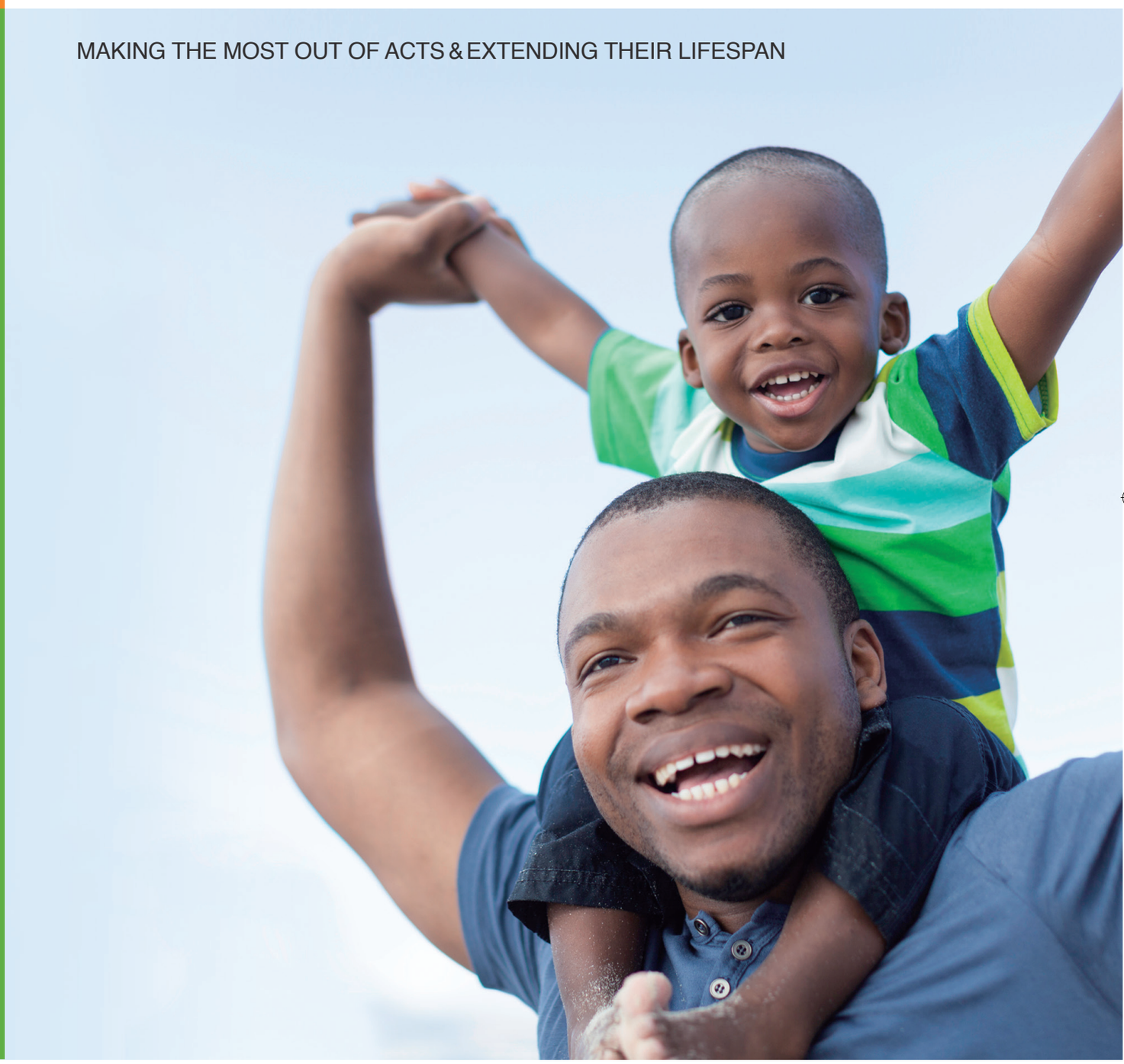
BEYOND EFFICACY, TOWARD PATIENT

MAKING THE MOST OUT OF ACTS & EXTENDING THEIR LIFESPAN



SHIN POONG PHARM. CO., LTD.

Antimalarial

PYRAMAX® TABLET Granules for Oral Suspension

Pyronaridine tetraphosphate / Artesunate

MALARIA
FACING EMERGING CHALLENGES

Antimalarial drug resistance is not the only cause of "treatment failure"[…] Incorrect dosing, incomplete adherence (compliance)**, poor drug quality, interactions with other drugs, compromised drug absorption,** vomiting of the medicine, unusual pharmacokinetics or misdiagnosis of the disease are other causes. Treatment failure is dangerous for the patient and also for the community, as it increases malaria transmission and fuels the emergence and spread of antimalarial drug resistance.

Guidelines for the treatment of malaria, 3rd Edition 2015, WHO

MORE FREQUENT RECRUDESCENCE AND REINFECTION INCREASED RISK OF RESISTANCE THREAT?

In areas without known resistance, **Multi-First-line Therapy may delay the emergence of drug resistance** (modelling studies)

Countries that rely on a **single ACT first-line treatment are encouraged to add additional effective ACT treatments to the national treatment guidelines,**

- to delay potentially the onset of resistance
- and to respond to stock-outs of first-line treatment.

WHO Meeting – 2015 Technical Expert Group (TEG) on Drug Efficacy and Response (DER)

PYRAMAX®
THE RESULT OF A LONG-TERM PARTNERSHIP

PYRAMAX® Tablets and PYRAMAX® Granules for oral suspension are the result of a long-standing collaboration between Shin Poong Pharmaceutical and non-profit foundation Medicines for Malaria Venture (MMV) to develop a new, quality-assured artemisinin combination therapy for uncomplicated malaria

ROADMAP TO ACCESS

2000

R&D project with WHO-TDR.
Then, partnership between Shin Poong Pharmaceuticals/MMV/University of Iowa

2010

Submission of tablet dossier to EMA (Article 58)

2011

WANECAM longitudinal study of ACTs commenced

2012

EMA Positive Scientific Opinion for tablets (with restrictions on use)
WHO pre-qualification for tablets

2014

Submission of Granules for oral suspension dossier and tablet dossier with label variation
(EMA - Article 58)

2015

EMA Positive Scientific Opinion for granules & for tablets (without previous restrictions on use)

2016

WHO pre-qualification for Granules for oral suspension
WANECAM phase IIIb/IVSub-study publication Listed for procurement by The Global Fund

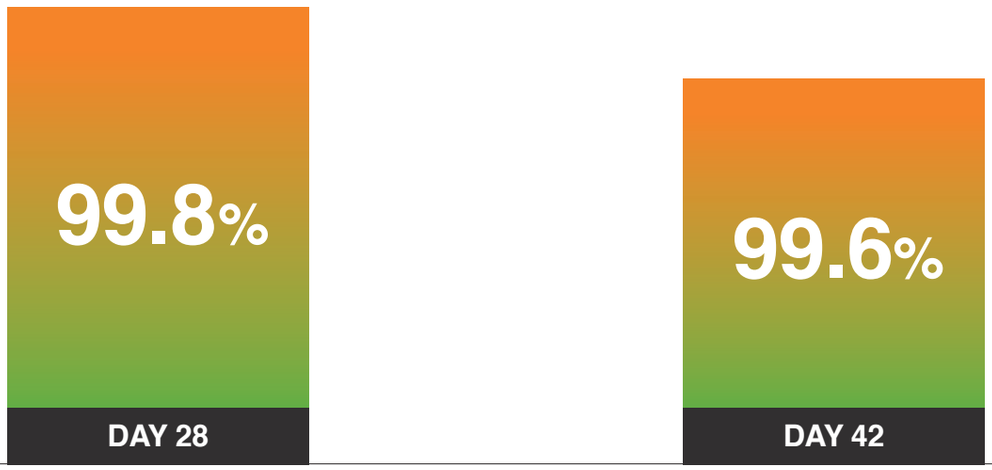
2017

Included in WHO's Essential Medicines Lists for adults & children Start of CANTAM cohort event monitoring study

PYRAMAX®
CONSISTENT AND RELIABLE EFFICACY OVER LONG TERM

EXCELLENT CURE RATES, SUSTAINED OVER TIME

PCR-adjusted ACPR in the per-protocol population for the first treatment episodes by Pyramax®



PCR-adjusted ACPR remains at day 28 and day 42 **≥ 99%** from 1st malaria episode and each retreatment episode

WANECAM STUDY (West African Network for Clinical Trials of Antimalarial Drugs)
A randomised controlled longitudinal design studies Pyramax® versus either AL or ASAQ for treatment of recurrent episodes in uncomplicated malaria patients over a 2-year period. From sites in Mali, Burkina Faso and Guinea: 673 and 671 in Pyramax® and AL with 669 and 668 with Pyramax® and ASAQ patients were dosed in the safety/ITT populations.

CLEARS PARASITES FASTER

HOURS	PA	AL
Median PCT (95% CI)	**24.7** hrs (24.3-26.1)	**34.5** hrs (34.2-35.1)

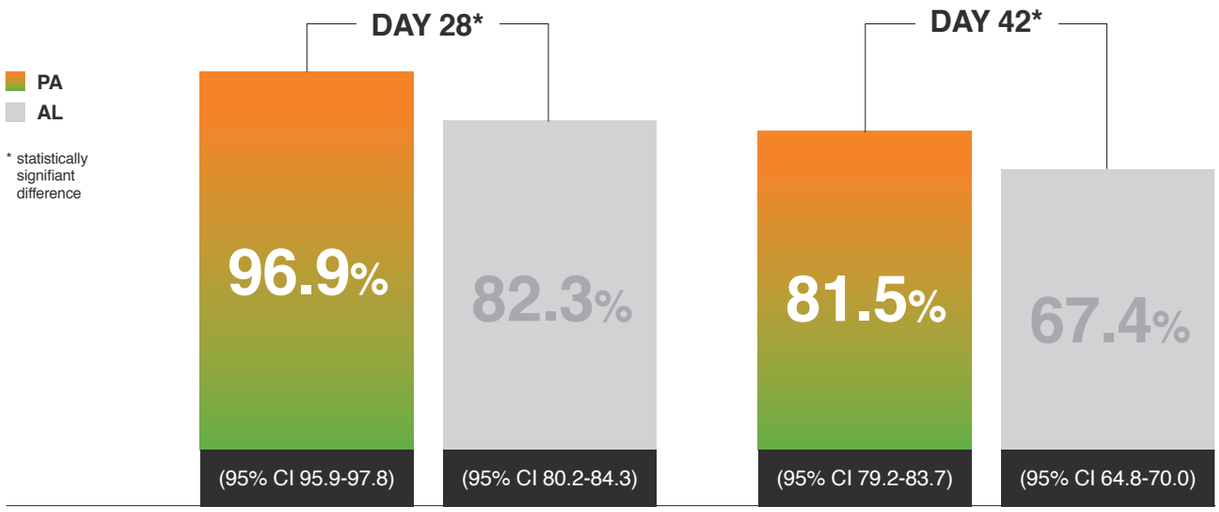
P<0.0001

P. falciparum parasite clearance time (PCT) for the first malaria episode in the Intent-To-Treat (ITT) population.

Data on file

PROVIDES LONG TERM PROTECTION WITH LESS REINFECTION

Crude (PCR-unadjusted) adequate clinical and parasitological response (ACPR) across all episodes at days 28 and 42 estimated using a general estimating equation (GEE), and between group comparisons (per-protocol population).



In this page, the result of Pyramax versus ASAQ is not shown.

Unadjusted ACPR rate in PP populations higher with Pyramax than AL.

The difference in crude ACPR resulted from a lower re-infection rate and recrudesence in the PYRAMAX® groupvs the AL group. It might be explained by the longer elimination half-life of pyronaridine (about 14 days) than of lumefantrine (3–4 days).

NON-INFERIORITY OVER 2 YEARS REPEAT MALARIA INCIDENCE TO STANDARD ACTS

PA	AL
Pyronaridine-artesunate	**Artemether-lumefantrine**
PA (N = 673)	AL (N = 671)
1.77	**1.87**
(95 % CI 1.63 - 1.93)	(95 % CI 1.72 - 2.03)

Data on file

PYRAMAX®
COMPARABLE SAFETY TO ARTEMETHER/LUMEFANTRINE

SIMILAR PROPORTION OF TREATMENT RELATED ADVERSE EVENTS BETWEEN PYRAMAX® AND AL AND BETWEEN THE EPISODES

- Pyramax® has lowest risk of QTc prolongation
- Pyramax® has higher liver enzymes rises rate but it is infrequent, without need for intervention and resolve by day 28 without clinical sequelae
- No difference between first and subsequent doses (non-inferiority)

The overall related serious adverse event profile was low and the incidence was similar between the groups[1]
Most common drug-related adverse events following treatment of uncomplicated Plasmodium spp. malaria with study drugs.

Treatment related AEs Adverse event, n(%)	PA versus AL	
	PA (N = 673)	AL (N = 671)
Anaemia	25 (3.7)	25 (3.7)
Monocytosis	18 (2.7)	21 (3.1)
Neutropenia	46 (6.8)	54 (8.0)
Thrombocytopenia	11 (1.6)	8 (1.2)
Abdominal pain	6 (0.9)	4 (0.6)
Vomiting	21 (3.1)	14 (2.1)
Fatigue	3 (0.4)	1 (0.1)
Hyperbilirubinaemia	2 (0.3)	2 (0.3)
Alanine aminotransferase (ALS) increased	35 (5.2)	11 (1.6)
Aspartate aminotransferase (AST) increased	39 (5.8)	17 (2.5)
Transaminases increased	2 (0.3)	1 (0.1)
Blood creatinine increased	8 (1.2)	8 (1.2)
Electrocardiogram QT prolonged	55 (8.2)	99 (14.8)
Electrocardiogram abnormal	4 (0.6)	0 (0.0)
Decreased appetite	1 (0.1)	0 (0.0)
Hypercreatininaemia	36 (5.3)	43 (6.4)
Headache	0 (0.0)	5 (0.7)
Somnolence	0 (0.0)	0 (0.0)

Statistical analysis confirmed a non-inferiority between re-treatment and first treatment suggesting no increase in hepatic adverse events on re-treatment with Pyramax® versus first treatment[2]

1 Data on File. **2** SAGARA ET AL. LANCET INFECT DIS 2016; 16: 189-98.

With Pyramax®, no need for routine monitoring (ECG, liver function…)

PYRAMAX®
A QUALITY-ASSURED ACT,
NOW READY TO MAKE THE MOST OUT OF ACTs IN YOUR REGION

- Approved by the EMA (Article 58)
- On The Global Fund List of Quality Assured Medicines
- On the WHO-Essential Medicines Lists
- Quality-assured, referenced on the WHO's list of prequalified medicines

Double-sided aluminium blister pack, stable in zone IV areas

EMA-GMP facility in South Korea

PYRAMAX®
OPTIMISING PATIENT ADHERENCE & COMFORT

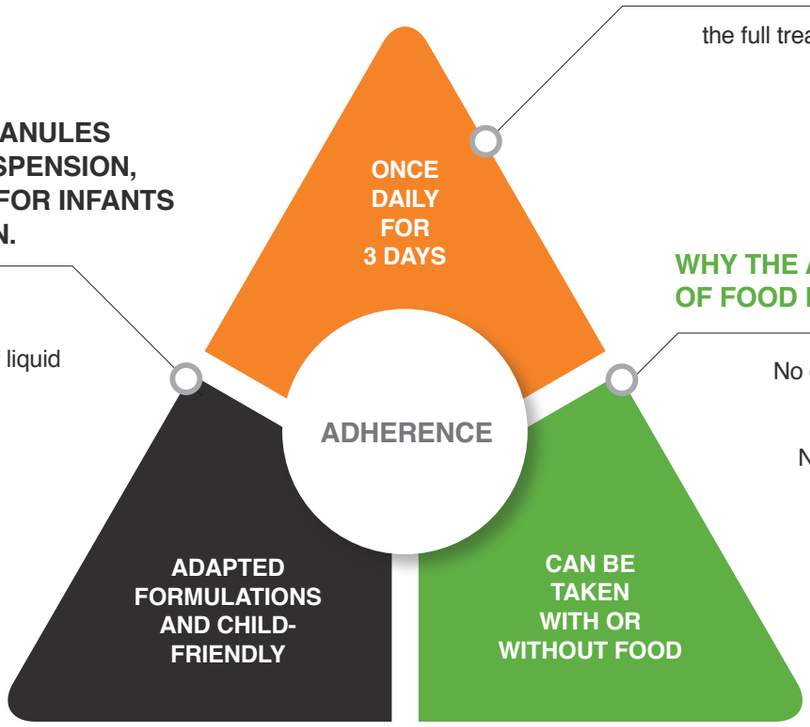
BENEFITS TO PATIENTS	PYRAMAX®	AL	DHA PQ
ONCE-DAILY	✓		✓
CHILD-FRIENDLY FORMULATION	✓	✓	
NO FOOD EFFECT	✓		

EASIER TO COMPLETE

the full treatment course

PYRAMAX® GRANULES FOR ORAL SUSPENSION, WELL SUITED FOR INFANTS AND CHILDREN.

Taste-masked
Suspends
in ~ 2 teaspoons of liquid



WHY THE ABSENCE OF FOOD EFFECT IS KEY:

No delay in first dosing
Ease of patient compliance
No variability in drug absorption

FEWER CONSTRAINTS, BETTER PATIENT ADHERENCE

PYRAMAX®
ADAPTED FOR BOTH CHILDREN & ADULTS

ONCE-DAILY

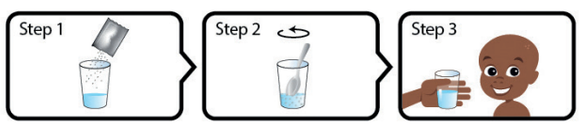
Can be taken with or without meals

Child-friendly granules for oral suspension for children weighing 5-19kg

Tablets for adults and children of 20kg+

RECOMMENDED DOSAGE

	Day 1	Day 2	Day 3
5kg-<8kg	3 Sachets		
8kg-<15kg	6 Sachets		
15kg-<20kg	9 Sachets		



Put the granule in a little of water.

Stir gently until a uniform suspension is obtained.

Give now. Make sure the child drinks all the medicine.*

*** IMPORTANT**
After step 3, add little water and repeat the administration steps until all medecine is taken.

RECOMMENDED DOSAGE

	Day 1	Day 2	Day 3
20kg-<24kg	3 Tablets		
24kg-<45kg	6 Tablets		
45kg-<65kg	9 Tablets		
≥65kg	12 Tablets		

The most efficient solution for children and adults

PYRAMAX®
THE MOST EFFICIENT SOLUTION FOR PATIENTS AND HCPs

- **BOX OF 90 TABLETS WITH DISPENSING ENVELOPES**
- **10 BLISTERS OF 9 TABLETS**

User-friendly packaging

From hospital to home-based management

- **BOX OF 90 SACHETS WITH DISPENSING ENVELOPES**
- **30 STRIPS OF 3 SACHETS**

A dispensing envelope with a pictorial posology table

- Facilitates dispensing by healthcare professionals
- Helps to improve the patient adherence
- Easy for Community Health Workers

CHOOSE PYRAMAX®
A NEW AND OPTIMIZED ACT

PYRAMAX® GOES...

BEYOND EFFICACY

- **Less re-infection of malaria**
- **Fast and long-term protection**
- **Quality assured by WHO-PQ & EMA**
- **Potential to delay the onset of resistance**

TOWARD PATIENT

- **Once daily**
- **Child-friendly (taste masked)**
- **No need for routine monitoring**
- **Ensures optimal efficacy through no food effect**
- **The most efficient adapted packaging for HCPs and patients**

SHIN POONG IS HIGHLY COMMITTED TO IMPROVING QUALITY OF LIFE IN THE GLOBAL COMMUNITY

With more than **50 years of experience,**
Shin Poong is a Korean pharmaceutical company having a global presence in **45 countries worldwide** and is specialized in anti-infectives medicines.

50
45

6 manufacturing site in the world.
3 SITES IN KOREA
3 SITES ABORAD- CHINA, SUDAN, VIETNAM

6

Overseas branches and R&D focused company

5

Prescribing information

NAME OF THE MEDICINAL PRODUCT
Pyramax 180 mg/60 mg Film-coated tablet
Pyramax 60 mg/20 mg Granules for oral suspension

QUALITATIVE AND QUANTITATIVE COMPOSITION
Each Pyramax tablet contains 180 mg Pyronaridine tetraphosphate and 60 mg Artesunate.
Each sachet of Pyramax Granules for oral suspension contains 60 mg Pyronaridine tetraphosphate and 20 mg Artesunate

THERAPEUTIC INDICATIONS
Pyramax tablets are indicated in the treatment of acute, uncomplicated malaria infection caused by Plasmodium falciparum or by Plasmodium vivax in adults and children weighing 20 kg or more.
Pyramax Granules for oral suspension are indicated in the treatment of acute, uncomplicated malaria infection caused by Plasmodium falciparum or by Plasmodium vivax in children and infants weighing 5 kg to under 20 kg.

POSOLOGY AND METHOD OF ADMINISTRATION
Mode of administration
The dose should be taken orally once a day for three days with or without food.
Posology
Dosage in adults and children
Pyramax tablets should be taken orally as a single daily dose for three consecutive days.

Body weight	Number of tablets	Regimen
20 - < 24 kg	1 tablet	Daily for 3 days
24 - <45 kg	2 tablet	Daily for 3 days
45 - < 65 kg	3 tablet	Daily for 3 days
≥ 65 kg	4 tablet	Daily for 3 days

Dosage for Granules for oral suspension in children and infants
Pyramax Granules for oral suspension should be taken orally as a single daily dose for three consecutive days.

Body weight	Number of granules sachets	Regimen
5 - < 8 kg	1 sachet	Daily for 3 days
8 - < 15 kg	2 sachet	Daily for 3 days
15 - < 20 kg	3 sachet	Daily for 3 days

Administration of Pyramax Granules; suspend the granules in a small amount of water (approximately 10 ml i.e. 2 teaspoons) into a small cup and administer, rinse cup and administer.

CONTRAINDICATIONS
- Known hypersensitivity to pyronaridine or artesunate or any component of the formulation.
- Patients with clinical signs or symptoms of hepatic injury (such as nausea and/or abdominal pain associated with jaundice) or known severe liver disease (i.e. decompensated cirrhosis, Child-Pugh stage B or C).
- Severe renal impairment

SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Pyramax tablets should not be used as a prophylactic treatment of malaria.
Specific caution should be taken in the case of:
- underlying hepatic injury, clinical signs or symptoms of hepatic injury or known severe liver disease; elevated transaminases
- co-infections (HBV, HCV, HIV); co- administration of drugs associated with mitochondrial toxicity (i.e. valproate, antiretroviral drugs), use of herbal medicines, patients with malnutrition or patients with other hepatic underlying conditions (i.e. ethanol intoxication, hepatic steatosis).
- known history or evidence of clinically significant cardiovascular disorders (including arrhythmia, QTc interval ≥450 milliseconds)
- initial low haemoglobin levels
- treatment of malaria in the first trimester of pregnancy
- Pyramax granules contains tartrazine (E102) and sunset yellow (E110) as colouring agents which may cause allergic reactions which may manifest as flushing, the appearance of wheals/urticarial, breathlessness, faintness and/or fall in blood pressure.

Pyramax should not be used for the treatment of severe malaria, cerebral malaria or other severe manifestations of complicated malaria, including hyperparasitaemia, pulmonary oedema, severe anaemia, renal or hepatic failure.
In the treatment of P. vivax malaria, radical cure requires Pyramax coadministration with a hypnozoitocidal drug such as primaquine.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION
Caution is advised in case of co-administration of drugs such as valproate, antiretroviral drugs), herbal medicines; paracetamol; metoprolol given in cardiac failure; flecainide and propafenone, antiarrhythmics; substrates for P-gp such as digoxin and dabigatran; CYP1A2 metabolisers such as theophylline; Enzyme inducing medicinal products such as rifampicin, carbamazepine, phenytoin, phenobarbital, St. John's wort (Hypericum perforatum).

FERTILITY, PREGNANCY AND

LACTATION
Pyramax cannot be recommended for treatment of malaria in the first trimester of pregnancy. However, they should not be withheld if treatment is considered lifesaving for the mother and other antimalarials are considered unsuitable.
Because of the limited safety data, Pyramax should only be used in the second and third trimesters of pregnancy when other treatments are considered unsuitable.
Pyronaridine may be excreted into breast milk. The benefits of breastfeeding to mother and infant should be weighed against potential risk from infant exposure to pyronaridine through breast milk.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Pyramax can uncommonly result in dizziness, fatigue, asthenia and somnolence. Patients should be warned not to drive or use machines if they feel tired or dizzy.

UNDESIRABLE EFFECTS
The safety of pyronaridine tetraphosphate and artesunate for treatment of malaria has been evaluated in clinical trials of more than 4000 patients. Pyramax was similarly well tolerated on single and repeat administration within as short as 28 days.
The most commonly reported (>1/100 to <1/10) adverse events were headache, eosinophilia, neutropenia, anaemia, increased platelet count, vomiting, abdominal pain, bradycardia, transaminase increases and hypoglycaemia.
Changes in haematology parameters were generally of similar magnitude in all treatment groups and are expected consequences of malaria infection and treatment. Overall, white cell counts remained constant throughout treatment with falls in neutrophils and compensatory rises in lymphocytes and eosinophils; reductions in haemoglobin of up to 2 g/dL.
Pyramax treatment was associated with mostly transient ALT elevations, with elevations of >3x upper limit of normal (ULN) and uncommonly, >10x ULN, with early onset peaking between Day 3 and 7 and normalising by Day 28.
Cases of syncope and isolated prolonged QTc were uncommonly reported for Pyramax. Mean decreases in heart rate were observed in all treatment groups and corresponded to reduction in the fever associated with the malaria infection.

System Organ Class	Common	Uncommon	Rare
Blood and lymphatic	Anaemia, eosinophilia, neutropenia, increased platelet count*	Basophilia, leukocytosis, leukopenia, lymphocytosis, monocytosis, splenomegaly, thrombocytopenia	Lymphopenia, pancytopenia
General disorders and administration site conditions		Asthenia, fatigue	Chest pain, chills, hypothermia, pyrexia
Hepatobiliary disorders		Hepatomegaly	Hepatosplenomegaly, liver tenderness
Immune system disorders			Hypersensitivity
Infections and infestations		Gastroenteritis, malaria, oral herpes, respiratory tract infection, tinea capitis, upper respiratory tract infection, urinary tract infection	Bronchitis, bronchopneumonia, infection parasitic, pharyngitis, pharyngotonsillitis, Plasmodium falciparum infection, pneumonia, rhinitis, subcutaneous abscess, tracheobronchitis
Investigations	Transaminases increased (See section 4.4)	Blood albumin decreased, blood alkaline phosphatase increased, blood creatine phosphokinase increased, blood creatinine decreased, blood sodium increased, electrocardiogram abnormal, electrocardiogram QT prolonged (see section 4.4), liver function test abnormal	Blood albumin increased, blood bilirubin decreased, blood bilirubin increased, blood creatinine increased, blood potassium decreased, haematocrit increased, red blood cell count increased, white blood cells urine
Metabolism and nutrition disorders	Hypoglycaemia	Anorexia, hyperkalaemia	Decreased appetite, hyperglycaemia
Musculoskeletal and connective tissue disorders		Myalgia	Arthralgia, back pain
Nervous system disorders	Headache	Dizziness, Dysgeusia, Paraesthesia	Somnolence
Pregnancy, puerperium and perinatal conditions			Abortion complete
Psychiatric disorders		Insomnia	Sleep talking
Renal and urinary disorders		Haematuria, proteinuria	Ketonuria
Reproductive system and breast disorders			Vulvovaginal pruritus
Respiratory, thoracic and mediastinal disorders		Cough	Asthma, epistaxis, haemoptysis, rhinorrhoea
Skin and subcutaneous tissue disorders		Hyperhidrosis, pruritus, rash	Blister, dermatitis, urticaria papular
Vascular disorders			Hypertension, hypotension

The frequency, type and severity of adverse reactions in children over 20 kg in body weight are expected to be similar to adults. Repeat dosing did not demonstrate a significant increase in adverse events versus one-time treatment with Pyramax tablets including in liver function changes.
No unexpected or clinically significant differences were observed in the analysis of adverse events and laboratory values by intrinsic factors (age group, gender, race, weight), extrinsic factors (region, study drug dose) or disease severity factors (previous malaria episode, number of previous malaria episodes in the last 12 months, baseline parasitaemia). In particular, patients with higher parasite loads (≥80.000/µL) were not at greater risk of adverse events, laboratory changes or electrocardiogram and cardiac events.

* A rise in platelets generally from a low to normal level was commonly reported (>1/100 to <1/10)

SHELF LIFE
2 years.

SPECIAL PRECAUTIONS FOR STORAGE
Do not store above 30°C. Store in the original package.

SUPPLIER
Shin Poong Pharmaceutical Co., Ltd
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Gangnam-gu Seoul
South Korea

For the map of the countries where PYRAMAX® is registered, please visit https://www.mmv.org/access/product-maps/pyramax-map

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