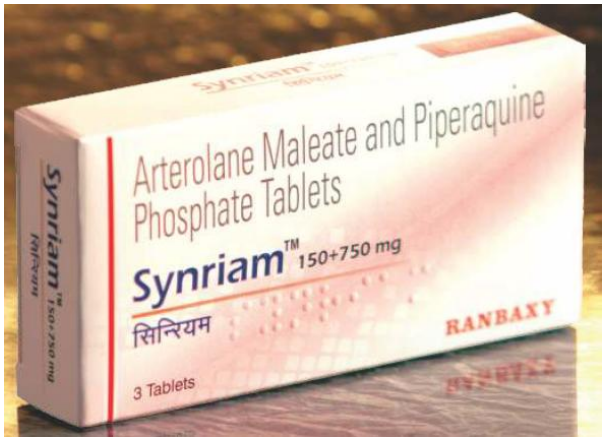
RANBAXY

Trusted medicines.Healthier lives




# Synriam™

Arterolane maleate 150 mg + Piperaquine phosphate 750 mg

## For the Treatment of Malaria

*Dr. Sanjukta Bhattacharyya*

**Ranbaxy Laboratories Ltd., India**

# Program Goal

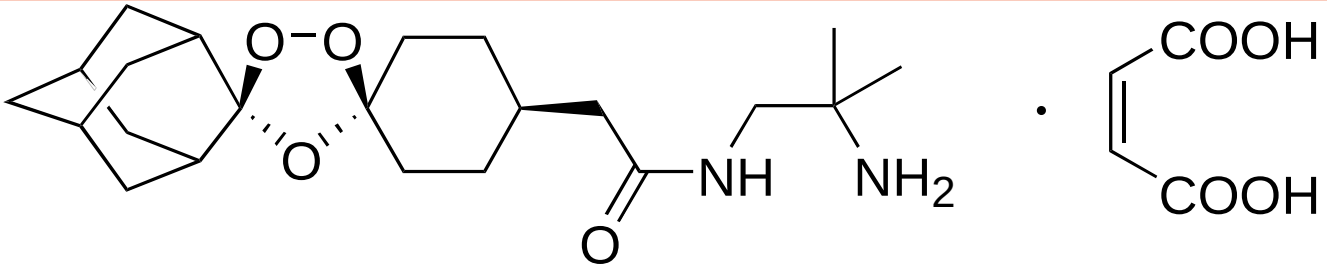
- To develop an oral fixed-dose combination product for *P. falciparum* and *P. vivax* malaria (adult & pediatric)
- Should show activity against resistant parasites
- Should have low propensity for development of resistance
- Effective vis-à-vis current benchmarks
- Convenient dosing: *once daily for 3 days*
- Affordable
- Easily available

# Collaborations

| | |
|---|---|
| **2003 to 2007** | Medicines of Malaria Venture, Switzerland |
| **2007 to Present** | Dept. of Science & Technology<br>Government of India |

Commitment to supply Synriam™ to Govt. of India for public use

# Arterolane maleate




**Chemical Name** : cis-Adamantane-2-spiro-3'-8'-[[[(2'-amino-2'-methylpropyl)amino] carbonyl] methyl]-1',2',4- trioxaspiro[4.5]decane hydrogen maleate

**Molecular Formula** : $C_{26}H_{40}N_2O_8$

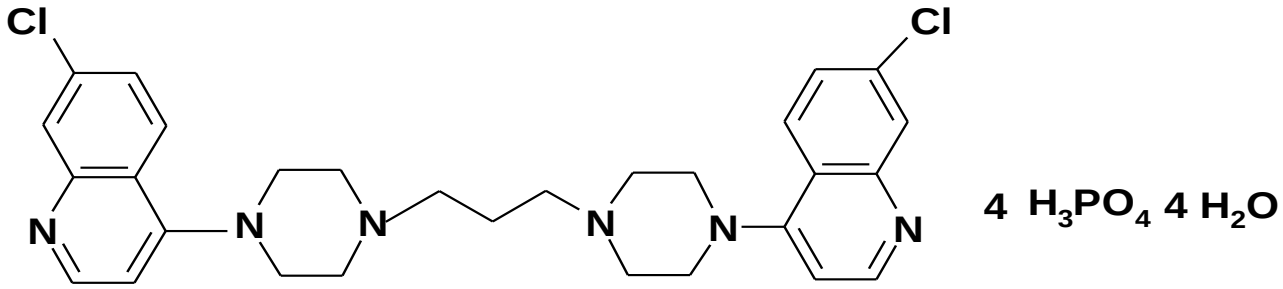
**Covergent synthesis** : 1+5 steps

**Overall Yield** : 48%

**Manufacturing** : At cGMP facility

- Totally synthetic
- Inexpensive
- Rapidly acting oral drug

# Piperaquine phosphate




**Chemical Name** : 1,3-Bis[4-(7-chloro quinolinyl-4)-piperazinyl-1]propane tetra phosphate tetra hydrate

**Molecular Formula** : $C_{29}H_{32}Cl_2N_6\ 4H_3PO_4\ 4H_2O$

**Molecular Weight** : 999.56 (Free Base: 535.52)

**Manufacturing** : At cGMP facility

- Proven effectiveness
- Established safety profile
- Cost-effective

# Mode of Action

## Arterolane

- A synthetic peroxide anti-malarial, is a rapidly acting blood schizonticide against all blood stages of P. falciparum without effect on liver stages.
- Arterolane is an active moiety which gets accumulated either in cytosol or food vacuole of the parasite.
- Acts by inhibition of PfATP6, a sarcoplasmic endoplasmic reticulum calcium ATPase encoded by P. Falciparum.
- In the food vacuole of parasite reductive cleavage of peroxide bond of arterolane by ferrous iron (fenton reaction) occurs. This irreversible redox reaction produces free radicals that alkylate the membrane associated parasite proteins. The reactive species inhibits an ATP-dependent Ca2+ pump located on the endoplasmic reticulum, PfATP6. The pump, called PfATP6, is a homologue of a mammalian sarcoplasmic /endoplasmic reticulum Ca2+ ATPase (SERCA).
- The reactive C radicals are thought to subsequently react more or less indiscriminately with different protein targets as well as with ferriprotoporphyrin IX itself, thus preventing heme detoxification and inhibiting a multitude of enzymes.

## Piperaquine

- Piperaquine is a bisquinoline anti-malarial drug and shows good activity against chloroquine-resistant Plasmodium strains.
- Evidence suggesting the inhibition of the heme-digestion pathway in the parasite food vacuole is most convincing.
- Piperaquine's bulky bisquinoline structure may be important for activity against chloroquine resistant strains and may act by inhibition of the transporters that efflux chloroquine from the parasite food vacuole.

Arterolane kills the malarial parasite in the blood, providing fast relief from symptoms of malaria like fever and chills. Piperaquine, on the other hand, has a longer-lasting effect than arterolane and kills residual parasites, preventing the recurrence of malaria.

# Formulations

- **Adult patients:** FDC tablets of Arteronale maleate (150mg) and Piperaquine phosphate (750mg)

- **Pediatric patients:** Dispersible FDC of Arterolane maleate (37.5mg) and Piperaquine phosphate (187.5 mg)

  - Taste masked. Sweet orange flavour
  - Clinical development ongoing
  - Dosing based on age-category of patients

| Age Category | No. of dispersible FDC tablets |
|---|---|
| 6 months to < 2 years | 1 |
| 2 years to < 6 years | 2 |
| 6 years to ≤ 12 years | 3 |

# Development Path

## Arterolane maleate

Pre-clinical → Phase I → Phase II

## Synriam™

[Arterolane maleate + PQP]

Pre-clinical → Phase I

## Piperaquine phosphate (PQP)

Pre-clinical → Phase I → Phase II*

## P - falciparum

- Ph III# (Adult) → Filing # → PM CT
- Ph II (Ped) → Ph III (Ped) → Filing → PM CT

## P - vivax

- Ph III → Filing → PM CT

Completed

Ongoing

To be done

* Published data on Phase II PQP

*# NDA Submitted in India & approved for marketing*

# Pre-clinical Efficacy & Toxicology

| Parameter | Artesunate | Arterolane |
|---|---|---|
| **$IC_{50}$ (ng/mL) K1/NF54** | 1.4/1.5 | 0.6/0.6 |
| **ED50/ED90 (mg/kg)** | 4.7/19 | 0.8/2.0 |
| **Cross Resistance** | none | None |
| **Additive interaction on co-administration of Arterolane and Piperaquine** | | |

| Parameter | Arterolane | Piperaquine | Synriam™ |
|---|---|---|---|
| **NOAEL in Wistar Rats (mg/kg)** | 60 | <5 | 10 + 0.5 |
| **NOAEL in Beagle Dogs (mg/kg)** | 30 | 5 | 30 + 2.5 |
| **Ames Mutagenicity** | Non-mutagenic | Non-mutagenic | Non-mutagenic |
| **Ch. Aberration/Micronucleus assay** | Non-clastogenic | Non-clastogenic | Non-clastogenic |
| **Safety margin from pre-clinical species to human is in acceptable/high** | | | |

# Phase I Clinical Trials

| S. No. | Subjects | Dose (mg) | Site |
|---|---|---|---|
| **Arterolane alone** | | | |
| 1 | Healthy young males [18-45yrs} | 25, 50, 100, 150, 200, 300, 400 & 600 | UK |
| 2 | Healthy elderly males & females [> 65yrs; Single dose] | 100 | UK |
| 3 | PK study in Thai volunteers | | Thailand |
| **Piperaquine phosphate alone** | | | |
| 4 | Healthy young males [Single & Multiple doses] | 500, 750, 1000, 1250 & 1500 | Switzerland |
| **Arterolane + Piperaquine phosphate** | | | |
| 5 | Healthy young males [Rising Single Dose] | 100 + 500 to 200 + 1000 | Switzerland |
| 6 | Healthy young males [Rising Multiple Dose] | 100 + 750 , 200 + 750<br>200 + 1000 | India |
| 7 | BA study of FDC vs Co-administration | 150+750 | India |
| 8 | BA study of dispersible FDC | 37.5+187.5 | India |

# Phase II Clinical Trials

| S. No. | Subjects | Dose (mg) | Site |
|---|---|---|---|
| **Arterolane alone** | | | |
| 9 | Patients with uncomplicated *Plasmodium falciparum* malaria | 25,50,75,100 & 200 | Thailand |
| 10 | PK in presence and absence of parasitemia | 100 | Thailand |
| 11 | Patients with uncomplicated *Plasmodium falciparum* malaria | 50, 100, 200 | Thailand |
| 12 | Patients with uncomplicated *Plasmodium falciparum* malaria | 50,100 & 200 | Thailand, Tanzania & India |
| **Arterolane + Piperaquine phosphate** | | | |
| 13 | Patients with uncomplicated *Plasmodium falciparum* malaria | AM - 150<br>PQP – 750 | Thailand & India |

# Phase III Clinical trial
## *(India & South East Asia)*

# Phase III Study – Design & Conduct

## According to WHO Treatment Guidelines

- **Phase III, Double-blind, Randomized, Multicenter**
- **Non inferiority comparison to Coartem at Day 28**
- **Compare Day 28 PCR corrected ACPR**
- **Patients: Adults**

# Efficacy Summary: Phase III

| Efficacy Parameters | Synriam™ | Coartem® |
|---|---|---|
| FCT (hrs) | 18 | 24 |
| PCT (hrs) | 36 | 34 |
| ACPR on Day 28 (PCR corrected) | 97.9% | 98.9% |
| ACPR on Day 28 (PCR uncorrected) | 97.4% | 94.7% |

# Combined Success Rate

| Phase II + III | | |
|---|---|---|
| **Efficacy Parameters** | **Synriam™** | **Coartem®** |
| **FCT (hrs)** | **24** | **24** |
| **PCT (hrs)** | **31** | **31** |
| **PCR Corrected ACPR Day 28** | **98.8%** | **98.8%** |

# Safety Summary : Phase III

- **No deaths**
- **Treatment Emergent Adverse Events as per CTCAE v3**

| | Synriam™ | Coartem® |
|---|---|---|
| No. of subjects with at least one AE | 96.8% | 100% |
| Total no. of AEs | 1125 | 649 |
| SAEs | 0 | 2.8% |

- **Most of the AEs were Grade 1 or 2 in severity (84% in arterolane+PQP and 90% in Coartem)**

# Statistical Analysis & Approval

- Synriam™ (Arterolane + PQP) effectively cures *P. falciparum* malaria and attains acceptable level of cure at Day 28 (PCR corrected ACPR >95%)
- The drug is well tolerated
- Major expected benefit
  - Patient compliance - 3 tabs (test) vs 24 tabs (reference) over 3 days
  - Synthetic manufacture, available in adequate quantities & Cost benefit
- Drugs Controller General (India) approved Synriam™ for the treatment of *P. falciparum* adult malaria 09 March 2012.
- Marketed successfully in India

# Synriam™

## Synriam™
### One Tablet Once a Day for Three Days Regimen

- Simplified dosing regimen : Ensures Compliance
- One tablet once-a-day x 3 days dosing compared with Twice a day dosing of Artemether + Lumefantrine

**Launched in India for uncomplicated *P. falciparum* malaria on 25 April 2012**

# Synriam™: Comparison with Other Drugs

| | AS+SP | A+L | AS+MQ | Synriam™ |
|---|---|---|---|---|
| **Efficacy** | 82.6% (Metanalysis) | 97.4% (Metanalysis) | 96.9% (Metanalysis) | 97.9% |
| **Pack** | Co-blister; chance of monotherapy | FDC tablets | FDC tablets | FDC tablets |
| **Pill Burden (Total Number of tablets)** | 5 | 6 – 24 | 6 | 3 |
| **Food –Drug Interaction** | No | Prescribed with fatty food | No | No |

# IP Position & Regulatory Filings

**IP Position**

- **IP protected till 2022**
- **Rights solely owned by Ranbaxy**

**Filings**

- **Registration in African countries to commence in May – June 2013**
- **First wave countries: *Ivory Coast, DRC, Mali, Senegal, Malawi, Nigeria, Kenya, Tanzania, Uganda***

# On-going Clinical Trials

## Completed enrollment

| Trials | Status |
|---|---|
| **Phase III trial in *P.falciparum* malaria patients** | Completed enrollment from 8 sites in Africa<br>• Ivory Coast – 2 sites<br>• DRC – 2 sites<br>• Mali<br>• Senegal<br>• Mozambique<br>• Malawi |
| **Pediatric Phase II trial in *P.falciparum* malaria patients** | Completed enrollment from 3 sites in India and 3 sites in Africa<br>• Rawanda<br>• Ivory Coast – 2 |
| **Phase III trial in *P.vivax* malaria patients in India** | Completed enrollment from 8 sites in India |

# Phase III *P. falciparum* study (adult): Blinded Safety data

- No deaths
- Four SAEs
  - Prolongation of hospitalization due to abdominal pain at Ivory Coast. Resolved without sequelae. Not related
  - Spontaneous abortion at DRC. Resolved without sequelae. Not related
  - Hospitalization due to suspected meningial syndrome at Mozambique. Resolved without sequelae. Not related.
  - Hospitalization due to sepsis at Malawi. Resolved without sequelae Not related.
- Commonly reported Clinical AEs
  - Cold, rhinitis, sore throat, cough, nausea, abdominal pain and epigastric discomfort

# Phase II Pediatric Trial (P. *falciparum*): Efficacy & Safety

**Efficacy Result**

- 126/141 patients completed study
- ACPR on Day 28 achieved in 126 patients
- ACPR on Day 42 achieved in 125 patients
- One treatment failure on Day 40 from 6-12 year age group

**Safety Result**

- No deaths or SAEs
- Commonly reported Clinical AEs: vomiting, headache, cough, anemia

# Synriam™

Arterolane maleate 150 mg + Piperaquine phosphate 750 mg

Amazingly simple... just 1 tab for 3 days