Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Malarone 250 mg/100 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Malarone tablet contains 250 mg atovaquone and 100 mg proguanil hydrochloride.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film coated tablet.

Product imported from the UK
Round, bioconvex, pink tablets engraved 'GX CM3' on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Malarone is a fixed dose combination of atovaquone and proguanil hydrochloride which acts as a blood schizonticide and also has activity against hepatic schizonts of Plasmodium falciparum.

It is indicated for:

Prophylaxis of *Plasmodium falciparum* malaria.

Treatment of acute, uncomplicated *Plasmodium falciparum* malaria.

Because Malarone is effective against drug sensitive and drug resistant *P. falciparum* it is especially recommended for prophylaxis and treatment of *P. falciparum* malaria where the pathogen may be resistant to other antimalarials.

Official guidelines and local information on the prevalence of resistance to antimalarial drugs should be taken into consideration. Official guidelines will normally include WHO and public health authorities' guidelines.

4.2 Posology and method of administration

Method of administration

The daily dose should be taken with food or a milky drink (to ensure maximum absorption) at the same time each day.

If patients are unable to tolerate food, Malarone should be administered, but systemic exposure of atovaquone will be reduced. In the event of vomiting within 1 hour of dosing a repeat dose should be taken.

Posology

Prophylaxis:

Prophylaxis should

- commence 24 or 48 hours prior to entering a malaria-endemic area,
- continue during the period of the stay, **which should not exceed 28 days,**
- continue for 7 days after leaving the area.

In residents (semi-immune subjects) of endemic areas, the safety and effectiveness of Malarone has been established in studies of up to 12 weeks.

Dosage in Adults

One Malarone tablet daily.

Malarone tablets are not recommended for malaria prophylaxis in persons under 40 kg bodyweight.

Treatment

Dosage in Adults

Four Malarone tablets as a single dose for three consecutive days.

Dosage in Children

11-20 kg bodyweight. One tablet daily for three consecutive days.
21-30 kg bodyweight. Two tablets as a single dose for three consecutive days.
31-40 kg bodyweight. Three tablets as a single dose for three consecutive days.
>40 kg bodyweight. Dose as for adults.

Dosage in the Elderly

A pharmacokinetic study indicates that no dosage adjustments are needed in the elderly *(See Section 5.2).*

Dosage in Hepatic Impairment

A pharmacokinetic study indicates that no dosage adjustments are needed in patients with mild to moderate hepatic impairment. Although no studies have been conducted in patients with severe hepatic impairment, no special precautions or dosage adjustment are anticipated *(See Section 5.2).*

Dosage in Renal Impairment

Pharmacokinetic studies indicate that no dosage adjustments are needed in patients with mild to moderate renal impairment. In patients with severe renal impairment (creatinine clearance <30mL/min) alternatives to Malarone for treatment of acute *P. falciparum* malaria should be recommended whenever possible *(See Sections 4.4 and 5.2).* For prophylaxis of *P. falciparum* malaria in patients with severe renal impairment *see Section 4.3.*

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients.

Malarone is contra-indicated for prophylaxis of *P. falciparum* malaria in patients with severe renal impairment (creatinine clearance < 30mL/min).

4.4 Special warnings and precautions for use

The safety and effectiveness of Malarone (atovaquone 250 mg/proguanil hydrochloride 100 mg tablets) for prophylaxis of malaria in patients who weigh less than 40 kg has not been established.

Persons taking Malarone for prophylaxis or treatment of malaria should take a repeat dose if they vomit within 1 hour of dosing. In the event of diarrhoea, normal dosing should be continued. Absorption of atovaquone may be reduced in patients with diarrhoea or vomiting, but diarrhoea or vomiting was not associated with reduced efficacy in clinical trials of Malarone for malaria prophylaxis. However, as with other antimalarial agents, subjects with diarrhoea or vomiting should be advised to continue to comply with personal protection measures (repellants, bednets).

In patients with acute malaria who present with diarrhoea or vomiting, alternative therapy should be considered. If Malarone is used to treat malaria in these patients, parasitaemia should be closely monitored.

The safety and effectiveness of Malarone (atovaquone 250 mg/proguanil hydrochloride 100 mg tablets) for treatment of malaria in paediatric patients who weigh less than 11 kg has not been established.

Malarone has not been evaluated for the treatment of cerebral malaria or other severe manifestations of complicated malaria including hyperparasitaemia, pulmonary oedema or renal failure.

Occasionally, severe allergic reactions (including anaphylaxis) have been reported in patients taking Malarone. If patients experience an allergic reaction *(see section 4.8)* Malarone should be discontinued promptly and appropriate treatment initiated.

Parasite relapse occurred commonly when *P. vivax* malaria was treated with Malarone alone. Travellers with intense exposure to *P. vivax* or *P. ovale*, and those who develop malaria caused by either of these parasites, will require additional treatment with a drug that is active against hypnozoites.

In the event of recrudescent infections due to *P. falciparum* after treatment with Malarone, or failure of chemoprophylaxis, patients should be treated with a different blood schizonticide.
Parasitaemia should be closely monitored in patients receiving concurrent metoclopramide or tetracycline *(see section 4.5).*

The concomitant administration of Malarone and rifampicin or rifabutin is not recommended *(see section 4.5).*

In patients with severe renal impairment (creatinine clearance <30 mL/min) alternatives to Malarone for treatment of acute *P. falciparum* malaria should be recommended whenever possible *(see sections 4.2, 4.3 and 5.2).*

4.5 Interaction with other medicinal products and other forms of interaction

Proguanil may potentiate the anticoagulant effect of warfarin and other coumarin based anticoagulants. The mechanism of this potential drug interaction has not been established. Caution is advised when initiating or withdrawing malaria prophylaxis or treatment with atovaquone-proguanil in patients on continuous treatment with coumarin based anticoagulants.

Concomitant treatment with metoclopramide and tetracycline has been associated with significant decreases in plasma concentrations of atovaquone *(See Section 4.4).*

Concomitant administration of atovaquone and indinavir results in a decrease in the Cmin of indinavir (23% decrease; 90% CI 8-35%). Caution should be exercised when prescribing atovaquone with indinavir due to the decrease in the trough levels of indinavir.

Concomitant administration of rifampicin or rifabutin is known to reduce atovaquone levels by approximately 50% and 34%, respectively. *(See Section 4.4).*

Atovaquone is highly protein bound (> 99%) but does not displace other highly protein bound drugs *in vitro*, indicating significant drug interactions arising from displacement are unlikely.

4.6 Fertility, pregnancy and lactation

The safety of atovaquone and proguanil hydrochloride when administered concurrently for use in human pregnancy has not been established and the potential risk is unknown.

Animal studies showed no evidence for teratogenicity of the combination. The individual components have shown no effects on parturition or pre- and post-natal development. Maternal toxicity was seen in pregnant rabbits during a teratogenicity study *(See Section 5.3).* The use of Malarone in pregnancy should only be considered if the expected benefit to the mother outweighs any potential risk to the foetus.

The proguanil component of Malarone acts by inhibiting parasitic dihydrofolate reductase. There are no clinical data indicating that folate supplementation diminishes drug efficacy. For women of childbearing age receiving folate supplements to prevent neural tube birth defects, such supplements should be continued while taking Malarone.

Lactation

The atovaquone concentrations in milk, in a rat study, were 30% of the concurrent atovaquone concentrations in maternal plasma. It is not known whether atovaquone is excreted in human milk.

Proguanil is excreted in human milk in small quantities.

Malarone should not be taken by breast-feeding women.

4.7 Effects on ability to drive and use machines

Dizziness has been reported. Patients should be warned that if affected they should not drive, operate machinery or take part in activities where this may put themselves or others at risk.

4.8 Undesirable effects

The following table provides a summary of adverse reactions reported with Malarone, atovaquone or proguanil in clinical trials and spontaneous post-marketing reports. The following convention is used for the classification of frequency: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); not known (cannot be estimated from the available data).

In clinical trials of atovaquone-proguanil for treatment of malaria, the most commonly reported adverse events, independent of attributability, were abdominal pain, headache, anorexia, nausea, vomiting, diarrhoea and coughing, and were generally reported in a similar proportion of patients receiving atovaquone-proguanil or a comparator antimalarial drug.

In clinical trials of atovaquone-proguanil for prophylaxis of malaria, the most commonly reported adverse events, independent of attributability, were headache, abdominal pain and diarrhoea, and were reported in a similar proportion of subjects receiving atovaquone-proguanil or placebo.

System Organ Class	Very Common	Common	Uncommon	Unknown
Blood and lymphatic disorders		Anaemia[1] Neutropenia[2]		Pancytopenia in patients with severe renal impairment[4]

Immune system disorders		Allergic reactions		Angioedema[4] Anaphylaxis[3] Vasculitis[4]
Metabolism and nutrition disorders		Hyponatraemia[2] Anorexia[1]	Elevated amylase levels[2]	
Psychiatric disorders		Abnormal dreams[1] Depression[1]	Anxiety[1]	Panic attack[3] Crying[3] Hallucination[3] Nightmares[3]
Nervous system disorders	Headache[1]	Insomnia[1] Dizziness[1]		Seizure[3]
Cardiac disorders			Palpitations[1]	Tachycardia[3]
Gastrointestinal disorders	Nausea[2] Vomiting[1] Diarrhoea[1] Abdominal Pain[1]		Stomatitis[1]	Gastric intolerance[4] Oral ulceration[4]
Hepatobiliary disorders		Elevated liver enzymes[2,5]		Hepatitis[3] Cholestasis[4]
Skin and subcutaneous tissue disorders		Rash[1]	Hair loss[1] Urticaria[1]	Stevens-Johnson Syndrome[3] Erythema multiforme[3] Blister[3] Skin exfoliation[3]
General disorders and administration site conditions		Fever[1]		
Respiratory, thoracic and mediastinal disorders		Cough[1]		

1. Frequency calculated from Malarone clinical trials.
2. Frequency taken from atovaquone label. Patients participating in clinical trials with atovaquone have received higher doses and have often had complications of advance Human Immunodeficiency Virus (HIV) disease. Therefore, the causal relationship between the adverse experiences and atovaquone is difficult to evaluate. These events may have been seen at a lower frequency or not at all in clinical trials with atovaquone-proguanil.
3. Observed from post-marketing spontaneous reports and the frequency is therefore unknown.
4. Observed with proguanil and the frequency is therefore unknown.
5. Clinical trial data for atovaquone-proguanil indicated that abnormalities in liver function tests were reversible and not associated with untoward clinical events.

4.9 Overdose

No case of overdose has been reported. In cases of suspected overdosage symptomatic and supportive therapy should be given as appropriate.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: P01B B51
Pharmacotherapeutic group: antimalarials

Mode of Action

The constituents of Malarone, atovaquone and proguanil hydrochloride, interfere with two different pathways involved in the biosynthesis of pyrimidines required for nucleic acid replication. The mechanism of action of atovaquone against *P. falciparum* is via inhibition of mitochondrial electron transport, at the level of the cytochrome bc1 complex, and collapse of mitochondrial membrane potential. One mechanism of action of proguanil, via its metabolite cycloguanil, is inhibition of dihydrofolate reductase, which disrupts deoxythymidylate synthesis. Proguanil also has antimalarial activity independent of its metabolism to cycloguanil, and proguanil, but not cycloguanil, is able to potentiate the ability of atovaquone to collapse mitochondrial membrane potential in malaria parasites. This latter mechanism may explain the synergy seen when atovaquone and proguanil are used in combination.

Microbiology

Atovaquone has potent activity against *Plasmodium* spp (*in vitro* IC against *P. falciparum* 0.23-1.43ng/mL).

Atovaquone is not cross-resistant with any other antimalarial drugs in current use. Among more than 30 *P. Falciparum* isolates, *in vitro* resistance was detected against chloroquine (41% of isolates), quinine (32% of isolates), mefloquine (29% of isolates), and halofantrine (48% of isolates) but not atovaquone (0% of isolates).

The antimalarial activity of proguanil is exerted via the primary metabolite cycloguanil (*in vitro* IC against various *P. falciparum* strains of 4-20ng/mL; some activity of proguanil and another metabolite, 4-chlorophenylbiguanide, is seen *in vitro* at 600-3000ng/mL)

In *in vitro* studies of *P. falciparum* the combination of atovaquone and proguanil was shown to be synergistic. This enhanced efficacy was also demonstrated in clinical studies in both immune and non-immune patients.

5.2 Pharmacokinetic properties

There are no pharmacokinetic interactions between atovaquone and proguanil at the recommended dose. In clinical trials, where children have received Malarone dosed by bodyweight, trough levels of atovaquone, proguanil and cycloguanil in children are generally within the range observed in adults.

Absorption

Atovaquone is a highly lipophilic compound with low aqueous solubility. In HIV-infected patients, the absolute bioavailability of a 750 mg single dose of atovaquone tablets taken with food is 23% with an inter-subject variability of about 45%.

Dietary fat taken with atovaquone increases the rate and extent of absorption, increasing AUC 2-3 times and C_{max} 5 times over fasting. Patients are recommended to take Malarone tablets with food or a milky drink *(See Section 4.2).*

Proguanil hydrochloride is rapidly and extensively absorbed regardless of food intake.

Distribution

Apparent volume of distribution of atovaquone and proguanil is a function of bodyweight.

Atovaquone is highly protein bound (> 99%) but does not displace other highly protein bound drugs *in vitro*, indicating significant drug interactions arising from displacement are unlikely.

Following oral administration, the volume of distribution of atovaquone in adults and children is approximately 8.8 L/kg.

Proguanil is 75% protein bound. Following oral administration, the volume of distribution of proguanil in adults and children ranged from 20 to 42 L/kg.

In human plasma the binding of atovaquone and proguanil was unaffected by the presence of the other.

Metabolism

There is no evidence that atovaquone is metabolised and there is negligible excretion of atovaquone in urine with the parent drug being predominantly (> 90%) eliminated unchanged in faeces.

Proguanil hydrochloride is partially metabolised, primarily by the polymorphic cytochrome P450 isoenzyme 2C19, with less than 40% being excreted unchanged in the urine.

Its metabolites, cycloguanil and 4-chlorophenylbiguanide are also excreted in the urine.

During administration of Malarone at recommended doses proguanil metabolism status appears to have no implications for treatment or prophylaxis of malaria.

Elimination

The elimination half life of atovaquone is about 2-3 days in adults and 1-2 days in children.

The elimination half lives of proguanil and cycloguanil are about 12-15 hours in both adults and children.

Oral clearance for atovaquone and proguanil increases with increased bodyweight and is about 70% higher in an 80 kg subject relative to a 40 kg subject. The mean oral clearance in paediatric and adult patients weighing 10 to 80 kg ranged from 0.8 to 10.8 L/h for atovaquone and from 15 to 106 L/h for proguanil.

Pharmacokinetics in the elderly

There is no clinically significant change in the average rate or extent of absorption of atovaquone or proguanil between elderly and young patients. Systemic availability of cycloguanil is higher in the elderly compared to the young patients (AUC is increased by 140% and Cmax is increased by 80%), but there is no clinically significant change in its elimination half-life *(see Section 4.2).*

Pharmacokinetics in renal impairment

In patients with mild to moderate renal impairment, oral clearance and/or AUC data for atovaquone, proguanil and cycloguanil are within the range of values observed in patients with normal renal function.

Atovaquone Cmax and AUC are reduced by 64% and 54%, respectively, in patients with severe renal impairment.

In patients with severe renal impairment, the elimination half lives for proguanil (t½ 39 h) and cycloguanil (t½ 37h) are prolonged, resulting in the potential for drug accumulation with repeated dosing *(see Section 4.2 and 4.4).*

Pharmacokinetics in hepatic impairment

In patients with mild to moderate hepatic impairment there is no clinically significant change in exposure to atovaquone when compared to healthy patients.

In patients with mild to moderate hepatic impairment there is an 85% increase in proguanil AUC with no change in elimination half life and there is a 65-68% decrease in Cmax and AUC for cycloguanil.

No data are available in patients with severe hepatic impairment *(see section 4.2).*

5.3 Preclinical safety data

Repeat dose toxicity:

Findings in repeat dose toxicity studies with atovaquone: proguanil hydrochloride combination were entirely proguanil related and were observed at doses providing no significant margin of exposure in comparison with the expected clinical exposure. As proguanil has been used extensively and safely in the treatment and prophylaxis of malaria at doses similar to those used in the combination, these findings are considered of little relevance to the clinical situation.

Reproductive toxicity studies:

In rats and rabbits there was no evidence of teratogenicity for the combination. No data are available regarding the effects of the combination on fertility or pre- and post-natal development, but studies on the individual components of Malarone have shown no effects on these parameters. In a rabbit teratogenicity study using the combination, unexplained maternal toxicity was found at a systemic exposure similar to that observed in humans following clinical use.

Mutagenicity:

A wide range of mutagenicity tests have shown no evidence that atovaquone or proguanil have mutagenic activity as single agents.

Mutagenicity studies have not been performed with atovaquone in combination with proguanil.

Cycloguanil, the active metabolite of proguanil, was also negative in the Ames test, but was positive in the Mouse Lymphoma assay and the Mouse Micronucleus assay. These positive effects with cycloguanil (a dihydrofolate antagonist) were significantly reduced or abolished with folinic acid supplementation.

Carcinogencity:

Oncogenicity studies of atovaquone alone in mice showed an increased incidence of hepatocellular adenomas and carcinomas. No such findings were observed in rats and mutagenicity tests were negative. These findings appear to be due to the inherent susceptibility of mice to atovaquone and are considered of no relevance in the clinical situation.

Oncogenicity studies on proguanil alone showed no evidence of carcinogenicity in rats and mice.

Oncogenicity studies on proguanil in combination with atovaquone have not been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core
Poloxamer 188
Microcrystalline Cellulose
Hydroxypropyl Cellulose
Povidone K30
Sodium Starch Glycollate (Type A)
Magnesium Stearate

Coating
Hypromellose
Titanium Dioxide E 171
Iron Oxide Red E 172
Macrogol 400
Polyethylene Glycol 8000

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

The shelf-life expiry date of this product is the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC aluminium foil blister pack/s containing 12 tablets in an overlabelled outer carton.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

PCO Manufacturing
Unit 10, Ashbourne Business Park
Rath
Ashbourne
Co. Meath

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 465/255/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1st October 2010

10 DATE OF REVISION OF THE TEXT

April 2011