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.

Excipients with known effect: each sachet contains 0.05 mg Sunset yellow FCF (E110) and 0.15 mg Tartrazine (E102).
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 liver toxicity 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 as a prophylactic treatment of malaria.

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 8 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). If a patient is already known to have elevated transaminases the use of Pyramax is not recommended.

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.

No data are available in patients with co-infections (HBV, HCV, HIV); those receiving co-administration of drugs known to be associated with mitochondrial toxicity (i.e. valproate, antiretroviral drugs), use of herbal medicines, patients with malnutrition or patients with other hepatic underlying conditions (i.e. ethanol intoxication, hepatic steatosis). Particular caution is advised in these patients regarding the risk of liver toxicity since these risk factors, also including co-administration of paracetamol, might produce a cumulative effect on the liver. 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 $\geq$ 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 recrudescent malaria infections 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. No 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. 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 (i.e. valproate, antiretroviral drugs), use of herbal medicines, and also co-administration of paracetamol (see section 4.4).

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

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.

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

Pregnancy register
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.

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 more than 4000 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	Bronchitis, bronchopneumonia, infection parasitic, pharyngitis, pharyngotonsillitis,

System Organ Class	Common	Uncommon	Rare
		infection	*Plasmodium falciparum* infection, pneumonia, rhinitis, subcutaneous abscess, tracheobronchitis
Investigations	Transaminases increased (See section 4.4)	Blood albumin decreased, blood alkaline phosphatase increased, blood creatine phosphokinase increased, blood creatinine decreased, blood sodium increased, electrocardiogram abnormal, electrocardiogram QT prolonged (see section 4.4), liver function test abnormal	Blood albumin increased, blood bilirubin decreased, blood bilirubin increased, blood creatinine increased, blood potassium decreased, haematocrit increased, red blood cell count increased, white blood cells urine
Metabolism and nutrition disorders	Hypoglycaemia	Anorexia, hyperkalaemia	Decreased appetite, hyperglycaemia
Musculoskeletal and connective tissue disorders		Myalgia	Arthralgia, back pain
Nervous system disorders	Headache	Dizziness, dysgeusia, paraesthesia	Somnolence
Pregnancy, puerperium and perinatal conditions			Abortion complete
Psychiatric disorders		Insomnia	Sleep talking
Renal and urinary disorders		Haematuria, proteinuria	Ketonuria
Reproductive system and breast disorders			Vulvovaginal pruritus
Respiratory, thoracic and mediastinal disorders		Cough	Asthma, epistaxis, haemoptysis, rhinorrhoea
Skin and subcutaneous tissue disorders		Hyperhidrosis, pruritus, rash	Blister, dermatitis, urticaria papular
Vascular disorders			Hypertension, hypotension

* 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, > 10x ULN 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 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.

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 plus 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 will be included in a pharmacovigilance study being 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.

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 faeces 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
Tartrazine (E102)

Sunset Yellow FCF (E110)
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