

# DATA SHEET

## MALARONE<sup>®</sup> TABLETS and MALARONE<sup>®</sup> JUNIOR TABLETS

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### Presentation

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MALARONE tablets are round, biconvex, pink film coated tablets, engraved on one side with "GX CM3".

Each MALARONE tablet contains atovaquone 250mg and proguanil hydrochloride 100mg. Do not halve tablet.

MALARONE JUNIOR tablets are round, biconvex, pink film coated tablets engraved on one side with "GX CG7".

Each MALARONE JUNIOR tablet contains atovaquone 62.5mg and proguanil hydrochloride 25mg. Do not halve the tablet.

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### Uses

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#### Actions

Pharmacotherapeutic Group: Antimalarials.

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 bc<sub>1</sub> 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<sub>50</sub> against *P. falciparum* 0.23-1.43ng/mL).

The antimalarial activity of proguanil is exerted via the primary metabolite cycloguanil (*in vitro* IC<sub>50</sub> 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.

### **Pharmacokinetics**

There are no pharmacokinetic interactions between atovaquone and proguanil at the recommended dose. In clinical trials, trough levels of atovaquone, proguanil and cycloguanil in children (weighing 5-40kg) are within the effective range observed in adults after adjusting for bodyweight.

**Absorption:** Atovaquone is a highly lipophilic compound with low aqueous solubility.

The pharmacokinetics of atovaquone are comparable between healthy subjects and HIV-infected patients. Although there are no atovaquone bioavailability data in healthy subjects, in HIV-infected patients the absolute bioavailability of a 750mg single dose of atovaquone tablets taken with food is 21% (90%CI: 17% - 27%).

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 Dosage and Administration).

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

**Distribution:** Apparent volume of distribution of atovaquone and proguanil is a function of body weight.

Atovaquone is highly protein bound (> 99%) but does not displace other highly protein bound medicines *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 8.8L/kg.

Proguanil is 75% protein bound. Following oral administration, the volume of distribution of proguanil in adults weighing 41 to 80kg is 42 to 27L/kg. The volume of distribution is approximately 42 to 20L/kg in children weighing 11 to 40kg, and is 79 to 45L/kg in children weighing 5 to 10kg.

In human plasma the binding of atovaquone and proguanil were 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 compound being predominantly (> 90%) eliminated unchanged in faeces.

Proguanil hydrochloride is partially metabolised 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.

Oral clearance of atovaquone and proguanil is a function of body weight.

Following oral administration, the clearance of atovaquone in adults and children weighing 41 to 80kg is approximately 0.16 to 0.05L/h/kg. The clearance is approximately 0.21 to 0.06L/h/kg in children weighing 11 to 40kg, respectively and 0.25 to 0.21L/h/kg in children weighing 5 to 10kg.

Following oral administration, the clearance of proguanil in adults weighing 41 to 80kg is 1.6 to 0.85L/h/kg. The clearance is approximately 1.5L/h/kg in children weighing 5 to 10kg.

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

**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, but there is no clinically significant change in its elimination half-life (see Dosage and Administration).

**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 increase in proguanil AUC with no change in its elimination half life and there is a decrease in C<sub>max</sub> and AUC for cycloguanil.

No data are available in patients with severe hepatic impairment. (see Dosage and Administration).

**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 C<sub>max</sub> and AUC are reduced in patients with severe renal impairment. The elimination half lives for proguanil and cycloguanil are prolonged in patients with severe renal impairment with corresponding increases in AUC, resulting in the potential of drug accumulation with

repeated dosing (see Dosage and Administration and Warnings and Precautions).

### **Indications**

MALARONE is a fixed dose combination of atovaquone and proguanil hydrochloride which acts as a blood schizonticide and also has activity against the hepatic forms of *Plasmodium falciparum*. It is indicated for:-

- Prophylaxis of *Plasmodium falciparum* malaria in adults and children.
- Treatment of *Plasmodium falciparum* malaria in adults and children.

Because MALARONE is effective against drug sensitive and drug resistant *P. falciparum* it is especially recommended for prophylaxis and treatment of *P. falciparum* malaria in areas 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.

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## **Dosage and Administration**

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The daily dose should be taken with food or a milky drink at the same time each day. Do not halve tablets.

In the event of vomiting within 1 hour of dosing a repeat dose should be taken.

MALARONE JUNIOR tablets should preferably be swallowed whole. If difficulties are encountered when dosing young children, the tablets may be crushed just before being taken and mixed with food or a milky drink.

### **Prophylaxis:**

Prophylaxis should start 1 to 2 days before entering a malaria-endemic area, and be continued daily until 7 days after leaving the area.

### **Dosage in Adults:-**

One MALARONE tablet (adult strength 250mg atovaquone/100mg proguanil) daily.

### **Dosage in Children:-**

11-20kg bodyweight	One MALARONE JUNIOR tablet (paediatric strength 62.5mg atovaquone/25mg proguanil) daily.
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21-30kg bodyweight	Two MALARONE JUNIOR tablets as a single dose daily.
31-40kg bodyweight	Three MALARONE JUNIOR tablets as a single dose daily.
> 40kg bodyweight	One MALARONE tablet (adult strength) daily.

***Treatment:***

*Dosage in Adults:-*

Four MALARONE tablets (adult strength; total daily dose 1g atovaquone/400mg proguanil hydrochloride) as a single dose for three consecutive days.

*Dosage in Children:-*

11-20kg bodyweight One MALARONE tablet (adult strength 250mg atovaquone/100mg proguanil) daily for three consecutive days.

21-30kg bodyweight	Two MALARONE tablets (adult strength) as a single dose for three consecutive days.
31-40kg bodyweight	Three MALARONE tablets (adult strength) as a single dose for three consecutive days.
> 40kg bodyweight	Four MALARONE tablets (adult strength) as a single dose for three consecutive days.

*Dosage in the Elderly (Prophylaxis and Treatment):-*

A pharmacokinetic study indicates that no dosage adjustments are needed in the elderly (see Pharmacokinetics).

*Dosage in Hepatic Impairment (Prophylaxis and Treatment):-*

A pharmacokinetic study indicates that no dosage adjustments are needed in patients with mild to moderate hepatic impairment. No studies have been conducted in patients with severe hepatic impairment (see Pharmacokinetics).

*Dosage in Renal Impairment (Prophylaxis and Treatment):-*

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 should be recommended for treatment of acute *P. falciparum* malaria whenever possible (see Warnings and Precautions and Pharmacokinetics). For prophylaxis of *P. falciparum* malaria in patients with severe renal impairment see Contraindications.

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## Contraindications

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MALARONE is contraindicated in individuals with known hypersensitivity to atovaquone or proguanil hydrochloride or any component of the formulation.

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

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## Warnings and Precautions

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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.

Safety and effectiveness of MALARONE for the treatment of malaria in paediatric patients who weigh less than 5kg, and prophylaxis of malaria in paediatric patients who weigh less than 11kg has not been established.

In the event of recrudescence of infections due to *P. falciparum* or failure of chemoprophylaxis, patients should be treated with a different blood schizonticide.

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 medicine such as primaquine, that is active against hypnozoites.

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, patients 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.

Parasitaemia should be closely monitored in patients receiving concurrent metoclopramide or tetracycline (see Interactions).

The concomitant administration of MALARONE and rifampicin or rifabutin is not recommended (see Interactions).

In patients with severe renal impairment (creatinine clearance < 30mL/min) alternatives to MALARONE should be recommended for treatment of acute *P.*

*falciparum* malaria whenever possible (see Dosage and Administration, Contraindications and Pharmacokinetics).

### ***Pregnancy and Lactation***

**Pregnancy:** The safety of atovaquone and proguanil hydrochloride when administered concurrently for use in human pregnancy has not been established.

Reproductive toxicity studies in animals did not indicate any teratogenic potential at dosages of atovaquone:proguanil hydrochloride of up to 50:20mg/kg/day in the rat or 100:40mg/kg/day in the rabbit. In rabbits given atovaquone alone at dosages up to 1200mg/kg/day, an increased incidence of resorptions and decreased length and weight of foetuses was noted. These effects were likely to be secondary to toxicity of atovaquone in maternal animals.

However, as animal studies are not always predictive of human response the use of MALARONE in pregnancy should only be considered if the expected benefit to the mother outweighs the 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 may 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.

It is not recommended that mothers receiving MALARONE breast feed their babies.

### ***Effects on Ability to Drive and Use Machines***

There have been no studies to investigate the effect of MALARONE on driving performance or the ability to operate machinery but a detrimental effect on such activities is not predicted from the pharmacology of the component medicines.

### ***Other***

#### ***Preclinical Safety Data***

**Repeat dose toxicity:** Findings in repeat dose studies with the atovaquone:proguanil hydrochloride combination were entirely proguanil related. As proguanil has been used extensively and safely in the treatment and prophylaxis of malaria at doses similar to those used in MALARONE, these findings are considered of little relevance in the clinical situation.

**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 folic acid supplementation.

**Carcinogenicity:** 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.

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## Adverse Effects

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Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common ( $\geq 1/10$ ), common ( $\geq 1/100$  and  $< 1/10$ ), uncommon ( $\geq 1/1000$  and  $< 1/100$ ), rare ( $\geq 1/10,000$  and  $< 1/1000$ ) and very rare ( $< 1/10,000$ ). Very common, common and uncommon events were determined from clinical trial data. Rare and very rare events were generally derived from spontaneous data. The frequency classification "Not known" has been applied to those events where a frequency could not be estimated from the available data.

MALARONE contains atovaquone and proguanil hydrochloride, therefore, the adverse effects associated with each of these compounds may be expected with MALARONE. At the doses employed for both treatment and prophylaxis of malaria, adverse events are generally mild and of limited duration. There is no evidence of added toxicity following concurrent administration of atovaquone and proguanil.

A summary of adverse events associated with the use of MALARONE, atovaquone or proguanil hydrochloride is provided below:

### *Blood and Lymphatic system disorders*

<i>Common:</i>	Anaemia <sup>1</sup> , neutropenia <sup>2</sup>
<i>Not known:</i>	Pancytopenia in patients with severe renal impairment <sup>4</sup>



### *Immune system disorders*

*Not known:* Angioedema<sup>4</sup>, anaphylaxis<sup>3</sup>, vasculitis<sup>4</sup>

### *Metabolism and nutritional disorders*

*Common:* Hyponatraemia<sup>2</sup>, anorexia<sup>1</sup>

*Uncommon:* Elevated amylase levels<sup>2</sup>

### *Psychiatric disorders*

*Rare:* Hallucinations<sup>1</sup>

### *Nervous system disorders*

*Very common:* Headache<sup>1</sup>

*Common:* Insomnia<sup>1</sup>, dizziness<sup>1</sup>

### *Gastrointestinal disorders*

*Very common:* Abdominal pain<sup>1</sup>, nausea<sup>2</sup>, vomiting<sup>1</sup>, diarrhoea<sup>1</sup>

*Uncommon:* Stomatitis<sup>1</sup>

*Not known:* Gastric intolerance<sup>4</sup>, oral ulceration<sup>4</sup>

### *Hepatobiliary disorders*

*Common:* Elevated liver enzyme levels<sup>2</sup>

*Not known:* Hepatitis<sup>3</sup>, Cholestasis<sup>4</sup>

Clinical trial data for Malarone indicated that abnormalities in liver function tests were reversible and not associated with untoward clinical events.

### *Skin and subcutaneous tissue disorders*

*Common:* Rash<sup>1</sup>

*Uncommon:* Hair loss<sup>1</sup>, urticaria<sup>1</sup>

*Not Known:* Stevens-Johnson syndrome<sup>3</sup>, erythema multiforme<sup>3</sup>

### *General disorders and administration site conditions*

*Common:* Fever<sup>1</sup>

### *Respiratory, thoracic and mediastinal disorders*

*Common:* Cough<sup>1</sup>

1. Frequency calculated from atovaquone-proguanil 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 advanced 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 Not known.
4. Observed with proguanil and the frequency is therefore Not known.

In clinical trials of MALARONE 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 MALARONE or placebo.

In clinical trials of MALARONE 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 MALARONE or a comparator antimalarial medicine.

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## Interactions

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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 Malarone in patients on continuous treatment with coumarin based anticoagulants.

Concomitant treatment with tetracycline, metoclopramide, rifampicin and rifabutin have been associated with significant decreases in plasma concentrations of atovaquone. (see Warnings and Precautions).

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

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

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## Overdosage

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In cases of suspected overdosage, symptomatic and supportive therapy should be given as appropriate.

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## Pharmaceutical Precautions

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### *Incompatibilities*

None known.

### *Shelf Life*

5 years.

### *Special Precautions for Storage*

Store below 30°C.

### *Instructions for Use/Handling*

None.

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## Medicines Classification

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Prescription Medicine

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## Package Quantities

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PVC aluminium foil blister packs or PVC-aluminium/paper child-resistant foil blister packs containing 12 tablets.

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## Further Information

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### *List of Excipients*

**Core:** Poloxamer 188, Microcrystalline Cellulose, Low-substituted Hydroxypropyl Cellulose, Povidone K30, Sodium Starch Glycollate, Magnesium Stearate.

**Coating:** Hypromellose, Titanium Dioxide, Iron Oxide Red E172, Macrogol 400, Macrogol 8000.

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## Name and Address

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GlaxoSmithKline NZ Limited  
Private Bag 1006600  
Downtown Auckland  
NEW ZEALAND

Phone (09) 367 2900  
Fax: (09) 367 2910

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## **Date of Preparation**

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8 April 2016

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