APPLICATION FOR INCLUSION OF

PYRONARIDINE TETRAPHOSPHATE / ARTESUNATE FIXED DOSE COMBINATION TABLETS AND GRANULES

IN THE WHO MODEL LIST OF ESSENTIAL MEDICINES (EML) AND MODEL LIST OF ESSENTIAL MEDICINES FOR CHILDREN (EMLc)
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   Therapeutic indications
   Posology and method of administration
   Contraindications
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   Interaction with other medicinal products and other forms of interaction
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1. SUMMARY STATEMENT OF THE PROPOSAL FOR INCLUSION

The WHO Guidelines for the Treatment of Malaria Third Edition, 2015 describe the nature of the malaria clinical disease, which depends strongly on the background level of acquired protective immunity, as a consequence of the pattern and intensity of malaria transmission in the area of residence of the affected individuals.

Artemisinin derivatives are widely used anti-malarial drugs with a history of clinical use both alone and in combination with other drugs, mainly to treat *P. falciparum* malaria, but also *P. vivax* malaria. Artemisinin derivatives clear parasites rapidly; however, conventional 7-day monotherapy regimens are associated with recrudescence. To combat resistance to anti-malarial monotherapy, combinations of anti-malarial drugs are recommended by the World Health Organization (WHO) in their malaria treatment guidelines dating back to 2006, 2010 and most recently updated in 2015. Artemisinin-based combination therapies (ACTs) have been increasingly used to treat uncomplicated *P. falciparum* malaria and have been shown to slow or reverse the emergence of resistance. When administered with rapidly eliminated compounds (e.g. tetracyclines, clindamycin), a 7-day course of treatment is required. However, when administered with a more slowly eliminated anti-malarial drug, a 3-day course of treatment is effective. The objective of ACT treatment is for a 3-day course to act over 2 asexual cycles to substantially reduce parasite numbers, ensuring a rapid clinical response.

PYRAMAX® (pyronaridine-artesunate) has been developed as a new fixed-dose oral formulation for the treatment of *P. falciparum* uncomplicated malaria and for the blood stages of *P. vivax* malaria. It is presented as a combined tablet or granule formulation, enabling adults, children as well as infants of 5 kg and over to be treated. The combination preparation is made of pyronaridine tetraphosphate, and resin-coated granules of artesunate in a 3:1 ratio. Both formulations can be stored up to 30°C in the original package, in order to protect them from heat and humidity.

The drug development programme for PYRAMAX® was designed to support the target product profile for treatment of a once-daily three day administration of a fixed-dose tablet or granule paediatric formulation of oral PYRAMAX® for use in infants, children and adults to treat acute, uncomplicated malaria for both *P. falciparum* and blood stages of *P. vivax* as an alternative to current malaria treatments. PYRAMAX® is presented as a combined, fixed-dose tablet or granule formulation in sachet, enabling adults as well as infants to be treated both in the presence and absence of food.

Shin Poong Pharmaceutical Co., Ltd is a pharmaceutical company established in Seoul, South Korea since 1962 that develops and manufactures medicines in their own facilities and markets them in many regions. Shin Poong has a long history of manufacturing products for neglected diseases including schistosomiasis where it has had a long standing collaboration with World Health Organization. Shin Poong is the Scientific Opinion Holder of the European Medicines Agency (EMA) Article 58 Positive Opinion for PYRAMAX®. The development has been undertaken in partnership with the Medicines for Malaria Venture (MMV), a
not-for-profit foundation based in Geneva, Switzerland. The programme has been managed by a drug development team which has received input from a wide range of experts including MMV’s Expert Scientific Advisory Committee, the World Health Organization (WHO) Roll Back Malaria Partnership and Global Malaria Programme, as well as malaria specialists from Africa and South East Asia. Under the Article 58 mechanism of EMA, Shin Poong has built a strong collaborative relationship with EMA.

Shin Poong manufactured PYRAMAX® for clinical studies and commercial use at their European-GMP compliant facilities in South Korea. Preclinical studies have been performed to ICH standards both with the individual active substances and with the combination as appropriate. Clinical studies for phases I, II and III have been completed with both the tablet and the granule formulation to GCP standards. The Company holds a New Drug Application (K-NDA) for PYRAMAX® Tablets from the Korean regulatory agency (August 2011) with a regulatory Variation filing submitted for repeated dosing administration.

PYRAMAX® Tablets were the first innovative medicinal products for the treatment of malaria to receive a Positive Opinion under the collaborative EMA/WHO mechanism for regulatory approval. PYRAMAX® was granted a positive Scientific Opinion under Article 58 for efficacy, safety and quality from EMA in February 2012 for the treatment of P. falciparum and blood stages of P. vivax in adult and children over 20 kg. On the basis of the EMA’s Positive Opinion, PYRAMAX® Tablets were included on WHO’s list of Pre-Qualified anti-malarials in May 2012. PYRAMAX® Tablets were officially launched in Korea in August 2012. In November 2015, a further Positive Opinion was granted from EMA for the paediatric formulation as PYRAMAX® granules for oral suspension for repeated dosing in children and infants from 5 kg to 20 kg for both P. falciparum and blood stages of P. vivax malaria. Furthermore a Label Variation was received from EMA at the same time for repeated dosing of PYRAMAX® Tablets. Additionally a number of limitations from the original product label were removed by EMA following a detailed review of the evidence presented by Shin Poong, notably the removal of the limitations on geographical region, requirements for liver function tests and the limit to just a single dosing regimen to cover repeated dosing within a minimum period of 28 days.

In March 2016, PYRAMAX® granules for oral suspension were included on WHO’s list of Pre-Qualified anti-malarials.

**Proof of efficacy and safety:**

In the Phase III studies to support the initial Positive Opinion from EMA, PYRAMAX® was shown to have good efficacy, safety and tolerability profiles in children and adults patients for the treatment of acute, uncomplicated P. falciparum (Tshefu et al., 2010, Rueangweerayut et al., 2012, Kayentao et al 2012) or blood stage P. vivax (Poravuth et al., 2011) malaria in endemic regions in Africa, South East Asia and India.
Overall comparative efficacy of PYRAMAX® tablets and granules:

In the individual Phase III studies, the primary end point in the P. falciparum populations was PCR-adjusted adequate clinical and parasitological response (ACPR) on Day 28 in the efficacy evaluable (EE) population. In each of the 3 P. falciparum studies, non-inferiority of PYRAMAX® vs. the comparator was demonstrated for the PCR-adjusted ACPR on Day 28 in the EE population. In the paediatric trial versus Coartem (SP-C-007-07), the primary analysis evaluated whether the PCR-adjusted ACPR in the PYRAMAX® group was statistically significantly >90%. In that study, the PCR-adjusted ACPR was statistically significantly >90% in the PYRAMAX® group by the exact binomial test. Non-inferiority of PYRAMAX® to comparators was also demonstrated in the ITT population on Day 28.

In an integrated analysis of all PYRAMAX® and comparator groups Phase III patients, the ITT population was considered the primary analysis population, in contrast to the individual studies, given the variability of the EE population criteria across studies. In the integrated analysis of the Phase III P. falciparum studies population, no notable differences in PCR-adjusted ACPR were observed between the PA group and the artemether-lumefantrine (AL) or mefloquine plus artesunate (MQ + AS) treatment groups at any time point in the ITT population. PCR-adjusted ACPR decreased over time in each treatment group, with notably lower cure rates observed on Day 35 and/or Day 42 compared with Days 14, 21, and 28 (Duparc et al, 2013).

Based on Kaplan-Meier estimates, time to parasite clearance was statistically significantly shorter in the PYRAMAX® group compared with AL group (SP-C-005-06 and SP-C-007-07) and chloroquine group (SP-C-006-06), based on the log-rank test. Time to parasite clearance was similar in the PYRAMAX® and MQ + AS groups (SP-C-004-06). In the pooled analysis, median time to parasite clearance was 24 hours in the PYRAMAX® and AL groups and 32 hours in the MQ + AS and chloroquine groups.

The clinical study programme undertaken for PYRAMAX® demonstrated conclusively that for the primary endpoint of PCR-adjusted ACPR at 28 days, pyronaridine-arpesunate was not inferior to MQ + AS or AL for the treatment of P. falciparum. At 28 days post-dosing, the cure rate for PYRAMAX®, MQ + AS, and AL was very high and, whilst the cure rates declined over time, PYRAMAX® was actually superior to AL at Day 35 in the study of adults and children (although not the paediatric-only study). PYRAMAX® demonstrated superiority in parasite clearance time, being statistically significant versus AL, although fever clearance time was faster in the AL group. In addition, time to P. vivax parasite clearance and time to fever clearance were statistically significantly shorter in the PYRAMAX® group compared with the chloroquine group, findings that were not unexpected due to the rapid action of AS.

PYRAMAX® was shown to provide greater protection than comparators against recrudescence and new infections in subjects treated for P. falciparum malaria. In addition, PYRAMAX® demonstrated gametocytocidal activity in the Phase III P. falciparum studies, establishing it as a transmission-blocking agent.

Although SP-C-006-06 was a study of uncomplicated malaria with P. vivax (mixed infections not allowed), a post hoc analysis also demonstrated that the risk of subsequent infection with P. falciparum was statistically significantly lower with PYRAMAX® than with chloroquine (p=0.0481), providing a further benefit after resolution of the original malaria infection.
In the PYRAMAX® clinical studies, there was a mixture of subjects from Asia, India and Africa, children and adults, and subjects with and without previous experience with malaria. Parasite clearance time and fever clearance time were shorter among subjects from Africa and among Black subjects compared with Asian/Oriental subjects, and time to recrudescence was longer among subjects from Africa and among Black subjects compared with Asian/Oriental subjects. Time to recrudescence where this occurred was longer in adults than children. Parasite clearance time and fever clearance time were longer and recrudescence rates were higher for subjects who had no previous episodes of malaria compared with subjects who had previously had malaria. These differences suggest that previous exposure allows the development of immunity and this, which is more established in adults than children, may contribute to the faster parasite clearance time. Whilst these times may vary, the effectiveness of PYRAMAX® in subjects with de novo malaria or those who had been previously exposed was extremely high.

**Overall comparative safety of PYRAMAX® tablets and granules:**

The safety database for the Phase II/III PYRAMAX® clinical programme included 3017 subjects who received at least 1 dose of PYRAMAX®, administered either as the fixed-dose co-formulation or as PP + AS across 7 Phase I, 2 Phase II, and 5 Phase III studies, or in the case of the mass balance study, pyronaridine alone. The adverse event profile of PYRAMAX® in the individual studies and in the integrated analysis of all Phase II/III studies was consistent with profiles reported for pyronaridine and artemisinins as monotherapy [Price, 1999; Ringwald, 1996; Looareesuwan, 1996, Ribeiro, 1998]. PA treatment was generally well tolerated with the vast majority of AEs being of mild or moderate intensity, with headache and gastrointestinal symptoms occurring most frequently.

The only notable safety finding that was more prevalent for subjects treated with PYRAMAX® was the finding of significant transient transaminase elevations in a relatively small proportion of subjects. However, the early onset (Day 3-7) and rapid resolution of the transaminase elevations are consistent with a direct, low-level toxicity. The risk associated with this finding also took into account subjects who had rises, after their first episode of treatment, >3x but ≤5x (2.1%), >5x but ≤10x (1%), and >10xULN (0.4%) for transaminases, as well as those subjects (0.2%) who might qualify as Hy’s law candidates (ALT >3xULN and total bilirubin >2xULN) when assessing the potential of PYRAMAX® to produce liver injury [Temple, 2001; Reuben, 2004] The data were rigorously reviewed by an Independent Safety Review Board consisting of 3 hepatologists, an epidemiologist and an independent statistician. Upon review of all the data, including the follow-up information on subjects with clinically significantly raised values, the board concluded that the risk of progressive liver injury, especially for a 3-day course of treatment, was very low. Their view was that serious idiosyncratic hepatotoxicity typically begins weeks or months after starting therapy. Of note in the cases that occurred in the PYRAMAX® study programme, all of the raised values returned to normal, the vast majority being normal at 28 days. Some returned to normal earlier, but for most studies, the blood draws were performed at 3, 7, 28, and 42 days. Overall, changes in liver function tests in terms of drug-induced liver injury were in the main mild with a small number of moderate cases (based on peak total bilirubin levels) based on the criteria of the Drug Induced Liver Injury Network (Fontana 2010). Furthermore there were no cases of liver failure, no encephalopathy, no evidence of coagulopathy and no evidence of a delayed effect.
Quality:

Pyronaridine tetraphosphate/artesunate - PYRAMAX® tablets and granules are manufactured by:
Shin Poong Pharmaceutical Co., Ltd
161, Yeoksam-ro
Gangnam-gu
Seoul
South Korea

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

This facility has been constructed and equipped in line with EU Good Manufacturing Practice (GMP) and granted EU GMP for API and FDF in April 2011 and May 2011 respectively. PYRAMAX® Tablets have been included on WHO’s list of Pre-Qualified anti-malarials in May 2012. Further GMP Inspections by EMA took place in July 2015 and April 2015. Both pyronaridine tetraphosphate and artesunate are manufactured at the same site as the tablet and granule formulations. Active ingredients are GMP compliant. PYRAMAX® Granules for oral suspension have been included on WHO’s list of Pre-Qualified anti-malarials in March 2016.
2. NAME OF THE WHO TECHNICAL DEPARTMENT AND FOCAL POINT SUPPORTING THE APPLICATION

Not applicable
3. NAME OF THE ORGANISATION(S) CONSULTED AND/OR SUPPORTING THE APPLICATION

Co-development partner for development of PYRAMAX® Tablets and Granules:

Medicines for Malaria Venture (MMV)
International Center Cointrin (ICC) Building
20, route de Pré-Bois
CH-1215 Geneva 15
Switzerland

PYRAMAX® Tablets and Granules were developed in conjunction with the expertise and support of malaria experts from endemic countries through their involvement in guiding the development of the most appropriate antimalarial product.
4. INTERNATIONAL NON-PROPRIETARY NAME (INN, GENERIC NAME) AND ATC CODE OF THE MEDICINE

PYRAMAX®, Pyronaridine/Artesunate tablets and granules are a fixed dose combination of two antimalarial drugs pyronaridine tetraphosphate (INN) and artesunate (INN).

Anatomical Therapeutic Chemical (ATC) code of is P01BF06.
5. FORMULATION AND STRENGTH PROPOSED FOR INCLUSION INCLUDING ADULT AND PAEDIATRIC

5.1 Rationale on the PYRAMAX® formulation

The goal of anti-malarial drug development is to develop potent, safe, easy-to-administer, field-adapted and inexpensive combination therapies. There is a need for new drugs that are efficacious against both *P. falciparum* and blood stages of *P. vivax*, because in areas where both species exist and health systems are under sourced, it is often not possible to distinguish between the two species at the initial diagnosis. Given the data accumulated to date, it has been demonstrated in clinical trials that the combination of pyronaridine tetraphosphate (PP) and artesunate (AS), as a new ACT, fulfils these needs, addressing the needs of the patients infected the two most prevalent malaria species.

Since endemic areas of malaria are mainly in underdeveloped regions of the world such as sub-Saharan Africa and remote regions of South East Asia any new dosage form of an anti-malarial medicine should be designed to achieve safe and effective therapy with easy to dose medicine designed to optimise patient compliance.

The rationale for the 3:1 ratio of pyronaridine to artesunate was based on prior existing clinical data and clinical practice. The recommended dose for artesunate in combination is 4 mg/kg and pyronaridine has been shown to be effective in doses of about 6-12 mg/kg per day. Therefore, the combination of the 2 drugs in approximately the same proportions seemed logical to take advantage of the short half-life of the artesunate combined with the longer half-life of the pyronaridine; this was further justified in the PYRAMAX® development programme by the absence of any pharmacokinetic interaction. The combination of the 2 drugs in a 3:1 ratio exhibited comparable onset of action and curative activity after both single and 3-dose oral treatment regimens in a rodent model and showed superior efficacy in comparison with the drugs alone. The dose escalation proposed in the Phase I and II studies was designed to assess the safety and the efficacy of a 3-day course of these drugs in achieving a sustainable cure rate of >90% at 28 days for falciparum malaria. Repeated 3-day administrations with the combination provides the supportive evidence for the extension to the label for both tablets and granules.

The current approved label by European Medicines Agency (EMA) is for repeated dosing of PYRAMAX® in patients with uncomplicated *P. falciparum* and blood stage *P. vivax* malaria in patients from 5 kg in body weight. PYRAMAX® is given once a day for three days and the drug can be given with no regard to food intake, which is a particular benefit compared to recently approved ACTs. Regulatory approvals for the revised label are being sought at a National level in Endemic Countries.

The approved formulations by European Medicines Agency are for:

- Single strength of immediate release film-coated pyronaridine-artesunate PYRAMAX® TABLET containing 180 mg pyronaridine tetraphosphate and 60 mg artesunate.
5.2 Chemical characteristics

Pyronaridine is a benzophenanthridine derivative first synthesized in 1970 at the Institute of Chinese Parasitic Disease, Chinese Academy of Preventive Medicine (Zheng et al., 1982; Zheng et al., 1979; Chen & Zheng, 1992). The pyronaridine nucleus is based on mepacrine (a 9-aminoacridine) with the addition of an amodiaquine-like side chain (Chang et al., 1992; Chen & Fleckenstein, 2001). The drug is formulated as pyronaridine tetraphosphate, a yellow, odourless powder with a bitter taste (Chang et al., 1992). As the use of pyronaridine for the treatment of malaria has been limited to China, where it has been used during 40 years, it is expected that resistance will be slow to develop across other malarial regions of the world.

Artemisinin is an antimalarial drug consisting of a sesquiterpene lactone ring with a unique endoperoxide dioxygen bridge in which the antimalarial activity resides. Extracts of artemisinin or ‘qinghaosu’ have been utilised for hundreds of years as antipyretic herbal remedies in China. However, it was not until 1971 that the antimalarial property of artemisinin was described (Anon, Qinghaosu antimalarial co-ordinating group, 1982). Artemisinin is readily purified from Artemisia annua (sweet wormwood) and has been used to treat malaria in China since the early 1970’s (Meshnick et al., 1996; Van Agtmael et al.; 1999; Price, 2000). Since this initial discovery a number of semi synthetic oil and water soluble derivatives of artemisinin have been developed with a variety of formulations entering clinical studies. In vivo, artemisinin and its derivatives are rapidly converted to dihydroartemisinin (DHA), the active metabolite.

Artesunate is the most widely used member of the artemisinin derivative drugs. It is effective against strains of P. falciparum resistant to all other antimalarial drugs in common clinical practice, as well as P. vivax.

Pyronaridine tetraphosphate is a blood schizonticide antimalarial therapy synthesised in China in 1970. Available data indicate that pyronaridine is effective in cases of chloroquine resistance and seems to be satisfactorily tolerated (Zheng et al, 1982). Pyronaridine (oral and injectable formulations) is currently marketed in China under the trade name Malaridine and was administered in combination with other agents with the aim of preventing the appearance of drug resistance (Ringwald et al, 1999, Chen and Zheng, 1992). The physicochemical properties of pyronaridine have been determined (Olajire et al, 2006).

5.3 The formulation for inclusion:

Pyronaridine/ artesunate are antimalarial agents with a history of clinical use both separately and in combination with other drugs. Each drug has powerful schizonticidal actions but the combination of the two is expected to show pharmacological addition in man. The action of
artesunate is a rapid knock-down of the parasites, after which the drug is rapidly cleared as it has a short systemic half-life. Pyronaridine is also effective in the short-term but has an intermediate blood half-life thus providing a sustained schizonticidal effect. The aim of the fixed dose combination of pyronaridine/artesunate in the treatment of uncomplicated acute malaria is to provide a rapid reduction in parasitaemia with a three-day regimen, thereby improving compliance and reducing the risk of recrudescence through the slower elimination of pyronaridine.

Based on existing clinical data and clinical practice, the ratio of pyronaridine to artesunate of 3:1 w/w was considered for development. Doses were originally selected to be in line with prescribing practice for the agents when used as monotherapy. The drug development programme for PYRAMAX® was designed to meet a target product profile for curative treatment of a once daily administration of a fixed dose tablet formulation pyronaridine/artesunate, for 3 days to patients with acute uncomplicated *P. falciparum* and blood stage *P. vivax* malaria. To meet more recent requirements, an additional target profile for repeated dosing was met.

The drug materials have been produced to European GMP standard by the Sponsor, Shin Poong Pharmaceutical Co., Ltd (SPP). The combination product has been developed by SPP in conjunction with Medicines for Malaria Venture (MMV) as a public private partnership.

### 5.3.1 Posology

PYRAMAX® tablets contain:

- The active substances of pyronaridine tetraphosphate and artesunate.
- Other ingredients of microcrystalline cellulose, crospovidone, mannitol (E421), magnesium stearate, talc, hypromellose, macrogol, hypromellose, titanium dioxide, tartrazine (E102), sunset yellow FCF (E110).

PYRAMAX® Granules for oral suspension contain:

- The active substances of pyronaridine tetraphosphate and artesunate.
- Other ingredients of mannitol, talc, ethyl cellulose, macrogol, hypromellose 2910, tartrazine (E102), sunset Yellow FCF (E110) and acesulfame potassium.

The food effect study did not suggest any clinically relevant effect of food on the bioavailability of either compound and therefore Pyramax can be taken with or without food. The tablets and granules should be stored in their original pack until use.

**PYRAMAX® tablets** are immediate release, orange, round, film-coated tablets. Each tablet contains 180 mg of pyronaridine tetraphosphate and 60 mg of artesunate. The tablet is a non-scored, single dose strength, to be administered once a day, by weight (20 to <90 kg) in ranges of 1 to 4 tablets.
<table>
<thead>
<tr>
<th>Weight</th>
<th>No. of Tablets</th>
<th>Pyronaridine (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 - &lt; 24 kg</td>
<td>1</td>
<td>7.5 – 9.0</td>
</tr>
<tr>
<td>24 - &lt; 45 kg</td>
<td>2</td>
<td>8.0 – 15.0</td>
</tr>
<tr>
<td>45 - &lt; 65 kg</td>
<td>3</td>
<td>8.3 – 12.0</td>
</tr>
<tr>
<td>≥65 kg</td>
<td>4</td>
<td>8.0 – 11.1</td>
</tr>
</tbody>
</table>

PYRAMAX® granules: Each sachet of PYRAMAX® Granules for oral suspension contains 60 mg pyronaridine tetraphosphate and 20 mg artesunate. PYRAMAX® granules for oral suspension are orange coloured granules. PYRAMAX® Granules for oral suspension should be taken orally as a single daily dose for three consecutive days, by weight ranges from 5 kg to under 20 kg.

<table>
<thead>
<tr>
<th>Weight</th>
<th>No. of Granule Sachets</th>
<th>Pyronaridine (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 - &lt; 8 kg</td>
<td>1</td>
<td>7.6 – 12.0</td>
</tr>
<tr>
<td>8 - &lt; 15 kg</td>
<td>2</td>
<td>8.1 – 15.0</td>
</tr>
<tr>
<td>15 - &lt; 20 kg</td>
<td>3</td>
<td>9.0 – 12.0</td>
</tr>
</tbody>
</table>

5.4 Stability of the formulations

PYRAMAX® tablets

PYRAMAX® tablets are packaged into tropical blister packs. One tropical blister pack contains 9 tablets in a 3 x 3 orientation. One or ten blister packs are inserted into a printed paper carton. The blister packs comprise of a thermoformed PVC film with an aluminium lid foil and an aluminium cold-formed laminate.

Based on the available data from the primary batches of drug product, the Sponsor has assigned a 24 month shelf-life to PYRAMAX® tablets when stored at or below 30°C and this shelf life has been approved by EMA.

PYRAMAX® granules

PYRAMAX® granules are packaged into square shaped pack sachets. One sachet contains 60mg pyronaridine tetraphosphate and 20mg artesunate.

The number of sachets required are inserted into a printed paper envelope by the prescribing health worker.

The sachet packs comprise special sealant (Polyethylene/Surlyn), aluminium foil and PET.

Based on available data from the primary batches of drug product, the Sponsor has assigned a 24 month shelf-life to PYRAMAX® sachets when stored at or below 30°C and this has been accepted by EMA.
Storage conditions
The manufacturer recommends that the drug is stored below 30°C in the original package.

5.5 PYRAMAX® Manufacturer

PYRAMAX® tablets and granules are manufactured by:

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

This facility has been specifically constructed for production of API and FDF and equipped in line with EU Good Manufacturing Practice (GMP) and granted EU GMP for API and FDF in April 2011 and May 2011 respectively. PYRAMAX® Tablets have been included on WHO’s list of pre-qualified anti-malarials in May 2012. Further EU GMP Inspections for API and FDF were conducted in July 2015 and April 2015. PYRAMAX® Granules for oral suspension have been included on WHO’s list of Pre-Qualified anti-malarials in March 2016.

Sufficient quantities of tablets and granules have been manufactured to meet expected needs.

In order to address the concerns of access to product, availability of stock and quality, Shin Poong from the outset chose to manufacture pyronaridine tetrathosphate and artesunate by itself; controlling the sourcing of starting materials through to distribution employing its own processes and network. In this way Shin Poong can assure adequate production and can be sufficiently flexible to meet market demands.

The development of pyronaridine tetrathosphate and artesunate tablet and granules was conducted to meet the stringent requirements of the EMA as competent regulatory authority. Nonetheless Shin Poong set out to conduct GCP clinical trials in a broad range of malaria endemic countries such that the product could be tested in the widest range of settings. Shin Poong were committed to ensure that both Plasmodium species should be fully tested to provide physicians with greater treatment flexibility in regions where mixed plasmodium and vivax infection is prevalent. Furthermore, the development phase of the tablet and the granules formulations took place in parallel, so that the target population of children could be exposed to the drug within the same timeframe as the adult.

Shin Poong elected to follow the newly created Article 58 Opinion Route for product registration as it provided for involvement of WHO both in the review of the registration dossier as well as facilitating WHO prequalification for Artemisinin based antimalarial products.

A submission to Minister of Food and Drug Safety (MFDS) in Korea took place in June 2010,
in parallel to that of EMA, with regulatory approval in August 2011. Subsequent registrations have been sought by Shin Poong in malaria endemic countries. PYRAMAX® granules have been approved by MFDS in May 2016.
6. LISTING AS AN INDIVIDUAL MEDICINE OR A PHARMACOLOGICAL CLASS

Pyronaridine tetraphosphate/artesunate (PYRAMAX®) tablets and granules are Artemisinin Containing Therapies (ACT) for malaria treatment and are submitted for inclusion in the 21st WHO Expert Committee Model Lists of Essential Medicines for both Adults and Children. It is proposed that inclusion is made in sub-section 6.5.3: antimalarial medicines – curative treatments in “antimalarial medicines for curative treatment”.

The combination of the most widely used artemisinin, artesunate, and an established anti-malarial agent, pyronaridine (i.e. pyronaridine tetraphosphate), forms a novel ACT. Pyronaridine tetraphosphate is a blood schizonticidal antimalarial therapy originally synthesised in China in 1970. Early data indicated that pyronaridine is effective in cases of chloroquine resistance and seemed to be satisfactorily tolerated. Pyronaridine (oral and injectable formulations) had been marketed in China under the trade name Malaridine and had been administered in combination with other agents with the aim of preventing the appearance of drug resistance. Because pyronaridine has an intermediate half-life (approximately 14 days), compared with other anti-malarials with substantially longer half-lives, such as chloroquine and mefloquine (MQ) or substantially shorter half-lives such as lumefantrine, it is an ideal partner drug for artesunate, which is rapidly effective and rapidly cleared due to its short systemic half-life. Pyronaridine had been used in China for over 40 years; initial clinical trials conducted in China demonstrated its safety and efficacy by oral and parenteral routes against both P. falciparum and P. vivax. The drug had also been shown to be satisfactorily tolerated and highly effective in treating malaria patients in other endemic regions. Available data also indicate that pyronaridine is effective in cases of drug resistance for all malaria species. Although pyronaridine is effective in the short term, it also provides a sustained schizonticidal effect due to its intermediate blood half-life. Furthermore, on repeated dosing to treat subsequent malaria episodes, pyronaridine was shown to be safe and effective.

In the 19th WHO Model List of Essential Medicines (April 2015), the following 3 ACTs are reported as being listed:

- artemether + lumefantrine* Tablet: 20 mg + 120 mg. Tablet (dispersible): 20 mg + 120 mg [c]. * Not recommended in the first trimester of pregnancy or in children below 5 kg.
- artesunate + amodiaquine* Tablet: 25 mg + 67.5 mg; 50 mg + 135 mg; 100 mg + 270 mg.
- artesunate + mefloquine Tablet: 25 mg + 55 mg; 100 mg + 220 mg.

While these other fixed dose combination ACTs are listed in the Essential Medicines List PYRAMAX® provides the advantage that it is the only ACT with stringent regulatory approval such that it can be prescribed for both P. falciparum and P. vivax malaria. The two formulations also provide the prescriber with greater options when treating younger children, as the target population. The weight based treatment bands for dosing and once a day dosing provide further advantages and should improve treatment compliance. Furthermore
PYRAMAX® has the advantage over other ACTs of being able to be administered with or without the intake of food.

Artemether-lumefantrine (Riamet®, Coartem®) and Dihydroartemisinin-piperaquine (Eurartesim®) are currently the only other fixed-dose, artemisinin based combinations registered with a competent stringent regulatory Authority. Riamet is available in developed, non-endemic countries and Coartem is registered and marketed in malaria-endemic countries. Coartem Dispersible, a paediatric formulation for infants and children under 11 kg has been approved and is currently deployed in malaria-endemic countries. Both Coartem and dihydroartemisinin-piperaquine have food constraints, the former to be given with food and the latter not to be given with food which adds complexity in the treatment of children with malaria. Dihydroartemisinin-piperaquine additionally has a product label warning in terms of the potential cardiovascular risk.

The aim of the fixed-dose combination of pyronaridine tetrathosphate and artesunate as PYRAMAX® in the treatment of uncomplicated acute malaria is to provide a rapid reduction in parasitaemia with a 3-day regimen, thereby improving compliance and reducing the risk of recrudescence through the slower elimination of pyronaridine.

The following are the key features of PYRAMAX®

- **Once a Day - for 3 Days**
- **Label indication for both *P falciparum* and *P vivax* infection**
- **Can be administered with or without food**
- **No safety tests required before administration**
- **Weight adjusted streamlined dosing regimen to as low as 5kg**
- **Simple dosage and regimen**
- **Weight neutral package resulting in less stock out**
7. TREATMENT DETAILS: PYRAMAX® TABLETS AND GRANULES

7.1 Therapeutic Indications

PYRAMAX® TABLETS
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.

PYRAMAX® Granules for oral suspension
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.

7.2 Posology and method of administration

PYRAMAX® TABLETS
*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.

<table>
<thead>
<tr>
<th>Body weight</th>
<th>Number of tablets</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 - &lt; 24 kg</td>
<td>1 tablet</td>
<td>Daily for 3 days</td>
</tr>
<tr>
<td>24 - &lt; 45 kg</td>
<td>2 tablets</td>
<td>Daily for 3 days</td>
</tr>
<tr>
<td>45 - &lt; 65 kg</td>
<td>3 tablets</td>
<td>Daily for 3 days</td>
</tr>
<tr>
<td>≥ 65 kg</td>
<td>4 tablets</td>
<td>Daily for 3 days</td>
</tr>
</tbody>
</table>

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.
**Elderly**
Clinical studies did not include patients aged 65 years and over. No dosing adjustments would be 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 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.

**PYRAMAX® GRANULES**

**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.

<table>
<thead>
<tr>
<th>Body weight</th>
<th>Number of granules sachets</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 - &lt; 8 kg</td>
<td>1 sachet</td>
<td>Daily for 3 days</td>
</tr>
<tr>
<td>8 - &lt; 15 kg</td>
<td>2 sachets</td>
<td>Daily for 3 days</td>
</tr>
<tr>
<td>15 - &lt; 20 kg</td>
<td>3 sachets</td>
<td>Daily for 3 days</td>
</tr>
</tbody>
</table>

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 < 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 < 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.

**7.3 Duration**

Pyronaridine-artesunate tablet or granules daily dose is to be administered on 3 consecutive days.

**7.4 WHO Guidelines**

The following WHO Guidelines were used in support of the strategy to develop the combination product of pyronaridine tetrathosphate and artesunate:


WHO 2014: World Malaria Report 2014 WHO/HTM/GMP/2015.2


7.5 Additional requirements

Not applicable

7.6 Core Listing

Not applicable.
8. INFORMATION SUPPORTING PUBLIC HEALTH RELEVANCE

*P. falciparum* is the most severe form of malaria affecting millions of people every year with its greatest prevalence in sub-Saharan Africa. Malaria is spread by the bite of the Anopheles mosquito. The disease mainly affects the under fives from about four months of age and children may have up to six episodes of malaria each year. Partial immunity develops later in childhood though repeated cycles of infection. More than 500,000 African children develop cerebral malaria (a severe form of the disease that affects the brain) each year, and 10-20% of these children die and approximately 7% are left with permanent neurological damage.

*P. falciparum* infection during pregnancy increases the chance of maternal anaemia, abortion, stillbirth, prematurity, intrauterine growth retardation, and low infant birth weight. Maternal anaemia, due to malaria, is estimated to cause as many as 10,000 maternal deaths each year in Africa. Malaria has been estimated to cause 8% to 14% of all low birth weight babies. Low infant birth weight is the greatest single risk factor for death in the first month of life.

Common co-morbidities found within the African population include malnourishment, low haemoglobin levels, HIV infection and tuberculosis (TB).

*P. vivax* represents a major health problem throughout the tropics. Outside of Africa, it accounts for over 50% of malaria cases, affecting an estimated 70-80 million people per year, notably in Southeast Asia, India and Central and South America, and has a particularly strong impact on the archipelago of Indonesia as well as in Papua New Guinea. In addition, it is estimated that 10-20% of the *P. vivax* cases occur in Eastern and Southern Africa, while *P. vivax* cases are extremely rare in the countries of sub-Saharan West Africa. This is apparently due to the high prevalence of the Duffy negative trait in West Africans, a phenotype that lacks the receptor for invasion of the human red blood cell (RBC) by *P. vivax* merozoites (Mendis K et al. 2001). Furthermore, in recent years the re-emergence of *P. vivax* has become a major problem in malaria-endemic areas, such as Korea or China, where the disease had been eradicated many years ago (Sleigh AC et al. 1998; Chai JY et al. 1999; Oh MD et al. 2001).

The *P. vivax* infection is rarely life-threatening, but is responsible for an important morbidity in all age groups (Karunaweera ND et al. 2003). *P. vivax* forms persistent hypnozoite parasite stages in the liver that can result in multiple relapses of infection weeks to months after the primary infection (Krotoski WA et al. 1982). Thus, a single infection causes repeated bouts of illness that significantly impact subjects’ health and ability to carry on activities of daily living. *P. vivax* causes a debilitating febrile illness with fevers as high as 39-41°C. Other major symptoms include headache, myalgia, nausea, diarrhoea, and vomiting. In the majority of cases, *P. vivax* malaria is benign and vital organ dysfunction is very rare. Nevertheless, reports of cases of severe *P. vivax* malaria have been published and acute respiratory distress syndrome seems to be one of the more common complications (Kochar DK et al. 2005).
<table>
<thead>
<tr>
<th>Indication/target population</th>
<th>Uncomplicated malaria caused by <em>P. falciparum</em> and blood stage of <em>P. vivax</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of target indication</td>
<td>The World Malaria Report 2015 states that the number of malaria cases globally fell from an estimated 262 million in 2000 (range: 205–316 million), to 214 million in 2015 (range: 149–303 million), a decline of 18%. Most cases in 2015 are estimated to have occurred in the WHO African Region (88%), followed by the WHO South-East Asia Region (10%) and the WHO Eastern Mediterranean Region (2%). The incidence of malaria, which takes into account population growth, is estimated to have decreased by 37% between 2000 and 2015. In total, 57 of 106 countries that had ongoing transmission in 2000 have reduced malaria incidence by &gt;75%. A further 18 countries are estimated to have reduced malaria incidence by 50–75%.</td>
</tr>
<tr>
<td>Prevalence/Incidence of target indication and potential health risk</td>
<td>There are divergent sources of information for the estimation of the mortality, including the WHO Global Malaria Report 2015 and the paper published in the Lancet (Murray et al. 2012). The actual incidence is probably somewhere between the two and both are quoted for completeness. Global malaria deaths increased from 995,000 (95% uncertainty interval 711,000–1,412,000) in 1980 to a peak of 1,817,000 (1,430,000–2,366,000) in 2004, decreasing to 1,238,000 (929,000–1,685,000) in 2010. In Africa, malaria deaths increased from 493,000 (290,000–747,000) in 1980 to 1,613,000 (1,243,000–2,145,000) in 2004, decreasing by about 30% to 1,133,000 (848,000–1,591,000) in 2010 according to the analysis of global malaria mortality (Murray et al. 2012). The WHO World Malaria Report states that the number of malaria deaths globally fell from an estimated 839,000 in 2000 (range: 653,000–1.1 million), to 438,000 in 2015 (range: 236,000–635,000), a decline of 48%. Most deaths in 2015 were in the WHO African Region (90%), followed by the WHO South-East Asia Region (7%) and the WHO Eastern Mediterranean Region (2%). The malaria mortality rate, which takes into account population growth, is estimated to have decreased by 60% globally between 2000 and 2015. The number of malaria deaths in children aged under 5 years is estimated to have decreased from 723,000 globally in 2000 (range: 563,000–948,000) to 306,000 in 2015 (range: 219,000–421,000). The bulk of this decrease occurred in the WHO African Region, where the estimated number of deaths fell from 694,000 in 2000 (range: 569,000–901,000) to 292,000 in 2015 (range: 212,000–384,000). As a result, malaria is no longer the leading cause of death among children in sub-Saharan Africa. In 2015, malaria was the fourth highest cause of death, accounting for 10% of child deaths in sub-Saharan Africa; malaria remains a major killer of children, particularly in sub-Saharan Africa, taking the life of a child every 2 minutes. The proportion of children infected with malaria parasites has halved in endemic areas of Africa since 2000. Infection...</td>
</tr>
</tbody>
</table>
prevalence among children aged 2–10 years is estimated to have declined from 33% in 2000 to 16% in 2015. In sub-Saharan Africa, it is estimated that malaria control interventions accounted for 70% of the 943 million fewer malaria cases occurring between 2001 and 2015, averting 663 million malaria cases (range: 542–753 million). Of the 663 million cases averted due to malaria control interventions, it is estimated that 69% were averted due to use of insecticide-treated mosquito nets, 21% due to artemisinin-based combination therapy (ACT) and 10% due to indoor residual spraying.

Target Population

PYRAMAX® is a fixed dose combination of pyronaridine tetraphosphate and artesunate which acts as a blood schizonticide on P. falciparum and P. vivax malaria. PYRAMAX® tablets are indicated for the treatment of acute, uncomplicated malaria infection caused by P. falciparum or by P. vivax in patients weighing 20 kg or more. PYRAMAX® granules are indicated for the treatment of acute, uncomplicated malaria infection caused by P. falciparum in patients weighing 5 kg - < 20 kg.

PYRAMAX® is effective against drug susceptible and drug resistant P. falciparum malaria and can be used to treat patients where resistance to other agents is known.

Rationale on ratio/dose

The single strength of pyronaridine-artesunate (PYRAMAX®) TABLET contains 180 mg pyronaridine tetraphosphate and 60 mg artesunate.

The single strength of pyronaridine-artesunate (PYRAMAX®) GRANULES contains 60 mg pyronaridine tetraphosphate and 20 mg artesunate.

It has been shown that pyronaridine is active in vitro against Plasmodia species, laboratory and field isolates, both sensitive and resistant to other agents such as chloroquine with an IC₅₀ of the order of 8 nmol/l. Artesunate, and its active metabolite dihydroartemisinin (DHA), are also active against a similar range of Plasmodia species with IC₅₀ values of the order of 4 and 1.5 nmol/l, respectively.

Pyronaridine-artesunate alone inhibited P. chabaudi in mice at 12 and 4 mg/kg, respectively for three days. A combination of a 3:1 ratio of the two drugs was equally active at 8 mg/kg (6 + 2 mg/kg).

Ringwald et al. (1999) previously reported weak antagonism when a combination of pyronaridine and dihydroartemisinin were examined against chloroquine-sensitive and resistant isolates of P. falciparum in vitro. Similarly, mild antagonism has been reported by other investigators using a similar combination against P. falciparum (Davis et al, 2006; Vivas et al, 2008).

In contrast, when 3 strains of P. falciparum were incubated for 48 hours with a combination of pyronaridine and artemisinin, the data indicated at least an additive but, predominantly, a
synergistic effect of this combination (Gupta et al, 2002). The authors suggested that the differences between these findings may be explained by differences in methodology and modes of calculation. Moreover, it should be noted that whilst antagonism has been reported between pyronaridine and artemisinin in vitro this is not usually translated in vivo (Vivas et al, 2008).

The efficacy of combinations of pyronaridine with both artemisinin and artesunate has been studied in vivo. In mice infected with chloroquine-sensitive P. yoelii ssp. [either NS or one of two lines derived from it namely ART (resistant to artemisinin) or SPN (resistant to pyronaridine)], the blood schizontocidal effects of subcutaneously administered combinations of artemisinin and pyronaridine (using the ED90’s for either compound) were evaluated. Combinations of artemisinin and pyronaridine were additive against P. yoelii NS but, showed marked synergy (as assessed using isoboles) against both the ART and SPN lines (Peters and Robinson, 1997).

Additional studies in mice infected with chloroquine sensitive-P. berghei (N strain) demonstrated that a combination of artesunate with pyronaridine impeded the selection of resistance to these compounds in P. berghei (Peters and Robinson, 2000).

The efficacy and PK/PD interactions of orally administered pyronaridine in combination with either artesunate or dihydroartemisinin (DHA) in a 3:1 ratio were compared with each drug administered alone in mice infected with P. berghei or P. chabaudi (Vivas, 2008). In the standard 4-day suppressive test, compared to monotherapy, combinations of pyronaridine-artesunate and pyronaridine / DHA showed comparable efficacy against all parasite strains tested (mean ED90 2.9:0.93 mg/kg and 2.8:0.95 mg/kg) respectively. Indeed, both combinations were more efficacious against the P. berghei NY drug sensitive strain, the artesunate resistant P. berghei SANA strain, the pyronaridine resistant strain P. berghei NPN and the drug-sensitive P. chabaudi AS strain when compared to monotherapy.

Pyronaridine-artesunate are antimalarial agents with a history of clinical use both separately and in combination with other drugs. Each drug has powerful schizonticidal actions but the combination of the two is expected to show pharmacological addition in man. The action of artesunate is a rapid knock-down of the parasites, after which the drug is rapidly cleared as it has a short systemic half-life. Pyronaridine is also effective in the short-term but has an intermediate blood half-life thus providing a sustained schizonticidal effect. The aim of the fixed dose combination of pyronaridine/artesunate in the treatment of uncomplicated acute malaria is to provide a rapid reduction in parasitaemia with a three-day regimen, thereby improving compliance and reducing the risk of recrudescence through the slower elimination of pyronaridine.

Based on existing clinical data and clinical practice, the ratio of pyronaridine to artesunate of 3:1 w/w was developed. Doses were selected to be in line with current prescribing practise for artesunate and literature-based for pyronaridine when used as monotherapy.
9. REVIEW OF BENEFITS: SUMMARY OF COMPARATIVE EFFECTIVENESS IN A VARIETY OF CLINICAL SETTINGS

The PYRAMAX® clinical study programme consists of the following studies. These studies provide information regarding the pharmacokinetics, safety, and efficacy of PYRAMAX®

Phase I studies in healthy volunteers:

- **Study SP-C-001-03** – A Phase I clinical study to assess the safety, tolerability, pharmacokinetics as well as for potential interaction of orally administered pyronaridine-artesunate in Healthy Korean Subjects (Tan et al. 2009).

- **Study SP-C-009-08** - Bioequivalence of pyronaridine-artesunate to-be-marketed tablet to the clinical trial reference tablet in Healthy European Subjects

- **Study SP-C-010-10** - A randomized, multiple dose, parallel group study of drug-drug interaction between pyronaridine-artesunate and the protease inhibitor ritonavir in Healthy European Subjects (Morris et al. 2012).

- **Study SP-C-012-11** - A mass balance study in 6 Healthy European Subjects who received a single dose of 720 mg of pyronaridine orally administered together with \(^{14}\text{C}\text{pyronaridine (approximately 100 μg, 800 nCi [29600 Bq]) (Morris et al. 2014).}}

- **Study SP-C-014-11** - An open label parallel group study to evaluate any drug interaction between CYP2D6 substrate metoprolol and pyronaridine-artesunate in healthy volunteers and to determine the safety of redosing a 3-day regimen of pyronaridine-artesunate following 60 or 90 days in healthy volunteers. (Morris et al. 2014).

- **Study SP-C-016-11** - An open label, crossover study to characterise potential pharmacokinetic interactions between primaquine and pyronaridine-artesunate in healthy adult Thai subjects as well as to evaluate the safety and tolerability of co-administering primaquine and pyronaridine-artesunate.

- **Study SP-C-017-12** – An open-label, crossover study to assess the relative bioavailability of the fixed dose combination of pyronaridine-artesunate in tablet and granule formulations in healthy Asian adults.

Two dose-finding Phase II PYRAMAX® studies were conducted in patients with acute uncomplicated *P. falciparum* malaria:

- **Study SP-C-002-05** - A randomised, multi-centre, Phase II, dose-ranging clinical study to assess the safety and efficacy of fixed-dose, orally administered pyronaridine:artesunate (3:1) in Adult Subjects from Thailand, Indonesia, Cambodia, Gambia, Senegal and Uganda with acute uncomplicated *Plasmodium falciparum* malaria
- **Study SP-C-003-05** - An open-label, Phase II, dose escalation clinical study to assess the pharmacokinetics, safety, tolerability and pharmacodynamics of fixed-dose combination tablet of PA (3:1) in children from Gabon with acute uncomplicated *P. falciparum* malaria and to assess the relative bioavailability of a fixed dose granule formulation of pyronaridine:artesunate (60 mg:20 mg) for paediatric use, compared with tablets of the same dose in children with acute uncomplicated *P. falciparum* malaria (Ramharter et al. 2008).

**Phase III comparative studies were conducted with PYRAMAX®:**

- **Study SP-C-004-06** – An open label, Phase III Comparative, Randomised, Multi-Centre Clinical Study in South East Asia and in Africa to Assess the Safety and Efficacy of fixed dose formulation oral PYRAMAX® versus mefloquine + artesunate in children and adult patients with acute uncomplicated *P. falciparum* malaria. (Rueangweerayut et al. 2012).

- **Study SP-C-005-06** - A Phase III comparative, (double-blind, double-dummy), randomised, multi-centre, clinical study to assess the safety and efficacy of fixed dose formulation of oral PYRAMAX® tablet (180:60 mg) versus Coartem® (artemether-lumefantrine) in children and adult patients from Africa, Indonesia and the Philippines with acute uncomplicated *P. falciparum* malaria. (Tshefu et al. 2010).

- **Study SP-C-006-06** - A Phase III multi-centre, randomised, double-blind, double-dummy, comparative clinical study to assess the safety and efficacy of a fixed-dose formulation of oral PYRAMAX® (180:60 mg tablet) versus chloroquine (155 mg tablet), in children and adult patients from India and South East Asia with acute *P. vivax* malaria. (Poravuth et al. 2011).

- **Study SP-C-007-07** - A Phase III comparative, open-labelled, randomised, multi-centre clinical study to assess safety and efficacy of a fixed dose of oral PYRAMAX® granule formulation (60:20 mg) (paediatric PYRAMAX®) versus Coartem crushed tablets in infants and children from Africa and the Philippines with acute uncomplicated *P. falciparum* malaria. (Kayentao et al. 2012)

- **Study SP-C-008-07** - A Phase III multi-centre, randomised, double-blind, double-dummy, comparative clinical study to assess the safety and efficacy of a fixed-dose formulation of oral PYRAMAX® (180:60 mg tablet) versus chloroquine (155 mg tablet), in children and adult patients from Korea with acute *P. vivax* malaria.
Further studies conducted with PYRAMAX®

- **Study SP-C-018-13** - Randomized trial of primaquine hypnozoitocidal efficacy when administered with artemisinin combined blood schizontocides for radical cure of *Plasmodium vivax* in Indonesia, explored the administration of PYRAMAX® in conjunction with primaquine in adult subjects with *P. vivax* malaria. This study demonstrated a benefit of the co-administration of PYRAMAX® with primaquine. (Newlan et al. 2016)

- **Study SP-C-0-019-13** - Efficacy and safety of artesunate-pyronaridine for the treatment of *Plasmodium falciparum* in western Cambodia has been undertaken in a region of Cambodia where *P. falciparum* resistance has been reported. This was conducted to investigate the efficacy of PYRAMAX® in a specific region of Cambodia where the Phase II had been investigated a decade earlier. (Leang et al. 2016)

Furthermore peri-approval studies are ongoing.

- **Study SP-C-013-11** - A comparative, randomised, multi-centre, open label parallel 3-arm clinical study to assess the safety and efficacy of repeated administration of PA, DHA-PQP or AL or ASAQ over a 2-year period in children and adult patients with acute uncomplicated *Plasmodium* sp. malaria. PYRAMAX® is being compared to either AL or ASAQ depending on the site and first line therapy. Interim sub-study analyses have been conducted on the PYRAMAX® versus comparator sub-groups to support the repeated dosing of Pyramax in regulatory submissions to EMA to extend the product label. The study is in reporting phase. Sub-study published (Sagara et al. 2016).

- **Study SP-C-020-15** - Pyronaridine-artesunate and artemether-lumefantrine for the treatment of paediatric uncomplicated *falciparum* malaria in Western Kenya. This study has been initiated in September 2015 and is ongoing.

- **Study SP-C-021-15** - Phase IIIb/IV Cohort Event Monitoring study to evaluate, in real life setting, the safety and tolerability in patients in Central Africa of the fixed-dose Artemisinin-based Combination Therapy PYRAMAX® (pyronaridine-artesunate). This study is in the planning phase.

**Phase II Adult Study of PYRAMAX®**

In the phase II programme, the strategic focus for the development plan was three-fold. Firstly, this was to enable the dose-finding study which showed that pyronaridine-artesunate cleared parasites from uncomplicated malaria patients within a range of 24 to 28 hours and that the fixed dose combination was both safe and well tolerated at all doses studied. Secondly, it was to justify the tablet strength (180:60 mg) and the dose level of pyronaridine:artesunate fixed combination for use in phase III study and marketing. Thirdly, it was to test pyronaridine-artesunate as a fixed-dose combination in the age range of patients which are the most affected by malaria and to conduct such trials in endemic regions, including those in areas of known current antimalarial resistance.
**Phase II double blind dose ranging study**

The phase II double blind dose ranging study has been conducted comparing safety and efficacy of one of three doses of the fixed pyronaridine-artesunate combination (6:2mg/kg, 9:3mg/kg, 12:4mg/kg) as a once daily oral dose for the treatment of uncomplicated acute *P. falciparum* malaria. The trial was conducted in 6 countries in South East Asia and Africa. The study commenced mid July 2005 and was completed in mid-April 2006. Primary outcome measure was PCR-adjusted adequate clinical and parasitological response (ACPR) at Day 28. Other outcome efficacy and safety assessments included ACPR on Day 42, parasite clearance time (PCT), fever clearance time (FCT) as well as ECG, clinical laboratory findings and adverse events, plus pharmacokinetics in a sub-group. Four Hundred and Seventy Seven (477) patients were treated in the trial at doses of 6:2, 9:3 or 12:4 mg/kg (160:157:160 patients respectively).

**Efficacy analysis**

In the per protocol analysis (EE population), at doses of 6:2, 9:3 or 12:4 mg/kg of pyronaridine-artesunate, PCR-adjusted ACPR was 100 % at Day 14, 96.5%, 99.3%, 99.3% respectively at Day 28 and 94.9%, 97.9%, 97.9% respectively at Day 42. Parasites were cleared by 30 hours in each dose group. Fever clearance time was a mean of 25.8 hours across all dose groups. Any treatment failures were late clinical or late parasitological failures. There were no early treatment failures. There were no overall regional differences in the efficacy of pyronaridine-artesunate.

**Pharmacokinetic analysis**

With regard to the pharmacokinetics of pyronaridine in this Phase II study of pyronaridine-artesunate, it was seen that the $T_{\text{max}}$ after the third dose was approximately 6 hours after oral administration. The mean $C_{\text{max}}$ values after the third dose were 91.9, 156.8 and 226.1 ng/ml at the 6, 9 and 12 mg/kg dose level, respectively. The pyronaridine half-life was approximately 10.4 to 15.1 days. This elimination half-life is similar to that found in a bioequivalence study where the average elimination half-life was 14.1-14.2 days. This elimination half-life is longer compared to healthy adult subjects (6.6 to 9.7 days) and children with malaria (6.6 to 9.0 days), which may be a reflection of the longer blood sampling period used in this study. Compared with phase I results, AUC values were slightly lower in malaria patients, which may reflect a larger pyronaridine volume of distribution in malaria patients.

Considering the efficacy and the safety findings, both the 9:3 mg/kg dose and the 12:4 mg/kg dose are clinically useful and safe in the treatment of *P. falciparum* malaria. The 6:2 mg/kg dose is also effective and safe but was not demonstrated to result in a PCR-adjusted ACPR statistically significantly greater than 95%.
**Phase II Paediatric Study of PYRAMAX®**

A dose rising paediatric study in uncomplicated *Plasmodium falciparum* malaria was conducted at Albert Schweitzer Hospital in Lambaréné, Gabon, from June to December 2006 in children over 2 years old and between 10 and 40 kg. A total of 59 patients (60 planned) received one of the three doses of the pyronaridine-artesunate tablet combination (6:2 mg/kg, 9:3 mg/kg, 12:4 mg/kg) or a 9:3 mg/kg granule formulation as a once daily oral dose for the treatment of uncomplicated disease in a hospital in-patient setting. Fifteen patients per dose were studied with a safety review prior to dose escalation. Treatment was administered once daily for three days and patients were followed up weekly for a 6 week period with a primary endpoint of 28 day PCR-adjusted ACPR.

The objective of the trial was to determine pharmacokinetics as well as safety and tolerability of the three doses and two formulations. Efficacy was evaluated to include the proportion of patients with PCR-adjusted ACPR on Day 28, parasite clearance time, fever clearance time, proportion of treatment success/failures and central ECG review.

**Efficacy analysis**

The overall PCR-adjusted day 28 cure rate was 100% in per protocol analysis at all dose levels. There were no treatment failures in the per protocol population up to Day 28. Three subjects, all from the 9+3 mg/kg tablet group, had re-appearance of parasitaemia, all detected on Day 28. All of these re-appearances were confirmed as new infections by PCR and classed as treatment success.
The PCR-adjusted ACPR at Day 42 was 100% in the 6:2 mg/kg and 12:4 mg/kg tablet groups, 88.9% in the 9:3 mg/kg tablet group, and 92.9% in the 9:3 mg/kg granule group. An additional 10 subjects (18.9% of the per protocol population) had re-appearance of parasitaemia during the course of the study after Day 28: 2 (3.8%) on Day 35 (1 from the 9:3 mg/kg tablet group and 1 from the 9:3 mg/kg granule group) and 8 (15.1%) on Day 42 (3 from the 6:2 mg/kg tablet group, 2 from the 9:3 mg/kg tablet group, 2 from the 12:4 mg/kg tablet group, and 1 from the 9:3 mg/kg granule group). Only 2 of these reappearances were confirmed by PCR as recrudescence (on Days 35 and 36). Furthermore, there was 1 subject from the 6:2 mg/kg group who had a PCR-confirmed new infection on Day 21. This subject was not included in the per protocol population due to the anti-malaria treatment administered for this new infection.

In all treatment groups, rapid parasite clearance was achieved. Median parasite clearance time (PCT) was 16.4 hours at 6:2 mg/kg, 16.1 hours at 9:3 mg/kg, 8.1 hours at 12:4 mg/kg for tablets and 8.3 hours for the 9:3 mg/kg paediatric granule formulation (per-protocol population).

Time to fever clearance was only summarised for subjects who had fever at baseline or within the first 24 hours after the start of study treatment. Since only 12 subjects in total had fever during this time, the time to fever clearance estimates are not very meaningful. Median FCT was between 8.2 hours and 8.6 hours in all treatment groups.

**Pharmacokinetic analysis**

A comparison of the individual pyronaridine levels 24 hours after doses 1, 2 and 3 for adults and children is shown in Figure 9-2 for the 9 mg/kg dose level. While there is considerable variability, on the average children, have slightly higher blood pyronaridine concentrations.
Figure 9-2. Pyronaridine Levels in Adults vs. children (9 mg/kg)

Individual pyronaridine levels 24 hours after dose 1, 2 and 3. Adult vs Children Malaria Patients (9 mg/kg Tablets)

Pharmacokinetic analyses were performed in the two formulations (tablets and granules) and results were comparable (Figure 9-3 and Figure 9-4).

Figure 9-3. Summary of Artesunate Plasma Levels in Tablet vs. Granules

Comparison of Artesunate Levels in Tablet vs. Granules (3 mg/kg Artesunate). Mean +/- SD
Figure 9-4. Summary of Pyronaridine Levels in Tablet vs. Granules

Comparison of Pyronaridine Levels for Tablets vs. Granules (9 mg/kg Pyronaridine) Mean +/- SD

For artesunate and its active metabolite DHA, a dose-related linear increase in $C_{\text{max}}$ and AUC was observed after oral administration of the 6.2 mg/kg, 9.3 mg/kg, and 12.4 mg/kg tablets. The mean $T_{\text{max}}$ for artesunate and DHA ranged from 0.5 to 1.03 hours and 1.31 to 1.7 hours, respectively. The mean half-life for artesunate and DHA ranged from 0.54 to 1.18 hours and 0.91 to 1.18 hours, respectively. No significant difference in the bioavailability of artesunate or DHA following was observed after oral administration of either the 9.3 mg/kg tablet or granule formulations.

A dose-related linear increase in $C_{\text{max}}$ and AUC was observed for pyronaridine after oral administration of the 6.2 mg/kg, 9.3 mg/kg and 12.4 mg/kg tablets. The mean $T_{\text{max}}$ for pyronaridine ranged from 2.4 to 3.2 hours and the mean half-life ranged from 6.6 to 9.0 days. There was no significant difference in pyronaridine AUC between the tablet and granule formulations; however, $C_{\text{max}}$ after the first dose was significantly higher for the granule formulation.

The Pyronaridine PK data for the Phase II are similar to those of the healthy volunteer Phase I study (Table 9-1).
Table 9-1 Pyronaridine PK parameters Phase II

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>$T_{\text{max}}$ (h)</th>
<th>$C_{\text{max}}$ (ng/ml)</th>
<th>AUC (ng/ml*d)</th>
<th>$T_{\frac{1}{2}}$ (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>5.3 ±2.0</td>
<td>91.9 ±30.8</td>
<td>749 ±603</td>
<td>19.1 ±5.9</td>
</tr>
<tr>
<td>9</td>
<td>6.2 ±6.3</td>
<td>156.8 ±57.1</td>
<td>1036 ±286</td>
<td>15.9 ±5.0</td>
</tr>
<tr>
<td>12</td>
<td>7.6 ±4.9</td>
<td>226.1 ±157.5</td>
<td>1134 ±624</td>
<td>14.6 ±6.6</td>
</tr>
</tbody>
</table>

**Overall conclusion from phase II studies**

The outcome of the phase II dose ranging trials provided sufficient confidence to move into expanded phase III confirmatory trials. Although the sample size within each dose group was small in the paediatric trial, 28-day PCR-adjusted ACPR as well as parasite clearance time showed promising efficacy of a fixed dose combination of pyronaridine-artesunate in younger patients. All doses of pyronaridine-artesunate were well tolerated. Although no major differences between the doses employed in the study were apparent there appeared to be more cases of malaria reported as AEs in the lowest dose and the adverse event/laboratory parameter profile was marginally worse in the highest dose group. Therefore the dose ratio of 9:3 mg/kg of pyronaridine-artesunate was selected for phase III.

**Phase III studies with PYRAMAX®**

Phase III comparative study of pyronaridine-artesunate with mefloquine+artesunate in children and adults ($P. falciparum$)

The main objectives of this open label Phase III comparative, randomised, multi-centre, clinical study in South East Asia and Africa, were to compare the efficacy and safety of the fixed combination of pyronaridine-artesunate tablets with that of mefloquine and artesunate (MQ + AS) in subjects with acute, uncomplicated $P. falciparum$ malaria and to confirm that pyronaridine-artesunate was non-inferior to MQ + AS in terms of efficacy.

The study was conducted in a total of 1271 male and female, children and adults subjects, recruited from 9 sites in Thailand, Vietnam, Cambodia, India, Ivory Coast, Burkina-Faso and Tanzania, and took place from late January 2007 to early October 2008. The majority of subjects were from Asia (81.3%).

Subjects were randomised in a 2:1 ratio (848 in the pyronaridine-artesunate group and 423 in the MQ + AS group) to receive either oral pyronaridine-artesunate (180:60-mg tablets) once a day for 3 consecutive days (Days 0, 1, and 2) or mefloquine (MQ) (250-mg tablets) plus artesunate (AS) (100 mg tablets) once a day for 3 consecutive days (Days 0, 1, and 2). For pyronaridine-artesunate, the actual dose range covered by this regimen was 7.2:2.4 mg to 13.8:4.6 mg. Posology was based on body weight ranges for both pyronaridine-artesunate and MQ + AS regimens.
Subjects were followed for 42 days, with the primary efficacy end point of PCR-adjusted ACPR occurring 28 days after initiation of study drug administration. Subjects were confined to the study facility for ≥4 days (Days 0, 1, 2 and 3) and ideally remained in the vicinity of the study site for ≥7 days or until fever and parasite had been cleared for ≥24 hours, whichever occurred later. The subject was to return to the study site for all scheduled follow-up visits until completion of the study on Day 42.

Most subjects were male (75.8%) and Asian/Oriental (81.3%); mean age was 25.1 years. The majority of subjects completed treatment (99.1%) and completed the study (85.0%). The most common reasons for withdrawing from the study were *P. falciparum* parasite re-appearance.

**Efficacy analysis**

For the primary end point, non-inferiority of pyronaridine-artesunate (PA) compared with MQ + AS was demonstrated for PCR-adjusted ACPR on Day 28 in the EE population (99.2% PA, 98.1% MQ + AS). In the same population, non-inferiority of PA to MQ + AS was also concluded at Days 14, 21, and 35 for PCR-adjusted ACPR (Figure 9-5), but not at day 42 (88.3% in the PA group and 89.9% in the MQ + AS group). For crude ACPR, PA was non-inferior to MQ + AS at all time points, with the cure rate in the PA group statistically significantly superior to that in the MQ + AS group on Day 28 (98.7% vs. 96.7%). In the ITT population (Figure 6), PCR-adjusted and crude cure results were similar, and non-inferiority was also demonstrated at day 42 in both PCR-adjusted and crude ACPR. No clinically important subgroup (region, age, gender, actual study drug dosing, and previous episode of malaria) differences in Day 28 PCR-adjusted ACPR were observed.

**Figure 9-5. Days 14, 21, 28, 35, and 42 ACPR – EE Population**
Note: The Day 21 and Day 35 analyses were performed post hoc.
a. Non-inferiority of PA to MQ + AS was concluded because the lower limit of the 2-sided 95% CI for the difference was >-5%.
b. Superiority of PA over MQ + AS was concluded.

**Figure 9-6. Days 14, 21, 28, 35, and 42 ACPR – ITT Population**
Note: The Day 21 and Day 35 analyses were performed post hoc.

a. Non-inferiority of PA to MQ + AS was concluded because the lower limit of the 2-sided 95% CI for the difference was >-5%.

The parasitology re-appearance (new infection or recrudescence) rate and the recrudescence rate (Figure 9-7) were statistically significantly lower with pyronaridine-artesunate compared with MQ + AS based on Kaplan-Meier estimates through Day 42 (p ≤ 0.049). The rate of new infection was statistically significantly lower (p = 0.041) with pyronaridine-artesunate compared with MQ + AS through Day 28, but not through Day 42.

Figure 9-7. Kaplan-Meier Estimates of Recrudescence Rate – ITT Population

Pyronaridine-artesunate and MQ + AS groups were rapidly effective. Parasite count (P. falciparum asexual forms) decreased rapidly (during the first 16 hours) in both the pyronaridine-artesunate and MQ + AS groups; time to parasite clearance was not statistically significantly different between the 2 groups. However, a greater percentage of pyronaridine-artesunate subjects vs. MQ + AS subjects achieved parasite clearance 24 hours after the first dose (38.5% vs. 31.6%). One difference from the main results was that the PCT was prolonged in Pailin (Cambodia) with a median of 64.0h for pyronaridine-artesunate and 64.2h for MQ + AS compared to 31.1h and 31.8h respectively in the other centres. The percentage of patients able to clear their parasites 72h following treatment initiation in Pailin...
was only 62.9% (95% CI: 54.9-70.8) with pyronaridine-artesunate and 62.0% (95% CI: 50.9-73.1) with MQ + AS. This would appear to represent some evidence of altering sensitivity to artesunate.

Time to fever clearance was similar in the pyronaridine-artesunate and MQ + AS groups.

**Phase III comparative study of Pyronaridine-Artesunate with Artemether-Lumefantrine (Coartem) in children and adults (P. falciparum)**

This study was a multi-centre, comparative, randomised, (double-blind, double-dummy), parallel-group, non-inferiority study which main objectives were to compare the efficacy and safety of the fixed combination of pyronaridine-artesunate with that of Coartem® (i.e., the combination of artemether-lumefantrine [AL]) in subjects with acute, uncomplicated *P. falciparum* malaria and to confirm that pyronaridine-artesunate was non-inferior to AL in terms of efficacy.

The study was conducted in a total of 1269 male and female subjects including children (≥20 kg body weight) and adults suffering from acute symptomatic uncomplicated *P. falciparum* malaria recruited from 10 study sites located in Africa and South East Asia (Democratic Republic of Congo, The Gambia, Ghana, Indonesia, Kenya, Mali, Mozambique, The Philippines, and Senegal) from January 2007 to April 2008.

Subjects were randomised to receive either oral pyronaridine-artesunate (180:60-mg tablets) once a day plus AL-placebo (twice a day) for 3 consecutive days (Days 0, 1, and 2) or AL twice a day plus pyronaridine-artesunate-placebo (once a day) for 3 consecutive days (Days 0, 1, and 2) in a 2:1 ratio. The actual dose range of pyronaridine-artesunate covered by this regimen was 7.2:2.4 mg/kg to 13.8:4.6 mg/kg, respectively, which has been shown to be effective and safe in Phase I and II studies. Posology was based on body weight ranges for both the pyronaridine-artesunate and AL regimens.

Subjects were followed for 42 days, with the primary efficacy end point occurring 28 days after initiation of study drug administration. Subjects were confined to the study facility for ≥4 days (Days 0, 1, 2, and 3) and ideally remained in the vicinity of the study site for ≥7 days or when fever and parasite had been cleared for ≥24 hours, whichever occurred later. The subject was to return to the study site for all scheduled follow-up visits until completion of the study on Day 42.

A total of 849 and 423 subjects were randomised to the pyronaridine-artesunate and AL treatment groups, respectively. The majority of subjects were from Africa (84.9%). Most subjects were male (56.7%) and black (84.9%); mean age was 17.5 years. The majority of subjects completed treatment (97.3%) and completed the study (86.3%). The most common reasons for withdrawing from the study were *P. falciparum* parasite re-appearance.

**Efficacy analysis**

Pyronaridine-artesunate was shown to be at least as effective as AL for the treatment of patients with acute, uncomplicated *P. falciparum* malaria. Non-inferiority of pyronaridine-artesunate to AL was demonstrated for PCR-adjusted ACPR on Day 28 in the EE (and ITT) population (Figures 9-8 and 9-9). Non-inferiority of pyronaridine-artesunate to
AL was also demonstrated at all other time points from Day 21 to Day 42 in the EE population and was maintained in the ITT population. PCR-adjusted ACPR was >99% for both treatment groups on Days 14, 21, and 28, and was statistically significantly superior in the pyronaridine-artesunate group compared with the AL group on Day 35 (97.7% vs. 94.8%) and Day 42 (93.2% vs. 88.1%) in the EE population (similar results were observed in the ITT population). A similar pattern of results was observed for crude ACPR (EE and ITT populations).

**Figure 9-8. Days 14, 21, 28, 35, and 42 ACPR – EE Population**
Figure 9-9. Days 14, 21, 28, 35, and 42 ACPR – ITT Population

No clinically important subgroup (region, age, gender, actual study drug dosing, and previous episode of malaria) differences in Day 28 PCR-adjusted ACPR were observed.

There was no statistically significant difference between the pyronaridine-artesunate and AL groups in the Kaplan-Meier estimate of recrudescence rate through Day 28 or Day 42. However, rates of new infection and parasitology re-appearance (new infection or recrudescence) were statistically significantly lower with pyronaridine-artesunate compared with AL (p<0.008) through Day 28 and Day 42. The superiority of pyronaridine-artesunate compared with AL for cure rate on Day 42 was likely due to the longer half-life of pyronaridine (17.0 ± 5.9 days in adults and 16.7 ± 9.5 days in children under 14 years old, per a phase II – phase III population pharmacokinetics analysis, unpublished data) compared with artemether (3-7 hours), its metabolite dihydroartemisinin (40-60 minutes), or lumefantrine (4-6 days) (Davis et al, 2005). The comparatively longer half-life of pyronaridine also likely resulted in the statistically significantly decreased risk of new infection and parasitology.
re-appearance compared with AL treatment (Figure 9-10).

**Figure 9-10. - Kaplan-Meier Estimates of New Infection Rate – ITT Population**

Pyronaridine-artesunate and AL were rapidly effective. Parasite count (*P. falciparum* asexual forms) decreased rapidly (during the first 16 hours) in both the pyronaridine-artesunate and AL groups. This was not unexpected as the clinical efficacy of the artemisinin derivatives is characterised by an almost immediate onset and rapid reduction of parasitaemia (deVries *et al.*, 1996). Time to parasite clearance was statistically significantly (p<0.001) shorter in the pyronaridine-artesunate group compared with the AL group. A greater percentage of pyronaridine-artesunate subjects vs. AL subjects achieved parasite clearance 24 hours after the first dose (68.1% vs. 52.8%). Time to fever clearance was similar in the pyronaridine-artesunate and AL groups.

**Phase III comparative study of pyronaridine-artesunate with chloroquine in adults (*P. vivax*)**

The main objectives of this multi-centre, randomised, double-blind, double-dummy, parallel group comparative trial were to compare the efficacy and safety of the fixed combination of pyronaridine-artesunate (180:60 mg) with that of chloroquine tablets (155 mg), in subjects with acute, uncomplicated *P. vivax* malaria and to confirm that pyronaridine-artesunate was non-inferior to chloroquine in terms of efficacy.

This study was conducted in a total of 456 male and female children (≥20 kg body weight) and adult subjects suffering from acute symptomatic uncomplicated *P. vivax* malaria recruited from study sites located in Cambodia, Thailand, Indonesia and India, from mid March 2007 to
end of March 2008. Subjects were randomised in a 1:1 ratio to receive either oral pyronaridine-artesunate (180:60-mg tablets) plus chloroquine-placebo or oral chloroquine (155 mg tablets) plus pyronaridine-artesunate/placebo, once a day for 3 consecutive days (Days 0, 1, and 2).

For subjects who completed the study up to Day 28 and who had normal glucose-6-phosphate dehydrogenase (G-6-PD) activity, a 14-day course of primaquine (15 mg/day) was administered starting on Day 28, after all required assessments had been performed, to complete their radical cure. Subjects who were deficient in G-6-PD and who completed the study up to Day 28 were treated per country policy.

For pyronaridine-artesunate, subjects received 1 to 4 tablets depending on their body weight. The actual dose range covered by this regimen was 7.2:2.4 mg/kg to 13.8:4.6 mg/kg, which has been shown to be effective and safe in Phase I and II studies. The chloroquine daily dose was 10 mg/kg on Days 0 and 1 and 5 mg/kg on Day 2 for children and 620 mg on Days 0 and 1 and 310 mg on Day 2 for adults.

Subjects were followed for 42 days, with the primary efficacy end point occurring 14 days after initiation of study drug administration. Subjects were confined to the study facility for $\geq 4$ days (Days 0, 1, 2, and 3) and ideally remained in the vicinity of the study site for $\geq 7$ days or when fever and parasite had been cleared for $\geq 24$ hours, whichever occurred later. The subject was to return to the study site for all scheduled follow-up visits until completion of the study on Day 42.

Overall, 33.8% of subjects participated at a site in Cambodia, 17.5% at a site in India, 5.3% at a site in Indonesia, and 43.4% at two sites in Thailand. Most subjects were male (73.7%); mean age was 26.7 years. The majority of subjects completed treatment (97.8%) and completed the study (83.3%). A greater percentage of chloroquine subjects than pyronaridine-artesunate subjects prematurely discontinued, primarily due to infection with $P. falciparum$ (6.1% vs. 2.2%).

**Efficacy analysis**

For the primary end point, non-inferiority of pyronaridine-artesunate compared with chloroquine at Day 14 in the EE population was demonstrated for crude cure (99.5% pyronaridine-artesunate, 100.0% chloroquine). Results were similar on Days 21, 28, and 35 and all this results were maintained in the ITT population (Figures 9-11 and 9-12). The greatest difference between the pyronaridine-artesunate and chloroquine groups was observed for crude cure rate on Day 42 (95.5% and 92.1%, respectively). The non-inferiority of pyronaridine-artesunate compared with chloroquine was also demonstrated for the exploratory PCR-adjusted cure rate (100.0% PA, 99.5% chloroquine) on Day 14. No clinically important subgroup (county, age, gender, by baseline $P. vivax$ count, previous malaria infection, and amount of drug dosing) differences in Day 14 crude cure rate were observed.
**Figure 9-11. Days 14, 21, 28, 35, and 42 Cure Rate – EE and Exploratory EE Populations**

Note: The Day 35 analysis was performed post hoc.
a - Non-inferiority of PA to chloroquine was concluded because the lower limit of the 2-sided 95% CI for the difference was >-10%.
Figure 9-12. Days 14, 21, 28, 35, and 42 Cure Rate – ITT Population

Note: The Day 35 analysis was performed post hoc.

a. Non-inferiority of PA to chloroquine was concluded because the lower limit of the 2-sided 95% CI for the difference was >10%.

The non-inferiority of pyronaridine-artesunate compared with chloroquine was also demonstrated for the exploratory PCR-adjusted cure rate (100.0% PA, 99.5% chloroquine) on Day 14. Genotyping by PCR was used as an exploratory tool to differentiate re-infection (new infection) from recrudescence or relapse (relapse being parasitaemia originating from latent hypnozoites). Although a common technical protocol was used for PCR sampling and analysis, the evaluation of PCR-adjusted cure rate was an exploratory end point because the tests used to perform the analysis to date were and are still not fully validated.

Pyronaridine-artesunate and chloroquine were both rapidly effective. *P. vivax* parasite count decreased rapidly (during the first 16 hours) in both the pyronaridine-artesunate and chloroquine groups. Time to parasite clearance was statistically significantly (p<0.0001) shorter in the pyronaridine-artesunate group compared with the chloroquine group. A greater
percentage of pyronaridine-artesunate subjects vs. chloroquine subjects achieved parasite clearance 24 hours (71.6% vs. 30.6%) and 48 hours (99.5% vs. 88.0%) after the first dose.

The clinical efficacy of the artemisinin derivatives is characterised by an almost immediate onset and rapid reduction of parasitaemia (deVries et al, 1996). The shorter times to parasite clearance and fever clearance with pyronaridine-artesunate treatment were expected, as studies of AS monotherapy for P. vivax infection have demonstrated rapid clearance of fever and parasites (Batty et al, 1998a; Pukrittayakamee et al, 2000; Hamedi et al, 2004).

Time to fever clearance was statistically significantly (p<0.0071) shorter in the pyronaridine-artesunate group compared with the chloroquine group (medians: 15.8 vs. 23.8 hours).

Risk of infection with P. falciparum was statistically significantly lower (p=0.0481) with pyronaridine-artesunate than with chloroquine, based on Kaplan-Meier estimates (Figure 13). The lower risk of infection with pyronaridine-artesunate compared with chloroquine may be due to the increased resistance of P. falciparum to chloroquine (Fu and Xiao, 1991; Chen et al, 1992).

Figure 9-13. Kaplan-Meier Estimates of P. falciparum Infection Rate – ITT Population

The results of this study suggest that pyronaridine-artesunate is well suited to be used as an anti-malarial drug in areas where mixed infections occur.

**Phase III comparative study of paediatric pyronaridine-artesunate granules with artemether-lumefantrine (Coartem®) crushed tablets in infants and children with P. falciparum malaria**

The main objectives of this Phase III comparative, open-labelled, randomised, multi-centre clinical study were to demonstrate the efficacy of a fixed combination of pyronaridine-artesunate granule formulation (60:20 mg), by showing a polymerase chain reaction (PCR)-adjusted adequate clinical and parasitological cure rate of more than 90%, and
to compare the efficacy (non-inferiority) and safety of pyronaridine-artesunate granule formulation with that of Coartem® (i.e., the combination of artemether-lumefantrine [AL]) crushed tablets in a paediatric population; and also to assess the safety of pyronaridine-artesunate granule formulation in infants and children subjects with acute, uncomplicated *P. falciparum* malaria.

The study was conducted in a total of 535 infant and children subjects (≤12 years of age) suffering from acute, uncomplicated *P. falciparum* malaria, recruited from 7 sites in Burkina Faso, the Democratic Republic of Congo, Gabon, Ivory Coast, Kenya, Mali, and the Philippines. Subjects were randomised in a 2:1 ratio to receive either oral pyronaridine-artesunate (60:20-mg granules in sachets) once a day for 3 consecutive days (Days 0, 1, and 2) or AL (20:120-mg crushed tablets) twice a day for 3 consecutive days (Days 0, 1, and 2). For pyronaridine-artesunate, the actual range covered by this regimen was 7.0:2.3 mg to 13.3:4.4 mg. Posology was based on body weight ranges for the pyronaridine-artesunate and AL regimens. Depending on body weight and randomisation, subjects received between 1 and 3 sachets of pyronaridine-artesunate granules or 1 or 2 crushed tablets twice a day of AL.

Subjects were followed for 42 days, with the primary efficacy end point occurring 28 days after initiation of study drug administration (Day 28). Subjects were confined to the study facility for ≥4 days (Days 0, 1, 2 and 3) and ideally remained in the vicinity of the study site for ≥7 days or when fever and parasite had been cleared for ≥24 hours, whichever occurred earlier. The subject was to return to the study site for all scheduled follow-up visits until completion of the study on Day 42.

A total of 355 and 180 subjects were randomised to the pyronaridine-artesunate and AL treatment groups, respectively. There were approximately equal percentages of male and female subjects and most subjects were Black (96.1%) and between 5 and 12 years of age. The majority of subjects completed treatment (97.8%) and completed the study (77.8%). The most common reason for withdrawing from the study was *P. falciparum* parasite re-appearance.

**Efficacy analysis**

For the primary end point, the PCR-adjusted ACPR on Day 28 was statistically significantly >90% in the pyronaridine-artesunate group (97.6%) by the exact binomial test, and was demonstrated to be non-inferior to the PCR-adjusted ACPR in the AL group (98.8%) (Figures 14 and 15). PCR-adjusted ACPR was also statistically significantly >90% (i.e., >97%) in the pyronaridine-artesunate treatment group on Days 14 and 21. Non-inferiority of pyronaridine-artesunate to AL was concluded at each time point in both EE and ITT populations. A similar pattern of results was observed for crude ACPR. No clinically important subgroup (region, age, gender, previous malaria infection, and dose of study drug) differences in Day 28 PCR-adjusted ACPR were observed.
Figure 9-14. Days 14, 21, 28, 35, and 42 ACPR – EE Population

Note: The Day 21 and Day 35 analyses were performed post hoc.

a. Non-inferiority of PA to AL was concluded because the lower limit of the 2-sided 95% CI for the difference was >-10%.

b. The hypothesis that the ACPR in the PA group is ≤90% was rejected because the p-value associated with the 1-sided test was ≤0.025.
Pyronaridine-artesunate were rapidly effective. Parasite count decreased rapidly (during the first 16 hours) in both the pyronaridine-artesunate and AL groups. This was not unexpected as the clinical efficacy of the artemisinin derivatives is characterised by an almost immediate onset and rapid reduction of parasitaemia (de Vries et al, 1996). Time to parasite clearance was slightly statistically significantly ($p=0.0459$) shorter in the pyronaridine-artesunate group compared with the AL group. A greater percentage of pyronaridine-artesunate subjects vs. AL subjects achieved parasite clearance 24 hours after the first dose (49.9% vs. 43.7%).

Time to fever clearance was similar in the pyronaridine-artesunate and AL groups.
No statistically significant difference between the pyronaridine-artesunate and AL groups was observed for the Kaplan-Meier estimates of new infection (p=0.7740), recrudescence (p=0.5263) (Figure 9-16), or parasite re-appearance (p=0.9800), as determined by PCR analysis. However, among ITT subjects, a greater percentage of AL than pyronaridine-artesunate subjects (2.8% vs. 0.6%) was treatment failures in the PCR-adjusted ACPR analysis due to new infection before Day 28.

**Figure 9-16. Kaplan-Meier Estimates of Recrudescence Rate – ITT Population**

![Kaplan-Meier Estimates of Recrudescence Rate](image)

**Immunity statement**

Immunity can play an important part of how patients respond to malaria treatment. In the pyronaridine-artesunate clinical studies there was mixture of patients from Asia and Africa, children and adults and previous experience with malaria. Patients who were Asian had slower parasite and fever clearance time when compared to Africans. Recrudescence rate were lower for Africans compared with Asians and for adults compared with children. Recrudescence rates for patients who had no previous episodes of malaria were higher. These differences although not statistically significant point out the effect of immunity on outcomes in the pyronaridine-artesunate studies, but overall pyronaridine-artesunate showed excellent activity against malaria in patients with immunity and those without immunity.
Phase III comparative study of PYRAMAX with chloroquine in Korean adults and children 

(P. vivax)

Study SP-C-008-07 was a multi-centre, randomised, double-blind, double-dummy comparative trial in male and female subjects between the ages of 3 and 60 years, inclusive, with body weight between 20 and 90 kg, no clinical evidence of severe malnutrition, and acute uncomplicated P. vivax mono-infection. This study was conducted at 2 investigative sites in Korea.

Subjects were randomised to receive either oral PYRAMAX (180:60-mg tablets) plus chloroquine-placebo or oral chloroquine (155-mg tablets) plus PYRAMAX-placebo, once a day for 3 consecutive days (Days 0, 1, and 2).

For subjects who completed the study up to Day 28 and who had normal G-6-PD activity, a 14-day course of primaquine (15 mg/day) was administered starting on Day 28, after all required assessments had been performed, to complete their radical cure. Subjects who were deficient in G-6-PD and who completed the study up to Day 28 were treated per country policy.

Depending on their body weight, subjects received between 1 and 4 tablets of PYRAMAX. The dose range covered by this regimen was 7.2:2.4 mg/kg/dose to 13.8:4.6 mg/kg/dose, which has been shown to be effective and well tolerated in Phase I and II studies (actual range received by subjects was 3.3-13.8 mg/kg/dose PP and 1.1-4.6 mg/kg/dose AS). The chloroquine daily dose was 10 mg/kg on Days 0 and 1 and 5 mg/kg on Day 2 for children and 620 mg on Days 0 and 1 and 310 mg on Day 2 for adults.

Subjects were confined to the study facility for ≥4 days (Days 0, 1, 2, and 3). The subject was to return to the study site for all scheduled follow-up visits until completion of the study on Day 42.

The primary efficacy end point for the study was the cure rate on Day 14. Due to the lack of validated molecular tools, the primary end point was based on a crude cure rate on Day 14. Secondary end points were: Cure rate on Day 28, defined in the same way as cure rate on Day 14, PCT, FCT, proportion of subjects with cleared parasites on Days 1, 2, and 3, proportion of subjects with fever cleared on Days 1, 2, and 3. Exploratory end points included proportion of subjects with PCR-adjusted cure on Days 14, and 28, and cure rate and PCR-adjusted cure rate on Day 42. Safety was assessed by physical examinations, AEs, vital signs, laboratory assessments (haematology, chemistry, urinalysis), clinical signs and symptoms, and 12-lead ECG.

A total of 40 subjects were planned however due to prolonged recruitment this was stopped after 30 subjects were recruited (15 in the PYRAMAX group and 15 in the chloroquine group). All subjects completed treatment (100%) and completed the study (100%).

**Efficacy analysis**

The efficacy results of this study demonstrate that:
• PYRAMAX and chloroquine showed a 100% crude cure rate at all evaluated time points until Day 42.
• Time to parasite clearance (medians: 32.0 vs. 63.9 hours) was statistically significantly shorter in the PYRAMAX group than in the chloroquine group (p<0.0001).
• Time to fever clearance (medians: 16.0 vs. 31.9 hours) was shorter in the PYRAMAX group than the chloroquine group without being statistically significantly different (p=0.4105).

**Overall conclusions from Phase III studies supporting registration**

In the Phase III studies to support the initial Positive Opinion from EMA, PYRAMAX was shown to have good efficacy, safety and tolerability profiles in children and adults patients for the treatment of acute, uncomplicated *P. falciparum* or blood stage *P. vivax* malaria in endemic regions in Africa, South East Asia and India.

**Efficacy**

In the individual Phase III studies, the primary end point in the *P. falciparum* populations was PCR-adjusted adequate clinical and parasitological response (ACPR) on Day 28 in the efficacy evaluable (EE) population. In each of the 3 *P. falciparum* studies, non-inferiority of PYRAMAX vs. the comparator was demonstrated for the PCR-adjusted ACPR on Day 28 in the EE population. In SP-C-007-07, the primary analysis evaluated whether the PCR-adjusted ACPR in the PYRAMAX group was statistically significantly >90%. In that study, the PCR-adjusted ACPR was statistically significantly >90% in the PYRAMAX group by the exact binomial test. Non-inferiority of PYRAMAX to comparators was also demonstrated in the ITT population on Day 28.
### Table 9-2: PCR-Adjusted ACPR – Phase III *P. falciparum* studies (EE population)

<table>
<thead>
<tr>
<th>Day 28 PCR-adjusted ACPR</th>
<th>PA (N=749)</th>
<th>MQ + AS (N=368)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SP-C-004-06</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Available observations, n (%)</td>
<td>749 (100)</td>
<td>368 (100)</td>
</tr>
<tr>
<td>Number (% of subjects cured</td>
<td>743 (99.2)</td>
<td>360 (97.8)</td>
</tr>
<tr>
<td>95% CI&lt;sup&gt;a&lt;/sup&gt;</td>
<td>98.3, 99.7</td>
<td>96.1, 99.2</td>
</tr>
<tr>
<td>Between group comparison:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difference in cure rate (PA minus MQ + AS)</td>
<td>1.4</td>
<td>0.0, 3.5</td>
</tr>
<tr>
<td>95% CI&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conclusion&lt;sup&gt;#&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p-value&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td>0.053</td>
</tr>
</tbody>
</table>

| **SP-C-005-06**          |            |                 |
| Available observations, n (%) | 792 (100) | 388 (100) |
| Number (% of subjects cured | 780 (98.5) | 384 (99.0) |
| 95% CI<sup>a</sup>        | 98.7, 99.9 | 97.7, 99.8 |
| Between group comparison: |            |                 |
| Difference in cure rate (PA minus AL) | 0.5 | -1.8, 1.2 |
| 95% CI<sup>b</sup>        |            |                 |
| Conclusion<sup>#</sup>    |            |                 |
| p-value<sup>c</sup>       |            | 0.499           |

| **SP-C-007-07**          |            |                 |
| Available observations, n (%) | 339       | 167             |
| Number (% of subjects cured | 329 (97.1) | 165 (98.8) |
| 95% CI<sup>a</sup>        | 95.4, 99.0 | 95.7, 99.9 |
| p-value (exact binomial test)<sup>d</sup> | <0.0001 |                 |
| Between group comparison: |            |                 |
| Difference in cure rate (PA minus AL) | -1.8 | -4.3, 1.6 |
| 95% CI<sup>b</sup>        |            |                 |
| Conclusion<sup>#</sup>    |            |                 |
| p-value<sup>c</sup>       |            | 0.223           |

CI=confidence interval

- a. Exact 2-sided 95% CI (Pearson-Clopper).
- b. 2-sided CI for between-group comparison calculated using Newcombe-Wilson method.
- c. 2-sided Chi-square test for superiority performed only when non-inferiority was demonstrated.
- d. For the hypothesis that the ACPR in the PA group is ≤90%. The hypothesis was rejected if the p-value associated with the 1-sided test was ≤0.025.
- # Non-inferiority of PA to MQ + AS in SP-C-004-06 and to AL in SP-C-005-06 was concluded because the lower limit of the 2-sided 95% CI for the difference was >-5%. Non-inferiority of PA to AL in SP-C-007-07 was concluded because the lower limit of the 2-sided 95% CI for the difference was >-10%.

In an integrated analysis of all PYRAMAX and comparator groups Phase III patients, the ITT population was considered the primary analysis population, in contrast to the individual studies, given the variability of the EE population criteria across studies. In the integrated analysis of the Phase III *P. falciparum* studies population, no notable differences in PCR-adjusted ACPR were observed between the PA group and the AL or MQ + AS...
treatment groups at any time point in the ITT population. PCR-adjusted ACPR decreased over time in each treatment group, with notably lower cure rates observed on Day 35 and/or Day 42 compared with Days 14, 21, and 28.

Based on Kaplan-Meier estimates, time to parasite clearance was statistically significantly shorter in the PYRAMAX group compared with AL group (SP-C-005-06 and SP-C-007-07) and chloroquine group (SP-C-006-06), based on the log-rank test (Figure 9-17). Time to parasite clearance was similar in the PYRAMAX and MQ + AS groups (SP-C-004-06). In the pooled analysis, median time to parasite clearance was 24 hours in the PYRAMAX and AL groups and 32 hours in the MQ + AS and chloroquine groups.

Figure 9-17: Kaplan-Meier Survival curve for parasite clearance time – integrated Phase III studies (EE Population)
The clinical study programme undertaken for PYRAMAX demonstrated conclusively that for the primary endpoint of PCR-adjusted ACPR at 28 days, pyronaridine-artesunate was not inferior to MQ + AS or AL for the treatment of \textit{P. falciparum}. At 28 days post-dosing, the cure rate for PYRAMAX, MQ + AS, and AL was very high and, whilst the cure rates declined over time, PYRAMAX was actually superior to AL at Day 35 in the study of adults and children (although not the paediatric-only study). PYRAMAX demonstrated superiority in parasite clearance time, being statistically significantly shorter versus AL, although fever clearance time was faster in the AL group. In addition, time to \textit{P. vivax} parasite clearance and time to fever clearance were statistically significantly shorter in the PYRAMAX group compared with the chloroquine group, findings that were not unexpected due to the rapid action of AS.

PYRAMAX was shown to provide greater protection than comparators against recrudescence and new infections in subjects treated for \textit{P. falciparum} malaria. In addition, PYRAMAX demonstrated gametocytocidal activity in the Phase III \textit{P. falciparum} studies, establishing it as a transmission-blocking agent.

Although SP-C-006-06 was a study of uncomplicated malaria with \textit{P. vivax} (mixed infections not allowed), a post hoc analysis also demonstrated that the risk of subsequent infection with \textit{P. falciparum} was statistically significantly lower with PYRAMAX than with chloroquine (p=0.0481), providing a further benefit after presentation of the original malaria infection.

In the PYRAMAX clinical studies, there was mixture of subjects from Asia, India and Africa, children and adults, and subjects with and without previous experience with malaria. Parasite clearance time and fever clearance time were shorter among subjects from Africa and among Black subjects compared with Asian/Oriental subjects, and time to recrudescence was longer among subjects from Africa and among Black subjects compared with Asian/Oriental subjects. Time to recrudescence where this occurred was longer in adults than children. Parasite clearance time and fever clearance time were longer and recrudescence rates were higher for subjects who no previous episodes of malaria had compared with subjects who had previously had malaria. These differences suggest that previous exposure allows the development of immunity and this, which is more established in adults than children, may contribute to the faster parasite clearance time. Whilst these times may vary, the effectiveness of PYRAMAX in subjects with \textit{de novo} malaria or those who had been previously exposed was extremely high.

In order to broaden the original PYRAMAX indication and in particular to remove the restriction for single treatment only, data from an ongoing longitudinal Phase IIIb study in West Africa (SP-C-013-11) has been evaluated within an interim sub-study. The sub-study, with additional PCR analysis, has been published by Sagara \textit{et al} (2016). The ongoing SP-C-013-11 study is being conducted by the West African Network for Clinical Trials of Antimalarial Drugs (WANECAM) in Mali, Burkina Faso and Guinea. It examines the safety and efficacy of PYRAMAX or DHA-PQP, versus either ASAQ or AL, according to the standard of care at each participating site. (PYRAMAX and DHA-PQP are not being compared).
**SP-C-013-11 Sub-study**

The interim sub-study has focused on the safety of repeated dosing with PYRAMAX in particular in relation to hepatotoxic events. The interim analysis of the longitudinal study was based on a statistical approach agreed with the EMA Rapporteurs in April 2013. Efficacy was also assessed in the context of this sub-study to demonstrate that the safety findings, on repeat dosing, are not at the expense of a loss of efficacy.

In total, 1686 patients with acute, uncomplicated *Plasmodium* sp. malaria were eligible for the sub-study and were randomised and treated for an initial episode of malaria; 1015 patients were randomised to the PYRAMAX arm and 671 patients to the AL arm at the data cut-off of 31st October 2013. Of the 1015 patients with *P. falciparum* malaria treated at least once with PYRAMAX, 316 patients received at least two or more courses of PYRAMAX. 128 of the 393 patients, in the under 20 kg patient population, were dosed more than once over the analysis period, while in the 20 kg and over group 188 of 622 patients were dosed more than once. The median time between treatment episodes 1 and 2, episodes 2 and 3, episodes 3 and 4, and episodes 4 and 5 were broadly similar but differed by weight category. The median time between treatment episodes was longer for patients with body weight ≥20 kg than for patients with body weight <20 kg.

**Efficacy**

PYRAMAX demonstrated comparable efficacy at first and subsequent dosings. This was particularly notable in the higher weight group. The crude ACPR rate at Day 28 in the ≥20 kg group was 96.7%, compared to 97.6% in the pivotal SP-C-005-06 study (with patients 25 kg and over). The crude ACPR rate at Day 28 in the under 20 kg patients was 93.1% compared to 89.4% in the SP-C-007-07 study (with patients under 25 kg). There was no reduction in efficacy over the treatment period for Day 28 ACPR and this rate of efficacy was generally maintained over treatment episodes. The low number of patients after the second dosing means that it is more difficult to conclude, however the trends are favourable to maintenance of efficacy.

At Day 42 PYRAMAX efficacy, as assessed by crude cure rate, was lower than that at Day 28, but comparable from first to subsequent treatment episodes. For the higher weight group this was over 81% and in the under 20kg was generally 50-70%, with one outlier of 30%.

The sub-study was exclusively carried out in area of very high malaria incidence attack rate (Mali, Guinea and Burkina Faso) where the population develops a high level of new infections because of the high number of infected mosquito bites reported during the rainy season, while studies SP-C-005-06 and SP-C-007-07 were conducted in area of very high malaria incidence attack rate but also in area of lower malaria incidence attack rate, similar to that seen in countries from Central Africa. Based on this information, the rate of crude ACPR at 42 days is therefore expected to be lower in the setting of SP-C-013-11 as the crude ACPR does not allow to make the difference between recrudescence of the initial infection and new infection. Caution should be advised on over interpretation of the crude ACPR data as this is regarded as the worst case scenario. Inclusion of these efficacy parameters in a sub-study which is essentially focused on the safety of PYRAMAX on repeat dosing, in particular in relation to hepatotoxicity, does however demonstrate that efficacy is not reduced when PYRAMAX is administered for repeated episodes of uncomplicated malaria.
The inclusion of AL in the analysis provided a comparison with an ACT which is currently used as a first or second line commercial anti-malaria agent in the countries where the study was undertaken.

For both Day 28 and Day 42, crude ACPR was more favourable in the PYRAMAX group than in the AL group, for younger and older patients alike and both on the initial treatment as well as when used for repeat treatment. The shorter half-life of lumefantrine compared to pyronaridine would result in a shorter protection period against new infections.

The Generalised Estimating Equation (GEE) estimate of crude ACPR difference in Episode 1 for PYRAMAX minus AL was 12.6% (94.8% in the PYRAMAX arm and 82.2% in the AL arm) on Day 28 and 12.9% (80.5% in the PYRAMAX arm and 67.6% in the AL arm) on Day 42. These differences are statistically significant at 5% with 95%CI being (9.7%, 15.6%) and (8.7%, 17.2%), respectively.

Parasite clearance time (PCT) remained consistent across repeated treatment with PYRAMAX. Confidence intervals were tight around the median reflecting a good degree of confidence that variability between patients was not an issue. *P. falciparum* parasite clearance was consistently over 95% by 48 hours after first dose of each treatment episode out to at least 4 cycles of repeated treatment. PCT for AL showed more variability on repeated treatment cycles but with the exception of a longer PCT for the first episode the effectivity based on median PCT was in line with PYRAMAX.

In a sub-group of these patients who received the PYRAMAX paediatric formulation of granules for oral suspension for at least the first dosing episode of treatment for malaria, 376 patients weighing from 5 kg under 20 kg were dosed once, with 124 patients dosed at least twice and 35 patients at least 3 times. The median time for redosing in those patients who required a repeat dose was 41 to 49 days for each episode. The sub-group was analysed for any influence of patient weight (reflecting number of sachets 1 to 3) or dosing episode on outcome and neither was seen to affect the efficacy parameters.

Day 28 PCR adjusted ACPR in the ITT population for PYRAMAX was 93.3% in the first dosing episode, 94.2% in the second and 94.3% in the third while for the comparator AL this was 81.1% for the first dosing episode, 83.3% for the second and 70.0% for the third episode. Of note there were a higher proportion of early treatment failures with AL compared to PYRAMAX for each episode. Generalised Estimating Equation Estimates of crude ACPR on Day 28 (26.5%) and Day 42 (14.0%) for PYRAMAX minus AL was positive, i.e. the rates of treatment success were better in the PYRAMAX arm compared to AL.

Median parasite clearance time was marginally shorter in the PYRAMAX (34.1 hrs) arm than in the AL arm (35.3 hrs) during treatment episode 1 and was similar during the other treatment episodes, with no difference seen in weight categories. Time until recurrence of *P. falciparum* infection was statistically significantly longer in the PYRAMAX arm compared to the AL arm during the first 2 episodes (episode 1: p <0.0001, episode 2: p = 0.0182, log rank test).

The analyses showed that in the patients who received at least one dosing episode of PYRAMAX...
granules for oral suspension efficacy was maintained across repeated treatments and that each of the weight categories performed similarly. On each parameter PYRAMAX granules for oral suspension performed better than the comparator AL.
10. REVIEW OF HARMS AND TOXICITY: SUMMARY OF EVIDENCE ON SAFETY

10.1 Total patient exposure to date

The safety database for the Phase II/III PYRAMAX clinical programme included 3017 subjects who received at least 1 dose of PYRAMAX, administered either as the fixed-dose co-formulation or as PP + AS across 7 Phase I, 2 Phase II, 5 Phase III studies and 1 Phase IIIb/IV study where a sub-population of data are reported. In the case of the mass balance study this is with pyronaridine alone.

The exposure data includes both adult and paediatric patients supporting EML listing (Table 10-1, 10-2, 10-3).

The safety review presented provides the adverse events and frequency, summary of data, comparative safety and variation based on different populations.

Table 10-1 Estimates of cumulative subject exposure to pyronaridine-artesunate from company-sponsored clinical trials (I-III) by age and gender

<table>
<thead>
<tr>
<th>Age group (years of age)*</th>
<th>Persons (n)</th>
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</thead>
<tbody>
<tr>
<td>TOTAL (Phase I) all &gt;18 years of age</td>
<td>320</td>
</tr>
<tr>
<td>TOTAL (Phase II/III)</td>
<td>2830</td>
</tr>
<tr>
<td>&lt;1</td>
<td>9</td>
</tr>
<tr>
<td>1-&lt;5</td>
<td>173</td>
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<tr>
<td>5-12</td>
<td>704</td>
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<tr>
<td>&gt;12-&lt;18</td>
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<tr>
<td>≥18</td>
<td>1542</td>
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<table>
<thead>
<tr>
<th>Gender</th>
<th>M</th>
<th>F</th>
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<tbody>
<tr>
<td>Phase I</td>
<td>145</td>
<td>115</td>
</tr>
<tr>
<td>Phase II/III</td>
<td>1872</td>
<td>958</td>
</tr>
</tbody>
</table>
Table 10-2  Demographic and Baseline Characteristics of Phase IIIb/IV Repeat Dose study (SP-C-013-11 Sub-study Population)

<table>
<thead>
<tr>
<th>Variable/Statistic/Category</th>
<th>PYRAMAX (PA) (N=1015)</th>
<th>Coartem (AL) (N=671)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>506 (49.9)</td>
<td>352 (52.5)</td>
</tr>
<tr>
<td>Female</td>
<td>509 (50.1)</td>
<td>319 (47.5)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Available observations</td>
<td>1015</td>
<td>671</td>
</tr>
<tr>
<td>Mean</td>
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<tr>
<td>Standard deviation</td>
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<td>9.65</td>
</tr>
<tr>
<td>Minimum</td>
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<td>0</td>
</tr>
<tr>
<td>Q1</td>
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<td>5</td>
</tr>
<tr>
<td>Median</td>
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<td>9</td>
</tr>
<tr>
<td>Q3</td>
<td>13</td>
<td>15</td>
</tr>
<tr>
<td>Maximum</td>
<td>62</td>
<td>69</td>
</tr>
<tr>
<td>Age category, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;18 years</td>
<td>902 (88.9)</td>
<td>573 (85.4)</td>
</tr>
<tr>
<td>≤6 months</td>
<td>3 (0.3)</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>&gt;6 months - &lt;1 year</td>
<td>6 (0.7)</td>
<td>3 (0.5)</td>
</tr>
<tr>
<td>1-2 years</td>
<td>82 (9.1)</td>
<td>32 (5.6)</td>
</tr>
<tr>
<td>3-5 years</td>
<td>233 (25.8)</td>
<td>145 (25.3)</td>
</tr>
<tr>
<td>6-17 years</td>
<td>578 (64.1)</td>
<td>391 (68.2)</td>
</tr>
<tr>
<td>≥18 years</td>
<td>113 (11.1)</td>
<td>98 (14.6)</td>
</tr>
<tr>
<td>Gender</td>
<td>M</td>
<td>F</td>
</tr>
<tr>
<td></td>
<td>506</td>
<td>509</td>
</tr>
<tr>
<td>GRANULES sub-group*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PA</td>
<td>AL</td>
</tr>
<tr>
<td>(N=376)</td>
<td>(N=233)</td>
<td></td>
</tr>
<tr>
<td>Gender male/female</td>
<td>168/208 (45%/55%)</td>
<td>122/111 (52%/48%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>4.0</td>
<td>4.3</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>1.83</td>
<td>1.89</td>
</tr>
<tr>
<td>Minimum</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Age category, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤6 months</td>
<td>2 (0.5)</td>
<td>2 (0.9)</td>
</tr>
<tr>
<td>&gt;6 months - &lt;1 year</td>
<td>6 (1.6)</td>
<td>3 (1.3)</td>
</tr>
<tr>
<td>1-2 years</td>
<td>79 (21.0)</td>
<td>32 (13.7)</td>
</tr>
<tr>
<td>3-5 years</td>
<td>210 (55.9)</td>
<td>140 (60.0)</td>
</tr>
<tr>
<td>≥6 years</td>
<td>79 (21.0)</td>
<td>56 (24.0)</td>
</tr>
</tbody>
</table>
The granules sub-group consists of all patients who received PA granules from the sub-study. The paediatric presentation of AL was taken as the comparator.

Table 10-3  **Demographic and Baseline Characteristics – Granules Integrated Safety**

<table>
<thead>
<tr>
<th>Summary Population</th>
<th>PA (N=667)</th>
<th>AL (N=358)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Variable/Statistic/Category</strong></td>
<td><strong>Gender, n (%)</strong></td>
<td><strong>Age (years)</strong></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td><strong>Gender, n (%)</strong></td>
<td>310 (46.5)</td>
<td>357 (53.5)</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>183 (51.1)</td>
<td>175 (48.9)</td>
</tr>
</tbody>
</table>
10.2 Safety and tolerability

10.2.1 Overview of PYRAMAX Safety

The adverse event profile of PYRAMAX in the individual studies and in the integrated analysis of all Phase II/III studies was consistent with profiles reported for pyronaridine and artemisinins as monotherapy [Price, 1999; Ringwald, 1996; Looareesuwan, 1996, Ribeiro, 1998]. PA treatment was generally well tolerated with the vast majority of AEs being of mild or moderate intensity, with headache and gastrointestinal symptoms occurring most frequently.

The only notable safety finding that was more prevalent for subjects treated with PYRAMAX was the finding of significant transient transaminase elevations in a relatively small proportion of subjects. However, the early onset (Day 3-7) and rapid resolution of the transaminase elevations are consistent with a direct, low-level toxicity. The risk associated with this finding also took into account subjects who had rises, after their first episode of treatment, >3x but ≤5x (2.1%), >5x but ≤10x (1%), and >10xULN (0.4%) for transaminases, as well as those subjects (0.2%) who might qualify as Hy’s law candidates (ALT >3xULN and total bilirubin >2xULN) when assessing the potential of PYRAMAX to produce liver injury [Temple, 2001; Reuben, 2004] The data were rigorously reviewed by an independent safety review board consisting of 3 hepatologists, an epidemiologist and an independent statistician. Upon review of all the data, including the follow-up information on subjects with clinically significantly raised values, the board concluded that the risk of progressive liver injury, especially for a 3-day course of treatment, was very low. Their view was that serious idiosyncratic hepatotoxicity typically begins weeks or months after starting therapy. Of note in the cases that occurred in the PYRAMAX study programme, all of the raised values returned to normal, the vast majority being normal at 28 days. Some returned to normal earlier, but for most studies, the blood draws were performed at 3, 7, 28, and 42 days. Overall, changes in liver function tests in terms of drug-induced liver injury were in the main mild with a small number of moderate cases (based on peak total bilirubin levels) based on the criteria of the Drug Induced Liver Injury Network (Fontana 2010). Furthermore there were no cases of liver failure, no encephalopathy, no evidence of coagulopathy and no evidence of a delayed effect.

10.2.2 Common Adverse Events Phase II/III

Table 10-4 summarises treatment-emergent adverse events considered to be study drug-related occurring ≥1.0% of subjects and summarises treatment emergent SAEs (and also identifies those that were considered related to treatment). In these controlled studies the overall incidence of AEs was similar between the studies and when compared to the antimalarial control agent. Adverse events were considered to be of mild or moderate intensity and all resolved without sequelae. Table 10-5 summarises the treatment-emergent serious adverse events from Phase II/III studies.
### Table 10-4. Treatment-Emergent Adverse Events Considered to be Study Drug-Related Occurring in ≥1.0% of Subjects in PYRAMAX or ALL Comparator Groups – All Phase II/III Studies Population

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>PYRAMAX (N=2830)</th>
<th>All Comparators (N=1269)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N</td>
<td>(%)</td>
</tr>
<tr>
<td>≥1 treatment-related AE</td>
<td></td>
<td>715</td>
<td>(25.3)</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td></td>
<td>46</td>
<td>(1.6)</td>
</tr>
<tr>
<td>Eosinophilia</td>
<td></td>
<td>70</td>
<td>(2.5)</td>
</tr>
<tr>
<td>Lymphocytosis</td>
<td></td>
<td>20</td>
<td>(0.7)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td></td>
<td>53</td>
<td>(1.9)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td></td>
<td>39</td>
<td>(1.4)</td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td>63</td>
<td>(2.2)</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alanine Aminotransferase Increased</td>
<td></td>
<td>45</td>
<td>(1.6)</td>
</tr>
<tr>
<td>Aspartate Aminotransferase Increased</td>
<td></td>
<td>52</td>
<td>(1.8)</td>
</tr>
<tr>
<td>Blood albumin decreased</td>
<td></td>
<td>19</td>
<td>(0.7)</td>
</tr>
<tr>
<td>Blood glucose decreased</td>
<td></td>
<td>29</td>
<td>(1.0)</td>
</tr>
<tr>
<td>Haemoglobin decreased</td>
<td></td>
<td>30</td>
<td>(1.1)</td>
</tr>
<tr>
<td>Platelet count increased</td>
<td></td>
<td>40</td>
<td>(1.4)</td>
</tr>
<tr>
<td>Transaminase increased</td>
<td></td>
<td>35</td>
<td>(1.2)</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td></td>
<td>26</td>
<td>(0.9)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td></td>
<td>17</td>
<td>(0.6)</td>
</tr>
<tr>
<td>Headache</td>
<td></td>
<td>85</td>
<td>(3.0)</td>
</tr>
</tbody>
</table>

### Table 10-5. Treatment-Emergent Serious Adverse Events – All Phase II/III Studies Population

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>PYRAMAX (N=2830)</th>
<th>All Comparators (N=1269)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N</td>
<td>(%)</td>
</tr>
<tr>
<td>≥1 SAE</td>
<td></td>
<td>18</td>
<td>(0.6)</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaemia haemolytic autoimmune</td>
<td></td>
<td>1</td>
<td>(&lt;0.1)</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac failure</td>
<td></td>
<td>1</td>
<td>(&lt;0.1)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>System Organ Class</td>
<td>Preferred Term</td>
<td>PYRAMAX (N=2830)</td>
<td>All Comparators (N=1269)</td>
</tr>
<tr>
<td>--------------------</td>
<td>----------------</td>
<td>-------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N</td>
<td>(%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td></td>
<td>1</td>
<td>(&lt;0.1)</td>
</tr>
</tbody>
</table>

**General disorders and administration site conditions**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>N</th>
<th>(%)</th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrexia</td>
<td></td>
<td>2</td>
<td>(0.1)</td>
<td>0</td>
<td>(0.0)</td>
</tr>
</tbody>
</table>

**Immune system disorders**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>N</th>
<th>(%)</th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunosuppression</td>
<td></td>
<td>0</td>
<td>(0.0)</td>
<td>1</td>
<td>(0.1)</td>
</tr>
</tbody>
</table>

**Infections and infestations**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>N</th>
<th>(%)</th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abscess limb</td>
<td></td>
<td>1</td>
<td>(&lt;0.1)</td>
<td>0</td>
<td>(0.0)</td>
</tr>
<tr>
<td>Cerebral malaria</td>
<td></td>
<td>0</td>
<td>(0.0)</td>
<td>2</td>
<td>(0.2)</td>
</tr>
<tr>
<td>Cholera</td>
<td></td>
<td>1</td>
<td>(&lt;0.1)</td>
<td>0</td>
<td>(0.0)</td>
</tr>
<tr>
<td>Malaria</td>
<td></td>
<td>2</td>
<td>(0.1)</td>
<td>0</td>
<td>(0.0)</td>
</tr>
<tr>
<td>Paronychia</td>
<td></td>
<td>1</td>
<td>(&lt;0.1)</td>
<td>0</td>
<td>(0.0)</td>
</tr>
<tr>
<td>Parotitis</td>
<td></td>
<td>1</td>
<td>(&lt;0.1)</td>
<td>0</td>
<td>(0.0)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td></td>
<td>1</td>
<td>(&lt;0.1)</td>
<td>0</td>
<td>(0.0)</td>
</tr>
<tr>
<td>Pyelonephritis acute</td>
<td></td>
<td>1</td>
<td>(&lt;0.1)</td>
<td>0</td>
<td>(0.0)</td>
</tr>
<tr>
<td>Typhoid fever</td>
<td></td>
<td>2</td>
<td>(0.1)</td>
<td>0</td>
<td>(0.0)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td></td>
<td>2</td>
<td>(0.1)</td>
<td>0</td>
<td>(0.0)</td>
</tr>
<tr>
<td>Wound infection</td>
<td></td>
<td>1</td>
<td>(&lt;0.1)</td>
<td>0</td>
<td>(0.0)</td>
</tr>
</tbody>
</table>

**Investigations**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>N</th>
<th>(%)</th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic enzyme increased</td>
<td></td>
<td>1</td>
<td>(&lt;0.1)</td>
<td>0</td>
<td>(0.0)</td>
</tr>
</tbody>
</table>

**Nervous system disorders**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>N</th>
<th>(%)</th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Convulsion</td>
<td></td>
<td>0</td>
<td>(0.0)</td>
<td>1</td>
<td>(0.1)</td>
</tr>
</tbody>
</table>

**Pregnancy, puerperium and perinatal conditions**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>N</th>
<th>(%)</th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abortion complete</td>
<td></td>
<td>1</td>
<td>(&lt;0.1)</td>
<td>0</td>
<td>(0.0)</td>
</tr>
<tr>
<td>Abortion incomplete</td>
<td></td>
<td>1</td>
<td>(&lt;0.1)</td>
<td>0</td>
<td>(0.0)</td>
</tr>
</tbody>
</table>

**Psychiatric disorders**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>N</th>
<th>(%)</th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td></td>
<td>1</td>
<td>(&lt;0.1)</td>
<td>0</td>
<td>(0.0)</td>
</tr>
</tbody>
</table>

a. Considered by the Investigator to be at least possibly related to study drug.

No unexpected or clinically concerning results were observed in the analysis of adverse events and potentially clinically significant laboratory values by intrinsic factors (age group, gender, race, weight), disease severity factors (previous malaria episode, number of previous malaria episodes in the last 12 months, baseline parasitaemia), or extrinsic factors (region, study drug dose).

Mean decreases in heart rate were observed in all treatment groups, a finding that has been observed in other studies of malaria treatment. [Ribeiro, 1998; Karbwang, 1992; Karbwang, 1994; Sowunmi, 1996] Bradycardia was recorded as an adverse event for 1.1% of pyronaridine-artesunate subjects and 0.8% of AL subjects. The mean age of the subjects was
15 to 27 years across treatment groups. In relatively fit youths, a slow heart rate is not uncommon. Once the pyrexia of malaria, with its associated tachycardia, has been cleared, a slowing of the heart may suggest that treatment has resulted in the patient returning to his or her normal low heart rate.

Electrocardiogram findings of any significant abnormalities were low and do not suggest a safety concern with pyronaridine-artesunate treatment. QT was specifically measured in Phase I and in Phase II/III a review of QT was conducted for those subjects with adverse events identified in ICH Topic E14 as being those of particular risk for association with a prolonged QT. The conclusion of this detailed work is that pyronaridine-artesunate does not exhibit a potential to prolong QT/QTc.

The overall pattern of safety findings in subjects with a higher baseline parasitaemia did not appear to be associated with a different profile from that seen in the subject population as a whole.

10.2.3 Conclusions on PYRAMAX Safety from Phase II/III

- PYRAMAX and the comparator drugs (AL, MQ + AS, chloroquine) were well tolerated. The adverse event profiles of PYRAMAX and the comparator drugs were similar and consistent with those previously reported for pyronaridine, artemisinins, AL, MQ, and chloroquine.
- Changes in haematology parameters were generally of similar magnitude in all treatment groups and are expected consequences of malaria infection and treatment.
- PYRAMAX treatment was associated with transient ALT elevations in a small number of subjects. The early onset (Day 3-7) and rapid resolution are consistent with a direct, low-level toxicity and do not indicate a risk of progressive liver injury with 3-day pyronaridine-artesunate treatment.
- Other biochemistry laboratory observations, also expected consequences of malaria infection and treatment, were generally similar across treatment groups.
- No unexpected or clinically concerning results were observed in the analysis of adverse and laboratory values by intrinsic factors (age group, gender, race, weight), disease severity factors (previous malaria episode, number of previous malaria episodes in the last 12 months, baseline parasitaemia), or extrinsic factors (region, study drug dose).
- Mean decreases in heart rate were observed in all treatment groups, a finding that has been observed in other studies of malaria treatment. This is not unexpected in subjects who are responding to therapy and becoming afebrile.
- Electrocardiogram results do not suggest a safety concern with PYRAMAX treatment.

10.2.4 PYRAMAX Repeated Dosing

A longitudinal study was conducted to examine the effect of repeated doses of PYRAMAX over multiple seasons. Data presented here reflects that from the sub-study analysis was undertaken of this study SP-C-013-11 to facilitate an improved label for PYRAMAX Tablets.
In the sub-study, the proportions of treatment related adverse events were also similar between the treatment groups and between the malaria treatment episodes, being more frequent in the < 20 kg weight group and there was no difference in incidence between 1st and subsequent episodes. In episode 1, neutropenia was slightly more frequently related to treatment in the < 20 kg age group and QTc prolongation as assessed by the investigator was more common in the lighter group. Transaminases rises were considered related in similar proportions across the treatment groups and weights except for the AL group ≥20 kg where it was the least frequently reported. Vomiting was more frequent in the PYRAMAX <20 kg group than the others. In episode 2 the incidence of related adverse events was less than in episode 1 and in episode 3 single cases meant that the incidence was distorted in percentage terms but there was no obvious trend to increased events in either weight range. Episode 4 only had 1 case of related QTc prolongation reported for PYRAMAX. There were no related events for PYRAMAX in episodes 5 to 9.

Table 10-6. Incidence of Treatment –related adverse events by drug and weight category (SP-C-013-11 sub-study)

<table>
<thead>
<tr>
<th></th>
<th>PYRAMAX</th>
<th>Artemether-Lumefantrine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;20 kg</td>
<td>≥20 kg</td>
</tr>
<tr>
<td><strong>Primary system organ class</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preferred term</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td><strong>Treatment episode 1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients dosed</td>
<td>393 (100.0)</td>
<td>622 (100.0)</td>
</tr>
<tr>
<td>At least one adverse event</td>
<td>96 (24.4)</td>
<td>91 (14.6)</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>27 (6.9)</td>
<td>29 (4.7)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>13 (3.3)</td>
<td>13 (2.1)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>4 (1.0)</td>
<td>12 (1.9)</td>
</tr>
<tr>
<td>Monocytosis</td>
<td>8 (2.0)</td>
<td>3 (0.5)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>34 (8.7)</td>
<td>15 (2.4)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>26 (6.6)</td>
<td>4 (0.6)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>9 (2.3)</td>
<td>5 (0.8)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>6 (1.5)</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>Investigations</td>
<td>37 (9.4)</td>
<td>33 (5.3)</td>
</tr>
<tr>
<td>Electrocardiogram QT prolonged</td>
<td>21 (5.3)</td>
<td>6 (1.0)</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>9 (2.3)</td>
<td>17 (2.7)</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>9 (2.3)</td>
<td>18 (2.9)</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>1 (0.3)</td>
<td>7 (1.1)</td>
</tr>
<tr>
<td>Hypercreatininaemia</td>
<td>1 (0.3)</td>
<td>7 (1.1)</td>
</tr>
<tr>
<td><strong>Treatment episode 2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients dosed</td>
<td>128 (100.0)</td>
<td>188 (100.0)</td>
</tr>
<tr>
<td>At least one adverse event</td>
<td>23 (18.0)</td>
<td>15 (8.0)</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>7 (5.5)</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>2 (1.6)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Monocytosis</td>
<td>2 (1.6)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>4 (3.1)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Primary system organ class</td>
<td>PYRAMAX &lt;20 kg (%)</td>
<td>PYRAMAX ≥20 kg (%)</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>-------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>4 (3.1)</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (2.3)</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Investigations</td>
<td>11 (8.6)</td>
<td>18 (9.5)</td>
</tr>
<tr>
<td>Electrocardiogram QT prolonged</td>
<td>3 (2.3)</td>
<td>4 (2.1)</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>5 (3.9)</td>
<td>1 (1.2)</td>
</tr>
</tbody>
</table>

**Treatment episode 3**

<table>
<thead>
<tr>
<th>Patients dosed</th>
<th>37 (100.0)</th>
<th>47 (100.0)</th>
<th>20 (100.0)</th>
<th>61 (100.0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least one adverse event</td>
<td>4 (10.8)</td>
<td>4 (8.5)</td>
<td>4 (20.0)</td>
<td>7 (11.5)</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>1 (2.7)</td>
<td>1 (2.1)</td>
<td>1 (5.0)</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>1 (2.7)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>0 (0.0)</td>
<td>1 (2.1)</td>
<td>3 (15.0)</td>
<td>2 (3.3)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>0 (0.0)</td>
<td>1 (2.1)</td>
<td>2 (10.0)</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>0 (0.0)</td>
<td>1 (2.1)</td>
<td>1 (5.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Investigations</td>
<td>0 (0.0)</td>
<td>2 (4.3)</td>
<td>0 (0.0)</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Electrocardiogram QT prolonged</td>
<td>0 (0.0)</td>
<td>1 (2.1)</td>
<td>0 (0.0)</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Blood creatinine increased</td>
<td>0 (0.0)</td>
<td>1 (2.1)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>2 (5.4)</td>
<td>2 (4.3)</td>
<td>0 (0.0)</td>
<td>2 (3.3)</td>
</tr>
<tr>
<td>Hypercreatininaemia</td>
<td>2 (5.4)</td>
<td>2 (4.3)</td>
<td>0 (0.0)</td>
<td>2 (3.3)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>1 (2.7)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Dermatitis allergic</td>
<td>1 (2.7)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
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</tbody>
</table>

**Treatment episode 4**

<table>
<thead>
<tr>
<th>Patients dosed</th>
<th>9 (100.0)</th>
<th>19 (100.0)</th>
<th>2 (100.0)</th>
<th>18 (100.0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least one adverse event</td>
<td>1 (11.1)</td>
<td>1 (5.3)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Investigations</td>
<td>1 (11.1)</td>
<td>1 (5.3)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Electrocardiogram QT prolonged</td>
<td>1 (11.1)</td>
<td>1 (5.3)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

Table 10-7. Incidence of Serious Adverse Events by Primary System Organ Class and Preferred Term, by Treatment Episode (SP-C-013-11 Sub-study)
In the granules integrated safety (ISS) population, overall the treatment emergent AEs were similar for both PYRAMAX and comparator AL with the exception of drug-related AEs that were significantly more frequent for AL. For all case AEs in the granules ISS population vomiting was more common for PYRAMAX and QTc prolongation more common for AL. There were two deaths considered unrelated to study drug in the SP-C-013-11 sub-study; in the PYRAMAX arm, a multi-organ failure following a road traffic accident and in the AL arm, an HIV infection. There was one withdrawal due to an adverse event (vomiting) and this was from the PYRAMAX arm. Table 10-7 shows that in the sub-study there were 11 SAEs for PYRAMAX in episode 1 (1.1%) and 5 in AL (0.7%); these were mainly infections. In episode 2 there were 2 SAEs both infections in the PYRAMAX arm. There were no SAEs in later episodes. The only related SAEs occurred in episode 1 (4 PYRAMAX (0.4%) and 1 AL [0.1%]). The PYRAMAX related SAEs were raised transaminases x 2, Hy’s law, and anaemia; the AL-related SAE was Toxic epidermal necrolysis. The Hy’s law patient was re-dosed for a further malaria episode 60

There were no SAEs in later episodes in the all patient repeat dose population.

<table>
<thead>
<tr>
<th>Primary system organ class</th>
<th>Preferred term</th>
<th>PYRAMAX</th>
<th>AL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>1 (0.1)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Multi-organ failure</td>
<td>1 (0.1)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>1 (0.1)</td>
<td>1 (0.1)</td>
<td></td>
</tr>
<tr>
<td>Drug-induced liver injury</td>
<td>1 (0.1)</td>
<td>1 (0.1)</td>
<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>4 (0.4)</td>
<td>2 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Malaria</td>
<td>4 (0.4)</td>
<td>1 (0.1)</td>
<td></td>
</tr>
<tr>
<td>HIV infection</td>
<td>0 (0.0)</td>
<td>1 (0.1)</td>
<td></td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>1 (0.1)</td>
<td>1 (0.1)</td>
<td></td>
</tr>
<tr>
<td>Face injury</td>
<td>1 (0.1)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Tibia fracture</td>
<td>0 (0.0)</td>
<td>1 (0.1)</td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td>2 (0.2)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>1 (0.1)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>1 (0.1)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Transaminases increased</td>
<td>1 (0.1)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>0 (0.0)</td>
<td>1 (0.1)</td>
<td></td>
</tr>
<tr>
<td>Toxic epidermal necrolysis</td>
<td>0 (0.0)</td>
<td>1 (0.1)</td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>1 (0.1)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1 (0.1)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment Episode 2</th>
<th>Patients dosed</th>
<th>316 (100.0)</th>
<th>238 (100.0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least one serious adverse event</td>
<td>2 (0.6)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>2 (0.6)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Anal abscess</td>
<td>1 (0.3)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Malaria</td>
<td>1 (0.3)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
</tbody>
</table>
days later with only a minimal rise in ALT only (just above ULN).

The incidence of any post dose rise in ALT >3 x ULN was 2.3% and >5 x ULN was 1.3% respectively. This compares in the Phase II/III programme with any post dose rise in ALT >3 x ULN of 3.3% and 1.4% >5 x ULN of 1.4% respectively. The proportions of these rises were lower for episode 2 and subsequent episodes for patients weighing ≥20 kg and <20 kg. The pattern of ALT rises is similar in patients in both weight categories as well as the overall findings for the 1st and subsequent episodes. The ≥20 kg weight group makes up approximately 60% of the total patients in the safety population for this study. The <20 kg patients were those who were treated for the first episode with the granule formulation.

The general pattern of liver function changes was similar between PYRAMAX and AL in the SP-C-013-11 sub-study for episode 1. Overall changes were similar or less marked with subsequent episodes as shown in the scatter plots of peak bilirubin versus peak ALT ≥Day 3 and is shown in patients who received at least one repeat dose.

**Figure 10-1 Scatter Plot of Peak Bilirubin versus Peak ALT ≥Day 3, by Treatment Episode (SP-C-013-11 sub-study)**

No unexpected or clinically concerning results were observed in the analysis of AEs and potentially clinically significant laboratory values by extrinsic factors (region, study drug dose) or intrinsic factors (age group, gender, race, weight), disease severity factors (previous malaria episode, number of previous malaria episodes in the last 12 months, baseline parasitaemia). There was a slightly higher incidence of adverse events in patients < 20 kg versus those ≥ 20 kg mainly for anaemia and infections however, there was no difference between PYRAMAX and comparator for the same ranges.

Finally, there was not obvious increased risk for adverse events or changes in liver function with PYRAMAX when re-dosed within 5 half-lives of pyronaridine or longer.
10.3 Management of potential risks PYRAMAX® tablets and granules

In conjunction with EMA, a Risk Management Plan has been established for PYRAMAX® tablets and granules which allows for the ongoing monitoring of PYRAMAX with the six monthly reporting of exposure and safety to EMA. This plan covers the following:

- Routine pharmacovigilance for individual adverse reactions related to potential interactions (potentiation of effect)
- Literature review for reports of interactions with components of PYRAMAX®
- A pregnancy register to monitor the outcomes of pregnancies of women who are or become pregnant at the time of receiving PYRAMAX®
- Routine pharmacovigilance for individual case reports
- Reporting to EMA though 6 monthly cycle via Periodic Safety Update Reports (PSUR) to include updates from all studies being conducted with PYRAMAX®
- A post-registration study has been agreed with EMA. This is a Phase IIIb/IV cohort event monitoring study to evaluate, in real life setting, the safety and tolerability in malaria patients of the fixed-dose artemisinin-based combination therapy PYRAMAX®

10.4 Variation in safety that may relate to health systems and patient factors

10.4.1 Use in 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
The safety of pyronaridine tetraphosphate and artesunate when administered concurrently for use in human pregnancy has not been established and the potential risk is unknown.

A component of PYRAMAX® is artesunate, a recognized in vivo embryotoxic and teratogenic compound in animal models, including primate. 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. There are no data from the use of pyronaridine in pregnant women.

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. Because of the limited safety data, artemisinin compounds should only be used in the second and third trimesters of pregnancy when other treatments are considered unsuitable.
Pregnancy register
A pregnancy register 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.

10.4.2 Drug interactions

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.

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 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.

10.4.3 Other populations

No specific studies have been undertaken in the elderly, given that the target patient population is the younger malaria population. No specific studies have been undertaken in
hepatic or renal impairment.

10.5  Summaries of Evidence for Safety and Efficacy

A Cochrane Systematic Review (Interventional) has been conducted entitled "Artesunate plus pyronaridine for treating uncomplicated *Plasmodium falciparum* malaria" and authored by Hasifa Bukirwa, B Unnikrishnan, Christine V Kramer, David Sinclair, Suma Nair and Prathap Tharyan. The Cochrane Systematic Review was published in Cochrane Database of Systematic Reviews 2014, Issue 3.

The Cochrane Review presents the published data for PYRAMAX from six randomised controlled trials enrolling 3718 children and adults. Two authors independently assessed trial eligibility and risk of bias, and extracted data.

The authors combined dichotomous data using risk ratios (RR) and continuous data using mean differences (MD), and presented all results with a 95% confidence interval (CI). The GRADE approach to assess the quality of evidence.
11. SUMMARY OF AVAILABLE DATA ON COMPARATIVE COST AND COST - EFFECTIVENESS WITHIN THE PHARMACOLOGICAL CLASS OR THERAPEUTIC GROUP

(Currency: US$)

<table>
<thead>
<tr>
<th>WT</th>
<th>PY+AS</th>
<th>Price</th>
<th>AL</th>
<th>Price</th>
<th>ASAQ</th>
<th>Price</th>
<th>DHAPQP</th>
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</tr>
</thead>
<tbody>
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<td></td>
<td>Granule</td>
<td></td>
<td>Tablet</td>
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<td></td>
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<td></td>
<td>Disp 6</td>
<td></td>
<td>g</td>
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<td>1.5 tablet</td>
<td>DHA 20mg</td>
</tr>
<tr>
<td></td>
<td>Tablets</td>
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<td>tablet</td>
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<td></td>
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</tr>
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<tr>
<td></td>
<td>AS 20mg</td>
<td></td>
<td>tablet</td>
<td></td>
<td>3 tablet</td>
<td></td>
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<td>15-&lt;20</td>
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<td></td>
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<td>9 tablet</td>
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<td>AS 60mg</td>
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<td>3 tablet</td>
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<td>1.96</td>
<td>12 tablet</td>
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<td>24 tablet</td>
<td></td>
<td>6 tablet</td>
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<tr>
<td></td>
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<td></td>
<td>24 tablet</td>
<td></td>
<td>6 tablet</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-&lt;45</td>
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<td>75&lt;WT&lt;100</td>
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<td>-</td>
<td>12 tablet</td>
<td>DHA 40mg</td>
</tr>
<tr>
<td></td>
<td>AS 60mg</td>
<td></td>
<td>24 tablet</td>
<td></td>
<td>6 tablet</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Each price is US$ xxx per treatment in different weight band.
- AL: Artemether/Lumefantrine, ASAQ: Artesunate/Amodiaquine, DHAPQP: Dihydroartemisinin/Piperaquine, WT: body weight
- Bench mark price : Coartem of Novartis, Coarsucam/Winthrop of Sanofi Aventis, Eurartesim of Sigma-tau
- Price information of other ACTs : https://bip2-ext.theglobalfund.org/analytics/saw.dll?PortalPages

**Rationale on cost:**

In public sectors, Global prices of various different ACTs show stable behaviour in terms of price movement since the launching of AMFm. Strong buyer’s power has kept different ACT price at a minimum level while key raw material artemisinin price moves from US$200 up to US$600/Kg. Despite the price fluctuation of artemisinin, manufacturers manage the price volatility while keeping the price of ACT as low as they can manage.
Under this situation, pyronaridine/artesunate price should follow the global price trend in order to keep the product competitive in the different dimensions of the market place. Therefore, the price will be:

- Tablet Pyronaridine 180mg/Artesunate 60mg price will be U$0.60 – 2.40 per treatment in different weight band excluding delivery, cargo insurance and tax from country of origin in public sectors.
- Granule Pyronaridine 60mg/Artesunate 20mg price will be U$0.44 -1.33 per treatment in different body weight excluding delivery, cargo insurance and tax from country of origin in public sectors

To provide a historical perspective, WHO commissioned a report in 2002 (Deloitte and Touche: Report for the Review of Collaborating Partner product Pricing) which concluded that in the early days in which volumes were very low, Novartis could have charged over $3/treatment and still respected the no-profit-no-loss covenant with WHO.

Shin Poong production capacity is forecast as follows:

<table>
<thead>
<tr>
<th></th>
<th>Annual Capacity in 2016</th>
<th>Annual Capacity in 2019</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tablet</strong></td>
<td>29 Million treatments</td>
<td>59 Million treatments</td>
</tr>
<tr>
<td><strong>Granules</strong></td>
<td>15 Million treatments</td>
<td>44 Million treatments</td>
</tr>
</tbody>
</table>
12. REGULATORY INFORMATION

12.1 Summary of Regulatory status

PYRAMAX® was granted Marketing Approval by the Minister of Food and Drug Safety in Korea on August 2011. Positive Opinion under Article 58 by the European Medicines Agency on February 2012 for use of the tablet formulation in the treatment of acute uncomplicated *P. falciparum* and blood stage *P. vivax* patients over 20 kg, in areas of low transmission with evidence of artemisinin resistance. On the basis of the EMA Positive Opinion, PYRAMAX® tablets were included on WHO’s list of Pre-Qualified anti-malarials on May 2012 and PYRAMAX® granules were included on the Pre-Qualification list in March 2016.

PYRAMAX® tablets were officially launched in Korea in August 2012. PYRAMAX® tablets are undergoing national approvals in malaria endemic countries, approvals (A) and submissions (S) are shown below:

<table>
<thead>
<tr>
<th>Country</th>
<th>Invented Name</th>
<th>Authorisation Status - Date</th>
<th>Approval Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>EU</td>
<td>Pyramax</td>
<td>A -16 Feb 2012</td>
<td>EMEA/H/W/002319/001 (9 tablet pack)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>EMEA/H/W/002319/002 (90 tablet pack)</td>
</tr>
<tr>
<td>Korea</td>
<td>Pyramax</td>
<td>A -17 Aug 2011</td>
<td>5025</td>
</tr>
<tr>
<td>Cambodia</td>
<td>Pyramax</td>
<td>A –22 Aug 2014</td>
<td>CAM N0477IP-14</td>
</tr>
<tr>
<td>Ivory Coast</td>
<td>Pyramax</td>
<td>A –27 Aug 2014</td>
<td>E-2014-380</td>
</tr>
<tr>
<td>Myanmar</td>
<td>Pyramax</td>
<td>A – 4 Sep 2014</td>
<td>1909AA7914</td>
</tr>
<tr>
<td>Burkina Faso</td>
<td>Pyramax</td>
<td>A – 22 Sep 2014</td>
<td>2014-928/MS/CAB</td>
</tr>
<tr>
<td>Guinea</td>
<td>Pyramax</td>
<td>A –30 Jan 2015</td>
<td>064MS/DNPL/2014</td>
</tr>
<tr>
<td>Chad</td>
<td>Pyramax</td>
<td>A –12 Feb 2015</td>
<td>1053 001</td>
</tr>
<tr>
<td>Mozambique</td>
<td>Pyramax</td>
<td>A– 18 Mar 2015</td>
<td>4059</td>
</tr>
<tr>
<td>Gabon</td>
<td>Pyramax</td>
<td>A- 30 Mar 2015</td>
<td>7080/15</td>
</tr>
<tr>
<td>Country</td>
<td>Invented Name</td>
<td>Authorisation Status - Date</td>
<td>Approval Number</td>
</tr>
<tr>
<td>---------------------</td>
<td>---------------</td>
<td>-----------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>RCA (Central African Republic)</td>
<td>Pyramax</td>
<td>A – 12 Jun 2015</td>
<td>113</td>
</tr>
<tr>
<td>Congo</td>
<td>Pyramax</td>
<td>A – 30 Oct 2015</td>
<td>VC-PSM-SP/10.7.3B/No3 OELOPHS4</td>
</tr>
<tr>
<td>Niger</td>
<td>Pyramax</td>
<td>A – 15 Nov 2015</td>
<td>197/MSP/DGSP/DPH/MT</td>
</tr>
<tr>
<td>Kenya</td>
<td>Pyramax</td>
<td>A – 31 May 2016</td>
<td>341</td>
</tr>
<tr>
<td>Uganda</td>
<td>Pyramax</td>
<td>A – 16 Jun 2016</td>
<td>9362-06-16</td>
</tr>
<tr>
<td>Mauritania</td>
<td>Pyramax</td>
<td>A – 22 Jul 2016</td>
<td>00198/MS/DPL</td>
</tr>
<tr>
<td>Benin</td>
<td>Pyramax</td>
<td>A – 05 Aug 2016</td>
<td>594/2016/MS/DPMED/SLRGP/DA MM-R</td>
</tr>
<tr>
<td>Mali</td>
<td>Pyramax</td>
<td>A – 01 Nov 2016</td>
<td>201/MSHP-SG</td>
</tr>
<tr>
<td>Philippines</td>
<td>Pyramax</td>
<td>S – Nov 2011 &amp; May 2012</td>
<td></td>
</tr>
<tr>
<td>Thailand</td>
<td>Pyramax</td>
<td>S – Dec 2012</td>
<td></td>
</tr>
<tr>
<td>Tanzania</td>
<td>Pyramax</td>
<td>S – Dec 2013</td>
<td></td>
</tr>
<tr>
<td>Senegal</td>
<td>Pyramax</td>
<td>S – May 2014</td>
<td></td>
</tr>
<tr>
<td>Mali</td>
<td>Pyramax</td>
<td>S – May 2014</td>
<td></td>
</tr>
<tr>
<td>Cameroon</td>
<td>Pyramax</td>
<td>S – Jun 2014</td>
<td></td>
</tr>
<tr>
<td>Congo DEM</td>
<td>Pyramax</td>
<td>S – Jun 2014</td>
<td></td>
</tr>
<tr>
<td>Pakistan</td>
<td>Pyramax</td>
<td>S – Nov 2014</td>
<td></td>
</tr>
<tr>
<td>Rwanda</td>
<td>Pyramax</td>
<td>S – Apr 2015</td>
<td></td>
</tr>
<tr>
<td>Nigeria</td>
<td>Pyramax</td>
<td>S – Jul 2015</td>
<td></td>
</tr>
<tr>
<td>Laos</td>
<td>Pyramax</td>
<td>S – Jul 2015</td>
<td></td>
</tr>
</tbody>
</table>

Positive Opinion has been received from EMA under the Article 58 procedure in November
2015 for the repeated dose of tablets and for the granule formulation for PYRAMAX®.

The submission to Korea as manufacturing country origin was made and PYRAMAX® granules have been approved by MFDS in May 2016. PYRAMAX® granules are undergoing national approvals in malaria endemic countries, approvals (A) and submissions (S) are shown below:

<table>
<thead>
<tr>
<th>Country</th>
<th>Invented Name</th>
<th>Authorisation Status - Date</th>
<th>Approval Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>EU</td>
<td>Pyramax</td>
<td>A -19 Nov 2015</td>
<td>EMEA/H/W/002319/002 (90 sachet pack)</td>
</tr>
<tr>
<td>Korea</td>
<td>Pyramax</td>
<td>A - 18 May 2016</td>
<td>5129</td>
</tr>
<tr>
<td>Niger</td>
<td>Pyramax</td>
<td>A – 19 Aug 2016</td>
<td>175/MSP/DGSP/DPH/MT</td>
</tr>
<tr>
<td>Congo</td>
<td>Pyramax</td>
<td>A –05 Sep 2016</td>
<td>8311/6.MSP/DGMPL/DPM-16</td>
</tr>
<tr>
<td>Benin</td>
<td>Pyramax</td>
<td>S – 08 Aug 2016</td>
<td></td>
</tr>
<tr>
<td>Niger</td>
<td>Pyramax</td>
<td>S – 12 Aug 2016</td>
<td></td>
</tr>
<tr>
<td>Nigeria</td>
<td>Pyramax</td>
<td>S – Aug 2016</td>
<td></td>
</tr>
<tr>
<td>Mali</td>
<td>Pyramax</td>
<td>S –08 Sep 2016</td>
<td></td>
</tr>
<tr>
<td>Chad</td>
<td>Pyramax</td>
<td>S – 10 Aug 2016</td>
<td></td>
</tr>
<tr>
<td>Guinea</td>
<td>Pyramax</td>
<td>S – 16 Aug 2016</td>
<td></td>
</tr>
<tr>
<td>Ivory Coast</td>
<td>Pyramax</td>
<td>S – Oct 2016</td>
<td></td>
</tr>
<tr>
<td>RCA</td>
<td>Pyramax</td>
<td>S– 05 Sep 2016</td>
<td></td>
</tr>
<tr>
<td>Burkina Faso</td>
<td>Pyramax</td>
<td>S – Oct 2016</td>
<td></td>
</tr>
</tbody>
</table>

Country submissions for repeated dose of tablets and for the paediatric granule formulation are underway.

12.2 Proposed text for the WHO Model Formulary

NAME OF THE MEDICINAL PRODUCT

Pyramax 180 mg/60 mg Film Coated Tablets
Pyramax 60 mg/20 mg Granules in sachet

**QUALITATIVE AND QUANTITATIVE COMPOSITION**

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

Each Pyramax granule sachet contains 60 mg Pyronaridine tetraphosphate and 20 mg Artesunate.

**PHARMACEUTICAL FORM**

**TABLETS:**

Film coated tablets. Round, biconvex, orange coloured tablets.

**GRANULES:**

Orange coloured, mixture of powder and granules.

**Clinical particulars**

**Therapeutic indications**

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

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

Consideration should be given to official guidance on the appropriate use of antimalarial agents.

**Posology and method of administration**

**Mode of administration**

The dose should be taken orally once a day for three days with or without food.

**Dosage in adults and children**

Pyramax tablets should be taken orally as a single daily dose for three consecutive days.
Pyronaridine tetraphosphate / artesunate tablets and granule

<table>
<thead>
<tr>
<th>Body weight</th>
<th>Number of tablets</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 - &lt; 24 kg</td>
<td>1 tablet</td>
<td>Daily for 3 days</td>
</tr>
<tr>
<td>24 - &lt; 45 kg</td>
<td>2 tablets</td>
<td>Daily for 3 days</td>
</tr>
<tr>
<td>45 - &lt; 65 kg</td>
<td>3 tablets</td>
<td>Daily for 3 days</td>
</tr>
<tr>
<td>≥ 65 kg</td>
<td>4 tablets</td>
<td>Daily for 3 days</td>
</tr>
</tbody>
</table>

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 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.

<table>
<thead>
<tr>
<th>Body weight</th>
<th>Number of granules sachets</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 - &lt; 8 kg</td>
<td>1 sachet</td>
<td>Daily for 3 days</td>
</tr>
<tr>
<td>8 - &lt; 15 kg</td>
<td>2 sachets</td>
<td>Daily for 3 days</td>
</tr>
<tr>
<td>15 - &lt; 20 kg</td>
<td>3 sachets</td>
<td>Daily for 3 days</td>
</tr>
</tbody>
</table>

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
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. 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.

**Dosage in the elderly**
Clinical studies did not include patients aged 65 years and over. No dosing adjustments would be 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 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.

**Contraindications**

- Known hypersensitivity to pyronaridine or artesunate or any component of the formulation.

- Patients with clinical signs or symptoms of hepatic injury (such as nausea and/or abdominal pain associated with jaundice) or known severe liver disease (i.e. decompensated cirrhosis, Child-Pugh stage B or C).

- Severe renal impairment

**Special warnings and precautions for use**

Pyramax tablets and granules 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). 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 should be advised of the clinical signs of hepatotoxicity in order to monitor closely if such 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, prolonged QTc 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 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 \textit{P. vivax} and \textit{P. falciparum} infections. No data are available with Pyramax in the treatment of malaria due to \textit{Plasmodium malariae} or \textit{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.

\textbf{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.

Pyronaridine shows \textit{in vitro} CYP2D6 inhibitory potential that is confirmed \textit{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 applies to flecainide and propafenone as well, two antiarrhythmics exclusively metabolised by CYP2D6.

As pyronaridine shows \textit{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.

**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**
The safety of pyronaridine tetraphosphate and artesunate when administered concurrently for use in human pregnancy has not been established and the potential risk is unknown.

A component of Pyramax is artesunate, a recognized *in vivo* embryotoxic and teratogenic compound in animal models, including primate. 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. There are no data from the use of pyronaridine in pregnant women.

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. Because of the limited safety data, artemisinin compounds should only be used in the second and third trimesters of pregnancy when other treatments are considered unsuitable.

**Pregnancy register**
A pregnancy register 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.

**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.

**Undesirable effects**

The safety of pyronaridine tetráphosphate 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 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).

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Anaemia, eosinophilia, neutropenia, increased platelet count*</td>
<td>Basophilia, leukocytosis, leukopenia, lymphocytosis, monocytosis, splenomegaly, thrombocytopenia</td>
<td>Lymphopenia, pancytopenia</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Bradycardia</td>
<td>Palpitations, ventricular extrasystoles</td>
<td>Arrhythmia, atrioventricular block first degree, sinus arrhythmia</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>Vertigo</td>
<td></td>
<td>Ear pain, hearing impaired, tinnitus</td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
<td></td>
<td>Conjunctivitis</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Abdominal Pain, Vomiting</td>
<td>Constipation, Diarrhoea, Dyspepsia, Gastritis, Nausea</td>
<td>Abdominal Tenderness, Aphthous Stomatitis, Stomatitis, Stomach Discomfort, Tongue Ulceration</td>
</tr>
<tr>
<td>General</td>
<td>Asthenia, fatigue</td>
<td></td>
<td>Chest pain, chills,</td>
</tr>
<tr>
<td>System Organ Class</td>
<td>Common</td>
<td>Uncommon</td>
<td>Rare</td>
</tr>
<tr>
<td>--------------------------------------------</td>
<td>-------------------------------------------------------------------------</td>
<td>------------------------------------------</td>
<td>-------------------------------------------</td>
</tr>
<tr>
<td>disorders and administration site conditions</td>
<td></td>
<td></td>
<td>hypothermia, pyrexia</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
<td>Hepatomegaly</td>
<td>Hepatosplenomegaly, liver tenderness</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
<td>Hypersensitivity</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Gastroenteritis, malaria, oral herpes, respiratory tract infection, tinea capitis, upper respiratory tract infection, urinary tract infection</td>
<td>Blood albumin, bronchitis, bronchopneumonia, infection parasitic, pharyngitis, pharyngotonsillitis, <em>Plasmodium falciparum</em> infection, pneumonia, rhinitis, subcutaneous abscess, tracheobronchitis</td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td>Transaminases increased (See section 4.4)</td>
<td>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</td>
<td>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</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Hypoglycaemia</td>
<td>Anorexia, hyperkalaemia</td>
<td>Decreased appetite, hyperglycaemia</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Myalgia</td>
<td></td>
<td>Arthralgia, back pain</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache, Dysgeusia</td>
<td>Dizziness, Somnolence</td>
<td></td>
</tr>
<tr>
<td>System Organ Class</td>
<td>Common</td>
<td>Uncommon</td>
<td>Rare</td>
</tr>
<tr>
<td>--------------------</td>
<td>--------------------------------</td>
<td>----------------------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Paraesthesia</td>
<td>Abortion complete</td>
</tr>
<tr>
<td>Pregnancy, puerperium and perinatal conditions</td>
<td></td>
<td>Insomnia</td>
<td>Sleep talking</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td>Haematuria, proteinuria</td>
<td>Ketonuria</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td></td>
<td>Vulvovaginal pruritus</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td></td>
<td>Cough</td>
<td>Asthma, epistaxis, haemoptysis, rhinorrhoea</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td>Hyperhidrosis, pruritus, rash</td>
<td>Blister, dermatitis, urticaria papular</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
<td>Hypertension, hypotension</td>
</tr>
</tbody>
</table>

* 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, >10x ULN with early onset peaking between Day 3 and 7 and normalising by Day 28.
Pyranmax has been administered to patients who have had repeated episodes of malaria and has been shown to be similarly well tolerated on repeat dosing as for first administration with repeat dosing intervals as short as 28 days. In Phase IIIb following repeated dosing of Pyramax, a similar pattern was observed. Where transient ALT elevations occurred, the adverse event profile was similar with repeat administration for both adults and children.

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.).

**Paediatric population**

The frequency, type and severity of adverse reactions in children over 20 kg in body weight are expected to be similar to adults. Repeat dosing did not demonstrate a significant increase in adverse events versus one-time treatment with Pyramax tablets including in liver function changes.

**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) 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.

**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.

**PHARMACOLOGICAL PROPERTIES**

**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 (ED50; 8.3 nM), followed by schizonts (ED50; 11.6 nM) then trophozoites (ED50; 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 IC50s 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 have demonstrated high activity against pyronaridine of 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 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 repeat-dose longitudinal study of 1015 patients treated with Pyramax 
tablets and granules for oral suspension, examining safety and efficacy of repeat dosing; of the 
622 patients weighing ≥ 20 kg, 188 (30%) received at least one further treatment and, of these, 
25% 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 will be 
included in a pharmacovigilance study being conducted in endemic areas.

*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*.
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 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**

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

**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 (dihydroartesunate, 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.

Shelf life
2 years
Special precautions for storage
Do not store above 30°C.
Store in the original package.

Nature and contents of container

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

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

Special precautions for disposal <and other handling>
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.

MARKETING AUTHORISATION HOLDER
Shin Poong Pharmaceutical Co., Ltd
161, Yeoksam-ro
Gangnam-gu
Seoul
South Korea
13. AVAILABILITY OF PHARMACEUTICAL STANDARDS

Artesunate standards:
- Chinese Pharmacopoeia.
- In house Standard harmonised in accordance with International Pharmacopoeia.

Pyronaridine standards:
- Chinese Pharmacopoeia.
- In house Standard.

Fixed dose combination:
- In house standard
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