ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Pyramax 180 mg/60 mg Film-coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Pyramax tablet contains 180 mg Pyronaridine tetraphosphate and 60 mg Artesunate.

Excipients with known effect: each tablet contains 0.11 mg Sunset yellow FCF (E110) and 0.58 mg Tartrazine (E102).
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet
Round, biconvex, orange coloured tablet

4. CLINICAL PARTICULARS

4.1 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.

Consideration should be given to official guidance on the appropriate use of antimalarial agents (see section 4.4)

4.2 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 tablets	Daily for 3 days
45 - < 65 kg	3 tablets	Daily for 3 days
≥ 65 kg	4 tablets	Daily for 3 days

A granule formulation is available for children weighing between 5 kg to under 20 kg.

In the event of vomiting within 30 minutes of administration after the first dose, a repeat dose should be given. If the repeat dose is vomited, the patient should be given an alternative antimalarial drug. In the event of non-severe diarrhoea normal dosing should be continued.

If a dose is missed, it should be taken as soon as realised and then the recommended regimen continued until the full course of treatment has been completed.

Dosage in paediatrics population
Pyramax is dosed according to body weight. The safety and efficacy of Pyramax tablets has not been established in children below 20 kg body weight. The clinical studies conducted in *Plasmodium vivax* malaria, included only 13 patients below 12 years old (see section 5.1.)

Elderly
Clinical studies included 54 patients over 65 years of age. No dosing adjustments are necessary based on present knowledge and the short 3-day course of treatment. However, considering the possibility of age-associated decrease in hepatic and renal function, caution should be exercised when administering the product to the elderly.

Dosage in hepatic and renal impairment

There is no information on dosing in patients with hepatic impairment. Due to its potential hepatotoxicity, Pyramax is contraindicated in patients with signs of hepatic impairment or known significant liver function test abnormalities.

There is no information on dosing patients with severe renal impairment. Although excretion via faeces was the main route of elimination of pyronaridine-related material in a human mass balance study, significant urinary excretion was also observed. Pyramax is, therefore, contraindicated in the case of severe renal impairment and caution should be exercised when treating patients with mild or moderate renal impairment.

4.3 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

4.4 Special warnings and precautions for use

Pyramax tablets should not be used for malaria prophylaxis.

Pyramax has been associated, in some patients, with transient increases in liver enzymes without clinical signs (see section 4.8). Pyramax is contra-indicated in the case of underlying hepatic injury, clinical signs or symptoms of hepatic injury or known severe liver disease (see section 4.3).

Patients should be advised of the clinical signs and symptoms of hepatotoxicity in order to monitor closely if such signs or symptoms occur, especially in the first two weeks after Pyramax intake. It is recommended that, in patients who exhibit symptoms of hepatotoxicity following treatment with Pyramax, the liver function tests be monitored, if possible, until normalisation.

Insufficient data are available in patients with co-infections (HAV, HBV, HCV, HIV) and those receiving co-administration of drugs known to be associated with mitochondrial toxicity (i.e. valproate) or herbal medicines.

No data are available in other hepatic underlying conditions (i.e. ethanol intoxication, hepatic steatosis). Caution is advised when treating these patients with Pyramax since the risk of liver toxicity with these risk factors, also including co-administration of drugs known to be hepatotoxic is not known and might produce a cumulative effect on the liver (see section 4.5). Enhanced surveillance is warranted in young children in case of malnutrition.

No specific QT/QTc study has been performed to specifically assess the cardiac safety of Pyramax. Based on the available comparative clinical studies, this risk does not appear to be higher with single or repeat administration of Pyramax as compared to the other available antimalarial drugs used in these trials (artesunate + mefloquine, chloroquine, artemether-lumefantrine). However, patients with known history or evidence of clinically significant cardiovascular disorders (including arrhythmia, QTc interval ≥450 milliseconds) were excluded from these clinical studies. Therefore, caution should be exercised in at risk patients i.e. those:

- with congenital prolongation of QTc interval, hypokalaemia, dehydration, cardiac arrhythmia, heart failure, etc.
- treated concomitantly with other drugs that can block potassium channels, such as antiarrhythmics, neuroleptics, certain antimicrobial agents (e.g. macrolides, fluoroquinolones, imidazole and triazole antifungals, pentamidine, saquinavir) and non-sedating antihistamines, cisapride, domperidone or methadone,
- recently treated with medicinal products with long elimination half-life and known to prolong the QTc interval that may still be circulating at the time Pyramax treatment course is commenced (see section 4.8. and 5.1.).

A fall in haemoglobin may occur during treatment. There is very little information on the effect of this in patients with initial haemoglobin levels of less than 8 g/dl. Caution should be exercised in treating patients with a low haemoglobin.

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. Patients with severe malaria are not candidates for oral therapy.

In patients with acute malaria who present with severe diarrhoea and vomiting, alternative therapy should be considered. If Pyramax is used in these patients, the parasite load should be closely monitored.

Pyramax is a blood schizonticide and for the treatment of *P. vivax* malaria, a radical cure (to destroy the parasite in the liver and thus prevent relapse) is required with a hypnozoitocidal drug such as primaquine.

In the event of proven or suspected recurrent malaria infections within 28 days after treatment with Pyramax, patients should be treated with a different blood schizonticide.

Artemisinin compounds should not be used for treatment of malaria in the first trimester of pregnancy if other suitable and effective antimalarials are available (See Section 4.6).

There is no experience in the treatment of mixed *P. vivax* and *P. falciparum* infections. Limited data are available with Pyramax in the treatment of malaria due to *Plasmodium malariae* or *Plasmodium ovale*.

The safety and effectiveness of Pyramax for the treatment of malaria in patients with HIV/AIDS has not been established as very few patients with known HIV have been treated. If Pyramax is used in these patients, the parasite load should be closely monitored.

This medicine 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.

4.5 Interaction with other medicinal products and other forms of interaction

Particular caution is advised in case of co-administration of drugs known to be associated with mitochondrial toxicity (e.g., valproate, antiretroviral drugs), use of herbal medicines, and also co-

administration of other drugs known to be hepatotoxic (e.g. rifampin, carbamazepine, isoniazid, paracetamol) (see section 4.4 and section 4.8).

Pyronaridine shows *in vitro* CYP2D6 inhibitory potential that is confirmed *in vivo* using metoprolol as CYP2D6 probe. The study shows an increase of metoprolol Cmax around 50% but the overall exposure increases to a lesser extent. Caution is therefore advised when co-administering Pyramax with metoprolol given in cardiac failure, notably during the titration phase, and a possible dose adjustment may be required. This also applies to flecainide and propafenone, two antiarrhythmics exclusively metabolised by CYP2D6.

As pyronaridine shows *in vitro* P-gp inhibitory potential, substrates for P-gp such as digoxin and dabigatran may also require additional monitoring of blood levels and possible dose adjustment.

The combination of Pyramax and primaquine has shown neither clinically relevant pharmacokinetic variations nor any impaired tolerance. If needed, the two antimalarial drugs may be co-administered.

Dihydroartemisinin (DHA) administration may result in a slight decrease in CYP1A2 activity. Caution is therefore, advised when Pyramax is administered concomitantly with medicinal products metabolised by this enzyme that have a narrow therapeutic index, such as theophylline. Any effects are unlikely to persist beyond 24 hours after the last intake of DHA.

Enzyme inducing medicinal products such as rifampicin, carbamazepine, phenytoin, phenobarbital, St. John's wort (Hypericum perforatum) may lead to reduced DHA plasma concentrations.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are only limited data on the use of Pyramax in pregnancy.

A component of Pyramax is artesunate, a recognized *in vivo* embryotoxic and teratogenic compound in animal models, including primate (see section 5.3). There is a limited amount of data from the use of artesunate during the first trimester of pregnancy.

Pyronaridine did not show any teratogenic effects in animal studies.

Artemisinin compounds 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. Artemisinin compounds should only be used in the second and third trimesters of pregnancy when other treatments are considered unsuitable (see sections 4.4 and 5.3).

Pregnancy registry

A pregnancy registry to monitor all pregnancies and their outcomes has been set up by the supplier. In the event that a patient is found to be pregnant whilst receiving Pyramax or becomes pregnant within two months of treatment this must be reported to the supplier immediately.

Lactation

Studies in rats have shown that pyronaridine is 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.

Fertility

In animal studies, no effects on fertility and reproductive performance were observed. In these studies, the exposure to artesunate was below the human exposure; the maximum exposure to pyronaridine was 3-fold higher than the proposed human exposure.

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.

Dizziness, fatigue, asthenia and somnolence have been reported uncommonly or rarely following treatment with Pyramax. Patients should be warned not to drive or use machines if they feel tired or dizzy.

4.8 Undesirable effects

The safety of pyronaridine tetraphosphate and artesunate for treatment of malaria has been evaluated in clinical trials of approximately 12,200 patients.

Summary of the safety profile
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.

Tabulated list of adverse reactions
The following table provides a summary of adverse reactions reported with Pyramax in clinical trial reports. Adverse reactions are ranked under headings of frequency using the MedDRA frequency convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (<1/1000).

System Organ Class	Common	Uncommon	Rare
Blood and lymphatic system disorders	Anaemia, eosinophilia, neutropenia, increased platelet count*	Basophilia, leukocytosis, leukopenia, lymphocytosis, monocytosis, splenomegaly, thrombocytopenia	Lymphopenia, pancytopenia
Cardiac disorders	Bradycardia	Palpitations, ventricular extrasystoles	Arrhythmia, atrioventricular block first degree, sinus arrhythmia
Ear and labyrinth disorders		Vertigo	Ear pain, hearing impaired, tinnitus
Eye disorders			Conjunctivitis
Gastrointestinal disorders	Abdominal pain, vomiting	Constipation, diarrhoea, dyspepsia, gastritis, nausea	Abdominal tenderness, aphthous stomatitis, stomach discomfort, tongue ulceration
General disorders and administration site conditions		Asthenia, fatigue	Chest pain, chills, hypothermia, pyrexia
Hepatobiliary disorders		Hepatomegaly	Hepatosplenomegaly, liver tenderness

System Organ Class	Common	Uncommon	Rare
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, pharyngotonsilitis, *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

System Organ Class	Common	Uncommon	Rare
Skin and subcutaneous tissue disorders		Hyperhidrosis, pruritus, rash	Blister, dermatitis, urticaria papular
Vascular disorders			Hypertension, hypotension

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

Description of selected adverse reactions
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.

Treatment with Pyramax, in keeping with other antimalarials, has caused reductions in haemoglobin of up to 2 g/dL and sometimes more. These generally reached a nadir by Day 3, recovering by Day 28.

In Phase II/III clinical trials that evaluated one single 3-days treatment course, Pyramax treatment was associated with mostly transient ALT elevations, with elevations of >3x upper limit of normal (ULN) and uncommonly, >10xULN, with early onset peaking between Day 3 and 7 and normalising by Day 28.

In the Phase IIIb longitudinal study Pyramax was administered to patients experiencing single and repeated episodes of malaria and was shown to be similarly well tolerated on repeat administration as for first administration with repeat administration intervals as short as 28 days. The comparator arms of the study, artemether-lumefantrine or artesunate-amodiaquine, or a second study arm of DHA-piperaquine, also showed similar tolerability between initial and repeat administration. Where transient ALT elevations occurred, the adverse event profile was slightly higher with repeat administration for both adults and children.

In Episode 1, the percentage of patients with ALT > 1.5xULN and ≤ 3xULN for the 4 treatment arms was Pyramax 3.9%, artemether-lumefantrine 2.2%, artesunate-amodiaquine 1.2% and DHA-piperaquine 1.6%.

In Episode 2+, the percentage of patients with ALT >1.5xULN and ≤ 3xULN for the 4 treatment arms was Pyramax 5.1%, artemether-lumefantrine 2.2%, artesunate-amodiaquine 2.4% and DHA-piperaquine 2.2%.

Cases of syncope and isolated prolonged QTc were uncommonly reported in the available clinical trials 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 (see section 4.4. and 5.1.).

In the Phase IIIb longitudinal study, Pyramax compared favourably to the other treatment arms in terms of QTc (Bazett and Fridericia) both on initial or any repeat dose (measured centrally).

In Episode 1, the percentage of patients with QTc (Bazett) >450 msec for the 4 treatment arms was Pyramax 4.0%, artemether-lumefantrine 10.3%, artesunate-amodiaquine 24.2% and DHA-piperaquine 34.1% and QTc (Fridericia), 0%, 0%, 5% and 7.2% respectively. No Pyramax patients had a QTc >480 msec.

In Episode 2+, the percentage of patients with QTc (Bazett) >450 msec for the 4 treatment arms was Pyramax 7.2%, artemether-lumefantrine 10%, artesunate-amodiaquine 41.1% and DHA-piperaquine

48.5% and QTc (Fridericia), 1.6%%, 2.9%, 9.55% and 17.6% respectively. No Pyramax patients had a QTc >500 msec.

Paediatric population

The frequency, type and severity of adverse reactions in children over 20 kg in body weight are generally 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.

Other specific populations

Except for findings regarding significant transient transaminase rises in Caucasian healthy volunteers, which may be linked to differences of pharmacokinetics due to non-infected state of healthy volunteers rather than to the potential difference of metabolic pathways between ethnic origins, 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 than the main population as a whole. In the real-life Phase IIIb/IV study, 370 patients with malnutrition were enrolled. In these patients, there were no hepatotoxic events recorded and there was generally no difference in adverse events between those considered malnourished and those who were not.

The safety of concomitant use of paracetamol has been explored in relation to hepatic transaminases in 3135 patients in the Phase II/III programme. Of 2453 (78.2%) who received paracetamol, there was no difference to changes in transaminases compared to patients who did not receive paracetamol. Additionally, paracetamol or paracetamol-containing products were administered concomitantly with Pyramax in 2128 episodes of treatment (24.9%) in the Phase IIIb/IV real-life study, including in patients with raised transaminases prior to dosing (27.2%) without any clinical evidence of hepatic impairment.

A real-life Phase IIIb/IV study with the primary safety endpoint being the occurrence of clinical hepatotoxic events was conduct where 8560 episodes of malaria were treated with Pyramax, 158 episodes included patients who had an asymptomatic ALT and/or AST >2xULN. In these and any other patients, no clinically apparent hepatotoxic events occurred in the study and there was no evidence that asymptomatic raised transaminase levels at baseline were associated with clinical hepatoxicity on Pyramax treatment.

4.9 Overdose

No case of overdosage with Pyramax has been reported. In cases of suspected overdosage symptomatic and supportive therapy should be given as appropriate, transaminases (AST and ALT) should be monitored. If there are significant rises then serial total and direct bilirubin values should also be obtained to determine whether there is any change in liver function.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: pyronaridine in combination with artesunate, *an artemisinin derivative*, ATC Code: P01BF06

Mechanism of action

Pyronaridine inhibits the formation of β-haematin thus, preventing the malarial parasite from neutralizing haem, which is toxic to the parasite. Additionally, by forming a drug-haematin complex pyronaridine inhibits glutathione-dependent degradation of haematin and enhances haematin-induced lysis of red blood cells. Both these actions lead to parasite death.

Several mechanisms of action have been proposed to account for the activity of artemisinins; the generation of free radicals inside the parasite food vacuole and inhibition of the parasite's sarcoplasmic endoplasmic reticulum calcium-ATPase are widely accepted.

Pharmacodynamic effects

Whilst the outcome of *in vitro* studies using combinations of pyronaridine and artemisinin have reported mixed results, efficacy studies in rodent models of malaria using sensitive and resistant parasite strains have shown enhanced therapeutic effects using a combination of both compounds in a 3:1 ratio respectively.

Pyronaridine has potent *in vitro* activity against *P. falciparum* and *P. vivax* strains and clinical isolates including those resistant to other antimalarials. Against erythrocytic *P. falciparum* activity is greatest for the ring-form stage (ED_{50}; 8.3 nM), followed by schizonts ($ED_{50;}$ 11.6 nM) then trophozoites ($ED_{50;}$ 14.0 nM). Pyronaridine retains high activity against chloroquine resistant strains. *In vivo* efficacy of pyronaridine has been reported in mouse and non-human primate models of malaria.

Artesunate and its active principal metabolite dihydroartemisinin (DHA) show potent *in vitro* activity against multiple strains of *P. falciparum* and *P. vivax*, as well as against clinical isolates, including those resistant to other antimalarials. Reported IC_{50}s for inhibition of parasite multiplication are usually <19 nM. *In vivo* efficacy of artesunate has been reported in mouse, rat and non-human primate models of malaria.

Cross resistance

In vitro data from 181 clinical isolates showed that pyronaridine and artesunate were active against *P. falciparum* strains and isolates that were resistant to chloroquine, quinine, monodesethylamodiaquine, mefloquine or pyrimethamine and IC50 of both pyronaridine and artesunate were not affected by an increase in IC50 of chloroquine, monodesethylamodiaquine, mefloquine or pyrimethamine. In another *in vitro* study conducted against 104 multidrug resistant *P. falciparum* isolates from Southern Papua, pyronaridine demonstrated potent activity against isolates resistant to chloroquine, amodiaquine (another quinoline-type Mannich base) and piperaquine.

Cross resistance to other antimalarials cannot be ruled out.

Resistance to artemisinin has been reported in clinical isolates *in vitro* and genetically stable resistance has been observed in animal models. Resistance has been reported as labile and difficult to induce experimentally in animals; however, those data cannot be extrapolated to humans *in vivo*. The threshold for resistance of *P. falciparum* to artesunate remains indeterminate however, prolonged parasite clearance times in patients with apparent artemisinin resistance have recently been described in Western Cambodia.

Clinical efficacy

Plasmodium falciparum malaria:
Pyramax was demonstrated in Phase III clinical studies in both the Per Protocol (PP) and Intent to Treat (ITT) populations to be non-inferior to artemether-lumefantrine and mefloquine + artesunate in the treatment of acute uncomplicated *P. falciparum* in 2280 children and adults for the primary endpoint of polymerase chain reaction (PCR)-adjusted adequate clinical and parasitological response

(ACPR) at 28 days. In addition, Pyramax was also found to be non-inferior to the comparator agents for the secondary endpoints of parasite PCR-adjusted ACPR at 42 days. Pyramax was rapidly effective, with more than 90% of subjects clearing parasites and fever within 48 hours. Parasite count (*P. falciparum* asexual forms) decreased rapidly (during the first 16 hours) in both the Pyramax and comparator groups. Time to parasite clearance was statistically significantly shorter in the Pyramax group compared with artemether-lumefantrine group based on the log-rank test. In the integrated analysis of all Phase III studies with *P. falciparum*, no clinically important differences in PCR-adjusted ACPR were observed by region, age, gender, race, weight, previous malaria episode, baseline parasitaemia, or formulation. Crude cure rate results were also similar. The median time to fever clearance was 15.5 hours.

In all studies conducted in *P. falciparum* malaria, there was a marginal but consistently longer gametocytes clearance time in the Pyramax groups as compared to mefloquine + artesunate or artemether-lumefantrine groups. Further trials are awaited to address the mosquito infectivity.

In an analysis of a repeat-dose longitudinal study of 1342 patients treated with Pyramax tablets and granules for oral suspension, examining safety and efficacy of repeat dosing; of the 770 patients weighing ≥ 20 kg, 434 (56.4%) received at least one further treatment and 31.6% had a second or more re-treatment. Reasons for non-inclusion into the study or non re-treatment were complicated malaria or hyperparasitaemia or significantly raised liver enzymes as well as comorbidities such as HIV, hepatitis, or severe malnutrition. Efficacy findings were similar to those in pivotal trials and were maintained with repeated treatment episodes. Patients previously excluded or poorly represented in the clinical studies were included in the Phase IIIb/IV study conducted in endemic areas.

The PCR-adjusted ACPR at Day 28 for the initial malaria episode for all four treatment arms (all patients) were, respectively in ITT and PP population, 95.7% / 99.8% for Pyramax, 90.0% / 99.0% for artemether-lumefantrine, 94.1% / 99.8% for artesunate-amodiaquine as direct comparators, while it was 96.3% / 99.9% for DHA-piperaquine. At Day 42, these values were 85.6% / 99.6%, 73.5% / 99.0%, 80.5% / 99.4% and 92.0% / 99.9% respectively. Subsequent episodes in the ITT/PP population are shown to demonstrate similar outcomes.

For patients weighing ≥20 kg, in the ITT population, the PCR-adjusted ACPR at Day 28 for the four treatment arms were 97.1%, 93.7%, 95.2%, 97.3% respectively and at Day 42 were 91.8%, 79.1%, 82.8%, 94.2% respectively.

Phase IIIb/IV real-life safety study:
Patients previously excluded or poorly represented in the clinical studies were included in the Phase IIIb/IV real-life study conducted in endemic areas.

The primary objective was to assess the safety of Pyramax in real-life in particular in subjects with transaminase abnormality without clinical signs.

This large open-label non-randomised safety study included 7202 patients with 8609 episodes in total.

The PCR-adjusted cure rate at Day 28 was 98.6% (CI: 98.3, 98.9) in PP population (7746 malaria episodes) and 90.9% (CI: 90.2, 91.5) in microbiological ITT (8480 malaria episodes).
For patients receiving tablets i.e., >= 20 kg body weight, Day 28 PCR-adjusted cure rates were 99.4% (CI: 99.1, 99.6) in the PP population and 92.0% (CI: 91.3, 92.7) in the mITT population. All subgroups by age, nutritional status and formulation produced broadly similar efficacy results.

Overall, in this “real-life” safety study examining the effectiveness of *Pyramax*, the Day 28 cure rate was comparable to the parasitological cure rates reported in the previous Phase III studies performed in patients with uncomplicated malaria due to *P. falciparum*.

Plasmodium vivax malaria:
In the studies in subjects with *P. vivax* malaria, non-inferiority of Pyramax compared with chloroquine was demonstrated with respect to the crude cure rate on Day 14 in the efficacy evaluable population (in children and adults), which was the primary end point in that study. Results were maintained in the intent-to-treat population. A high crude cure rate (95.5%) was still observed at Day 42. Times to fever and parasite clearance were significantly shorter for Pyramax than chloroquine in this study. Only 13 patients less than 12 years old (no patient less than 7 years) were treated with Pyramax for *P. vivax* malaria. At the time the study was conducted, the areas where the studies were performed had low chloroquine resistance to *P. vivax*.

5.2 Pharmacokinetic properties

There is no pharmacokinetic interaction between pyronaridine tetraphosphate and artesunate at the recommended dose.

In clinical trials trough levels of pyronaridine and artesunate in children were generally within the range observed in adults.

Absorption

Following administration of Pyramax tablets to healthy volunteers and patients with malaria, peak plasma concentrations are generally reached between 0.5 and 1.0 hours post-dose for artesunate, between 1 and 2 hours post-dose for DHA and between 2 and 8 hours post-dose for pyronaridine. Exposure to artesunate and pyronaridine was increased by 34% and 20% respectively when Pyramax was administered with a high fat meal, however these effects were not judged clinically significant and patients can take Pyramax tablets without regard to meals (see section 4.2).

Distribution

Pyronaridine and its metabolites are extensively distributed into tissues, with highest concentrations achieved in the liver, spleen, adrenal gland, kidney and thyroid gland in the rat. There is evidence that pyronaridine binds to melanin in the eye. In the dog, approximately 6% of a single dose of pyronaridine remained in the liver 24 months after administration. The potential extrapolation to human is not elucidated but the very slow elimination of pyronaridine-related material from the body means that accumulation, with possible hepatotoxicity, cannot be ruled out if pyronaridine is readministered too early.

Pyronaridine preferentially associates with blood cells, exhibiting a whole blood/plasma concentration ratio of approximately 1.5:1. Pyronaridine is highly bound to human serum proteins *in vitro* (92 to 95%). Pyronaridine displays two-compartment pharmacokinetic characteristics with a blood level profile that has a distinct distribution phase.

Artesunate and its metabolites are primarily associated in the rat with tissues involved in absorption and excretion and high levels were also found in the spleen.

Plasma protein binding of artesunate and DHA is moderate (62 to 93%) and albumin is the principal binding protein for DHA in human plasma.

Biotransformation

Pyronaridine appears to have a large number of potential metabolites, with no clear major metabolic route. Human *in vivo* metabolic profiling was conducted in blood, urine, and faecal samples from six healthy male volunteers in a microdose radioactivity mass balance study. Pyronaridine (unchanged) and a total of thirteen metabolites were identified in one or more sample matrices. Proposed metabolic pathways include: *N*-dearylation, oxidation, de-methylation, glucuronidation, cysteine conjugation, acetylation and reduction.

Artesunate is very rapidly metabolized by esterases to the active metabolite dihydroartemisinin (DHA). DHA is subsequently conjugated with glucuronic acid via UGT1A9 and UGT2B7.

Elimination

Pyronaridine is eliminated slowly from blood, with an elimination half-life in adults of between 14 and 18 days for parent compound, and a mean of 33.5 days for total drug-related material. Urinary excretion of unchanged pyronaridine is <2% in healthy human subjects. Data from the mass balance study with pyronaridine in healthy volunteers indicates that faecal excretion is the main route of elimination of drug-related material. In this study, pyronaridine-related material was excreted both via faeces (47.8%) and urine (23.7%) after oral dosing of pyronaridine to healthy human subjects. Elimination occurred very slowly, the mean recovery of 71.5% (range 60.3%-82.2%) was achieved by 86 days after dosing.

In patients with uncomplicated malaria, artesunate and DHA are cleared from plasma with an elimination half-life of about 0.5 and 0.8 hours, respectively. No urinary excretion data are available for humans.

Hepatic and Renal Impairment

Pyramax has not been studied for efficacy and safety in patients with severe hepatic and/or severe renal impairment (see section 4.2).

Elderly Patients

No specific pharmacokinetic studies have been performed in patients older than 65 years of age.

5.3 Preclinical safety data

Repeat-dose toxicity studies with pyronaridine tetraphosphate:artesunate (3:1) in rats and dogs produced similar effects to those seen with each component individually.

The predominant feature in animals receiving repeated higher doses of pyronaridine tetraphosphate:artesunate (3:1) was related to the accumulation of pyronaridine.

Microscopically, after repeated dosing, this was seen as a widespread accumulation of basophilic material in many tissues and organs, sometimes present without associated inflammatory change (as for bone marrow and eye) but more often associated with dose-related inflammatory changes (as for liver, lung, spleen, gall bladder and kidney). It should be noted that, following a single 3-day cycle of treatment in dog, inflammatory changes were confined to liver and brain.

These inflammatory changes are considered secondary to the body's attempt to clear the accumulated material, and an increase in white blood cell count, predominantly in neutrophils and monocytes, is also considered a sequela of these changes. In more reactive tissues, notably rat liver, inflammatory and degenerate changes worsened over time in response to the prolonged presence of material, and this was correlated with increasing transaminase levels. This increase in severity was not evident following a single cycle of treatment.

Minimal to mild perivasculitis of the brain was noted in all repeat dose dog studies, including the single cycle study. This finding occurred with dose-related incidence, was not associated with relevant neurobehavioural changes and was not fully reversible.

Thymus atrophy was observed after administration of pyronaridine and artesunate to rats and dogs.

HERG studies were performed with pyronaridine, artesunate and dihydroartemisinin (DHA). Those studies showed that artesunate seldom had an effect on hERG tail current up to 300 μM (115.3 μg/mL) and that DHA and pyronaridine both inhibited hERG tail current with IC50s of 282.7 μM and 0.65 μM, respectively.

Pyronaridine was clastogenic in *in vitro* chromosome aberration tests and mouse lymphoma assays. The positive findings *in vitro* with mammalian cells are consistent likely related to the potential of pyronaridine for topoisomerase II inhibition. Pyronaridine was negative in the *in vivo* mouse bone marrow micronucleus test and rat liver *in vivo/in vitro* Unscheduled DNA Synthesis assay. In the rat liver comet assay negative results were obtained at liver concentrations 45-fold higher than the estimated liver concentrations reached in humans. Overall, the genotoxic risk associated with the proposed treatment cycle using pyronaridine should be no greater than that associated with other current therapies. Artesunate was not genotoxic in a standard package of genotoxicity assays. Carcinogenicity studies were not conducted since the treatment is limited to 3 days.

Neither pyronaridine tetraphosphate nor artesunate have effects on rat fertility. Artesunate is embryolethal at varying maternal dose levels and dosing regimens, depending on the nonclinical species. In fact, together with most other artemisinins (dihydroartemisinin, arteether, artemether) artesunate acts by depleting embryonic erythroblasts leading to severe anaemia. In cynomolgus monkeys, embryo lethality was observed in monkeys treated with artesunate for 30 days during the period of organogenesis, whereas no embryo lethality was observed in monkeys treated for a 3- or 7-day period during organogenesis, at comparable dose (which is 3 times the human dose based on mg/kg). In rats and rabbits, artesunate also caused embryolethality and foetotoxicity (decreased foetal body weight and increased skeletal and visceral variations).

Pyronaridine was shown to cross the placenta in rats. At maternally toxic doses, it caused early resorptions and abortions in rabbits, and decreased foetal body weight in rats and rabbits. There was no evidence of teratogenicity in both species.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Microcrystalline cellulose
Crospovidone
Mannitol (E421)
Magnesium stearate
Talc
Hypromellose
Macrogol 6000

Film coating
Hypromellose
Titanium dioxide
Tartrazine (E102)
Macrogol 6000
Sunset yellow FCF (E110)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months.

6.4 Special precautions for storage

Do not store above 30°C.
Store in the original package.

6.5 Nature and contents of container

Aluminium/PVC/Aluminium-oPA foil blisters containing 9 tablets.
The blisters are packed into cartons containing one or 10 blisters.

6.6 Special precautions for disposal

No special requirements.

Patients should be advised not to throw away any medicines via wastewater or household waste and ask their health provider how to dispose of unused medication.

7. SUPPLIER

Shin Poong Pharmaceutical Co., Ltd
161, Yeoksam-ro
Gangnam-gu
Seoul
South Korea

8. MARKETING AUTHORISATION NUMBER(S)

Not applicable.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Not applicable.

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency (EMA) http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Pyramax 60 mg/20 mg Granules for oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sachet of Pyramax Granules for oral suspension contains 60 mg Pyronaridine tetraphosphate and 20 mg Artesunate.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Pyramax granules for oral suspension
Orange coloured granules

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

Consideration should be given to official guidance on the appropriate use of antimalarial agents (see section 4.4).

4.2 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 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 sachets	Daily for 3 days
15 - < 20 kg	3 sachets	Daily for 3 days

A tablet formulation is available for children weighing 20 kg and over.

Administration of Pyramax Granules for oral suspension:

Add a small amount of water (approximately 10 ml i.e. 2 teaspoons) into a small cup. Put the contents of the required number of sachets (based on the weight of the child) into the cup and stir gently until the granules are suspended evenly. The granules will not dissolve. The patient should swallow the suspension immediately. Add a small amount of water (approximately 10 ml i.e. 2 teaspoons) to the cup to mix any remaining granules and the suspension should then be immediately swallowed by the patient. It is recommended to repeat this step until the patient has swallowed all the granules and no granules remain in the cup.

Only drinking water should be used for preparation of the oral suspension. Administration with feeding tubes has not been studied. Caution should be exercised to avoid the risk of aspiration in very young children.

In the event of vomiting within 30 minutes of administration after the first dose, a repeat dose should be given. If the repeat dose is vomited, the patient should be given an alternative antimalarial drug. In the event of non-severe diarrhoea normal dosing should be continued.

If a dose is missed, it should be taken as soon as possible and then the recommended regimen continued until the full course of treatment has been completed.

Dosage in paediatrics population
Pyramax is dosed according to body weight. Safety and efficacy of Pyramax granules for oral suspension has been established in infants and children weighing 5 kg to below 20 kg, but not in children less than 5 kg. The clinical studies conducted in *Plasmodium vivax* malaria, included only 13 patients below 12 years old (see section 5.1.)

Elderly
Not applicable. Pyramax Granules for Oral Suspension are intended for children and infants weighing 5 kg to under 20 kg.

Dosage in hepatic and renal impairment

There is no information on dosing in patients with hepatic impairment. Due to its potential hepatotoxicity, Pyramax is contraindicated in patients with signs of hepatic impairment or known significant liver function test abnormalities.

There is no information on dosing patients with severe renal impairment. Although excretion via faeces was the main route of elimination of pyronaridine-related material in a human mass balance study, significant urinary excretion was also observed. Pyramax is, therefore, contraindicated in the case of severe renal impairment and caution should be exercised when treating patients with mild or moderate renal impairment.

4.3 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.

4.4 Special warnings and precautions for use

Pyramax should not be used for malaria prophylaxis.

Pyramax has been associated, in some patients, with transient increases in liver enzymes without clinical signs (see section 4.8). Data are very limited for infants weighing less than 5 kg (see section 5.1). Pyramax is contra-indicated in the case of underlying hepatic injury, clinical signs or symptoms of hepatic injury or known severe liver disease (see section 4.3).

Patients or their parent/guardian should be advised of the clinical signs and symptoms of hepatotoxicity in order to monitor closely if such signs or symptoms occur, especially in the first two weeks after Pyramax intake. It is recommended that, in patients who exhibit symptoms of

hepatotoxicity following treatment with Pyramax, the liver function tests be monitored if possible, until normalisation.

Insufficient data are available in patients with co-infections (HAV, HBV, HCV, HIV) and those receiving co-administration of drugs known to be associated with mitochondrial toxicity (i.e. valproate) or herbal medicines.

No data are available in other hepatic underlying conditions (i.e. ethanol intoxication, hepatic steatosis). Caution is advised when treating these patients with Pyramax since the risk of liver toxicity with these risk factors, also including co-administration of drugs known to be hepatotoxic is not known and might produce a cumulative effect on the liver (see section 4.5). Enhanced surveillance is warranted in young children in case of malnutrition.

No specific QT/QTc study has been performed to specifically assess the cardiac safety of Pyramax. Based on the available comparative clinical studies, this risk does not appear to be higher with single or repeat administration of Pyramax as compared to the other available antimalarial drugs used in these trials (artesunate + mefloquine, chloroquine, artemether-lumefantrine). However, patients with known history or evidence of clinically significant cardiovascular disorders (including arrhythmia, QTc interval ≥ 450 milliseconds) were excluded from these clinical studies. Therefore, caution should be exercised in at risk patients i.e. those:

- with congenital prolongation of QTc interval, hypokalaemia, dehydration, cardiac arrhythmia, heart failure, etc.
- treated concomitantly with other drugs that can block potassium channels, such as antiarrhythmics, neuroleptics, certain antimicrobial agents (e.g. macrolides, fluoroquinolones, imidazole and triazole antifungals, pentamidine, saquinavir) and non-sedating antihistamines, cisapride, domperidone or methadone
- recently treated with medicinal products with long elimination half-life and known to prolong the QTc interval that may still be circulating at the time Pyramax treatment course is commenced (see section 4.8. and 5.1.).

A fall in haemoglobin may occur during treatment. There is very little information on the clinical effect of this in patients with initial haemoglobin levels of less than 8 g/dl. Caution should be exercised in treating patients with a low haemoglobin.

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. Patients with severe malaria are not candidates for oral therapy.

In patients with acute malaria who present with severe diarrhoea and vomiting, alternative therapy should be considered. If Pyramax is used in these patients, the parasite load should be closely monitored.

Pyramax is a blood schizonticide and for the treatment of *P. vivax* malaria, a radical cure (to destroy the parasite in the liver and thus prevent relapse) is required with a hypnozoitocidal drug such as primaquine.

In the event of proven or suspected recurrent malaria infections within 28 days after treatment with Pyramax, patients should be treated with a different blood schizonticide.

Artemisinin compounds should not be used for treatment of malaria in the first trimester of pregnancy if other suitable and effective antimalarials are available (See Section 4.6).

There is no experience in the treatment of mixed *P. vivax* and *P. falciparum* infections. Limited data are available with Pyramax in the treatment of malaria due to *Plasmodium malariae* or *Plasmodium ovale*.

The safety and effectiveness of Pyramax for the treatment of malaria in patients with HIV/AIDS has not been established as very few patients with known HIV have been treated. If Pyramax is used in these patients, the parasite load should be closely monitored.

4.5 Interaction with other medicinal products and other forms of interaction

Particular caution is advised in case of co-administration of drugs known to be associated with mitochondrial toxicity (e.g. valproate, antiretroviral drugs use of herbal medicines, and also co-administration of other drugs known to be hepatotoxic (e.g. rifampin, carbamazepine, isoniazid, paracetamol) (see section 4.4 and section 4.8).

Pyronaridine shows *in vitro* CYP2D6 inhibitory potential that was confirmed *in vivo* using metoprolol as CYP2D6 probe. The study showed an increase of metoprolol Cmax of around 50% but the overall exposure increased to a lesser extent. Caution is therefore advised when co-administering Pyramax with metoprolol given in cardiac failure, notably during the titration phase and a possible dose adjustment may be required. This applies to flecainide and propafenone as well, two antiarrhythmics exclusively metabolised by CYP2D6.

As pyronaridine shows *in vitro* P-gp inhibitory potential, substrates for P-gp such as digoxin and dabigatran may require additional monitoring of blood levels and possible dose adjustment as well.

The combination of Pyramax and primaquine has shown neither clinically relevant pharmacokinetic variations nor any impaired tolerance. If needed, the two antimalarial drugs may be co-administered.

Dihydroartemisinin (DHA) administration may result in a slight decrease in CYP1A2 activity. Caution is therefore, advised when Pyramax is administered concomitantly with medicinal products metabolised by this enzyme that have a narrow therapeutic index, such as theophylline. Any effects are unlikely to persist beyond 24 hours after the last intake of DHA.

Enzyme inducing medicinal products such as rifampicin, carbamazepine, phenytoin, phenobarbital, St. John's wort (*Hypericum perforatum*) may lead to reduced DHA plasma concentrations.

4.6 Fertility, pregnancy and lactation

Pregnancy
Not applicable. Pyramax Granules for Oral Suspension are intended for children and infants weighing 5 kg to under 20 kg.

Pregnancy registry
Not applicable. Pyramax Granules for Oral Suspension are intended for children and infants weighing 5 kg to under 20 kg.

Lactation
Not applicable. Pyramax Granules for Oral Suspension are intended for children and infants weighing 5 kg to under 20 kg.

Fertility
In animal studies, no effects on fertility and reproductive performance were observed. In these studies, the exposure to artesunate was below the human exposure; the maximum exposure to pyronaridine was 3-fold higher than the proposed human exposure.

4.7 Effects on ability to drive and use machines

Not applicable. Pyramax Granules for Oral Suspension are intended for children and infants weighing 5 kg to under 20 kg.

4.8 Undesirable effects

The safety of pyronaridine tetraphosphate and artesunate for treatment of malaria has been evaluated in clinical trials of approximately 12,200 patients.

Summary of the safety profile
The most commonly reported (≥1/100 to <1/10) adverse event were headache, eosinophilia, neutropenia, anaemia, increased platelet count, vomiting, abdominal pain, bradycardia, transaminase increases and hypoglycaemia.

Tabulated list of adverse reactions
The following table provides a summary of adverse reactions reported with Pyramax for both tablets and granules in clinical trial reports. Adverse reactions are ranked under headings of frequency using the MedDRA frequency convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (<1/1000).

System Organ Class	**Common**	**Uncommon**	**Rare**
Blood and lymphatic system disorders	Anaemia, eosinophilia, neutropenia, increased platelet count*	Basophilia, leukocytosis, leukopenia, lymphocytosis, monocytosis, splenomegaly, thrombocytopenia	Lymphopenia, pancytopenia
Cardiac disorders	Bradycardia	Palpitations, ventricular extrasystoles	Arrhythmia, atrioventricular block first degree, sinus arrhythmia
Ear and labyrinth disorders		Vertigo	Ear pain, hearing impaired, tinnitus
Eye disorders			Conjunctivitis
Gastrointestinal disorders	Abdominal pain, vomiting	Constipation, diarrhoea, dyspepsia, gastritis, nausea	Abdominal tenderness, aphthous stomatitis, stomach discomfort, tongue ulceration
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

System Organ Class	Common	Uncommon	Rare
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

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

Description of selected adverse reactions

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.

Treatment with Pyramax, in keeping with other antimalarials, has caused reductions in haemoglobin of up to 2 g/dL and sometimes more. These generally reached a nadir by Day 3 recovering by Day 28.

In Phase II/III clinical trials evaluating one single 3-day treatment course, Pyramax treatment was associated with mostly transient ALT elevations, with elevations of > 3x upper limit of normal (ULN) and uncommonly, > 10xULN with early onset peaking between Day 3 and 7 and normalising by Day 28.

In the Phase IIIb longitudinal study Pyramax was administered to patients experiencing single and repeated episodes of malaria and was shown to be similarly well tolerated on repeat administration, as for first administration with repeat administration intervals as short as 28 days. The comparator arms of the study, artemether-lumefantrine or artesunate-amodiaquine, or a second study arm of DHA-piperaquine, also showed similar tolerability between initial and repeat administration. Where transient ALT elevations occurred, the adverse event profile was similar with repeat administration for both adults and children based on data associated with the treatment of Episode 1 and any repeat treatment (Episodes 2+) for all treatment arms in terms of liver enzyme classifications for the highest post Day 0 values.

A sub analysis of liver function tests in the granules population of the longitudinal study was performed and the incidence of ALT values relative to the normal range, by body weight <10 kg or ≥10 kg for the three treatment arms using the highest post-Day 0 value were similar across the treatment groups and weight categories.

One potential Hy's law case on Pyramax were seen in the <10 kg body weight group occurring in Episode 3. There was one case of potential Hy's law case on Pyramax were seen in the ≥ 10 kg body weight group occurring in Episode 1 and, in this case, the patient was subsequently retreated with no recurrence of the hepatotoxicity. There were two Hy's law cases reported in the artemether-lumefantrine group in the ≥ 10 kg body weight group; one case occurring in Episode 1 and the other on re-treatment.

Cases of syncope and isolated prolonged QTc were uncommonly reported in the available clinical trials. Mean decreases in heart rate were observed in all treatment groups and corresponded to reduction in the fever associated with the malaria infection (see section 4.4. and 5.1.).

In the Phase IIIb longitudinal study, Pyramax compared favourably to the other treatment arms in terms of QTc (Bazett and Fridericia) both on initial or any repeat dose (measured centrally).

In Episode 1, the percentage of patients with QTc (Bazett) >450 msec for the 4 treatment arms was Pyramax 4.0%, artemether-lumefantrine 10.3%, artesunate-amodiaquine 24.2% and DHA-piperaquine 34.1% and QTc (Fridericia), 0%, 0%, 5% and 7.2% respectively. No Pyramax patients had a QTc >480 msec.

In Episode 2+, the percentage of patients with QTc (Bazett) >450 msec for the 4 treatment arms was Pyramax 7.2%, artemether-lumefantrine 10%, artesunate-amodiaquine 41.1% and DHA-piperaquine 48.5% and QTc (Fridericia), 1.6%%, 2.9%, 9.55% and 17.6% respectively. No Pyramax patients had a QTc >500 msec.

There were no post dose QTc (Bazett) values >500 msec and no post dose QTc (Fridericia) values >450 msec nor any increases of >60 msec from baseline in the granules population including patients less than 10 kg.

Paediatric population
The frequency, type and severity of adverse reactions in children 5 kg and over in body weight are generally similar to adults, however, to date, very few patients weighing less than 8 kg have been treated with Pyramax. Repeat dosing in the 128 children re-dosed at least once with Pyramax granules

did not demonstrate a significant increase in adverse events versus one-time treatment with Pyramax including in liver function changes.

Other specific populations
Except for findings regarding significant transient transaminase rises in Caucasian healthy volunteers - which may be linked to differences of pharmacokinetics due to non-infected state of healthy volunteers rather than to the potential difference of metabolic pathways between ethnic origins - no unexpected or clinically significant differences were observed in the analysis of adverse events and laboratory values by intrinsic factors (age group, gender, 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) and 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 than the main population as a whole.

In the real-life Phase IIIb/IV study, 370 patients with malnutrition were enrolled. In these patients, there were no hepatotoxic events recorded and there was generally no difference in adverse events between those considered malnourished and those who were not.

The safety of concomitant use of paracetamol has been explored in relation to hepatic transaminases in 3135 patients in the Phase II/III programme. Of 2453 (78.2%) who received paracetamol, there was no difference to changes in transaminases compared to patients who did not receive paracetamol. Additionally, paracetamol or paracetamol-containing products were administered concomitantly with Pyramax in 2128 episodes of treatment (24.9%) in the Phase IIIb/IV real-life study, including in patients with raised transaminases prior to dosing (27.2%) without any clinical evidence of hepatic impairment.

A real-life Phase IIIb/IV study with the primary safety endpoint being the occurrence of clinical hepatotoxic events was conduct where 8560 episodes of malaria were treated with Pyramax, 158 episodes included patients who had an asymptomatic ALT and/or AST >2xULN. In these and any other patients, no clinically apparent hepatotoxic events occurred in the study and there was no evidence that asymptomatic raised transaminase levels at baseline were associated with clinical hepatotoxicity on Pyramax treatment.

4.9 Overdose

No case of overdosage with Pyramax has been reported. In cases of suspected overdosage symptomatic and supportive therapy should be given as appropriate, transaminases (AST and ALT) should be monitored. If there are significant rises then serial total and direct bilirubin values should also be obtained to determine whether there is any change in liver function.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: pyronaridine in combination with artesunate, *an artemisinin derivative*, ATC Code: P01BF06

Mechanism of action

Pyronaridine inhibits the formation of β-haematin thus, preventing the malarial parasite from neutralizing haem, which is toxic to the parasite. Additionally, by forming a drug-haematin complex pyronaridine inhibits glutathione-dependent degradation of haematin and enhances haematin-induced lysis of red blood cells. Both these actions lead to parasite death.

Several mechanisms of action have been proposed to account for the activity of artemisinins; the generation of free radicals inside the parasite food vacuole and inhibition of the parasite's sarcoplasmic endoplasmic reticulum calcium-ATPase are widely accepted.

Pharmacodynamic effects

Whilst the outcome of *in vitro* studies using combinations of pyronaridine and artemisinin have reported mixed results, efficacy studies in rodent models of malaria using sensitive and resistant parasite strains have shown enhanced therapeutic effects using a combination of both compounds in a 3:1 ratio respectively.

Pyronaridine has potent *in vitro* activity against *P. falciparum* and *P. vivax* strains and clinical isolates including those resistant to other antimalarials. Against erythrocytic *P. falciparum* activity is greatest for the ring-form stage (ED_{50}; 8.3 nM), followed by schizonts ($ED_{50;}$ 11.6 nM) then trophozoites ($ED_{50;}$ 14.0 nM). Pyronaridine retains high activity against chloroquine resistant strains. *In vivo* efficacy of pyronaridine has been reported in mouse and non-human primate models of malaria.

Artesunate and its active principal metabolite dihydroartemisinin (DHA) show potent *in vitro* activity against multiple strains of *P. falciparum* and *P. vivax*, as well as against clinical isolates, including those resistant to other antimalarials. Reported IC_{50}s for inhibition of parasite multiplication are usually <19 nM. *In vivo* efficacy of artesunate has been reported in mouse, rat and non-human primate models of malaria.

Cross resistance

In vitro data from 181 clinical isolates showed that pyronaridine and artesunate were active against *P. falciparum* strains and isolates that were resistant to chloroquine, quinine, monodesethylamodiaquine, mefloquine or pyrimethamine and IC50 of both pyronaridine and artesunate were not affected by an increase in IC50 of chloroquine, monodesethylamodiaquine, mefloquine or pyrimethamine. In another *in vitro* study conducted against 104 multidrug resistant *P. falciparum* isolates from Southern Papua, pyronaridine demonstrated potent activity against isolates resistant to chloroquine, amodiaquine (another quinoline-type Mannich base) and piperaquine.

Cross resistance to other antimalarials cannot be ruled out.

Resistance to artemisinin has been reported in clinical isolates *in vitro* and genetically stable resistance has been observed in animal models. Resistance has been reported as labile and difficult to induce experimentally in animals; however those data cannot be extrapolated to humans *in vivo*. The threshold for resistance of *P. falciparum* to artesunate remains indeterminate however, prolonged parasite clearance times in patients with apparent artemisinin resistance have recently been described in Western Cambodia.

Clinical efficacy

Plasmodium falciparum malaria:
Pyramax was demonstrated in Phase III clinical studies in both the Per Protocol (PP) and Intent to Treat (ITT) populations to be non-inferior to artemether-lumefantrine and mefloquine + artesunate in the treatment of acute uncomplicated *P. falciparum* in 2280 children and adults for the primary endpoint of polymerase chain reaction (PCR)-adjusted adequate clinical and parasitological response (ACPR) at 28 days. In addition, Pyramax was also found to be non-inferior to the comparator agents for the secondary endpoints of parasite PCR-adjusted ACPR at 42 days. Pyramax was rapidly effective, with more than 90% of subjects clearing parasites and fever within 48 hours. Parasite count (*P. falciparum* asexual forms) decreased rapidly (during the first 16 hours) in both the Pyramax and comparator groups. Time to parasite clearance was statistically significantly shorter in the Pyramax group compared with artemether-lumefantrine group based on the log-rank test. In the integrated analysis of all Phase III studies with *P. falciparum*, no clinically important differences in PCR-adjusted ACPR were observed by region, age, gender, race, weight, previous malaria episode, baseline

parasitaemia, or formulation. Crude cure rate results were also similar. The median time to fever clearance was 15.5 hours.

In all studies conducted in *P. falciparum* malaria, there was a marginal but consistently longer gametocytes clearance time in the Pyramax groups as compared to mefloquine + artesunate or artemether-lumefantrine groups. Further trials are awaited to address the mosquito infectivity.

In an analysis of a longitudinal study of 1342 patients treated with Pyramax tablets and granules for oral suspension, examining safety and efficacy of repeat dosing; 572 patients were between 5 and under 20 kg. Three hundred and ninety-three (393) patients received treatment with Pyramax for more than one malaria episode (68.7%) and 277 (48.4%) were treated for 3 or more malaria episodes. To date 43 patients under 10 kg received Pyramax granules for oral suspension in the longitudinal study. Reasons for non-inclusion into the study or non re-treatment were complicated malaria or hyperparasitaemia or significantly raised liver enzymes as well as comorbidities such as HIV, hepatitis, or severe malnutrition. Efficacy findings were similar to those in pivotal trials and were maintained with repeated treatment episodes. Patients previously excluded or poorly represented in the clinical studies were included in Phase IIIb/V study conducted in endemic areas.

For patients weighing < 20 kg the PCR-adjusted ACPR in the ITT population at Day 28 for the four treatment arms were 94% Pyramax, 83.1% artemether-lumefantrine, 93.1% artesunate-amodiaquine, 95% DHA-piperaquine respectively and at Day 42 were 77.3%, 63%, 78.3%, 89.4% respectively.

Phase IIIb/IV real-life safety study:
Patients previously excluded or poorly represented in the clinical studies were included in the Phase IIIb/IV real-life study conducted in endemic areas.

The primary objective was to assess the safety of Pyramax in real-life in particular in subjects with transaminase abnormality without clinical signs.

This large open-label non-randomised safety study included 7202 patients with 8609 episodes in total.

The PCR-adjusted cure rate at Day 28 was 98.6% (CI: 98.3, 98.9) in PP population (7746 malaria episodes) and 90.9% (CI: 90.2, 91.5) in microbiological ITT (8480 malaria episodes).

All subgroups by age, nutritional status and formulation produced broadly similar efficacy results.

Overall, in this "real-life safety study examining the effectiveness of *Pyramax*, the Day 28 cure rate was comparable to the parasitological cure rates reported in the previous Phase III studies performed in patients with uncomplicated malaria due to *P. falciparum.*

Plasmodium vivax malaria:
In the studies in subjects with *P. vivax* malaria, non-inferiority of Pyramax compared with chloroquine was demonstrated with respect to the crude cure rate on Day 14 in the efficacy evaluable population (in children and adults), which was the primary end point in that study. Results were maintained in the intent-to-treat population. A high crude cure rate (95.5%) was still observed at Day 42. Times to fever and parasite clearance were significantly shorter for Pyramax than chloroquine in this study. Only 13 patients less than 12 years old (no patient less than 7 years) were treated with Pyramax for *P vivax* malaria. At the time the study was conducted, the areas where the studies were performed had low chloroquine resistance to *P vivax*.

5.2 Pharmacokinetic properties

Information on the pharmacokinetic of pyronaridine tetraphosphate and artesunate is mainly derived from the use of the tablet formulation.

There is no pharmacokinetic interaction between pyronaridine tetraphosphate and artesunate at the recommended dose.

In clinical trials trough levels of pyronaridine and artesunate in children were generally within the range observed in adults. Pyramax produces a uniform exposure across the weight ranges for the proposed labelled dosing of granules with no increased exposure seen in the younger patient range.

Absorption

Following administration of Pyramax tablets to healthy volunteers and patients with malaria, peak plasma concentrations are generally reached between 0.5 and 1.0 hours post-dose for artesunate, between 1 and 2 hours post-dose for DHA and between 2 and 8 hours post-dose for pyronaridine. Exposure to artesunate and pyronaridine was increased by 34% and 20% respectively when Pyramax was administered with a high fat meal, however these effects were not judged clinically significant and patients can take Pyramax tablets without regard to meals (see section 4.2).

Distribution

Pyronaridine and its metabolites are extensively distributed into tissues, with highest concentrations achieved in the liver, spleen, adrenal gland, kidney and thyroid gland in the rat. There is evidence that pyronaridine binds to melanin in the eye. In the dog, approximately 6% of a single dose of pyronaridine remained in the liver 24 months after administration. The potential extrapolation to human is not elucidated but the very slow elimination of pyronaridine-related material from the body means that accumulation, with possible hepatotoxicity, cannot be ruled out if pyronaridine is readministered too early.

Pyronaridine preferentially associates with blood cells, exhibiting a whole blood/plasma concentration ratio of approximately 1.5:1. Pyronaridine is highly bound to human serum proteins *in vitro* (92 to 95%). Pyronaridine displays two-compartment pharmacokinetic characteristics with a blood level profile that has a distinct distribution phase.

Artesunate and its metabolites are primarily associated in the rat with tissues involved in absorption and excretion and high levels were also found in the spleen.

Plasma protein binding of artesunate and DHA is moderate (62 to 93%) and albumin is the principal binding protein for DHA in human plasma.

Biotransformation

Pyronaridine appears to have a large number of potential metabolites, with no clear major metabolic route. Human *in vivo* metabolic profiling was conducted in blood, urine, and faecal samples from six healthy male volunteers in a microdose radioactivity mass balance study. Pyronaridine (unchanged) and a total of thirteen metabolites were identified in one or more sample matrices. Proposed metabolic pathways include: *N*-dearylation, oxidation, de-methylation, glucuronidation, cysteine conjugation, acetylation and reduction.

In vitro experiments indicate that CYP1A2, CYP2D6 and CYP3A4 could be involved in the metabolism of pyronaridine. *In vitro,* pyronaridine inhibits the activity of CYP2D6 at therapeutic plasma concentrations.

Artesunate is very rapidly metabolised by esterases to the active metabolite dihydroartemisinin (DHA). DHA is subsequently conjugated with glucuronic acid via UGT1A9 and UGT2B7.

Elimination

Pyronaridine is eliminated slowly from blood, with an elimination half-life in adults of between 14 and 18 days for parent compound, and a mean of 33.5 days for total drug-related material. The mean elimination half-life for paediatric malaria patients is 12.3 days. Urinary excretion of unchanged pyronaridine is <2% in healthy human subjects. Data from the mass balance study with pyronaridine

in healthy volunteers indicates that faecal excretion is the main route of elimination of drug-related material. In this study, pyronaridine-related material was excreted both via faeces (47.8%) and urine (23.7%) after oral dosing of pyronaridine to healthy human subjects. Elimination occurred very slowly, the mean recovery of 71.5% (range 60.3%-82.2%) was achieved by 86 days after dosing.

In patients with uncomplicated malaria, artesunate and DHA are cleared from plasma with an elimination half-life of about 0.5 and 0.8 hours, respectively. No urinary excretion data are available for humans.

Hepatic and Renal Impairment

Pyramax has not been studied for efficacy and safety in patients with severe hepatic and/or severe renal impairment (see section 4.2).

Elderly Patients

Pyramax granules are intended for patients weighing less than 20 kg only.

5.3 Preclinical safety data

Repeat-dose toxicity studies with pyronaridine tetraphosphate:artesunate (3:1) in rats and dogs produced similar effects to those seen with each component individually.

The predominant feature in animals receiving repeated higher doses of pyronaridine tetraphosphate:artesunate (3:1) was related to the accumulation of pyronaridine.

Microscopically, after repeated dosing, this was seen as a widespread accumulation of basophilic material in many tissues and organs, sometimes present without associated inflammatory change (as for bone marrow and eye) but more often associated with dose-related inflammatory changes (as for liver, lung, spleen, gall bladder and kidney). It should be noted that, following a single 3-day cycle of treatment in dog, inflammatory changes were confined to liver and brain.

These inflammatory changes are considered secondary to the body's attempt to clear the accumulated material, and an increase in white blood cell count, predominantly in neutrophils and monocytes, is also considered a sequela of these changes. In more reactive tissues, notably rat liver, inflammatory and degenerate changes worsened over time in response to the prolonged presence of material, and this was correlated with increasing transaminase levels. This increase in severity was not evident following a single cycle of treatment.

Minimal to mild perivasculitis of the brain was noted in all repeat dose dog studies, including the single cycle study. This finding occurred with dose-related incidence, was not associated with relevant neurobehavioural changes and was not fully reversible.

Thymus atrophy was observed after administration of pyronaridine and artesunate to rats and dogs.

HERG studies were performed with pyronaridine, artesunate and dihydroartemisinin (DHA). Those studies showed that artesunate seldom had an effect on hERG tail current up to 300 μM (115.3 μg/mL) and that DHA and pyronaridine both inhibited hERG tail current with IC50s of 282.7 μM and 0.65 μM, respectively.

Pyronaridine was clastogenic in *in vitro* chromosome aberration tests and mouse lymphoma assays. The positive findings *in vitro* with mammalian cells are consistent likely related to the potential of pyronaridine for topoisomerase II inhibition. Pyronaridine was negative in the *in vivo* mouse bone marrow micronucleus test and rat liver *in vivo/in vitro* Unscheduled DNA Synthesis assay. In the rat liver comet assay negative results were obtained at liver concentrations 45-fold higher than the estimated liver concentrations reached in humans. Overall, the genotoxic risk associated with the proposed treatment cycle using pyronaridine should be no greater than that associated with other

current therapies. Artesunate was not genotoxic in a standard package of genotoxicity assays. Carcinogenicity studies were not conducted since the treatment is limited to 3 days.

Neither pyronaridine tetraphosphate nor artesunate have effects on rat fertility. Artesunate is embryolethal at varying maternal dose levels and dosing regimens, depending on the nonclinical species. In fact, together with most other artemisinins (dihydroartemisinin, arteether, artemether) artesunate acts by depleting embryonic erythroblasts leading to severe anaemia. In cynomolgus monkeys, embryo lethality was observed in monkeys treated with artesunate for 30 days during the period of organogenesis, whereas no embryo lethality was observed in monkeys treated for a 3- or 7-day period during organogenesis, at comparable dose (which is 3 times the human dose based on mg/kg). In rats and rabbits, artesunate also caused embryolethality and foetotoxicity (decreased foetal body weight and increased skeletal and visceral variations).

Pyronaridine was shown to cross the placenta in rats. At maternally toxic doses, it caused early resorptions and abortions in rabbits, and decreased foetal body weight in rats and rabbits. There was no evidence of teratogenicity in both species.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Pyramax granules for oral suspension

Artesunate
Pyronaridine tetraphosphate
Mannitol
Talc
Ethyl cellulose
Macrogol 6000
Hypromellose 2910
Iron oxide yellow (E172)
Iron oxide red (E172)
Acesulfame potassium

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 30°C.
Store in the original package.

6.5 Nature and contents of container

Pyramax granules for oral suspension

Sachets consisting of layers of polyester, aluminium and polyethylene/Surlyn, containing granules. Each carton contains 90 sachets.

6.6 Special precautions for disposal

No special requirements.

Patients should be advised not to throw away any medicines via wastewater or household waste and ask their health provider how to dispose of unused medication.

7. SUPPLIER

Shin Poong Pharmaceutical Co., Ltd
161, Yeoksam-ro
Gangnam-gu
Seoul
South Korea

8. MARKETING AUTHORISATION NUMBER(S)

Not applicable.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Not applicable.

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency (EMA) http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. CONDITIONS AND REQUIREMENTS OF THE SCIENTIFIC OPINION HOLDER

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Shin Poong Pharmaceutical Co., Ltd.
70, Sandan-ro 19beon-gil
Danwon-gu
Ansan-si
Gyeonggi-do
South Korea

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.4)

C. OTHER CONDITIONS AND REQUIREMENTS OF THE SCIENTIFIC OPINION HOLDER

- **Periodic Safety Update Reports**

The scientific opinion holder shall submit the next PSUR, including safety data from 16 August 2020 to 15 August 2023, within 90 calendar days after its data lock point. Subsequently, the scientific opinion holder shall submit PSURs for this product every three years until otherwise agreed by the CHMP.

Pharmacovigilance system
The Scientific Opinion Holder must ensure that the system of pharmacovigilance presented in Module 1.8.1. of the Scientific Opinion Application is in place and functioning before and whilst the medicinal product is on the market.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The Scientific Opinion Holder shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Scientific Opinion and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

A. LABELLING – PYRAMAX – 9 Tablets

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON – 9 Tablets

1. NAME OF THE MEDICINAL PRODUCT

Pyramax 180 mg/60 mg Film-coated tablet

Pyronaridine tetraphosphate and Artesunate.

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each Pyramax tablet contains 180 mg Pyronaridine tetraphosphate and 60 mg Artesunate.

3. LIST OF EXCIPIENTS

Also contains: Tartrazine (E102) and Sunset yellow FCF (E110). See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film coated tablets.

9 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral Use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

Store in the original package.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF SUPPLIER

Shin Poong Pharmaceutical Co., Ltd
161, Yeoksam-ro
Gangnam-gu
Seoul
South Korea

12. MARKETING AUTHORISATION NUMBER(S)

Not applicable

13. BATCH NUMBER

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription under specific conditions.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Not applicable

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER – 9 Tablets

1. NAME OF THE MEDICINAL PRODUCT

Pyramax 180 mg/60 mg Film-coated Tablet

Pyronaridine tetraphosphate and Artesunate.

2. NAME OF SUPPLIER

Shin Poong Pharmaceutical Co., Ltd

3. EXPIRY DATE

4. BATCH NUMBER

5. OTHER

A. LABELLING – PYRAMAX – 90 Tablets

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON – 90 Tablets

1. NAME OF THE MEDICINAL PRODUCT

Pyramax 180 mg/60 mg Film-coated Tablet

Pyronaridine tetraphosphate and Artesunate.

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each Pyramax tablet contains 180 mg Pyronaridine tetraphosphate and 60 mg Artesunate.

3. LIST OF EXCIPIENTS

Also contains: Tartrazine (E102) and Sunset yellow FCF (E110). See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film coated tablets.

90 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral Use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

Store in the original package.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE SUPPLIER

Shin Poong Pharmaceutical Co., Ltd
161, Yeoksam-ro
Gangnam-gu
Seoul
South Korea

12. MARKETING AUTHORISATION NUMBER(S)

Not applicable

13. BATCH NUMBER

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription under specific conditions.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Not applicable

A. LABELLING – PYRAMAX – Granules for oral suspension

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON – 90 sachets of Granules

1. NAME OF THE MEDICINAL PRODUCT

Pyramax 60 mg/20 mg Granules for oral suspension

Pyronaridine tetraphosphate and Artesunate.

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sachet of Pyramax granules for oral suspension contains 60 mg Pyronaridine tetraphosphate and 20 mg Artesunate.

3. LIST OF EXCIPIENTS

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Granules for oral suspension

90 sachets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral Use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

Store in the original package.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF SUPPLIER

Shin Poong Pharmaceutical Co., Ltd
161, Yeoksam-ro
Gangnam-gu
Seoul
South Korea

12. MARKETING AUTHORISATION NUMBER(S)

Not applicable

13. BATCH NUMBER

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription under specific conditions.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Not applicable

MINIMUM PARTICULARS TO APPEAR ON SACHETS

SACHET as indiviual dosing unit

1. NAME OF THE MEDICINAL PRODUCT

Pyramax 60 mg/20 mg Granules for oral suspension

Pyronaridine tetraphosphate and Artesunate.

2. NAME OF SUPPLIER

Shin Poong Pharmaceutical Co., Ltd

3. EXPIRY DATE

4. BATCH NUMBER

5. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Pyramax 180 mg/60 mg Film Coated Tablets
Pyronaridine tetraphosphate and Artesunate

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you or your child. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours or your child's.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT PYRAMAX IS AND WHAT IT IS USED FOR

Pyramax belongs to a group of medicines known as anti-malarials.

Pyramax tablets are used in adults and children weighing 20 kg or more for the treatment of acute, uncomplicated malaria infection caused by parasites called *Plasmodium falciparum* or *Plasmodium vivax*.

Pyramax is not suitable for preventing malaria, nor for treating severe malaria (e.g. affecting the child's brain, kidneys, or lungs).

2. BEFORE PYRAMAX IS TAKEN

Do not take Pyramax if you or your child
- are allergic (hypersensitive) to pyronaridine tetraphosphate, artesunate, or any of the other ingredients of Pyramax listed at the end of this leaflet.
- known to have severe kidney disease.
- have a severe liver disease or you have clinical symptoms of hepatic dysfunction such as nausea or abdominal pain associated with jaundice (yellowing of the eyes and/or skin).

Take special care with Pyramax
Talk to your doctor or pharmacist before taking Pyramax if you or your child:

- have abnormal hepatic dysfunction notably elevated transaminases which can be shown after blood sample analysis
- are co infected with hepatitis B or C or HIV,
- are malnourished,
- use concomitant drug such as paracetamol, valproate (to treat epilepsy, a neurological disorder), antiretroviral drug (to treat HIV) or herbal medicines (see also Taking other medicines),
- are anaemic (to have a low red blood count – signs of anaemia include tiredness and lethargy (lack of energy), shortness of breath and a pale complexion)
- suffer from kidney disease.

You should monitor especially in the first 2 weeks after Pyramax intake any clinical signs or symptoms of hepatic dysfunction such as fatigue, nausea, abdominal pain, dark urine, putty or mastic coloured stools, jaundice (yellowing of the whites of the eyes or skin) and itching. Contact your doctor or pharmacist if you or your child experience such symptoms, particularly if you or your child get more than one of them. In this case, your doctor may request blood samples to test and monitor the liver function.

Taking other medicines
Please tell your doctor or pharmacist if the person taking the medicine (you or your child) are taking or have recently taken any medicines, including medicines obtained without a prescription, especially if you are being treated with any of the following:

- drugs used to treat HIV (such as ritonavir)
- drugs used to treat heart rhythm disorders
- drugs that are used for nervous diseases
- certain types of antibiotic and anti-fungal agents
- digoxin
- dabigatran
- ketoconazole
- flecainide
- metoprolol
- imipramine
- amitriptyline
- clomipramine
- herbal remedies
- valproate
- paracetamol

If you or your child are taking any of these medicines, tell your doctor **before taking this medicine** as your doctor may need to monitor you or your child more closely or carry out blood tests.

Pregnancy and breast-feeding
Tell your doctor if you are pregnant, or there is any possibility that you may be pregnant (even if you are not sure) or become aware that you are pregnant while taking Pyramax or soon after. Pyramax **must not be used** during the first three months of pregnancy unless your doctor has advised you that there is no alternative.

In the later stages of pregnancy, you can take Pyramax only if your doctor feels that alternative medicines would be unsuitable. Your doctor will discuss with you the potential risk of taking Pyramax during pregnancy and will want to keep seeing you until the baby is born.

The doctor will report your pregnancy to the manufacturer who is keeping a record of all pregnancies occurring if a patient is taking Pyramax. This is so that they can understand any effects that the treatment may have on the pregnancy and the baby.

If possible, you should not breastfeed while you are taking Pyramax as this medicine can pass into breast milk.

Driving and using machines
Pyramax may make you or your child feel dizzy, weak or sleepy. If this happens to you, you are advised not to drive or use any machines.

Important information about some of the ingredients of Pyramax
Pyramax contains Tartrazine (E102) and Sunset yellow FCF (E110) which may cause allergic reactions which may show as:
- Flushing (reddening of the skin especially around the face and upper chest)
- The appearance of wheals/urticaria (itchy blisters)
- Breathlessness
- Feeling faint or light-headedness

3. HOW TO TAKE PYRAMAX

Always take Pyramax exactly as your doctor has told you **and always finish the whole course of treatment**. You should check with your doctor or pharmacist if you are not sure.

Taking Pyramax
- the tablets are to be swallowed whole.
- the tablets should be taken with water.
- if you or your child are sick (vomit) within 30 minutes of taking the first dose take a repeated dose.
- if you or your child are sick (vomit) after taking the repeated dose do not take any more Pyramax and speak to your doctor who may need to give you or your child an alternative medicine to treat the malaria.
- if you or your child have mild diarrhoea, you or your child can continue to take Pyramax normally. However, if you suffer from severe diarrhoea you should speak to your doctor who may have to treat you or your child with an additional or alternative antimalarial.

How much to take
- the recommended dose should be taken once a day for three days without a break. You should try to take the medicine at the same time of day
- the number of tablets you can take depends on your weight:

  - **20 kg to less than 24 kg** body weight: take one tablet daily for three days
  - **24 kg to less than 45 kg** body weight: take two tablets daily for three days
  - **45 kg to less than 65 kg** body weight: take three tablets daily for three days
  - **65 kg** body weight **or greater**: take four tablets daily for three days

Pyramax tablets should not be given to children who weigh less than 20 kg. A granule formulation is available if your child weighs between 5 to under 20 kg.

No special precautions or dosage changes are considered to be necessary in patients who are more than 65 years old.

No special precautions or dosage changes are considered to be necessary if you have been told that you or your child have reduced liver function or reduced kidney function. This is because of the short three day course of treatment.

If you or your child take more Pyramax than you should
If you have accidentally taken too many tablets, **contact your doctor as soon as you can.**

If any of the Pyramax doses are forgotten
Try to make sure you or your child do not miss any doses. If however, you forget a dose of Pyramax, take or give to your child the missed dose as soon as you remember and then the next dose 24 hours later. Do not take a double dose to make up for a forgotten dose.

If you or your child stop taking Pyramax
Make sure you or your child finish the entire course of the treatment, even if you feel better, since the malaria infection may otherwise return. Therefore, do not stop taking your medicine unless your doctor tells you to.

If you or your child stop taking Pyramax before the course is finished for any reason other than because your doctor has told you to, you must contact your doctor who will want to give you or your child alternative treatment.

Always follow your doctor's instructions carefully, and complete the course of medication.
If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Pyramax can cause side effects, although not everybody gets them.

Although allergic reactions to Pyramax are very unusual if you or your child do experience the following symptoms of an allergic reaction:
- rash and itching,
- sudden wheezing, tightness of the chest or throat, difficulty swallowing or breathing
- swelling of the eyelids, face, lips, tongue or other part of the body

Tell your doctor immediately or go to the nearest hospital or clinic immediately and take this leaflet with you.

You should also tell your doctor if you or your child experience any of the following symptoms (particularly if you get more than one of them): fatigue, nausea, abdominal pain, dark urine, putty or mastic (very light coloured) stools, jaundice (yellowing of the whites of the eyes or skin) and itching.

Other possible side effects that you may notice are:

Common (affecting less than 1 in 10 patients)
- headache
  feeling or being sick
- abdominal pain
- changes in heart rate

- **Uncommon** (affecting less than 1 in 100 patients)
- feeling dizzy or weak
- tiredness, sleeping problems
- upset stomach, poor appetite, diarrhoea or constipation
- fever, excessive sweating, cough, respiratory infection, bladder infection or skin infection
- sore mouth or throat, aching muscles
- tingling and/or numbness
- decreased sense of taste
- heaviness in the abdomen that may be due to an enlarged liver or enlarged spleen
- rash, itching, cutaneous reaction

Rare (affecting less than 1 in 1000 patients)
- runny eyes or runny nose
- altered hearing or ringing in the ears
- feeling shivery, fever
- joint, back, or chest pain
- nose bleed or coughing up blood
- asthma

Other side effects:
There are side effects that you may not notice as they only show up on certain tests. If this occurs your doctor may want to do more tests to check that these abnormalities return to normal.

Common side effects which may show up in blood tests are:
- changes in liver enzymes
- changes in certain elements of white blood cells
- anaemia or worsening of anaemia
- the number of cells that help blood clotting (platelets) may change. If they fall too much you or your child may find that bleeding takes longer to stop
- changes in your blood sugar may occur

Less commonly your doctor or nurse may find:
- blood or protein in the urine or occasional white cells
- presence of ketones in the urine (ketonuria)
- small changes in blood pressure

Rarely:
- irregularity in your heart rhythm (arrhythmia)

If any of the side effects become troublesome, or if you notice any side effects not listed in this leaflet tell your doctor or pharmacist.

5. HOW TO STORE PYRAMAX

Keep out of the reach and sight of children.

Do not use Pyramax after the expiry date which is stated on the blister and carton. The expiry date refers to the last day of that month.
Do not store above 30°C.
Store in the original package.
Do not use Pyramax if you notice that the packaging is damaged or shows signs of tampering.
Medicines should not be disposed of via wastewater or household waste. Ask your healthcare provider how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Pyramax contains
- The active substances are pyronaridine tetraphosphate and artesunate.
- The other ingredients are:
  - Tablet - Microcrystalline cellulose, Crospovidone, Mannitol (E421), Magnesium stearate, Talc, Hypromellose, Macrogol 6000
  - Film coating – Hypromellose, Titanium dioxide, Tartrazine (E102), Macrogol 6000, Sunset yellow FCF (E110) (see section 2)

What Pyramax looks like and contents of the pack

Pyramax tablets are round, orange coloured tablets.
Pyramax tablets are available in tropical PVC/aluminium foil blisters containing 9 tablets. The blisters are packed into cartons containing one or 10 blisters.

Supplier
Shin Poong Pharmaceutical Co., Ltd
161, Yeoksam-ro
Gangnam-gu
Seoul
South Korea

Manufacturer
Shin Poong Pharmaceutical Co., Ltd.
70, Sandan-ro 19beon-gil
Danwon-gu
Ansan-si
Gyeonggi-do
South Korea

PACKAGE LEAFLET: INFORMATION FOR THE USER

Pyramax 60 mg/20 mg Granules for oral suspension
Pyronaridine tetraphosphate and Artesunate

Read all of this leaflet carefully before your child starts taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for your child. Do not pass it on to others. It may harm them, even if their symptoms are the same as your child's.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT PYRAMAX IS AND WHAT IT IS USED FOR

Pyramax belongs to a group of medicines known as anti-malarials.

Pyramax granules for oral suspension are used in children and infants weighing 5 kg or more up to 20 kg for the treatment of acute, uncomplicated malaria infection caused by parasites called *Plasmodium falciparum* or *Plasmodium vivax.*

Pyramax is not suitable for preventing malaria, nor for treating severe malaria (e.g. affecting the child's brain, kidneys, or lungs).

2. BEFORE PYRAMAX IS TAKEN

Pyramax should not be given to your child if your child
- is allergic (hypersensitive) to pyronaridine tetraphosphate, artesunate, or any of the other ingredients of Pyramax listed at the end of this leaflet.
- is known to have severe kidney disease.
- has a severe liver disease or has clinical symptoms of hepatic dysfunction such as nausea or abdominal pain associated with jaundice (yellowing of the eyes and/or skin).

Take special care with Pyramax
Talk to your doctor of pharmacist before Pyramax is taken if your child:

- has abnormal hepatic dysfunction notably elevated transaminases which can be shown after blood sample analysis
- is co infected with hepatitis B or C or HIV,
- is malnourished,
- is taking concomitant drug such paracetamol, valproate (to treat epilepsy, a neurological disorder), antiretroviral drug (to treat HIV) or herbal medicines (see also Taking other medicines),
- is anaemic (to have a low red blood count – signs of anaemia include tiredness and lethargy (lack of energy), shortness of breath and a pale complexion)
- suffers from kidney disease.

You should monitor your child especially in the first 2 weeks after Pyramax intake any clinical signs or symptoms of changed liver function such as fatigue, nausea, abdominal pain, dark urine, putty or mastic coloured stools, jaundice (yellowing of the whites of the eyes or skin) and itching. Contact your doctor or pharmacist if your child experiences such symptoms, particularly if your child gets more than one of them. In this case, your doctor may request blood samples to test and monitor the liver function.

Taking other medicines
Please tell your doctor or pharmacist if the person taking the medicine (your child) are taking or have recently taken any medicines, including medicines obtained without a prescription, especially if you are being treated with any of the following:

- drugs used to treat HIV (such as ritonavir)
- drugs used to treat heart rhythm disorders
- drugs that are used for nervous diseases
- certain types of antibiotic and anti-fungal agents
- digoxin
- dabigatran
- ketoconazole
- flecainide
- metoprolol
- imipramine
- amitriptyline
- clomipramine
- herbal remedies
- valproate
- paracetamol

If the person taking the medication are taking any of these medicines, tell your doctor before giving this medicine as your doctor may need to monitor your child more closely or carry out blood tests.

Pregnancy and breast-feeding
Not applicable.
Driving and using machines
Not applicable

3. HOW PYRAMAX IS TAKEN

Always take Pyramax exactly as your doctor has told you and always finish the whole course of treatment. You should check with your doctor or pharmacist if you are not sure.

Taking Pyramax
- the granules for oral suspension should be taken, as instructed by your doctor in a small amount of water as described below under Administration of Pyramax Granules for oral suspension.
- the granules can be taken with or without food.
- if your child is sick (vomits) within 30 minutes of taking the first dose, take a repeat dose.
- if your child is sick (vomits) after taking the repeated dose do not take any more Pyramax and speak to your doctor who may need to give your child an alternative medicine to treat the malaria.
- if your child has mild diarrhoea, your child can continue to take Pyramax normally. However, if your child suffers from severe diarrhoea you should speak to your doctor who may have to treat your child with an additional or alternative antimalarial.

How much to give:
- the recommended dose should be taken once a day for three days without a break. You should try to give the child the medicine at the same time of day

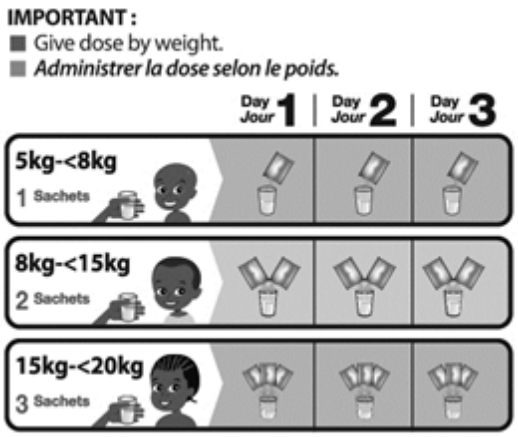
- **the number of sachets of granules for oral suspension which should be taken depends on the child's weight:**

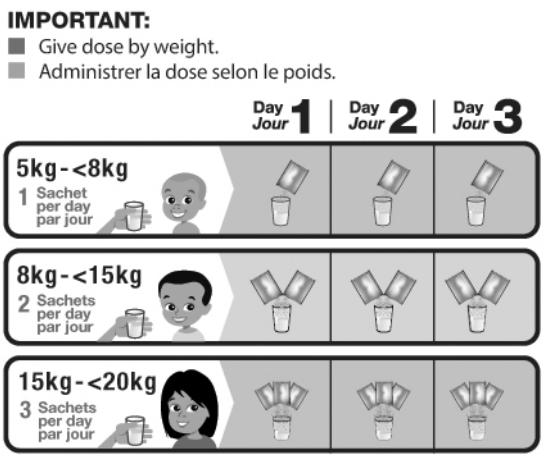
    - **5 kg to less than 8 kg body weight: give one sachet daily for three days**
    - **8 kg to less than 15 kg body weight: give two sachets daily for three days**
    - **15 kg to less than 20 kg body weight: give one sachet daily for three days**

A tablet formulation is available if your child weighs more than 20 kg.

Administration of Pyramax Granules for oral suspension:

Add a small amount of water (approximately 10 ml i.e. 2 teaspoons) into a small cup. Put the contents of the required number of sachets (based on the weight of the child) into the cup and stir gently until the granules are suspended evenly. The granules will not dissolve. The patient should swallow the suspension immediately. Add a small amount of water (approximately 10 ml i.e. 2 teaspoons) to the cup to mix any remaining granules and the suspension should then be immediately swallowed by the patient. It is recommended to repeat this step until the patient has swallowed all the granules and no granules remain in the cup. Only drinking water should be used for preparing the oral suspension. No studies have been conducted on administration with feeding tubes. Caution is needed to minimise the risk of inhaling the granules with very young children.





No special precautions or dosage changes are considered to be necessary if you have been told that your child has reduced liver function or reduced kidney function. This is because of the short three day course of treatment.

If your child takes more Pyramax than he/she should
If your child has accidentally taken too many granules, contact your doctor as soon as you can.

If any of the Pyramax doses are forgotten
Try to make sure you do not miss any doses. If however, you forget to give to your child a dose of Pyramax, give the missed dose as soon as you remember and then the next dose 24 hours later. Do not give a double dose to make up for a forgotten **dose**.

If your child stops taking Pyramax
Make sure your child finishes the entire course of the treatment, even if they feel better, since the malaria infection may otherwise return. Therefore, do not stop the medicine unless your doctor tells you to.

If you stop giving Pyramax before the course is finished for any reason other than because your doctor has told you to, you must contact your doctor who will want to give your child alternative treatment.

Always follow your doctor's instructions carefully, and complete the course of medication.
If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Pyramax can cause side effects, although not everybody gets them.

Although allergic reactions to Pyramax are very unusual if you do experience the following symptoms of an allergic reaction:
- rash and itching,
- sudden wheezing, tightness of the chest or throat, difficulty swallowing or breathing
- swelling of the eyelids, face, lips, tongue or other part of the body

Tell your doctor immediately or go to the nearest hospital or clinic immediately and take this leaflet with you.

You should also tell your doctor if your child experiences any of the following symptoms (particularly if your child get more than one of them): fatigue, nausea, abdominal pain, dark urine, putty or mastic (very light coloured) stools, jaundice (yellowing of the whites of the eyes or skin) and itching.

Other possible side effects that you may notice are:

Common (affecting less than 1 in 10 patients)
- headache
- feeling or being sick
- abdominal pain
- changes in heart rate

Uncommon (affecting less than 1 in 100 patients)
- feeling dizzy or weak
- tiredness, sleeping problems
- upset stomach, poor appetite, diarrhoea or constipation
- fever, excessive sweating, cough, respiratory infection, bladder infection or skin infection
- sore mouth or throat, aching muscles
- tingling and/or numbness
- decreased sense of taste
- heaviness in the abdomen that may be due to an enlarged liver or enlarged spleen
- rash, itching, cutaneous reaction

Rare (affecting less than 1 in 1000 patients)
- runny eyes or runny nose
- altered hearing or ringing in the ears
- feeling shivery, fever
- joint, back, or chest pain
- nose bleed or coughing up blood
- asthma

Other side effects:
There are side effects that you may not notice as they only show up on certain tests. If this occurs your doctor may want to do more tests to check that these abnormalities return to normal.

Common side effects which may show up in blood tests are:
- changes in liver enzymes
- changes in certain elements of white blood cells
- anaemia or worsening of anaemia
- the number of cells that help blood clotting (platelets) may change. If they fall too much you may find that bleeding takes longer to stop
- changes in blood sugar may occur

Less commonly your doctor or nurse may find:
- blood or protein in the urine or occasional white cells
- presence of ketones in the urine (ketonuria)
- small changes in blood pressure

Rarely:
- irregularity in your heart rhythm (arrhythmia)

If any of the side effects become troublesome, or if you notice any side effects not listed in this leaflet tell your doctor or pharmacist.

5. HOW TO STORE PYRAMAX

Keep out of the reach and sight of children.
Do not use Pyramax after the expiry date which is stated on the sachet and carton. The expiry date refers to the last day of the month.
Do not store above 30°C.
Store in the original package.
Do not use Pyramax if you notice that the packaging is damaged or shows signs of tampering.
Medicines should not be disposed of via wastewater or household waste. Ask your healthcare provider how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Pyramax contains
- The active substances are pyronaridine tetraphosphate and artesunate.
- The other ingredients are:
  - Granules for oral suspension: Mannitol, Talc, Ethyl cellulose, Macrogol 6000, Hypromellose 2910, Iron oxide yellow (E172), Iron oxide red (E172), Acesulfame potassium (see section 2)

What Pyramax looks like and contents of the pack
Pyramax granules for oral suspension are orange coloured granules
Pyramax granules for oral suspension are packaged in sachets consisting of layers of polyester, aluminium and polyethylene/Surlyn. Each carton contains 90 sachets.

Supplier
Shin Poong Pharmaceutical Co., Ltd
161, Yeoksam-ro
Gangnam-gu
Seoul
South Korea

Manufacturer
Shin Poong Pharmaceutical Co., Ltd
70, Sandan-ro 19beon-gil
Danwon-gu
Ansan-si
Gyeonggi-do
South Korea