and infestations			Filariasis, Malaria, Oral herpes, Respiratory tract infection, Rhinitis, Rickettsiosis

SOC	Very Common	Common	Uncommon
Investigations	Aspartate aminotransferase increased, Haematocrit decreased, Haemoglobin decreased, Reticulocyte count increased, Eosinophil count increased, Lymphocyte count increased, Monocyte count increased, Neutrophil count decreased	Alanine aminotransferase increased, Blood alkaline phosphatase increased, Blood bilirubin increased, Protein total decreased, Protein total increased, Blood albumin decreased, Blood creatinine increased, Blood urea decreased, Blood glucose decreased, Blood glucose increased, Blood potassium decreased, Blood potassium increased, Blood sodium decreased, Blood sodium increased, Electrocardiogram QT prolonged, Mean cell haemoglobin decreased, Reticulocyte count decreased, Mean cell volume decreased, Mean cell volume increased, White blood cell count decreased, White blood cell count increased, Basophil count increased, Lymphocyte count decreased, Monocyte count decreased, Neutrophil count increased, Platelet count decreased, Platelet count increased	Alanine aminotransferase decreased, Aspartate aminotransferase decreased, Blood alkaline phosphatase decreased, Blood bilirubin decreased, Blood albumin increased, Blood creatinine decreased, Blood urea increased, Blood chloride decreased, Cardiac murmur, Haematocrit increased, Haemoglobin increased, Mean cell haemoglobin concentration decreased, Mean cell haemoglobin increased, Red blood cell count decreased, Red blood cell sedimentation rate increased, Red cell distribution width increased, Reticulocyte percentage increased, Eosinophil count decreased, Blood urine present, Urobilin urine present

SOC	Very Common	Common	Uncommon
Metabolism and nutrition disorders		Hyperglycaemia, Hyperkalaemia, Hypernatraemia, Hypoalbuminaemia, Hypoglycaemia, Hypokalaemia, Hyponatraemia	Anorexia, Hyperalbuminaemia, Hypercalcaemia, Hyperproteinaemia, Increased appetite
Musculoskeletal and connective tissue disorders			Arthralgia, Back pain, Muscle spasms, Muscular weakness, Myalgia, Neck pain
Nervous system disorders		Dizziness, Headache	Dysgeusia, Paraesthesia
Psychiatric disorders			Insomnia
Renal and urinary disorders		Proteinuria	Glycosuria, Leukocyturia, Nephritis
Reproductive system and breast disorders			Galactorrhoea
Respiratory, thoracic and mediastinal disorders		Cough	Nasal congestion, Rhinorrhoea
Skin and subcutaneous tissue disorders			Hyperhidrosis, Pruritus, Rash, Urticaria
Vascular disorders			Hypertension, Hypotension
CTCAE was used to assess the severity of adverse events. Adverse events which were not listed in the CTCAE were assessed as per the CTEP, NCI guidelines CTCAE: Common Terminology Criteria for Adverse Events; CTEP: Cancer Therapy Evaluation Program; NCI: National Cancer Institute			

Post-marketing Experience

In a phase IV, post-marketing trial of **SYNRIAM™ 150+750 mg** in 410 patients with *P. vivax* malaria, majority of the reported adverse reactions were "mild" in intensity. All the adverse reactions were resolved by the end of the trial. None of the subject was withdrawn from the trial due to adverse reaction. No death was reported in the trial. Adverse reactions are presented below:

Gastrointestinal disorders: *Common:* vomiting; *Uncommon*: nausea, abdominal pain upper, gastritis

Ear and labyrinth disorders: *Uncommon:* vertigo

Nervous system disorders: *Uncommon:* headache, burning sensation

Musculoskeletal and connective tissue disorders: *Uncommon:* myalgia

Metabolism and nutrition disorders: *Uncommon:* decreased appetite

Respiratory, thoracic and mediastinal disorders: *Uncommon:* cough, rhinorrhea, dyspnea

Infections and infestations: *Uncommon:* furuncle

Blood and lymphatic system disorders: *Uncommon:* anaemia

Investigations: *Common:* electrocardiogram QT prolonged; *Uncommon:* aspartate aminotransferase increased, alanine aminotransferase increased, platelet count decreased
General disorders and administration site conditions: *Common:* pyrexia; *Uncommon:* asthenia, chills, pain

In a post-marketing surveillance study of **SYNRIAM™ 150+750 mg** in 336 patients with *P. falciparum* malaria, following adverse events were reported: vomiting, nausea, headache, abdominal pain, diarrhea, dizziness, and re-infection with *P. vivax* malaria.

The following additional adverse reactions have been reported during post-marketing use of **SYNRIAM™ 150+750 mg**. Because these spontaneously reported events are from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Eye disorders: eye irritation, ocular hyperaemia
Gastrointestinal disorders: gastritis, retching, gastric disorder, haemorrhoids, rectal haemorrhage
General disorders and administration site conditions: irritability
Infections and infestations: nasopharyngitis
Nervous system disorders: somnolence, confusional state, disorientation, dyskinesia, dystonia
Psychiatric disorder: nightmare
Hepatobiliary disorders: hepatitis, cholecystitis
Kidney and urinary disorders: polyuria
Musculoskeletal and connective tissue disorders: trismus
Investigations: blood pressure diastolic decreased

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via drugssafety@sunpharma.com or http://www.sunpharma.com/sunpharma-adverse-event.

4.9 Overdose

There is no information available on overdose of **SYNRIAM™**.

Single doses of 600 mg of arterolane and 1500 mg of piperaquine phosphate have been found to be well tolerated in humans.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of Action

SYNRIAM™ is a fixed dose combination containing arterolane maleate and piperaquine phosphate. Both components are blood schizontocides.

Arterolane maleate is a synthetic trioxolane compound. *In vitro* and *in vivo* studies have been performed with the human pathogen, *P. falciparum*, and the rodent specific species, *P. berghei*, respectively. In the efficacy models of *P. falciparum* malaria using Swiss mice infected with (intravenous) *P. berghei*, it was found to be more potent than the standard reference antimalarial drugs- chloroquine, mefloquine and artesunate.

Piperaquine phosphate is an established antimalarial drug in China and several Southeast Asian malaria endemic countries. It is a bisquinoline compound. It probably acts in a way similar to chloroquine i.e. by inhibiting haeme-digestion pathway in the parasite. It has antimalarial activity against both *P. vivax* and *P. falciparum*, including strains of chloroquine-resistant *P. falciparum*. Numerous *in vitro* studies have shown good antimalarial activity of piperaquine against chloroquine-resistant *Plasmodium* strains. The activity of piperaquine phosphate and other bisquinolines has also been examined against chloroquine in *P. berghei* strains in mice. Piperaquine demonstrated a significantly lower resistance index *in vitro* than chloroquine and good *in vivo* activity against *P. berghei* in mice without significant toxicity.

The potential interaction between arterolane maleate and piperaquine phosphate has been investigated using *in vitro* and *in vivo* malaria models. *In vitro* drug combination assays were performed against the laboratory *P. falciparum* strains NF54 (chloroquine-sensitive) and K1 (chloroquine-resistant) strains. A slight antagonism was observed. Murine model was used to verify if the slight antagonism present in the *in vitro* arterolane and piperaquine combination is also observed *in vivo*. A classical *in vivo* combination experiment using *P. berghei*-infected mice was performed with different ratios and different doses of each compound. An additive action was noticed between arterolane maleate and piperaquine phosphate.

In conclusion, arterolane maleate is rapid and short acting antimalarial while piperaquine phosphate is slow and long acting, and the combination provides antimalarial activity at different time windows.

The efficacy and safety of **SYNRIAM™** have been assessed in four randomised, clinical trials:

Adults and children more than 12 years
The safety and efficacy of fixed dose combination tablets of arterolane maleate and piperaquine phosphate (AM-PQP) was compared to artemether and lumefantrine tablets in patients with acute uncomplicated *P. falciparum* malaria in a phase III, double-blind, randomized, multi-center, multi-national trial. There were no early treatment failures. Late clinical failure and late parasitological failures were in 18 out of 714 patients treated with AM-PQP and in 28 out of 358 patients treated with artemether and lumefantrine. In per protocol (PP) population, AM-PQP was effective and attained Polymerase Chain Reaction corrected Adequate Clinical and Parasitological Response (ACPR) at Day 28 in 99.25% patients (659 out of 664) whereas 99.07% (320 out of 323) patients were considered to be cured after artemether and lumefantrine treatment.

For PCR corrected ACPR in PP population on Day 42, 98.61% (637 out of 646) patients were considered to be cured after AM-PQP treatment whereas 98.36% (300 out of 305) patients were considered to be cured after artemether and lumefantrine treatment.

Median parasite clearance time (PCT) and fever clearance time (FCT) for the combination of AM-PQP were 24 hours and 6 hours, respectively.

AM-PQP was found to be noninferior to artemether and lumefantrine considering uncorrected and corrected ACPR on Day 28. This was supported by survival analysis.

In another phase III, open-label, randomized, parallel group, multi-center trial, the safety and efficacy of AM-PQP was compared to chloroquine tablets in patients with acute uncomplicated *P. vivax* malaria. Outcomes for the primary endpoint defined as aparasitemic and afebrile patients at day 3 in per protocol population, achieved were 100%, (140/140; 95% CI 97.40, 100) in the AM-PQP group and 99.3%, (145/146; 95% CI 96.24, 99.98) in the chloroquine phosphate group. Median PCT was 24.0 hours in AM-PQP group and 26.0 hours in chloroquine group. Median FCT was similar (24.0 hours) in both the treatment groups. Day 28 cure rates were 100% in per protocol population in both the treatment groups.

Effects on the Electrocardiogram
See **section 4.4**

5.2 Pharmacokinetics properties

Absorption

Arterolane Maleate

Arterolane maleate is well absorbed with a relatively short $t_{1/2}$ of 2 to 4 h. The T_{max} in healthy young male subjects was observed to be 4.5 to 5.25 h. Secondary peaks were seen in arterolane plasma concentration time profiles that may be possibly related to regional absorption in the gut, enterohepatic cycling or variable gastric emptying. There is evidence of a greater than dose proportional increase in systemic exposure to arterolane maleate.

A 33% increase in systemic exposure to arterolane has been observed with food. The systemic exposure in elderly male subjects has been found to be similar to that in young, healthy, male subjects. Systemic exposure to arterolane in elderly females was higher than that in elderly males; however, these apparent differences were not statistically significant.

Plasma concentrations of arterolane in patients with uncomplicated *P. falciparum* malaria were observed to be significantly lower than those in healthy subjects. Parasitaemia and/or disease condition leads to lower exposure and higher clearance.

Results of a pharmacokinetic study in healthy Thai subjects illustrated that time of dosing, posture or ethnicity did not influence the pharmacokinetics of arterolane maleate.

Piperaquine Phosphate

Piperaquine is well absorbed following oral administration of single oral doses of piperaquine up to 1500 mg in young healthy male subjects, maximum plasma piperaquine concentrations (C_{max}) were attained on average (median), at 2.5 to 4.5 h (T_{max}) post dose. The plasma concentration time profiles of piperaquine indicated irregular absorption with a typical pattern of double or multiple peaks at each dose level. The initial peak was apparent at 2 to 4 h post-dose followed by a secondary peak at approximately 6 to 8 h post-dose. Due to this irregular absorption, the estimation of terminal half-life was not reliable. The individual terminal half-life ranged from 1.5 to 37 days, while mean values ranged from 11 to 18 days.

Following single (Day 1) and repeated (Day 3) oral doses of 500 to 1500 mg piperaquine phosphate, the mean systemic exposure (AUC_{0-24}) to piperaquine after once-daily dosing (Day 3) was 3-7 fold higher than that after a single dose (Day 1), consistent with the long elimination half-life relative to the dosing interval. Secondary peaks were observed in the plasma piperaquine concentration-time profiles. Plasma concentrations of piperaquine were measurable up to 60 days following single and multiple doses, with the lower limit of quantification as 1 ng/mL. The mean terminal

half-lives ranged from 11 to 18 days following single dose administration and from 17 to 23 days following multiple dose administration.

Arterolane Maleate and Piperaquine Phosphate

In healthy young male subjects exposure of arterolane is almost doubled upon co-administration with piperaquine phosphate. This increase in arterolane exposure is dose proportional when arterolane dose is increased from 100 to 200 mg. There is little if any, increase in exposure of arterolane with increase in the combination dose of piperaquine phosphate from 500 to 1000 mg (plateau effect).

Geometric mean of pharmacokinetic parameters for arterolane 150 mg and piperaquine phosphate 750 mg following single dose administration of FDC to young healthy male subjects under fasting condition are given below:

Table: Mean Pharmacokinetic Parameters of Arterolane, Piperaquine in Young Healthy subjects

Parameters	Arterolane	Piperaquine Phosphate
T_{max} (h)	3.38±1.63	4.59±1.24
C_{max} (ng/mL)	127.73±33.86	92.68±54.73
AUC_{0-t}(ng.h/mL)	1146.70±409.60	1431.48±854.02
$t_{1/2}$ (h)	3.98±0.57	-*

FDC: Fixed dose combination tablet of arterolane 150 mg and piperaquine phosphate 750 mg, as one tablet (n=16).
AUC_{0-t}: AUC 0 to last measurable concentration (sampling up to 96 h).
*$t_{1/2}$ not reported as it could not be reliably determined from 96 h sampling (reported piperaquine $t_{1/2}$ is ~15 days).

Patients with Acute Uncomplicated Plasmodium falciparum Malaria

Geometric mean of pharmacokinetic parameters for arterolane 150 mg and piperaquine phosphate 750 mg following administration of FDC to patients with *P. falciparum* malaria across sites in Africa and Asia are given below:

Table: Mean Pharmacokinetic Parameters of Arterolane, Piperaquine in Adult Patients with *P. falciparum* Malaria across Sites in Africa and Asia

Parameter	Arterolane		Piperaquine	
	C_{max} (ng/mL)	**AUC_{last} (h.ng/mL)**	**C_{max} (ng/mL)**	**AUC_{last} (h.ng/mL)**
Mean ± SD	61.02±39.86	1754.71±2154.86	238.88± 230.71	66843.90± 83039.69

Note: C_{max}: Maximum observed concentration (may not be "true" C_{max}) obtained in 202 patients and minimal profile to calculate AUC was obtained in 197 patients for arterolane and 662 patients and 660 patients respectively for Piperaquine. Pharmacokinetic parameters determined based on sparse sampling times and, from subjects who had 2-3 non below level of quantification (BLQ) concentrations.

The C_{max} and AUC_{last} of both arterolane and piperaquine in patients of uncomplicated falciparum malaria exhibited high variability when sparse samples were collected for pharmacokinetic analysis.

Patients with Acute Uncomplicated Plasmodium vivax Malaria
One hundred and twelve patients with uncomplicated *P. vivax* malaria were analyzed for pharmacokinetic analysis for FDC of arterolane maleate and piperaquine phosphate.

Pharmacokinetic results of arterolane indicate that C_{max} (ng/mL), AUC $_{48\text{-}72}$ (ng*h/mL), $t_{//2}$ (h) are 60.26, 377.46, 3.20 respectively. Piperaquine exposure increased on Day 2 following multiple dosing as compared to single dose exposure. The mean piperaquine C_{max} (ng/mL), $AUC_{48\text{-}72}$ (ng*h/mL), $t_{//2}$ (h) are 317.82, 4449.79 and 228.33 respectively.

Pharmacokinetic results through non-compartmental analysis indicate that the mean rate and extent of absorption for arterolane and piperaquine were apparently similar to those observed in patients treated for *P. falciparum* malaria. Parasite Clearance Time for patients treated with the FDC of arterolane maleate and piperaquine phosphate seem lower than that for the other treatment (Chloroquine phosphate). Exposures for chloroquine were higher as compared to piperaquine exposures.

Food effect on pharmacokinetics of co-administration of Arterolane Maleate and Piperaquine Phosphate
In presence of piperaquine phosphate, the normal fat food has no effect on exposure of arterolane i.e. arterolane maleate can be administered with or without food. Pharmacokinetic parameters of piperaquine phosphate are not affected by arterolane maleate. On the other hand, exposure of piperaquine phosphate is doubled in presence of food, similar to that observed when administered alone.

Distribution
Arterolane Maleate
The plasma protein binding of arterolane is ~93% in human at 200 and 2000 ng/mL concentrations.

Piperaquine Phosphate
Piperaquine phosphate is highly bound to plasma proteins (>99%) in all the species tested, including human in 100 to 1000 ng/mL concentration range. *In vitro* blood to plasma concentration ratio of piperaquine phosphate ranged between 0.99 to 1.20 for human, in 100 to 1000 ng/ml. These results suggest that piperaquine phosphate does not bind extensively to human red blood cells.

Elimination (Metabolism & Excretion)
Arterolane Maleate
In vitro metabolism studies with human liver microsomes showed that the major metabolic pathway is the oxidation of the adamantane moiety. Metabolism in human

cryopreserved hepatocytes demonstrated that the compound is fairly stable in human hepatocytes. Studies with purified cDNA expressed isozymes indicate CYP3A4 is the primary isozyme responsible for the metabolism. However, the *in vivo* interaction study with ketoconazole illustrated that CYP3A is unlikely to play a major role in the systemic clearance.

Piperaquine Phosphate
Piperaquine phosphate is fairly stable on incubation with hepatic microsomes. The *in vitro* degradation half-life of piperaquine phosphate in human microsomes was 41 minutes at 0.5 µM. The half-life increased with increase in concentration for human microsomes. The *in vitro* biotransformation study with five major recombinant human cytochrome P450 isozymes indicated that CYP3A4 is the primary isozyme responsible for the Phase I metabolism. However, the major metabolites of piperaquine phosphate generated by CYP3A4 are yet to be identified. The cleavage metabolite was not produced by CYP3A4, and the hydroxylated metabolite was formed at very low levels. Piperaquine phosphate also inhibits CYP3A4 with an IC_{50} of ~5µM. Observed metabolites from liver microsomes are monooxygenated and dioxygenation products.

The high molecular weight of piperaquine phosphate, together with its pharmacokinetic properties suggests that it may undergo enterohepatic recycling.

Combination of Arterolane Maleate and Piperaquine Phosphate
In vitro metabolism studies conducted in human liver microsomes have indicated that both arterolane maleate and piperaquine phosphate are substrates for cytochrome P450 3A4. Using heterologously-expressed recombinant human CYP3A4 microsomes, arterolane maleate was found to have no effect on the rate of metabolism of piperaquine phosphate (IC_{50} of 38 µM). In comparison, piperaquine phosphate reduced the rate of metabolism of arterolane maleate with an IC_{50} of 0.5 µM. Additional studies conducted using the same test system over a range of substrate (i.e. arterolane maleate) and inhibitor (i.e. piperaquine phosphate) concentrations indicated that the Ki for piperaquine inhibition of arterolane maleate metabolism by human CYP3A4 is approximately 0.1 µM.

Pharmacokinetics in Special Populations

Hepatic and Renal Impairment
No specific pharmacokinetic studies have been performed in patients with either hepatic or renal impairment.

Paediatric Patients
Pharmacokinetic parameters of arterolane and piperaquine were evaluated in paediatric patients with *P. falciparum* malaria following oral administration of 3 doses of **SYNRIAM™ Dispersible Tablet 37.5 + 187.5 mg** over 3 days period. Paediatric

patients aged 6 months to 2 years, 2 to 6 years and 6 to 12 years were treated with 1, 2 and 3 tablets daily, respectively. The mean C_{max} for arterolane was 57.90, 87.52 and 93.08 ng/mL and the mean exposure (AUC) of arterolane was 985.19, 2157.36 and 2158.47 h.ng/mL across age groups of 6 months to 2 years, 2 to <6 years and 6 to ≤12 years, respectively. Similarly, the mean C_{max} of piperaquine was from 315.08, 550.27 and 523.75 ng/mL and the mean exposure was from 38018.82 h.ng/mL, 74148.42 h.ng/mL and 77032.99 h.ng/mL across age groups of 6 months to 2 years, 2 to 6 years and 6 to 12 years, respectively.

Elderly Patients
No specific pharmacokinetic studies have been performed with arterolane maleate and piperaquine phosphate in patients older than 65 years of age.

The systemic exposure of arterolane in healthy elderly male subjects has been found to be similar to that in healthy young male subjects. Systemic exposure to arterolane in elderly females was higher than that in elderly males; however, these apparent differences were not statistically significant.

CYP Interaction
In vitro inhibition potential (IC_{50}) of arterolane maleate for CYP3A4, CYP1A2, CYP2C9 and CYP2D6 is greater than 40-50 µM. Hence, the compound is unlikely to inhibit these isozymes at therapeutic concentrations.

In vitro metabolism studies conducted in human liver microsomes have indicated that both arterolane maleate and piperaquine phosphate are substrates for cytochrome P450 3A4. However, the *in vivo* interaction study with ketoconazole in rats demonstrated that CYP3A is unlikely to play a major role in the systemic clearance of arterolane. Piperaquine phosphate is an inhibitor of cytochrome P450 3A4.

5.3 Preclinical safety data

Carcinogenesis, mutagenesis, impairment of fertility
Carcinogenesis
Carcinogenicity studies were not conducted.

Mutagenesis
Both, arterolane maleate and piperaquine phosphate were found to be non-mutagenic in bacterial reverse mutation (Ames) assay and non- clastogenic in *in-vitro* chromosomal aberration test in human lymphocytes and in *in-vivo* murine micronucleus induction assay, tested individually.

Reproductive Toxicity

Studies were conducted on arterolane maleate individually in rat and on combination of arterolane maleate and piperaquine phosphate in both rat and mouse.

The reproductive parameters viz. fertility, early embryonic and pre weaning development in rats were least affected in rats with arterolane alone and the No Observed Effect Level (NOEL) determined was 25 mg/kg body weight as compared to systemic effects (NOAEL 25 mg/kg body weight/day). The toxicity manifested at highest dose of 60 mg/kg was in form of marginally increased post implantation loss leading to reduced live birth index.

For the combination, the study in rat showed less toxicity to reproductive parameters (NOEL 25 + 1.25 mg/kg) than to systemic toxicity (NOAEL for parental toxicity 10 + 0.5 mg/kg). The toxicity at highest dose was manifested in form of adversely affected estrous cyclicity that resulted in slightly increased precoital duration. Piperaquine was found to induce vaginal anestrous and atrophy of uterus and ovaries in repeated dose study in rat. Further, the results of this study when compared with the results of arterolane maleate alone, it is clearly evident that additional toxicity for the combination was attributed to piperaquine. In mice, the NOAEL for both, reproduction and systemic toxicity was inferred to be 20 + 4 mg/kg.

For arterolane maleate, embryo-foetal toxicity study conducted in rabbit, did not reveal any teratogenic findings in spite of evidence of maternal toxicity, increased incidence of post-implantation loss and reduced foetal weights at the highest dose of 90 mg/kg. The NOEL of 30 mg/kg for foetal organisms was higher than that of maternal NOEL of 10 mg/kg. In rat, administration at similar highest dose (90 mg/kg), resulted in increased post-implantation loss, reduced body weight gain, reduced foetal weights and an increased incidence of interventricular septal defect (5/48 foetuses), dilated aortic arch (6/48 foetuses), reduced spleen size (4/48 foetuses), ductus arteriosus and/or pulmonary trunk narrowed (5/48 foetuses). At 30 mg /kg dose, an interventricular septal defect was noticed in 1/135 foetus examined. The NOEL determined for maternal organisms and reproductive parameters was 30 mg/kg and for foetal organisms as 10 mg/kg.

Other reproduction toxicity studies designed to evaluate potential risks to maternal health and to development of conceptuses, their birth, physical and functional growth, attainment of sexual maturity, mating ability and their reproductive competence was conducted in rats and mice. In rats, NOAEL for reproductive parameters was 60+3 mg/kg about 2.4 times higher than the dose level at which systemic toxicity (NOEL for systemic toxicity 25+1.25 mg/kg) was evident. In mice, the NOAEL for reproductive and parental toxicity was 25+5 mg/kg body weight/day.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose, Crospovidone, Magnesium stearate, Opadry 02B53782 (Orange), Purified water

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30°C, protected from moisture

6.5 Nature and contents of container

Desiccant Embedded cold form blister strip of 3 tablets (3's blister strip)

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Ranbaxy Nigeria Ltd.
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