AUSTRALIAN PRODUCT INFORMATION

MALARONE TABLETS (250/100) and MALARONE JUNIOR TABLETS (62.5/25) (atovaquone and proguanil hydrochloride) tablets

1 NAME OF THE MEDICINE

Atovaquone and proguanil hydrochloride

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

MALARONE TABLETS (250/100) and MALARONE JUNIOR TABLETS (62.5/25) are fixed combination products containing atovaquone and proguanil hydrochloride. Each MALARONE TABLETS (250/100) contains atovaquone 250 mg and proguanil hydrochloride 100 mg. Each MALARONE JUNIOR TABLETS (62.5/25) contains atovaquone 62.5 mg and proguanil hydrochloride 25 mg.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

MALARONE TABLETS (250/100): Round, biconvex, pink film-coated tablets, branded “GX CM3”. Each tablet contains the active ingredients atovaquone 250 mg and proguanil hydrochloride 100 mg.

MALARONE JUNIOR TABLETS (62.5/25): Round, biconvex, pink film-coated tablets, branded “GX CG7”. Each tablet contains the active ingredients atovaquone 62.5 mg and proguanil hydrochloride 25 mg.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

MALARONE is indicated for:

- Prophylaxis of *Plasmodium falciparum* malaria in adults and children ≥ 11 kg.
- Treatment of *Plasmodium falciparum* malaria in adults and children aged 3 years or older.

4.2 DOSE AND METHOD OF ADMINISTRATION

The daily dose should be taken with food or a milky drink at the same time each day.

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

MALARONE (250/100) or MALARONE JUNIOR TABLETS (62.5/25) should preferably be swallowed whole. If difficulties are encountered when dosing young children, the tablet(s)

may be crushed and added to a small amount of milk, all of which should be consumed immediately.

Prophylaxis:

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

If patients are unable to tolerate food, MALARONE TABLETS should be administered, but systemic exposure of atovaquone will be reduced.

Dosage in Adults:

One MALARONE TABLET (250/100) daily.

Dosage in Children:

Body weight (kg)	Single daily dosage
11-20	1 MALARONE JUNIOR TABLET (62.5/25)
21-30	2 MALARONE JUNIOR TABLETS (62.5/25)
31-40	3 MALARONE JUNIOR TABLETS (62.5/25)
>40	1 MALARONE TABLETS (250/100)

Treatment:

Dosage in Adults:

Four tablets as a single dose for three consecutive days.

Dosage in Children:

Body weight (kg)	Single dosage for 3 consecutive days
11-20	1 MALARONE TABLETS (250/100)
21-30	2 MALARONE TABLETS (250/100)
31-40	3 MALARONE TABLETS (250/100)
>40	4 MALARONE TABLETS (250/100)

Dosage in the Elderly (Prophylaxis and Treatment):

A pharmacokinetic study indicates that no dosage adjustments are needed in the elderly (see Section 5.2 PHARMACOKINETIC PROPERTIES).

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 Section 5.2 PHARMACOKINETIC PROPERTIES).

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 < 30 mL/min) alternatives to MALARONE should be recommended for the treatment of acute *P. falciparum* malaria whenever possible (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 5.2 PHARMACOKINETIC PROPERTIES). For prophylaxis of *P. falciparum* malaria in patients with severe renal impairment see Section 4.3 CONTRAINDICATIONS.

4.3 CONTRAINDICATIONS

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

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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 efficacy of MALARONE for the treatment and prophylaxis of malaria in paediatric patients who weigh less than 11 kg have not been established.

In the event of recrudescent 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 drug 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.

The co-administration of MALARONE with other antimalarial drugs has not been evaluated.

Parasitaemia should be closely monitored in patients receiving concurrent metoclopramide or tetracycline (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

The concomitant administration of MALARONE and rifampicin or rifabutin is not recommended (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS**)**.

Use in hepatic impairment

Pharmacokinetic studies indicate that no dosage adjustments are needed in patients with mild to moderate hepatic impairment. MALARONE has not been specifically studied in patients with severe hepatic impairment.

Use 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 < 30 mL/min) alternatives to MALARONE for treatment of acute *P. falciparum* malaria should be recommended whenever possible (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION, Section 4.3 CONTRAINDICATIONS and Section 5.2 PHARMACOKINETIC PROPERTIES).

Use in the elderly

Pharmacokinetic studies indicate that no dosage adjustments are needed in the elderly.

Paediatric use

Dosage recommendations in children are based on body weight (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Effects on laboratory tests

No data available

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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 concentration of atovaquone (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Concomitant administration of tetracycline and MALARONE reduced the plasma concentrations of atovaquone but had no effect on the efficacy of MALARONE in curing *Plasmodium falciparum* malaria.

Concomitant administration of atovaquone and indinavir results in a 23% decrease in the C_{min} of indinavir in healthy individuals. Caution should be exercised when prescribing atovaquone with indinavir due to the decrease in trough levels of indinavir.

In clinical studies of atovaquone in the treatment of diseases other than malaria, small decreases in plasma concentrations were associated with concomitant use of paracetamol, benzodiazepines, aciclovir, opiates, cephalosporins, antidiarrhoeal agents and laxatives. The implications of these observations for use with MALARONE are not known. In the same series of studies, the following medications were not associated with a change in steady state plasma concentrations of atovaquone: fluconazole, clotrimazole, ketoconazole, antacids, systemic corticosteroids, non-steroidal anti-inflammatory drugs, anti-emetic drugs (excluding metoclopramide) and H_2-antagonists.

There is no information available on whether interactions occur between atovaquone and terfenadine or cisapride.

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

Coadministration of efavirenz with MALARONE may result in a decrease in exposure to atovaquone and proguanil. When given with efavirenz or boosted protease-inhibitors, atovaquone concentrations have been observed to decrease as much as 75%. Since decreased concentrations of atovaquone and proguanil may result in a decrease of antimalarial efficacy, concomitant administration should be avoided whenever possible.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There are no data on the effect of atovaquone on human fertility. Data from animal studies show that atovaquone does not affect reproductive potential or performance at oral doses of up to 1000 mg/kg (approximately 6.5 times human exposure at the maximum recommended clinical treatment dose, based on AUC). A study in rats showed no impairment of male or female fertility at oral proguanil doses up to 16 mg/kg/day (approximately 0.03 times human exposure at the recommended clinical treatment dose, based on AUC). However, there is some evidence from published animal studies that proguanil and/or its main metabolite, cycloguanil, may cause impairment of fertility/early embryonic loss. No fertility studies have been performed in animals with atovaquone in combination with proguanil.

Findings in repeat dose studies with the atovaquone and 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.

Use in pregnancy

(Pregnancy Category B2)

The safety of the drug combination in human pregnancy has not been established. There is no information on effects of atovaquone administration during human pregnancy. Foetal death and malformation have rarely been reported in association with the use of proguanil. The relationship of these events to proguanil is not certain, and the overall number of reported events is low, given that the drug has been used in pregnant women for many years. Foetal loss is a known complication of *Plasmodium falciparum* malaria in pregnancy.

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.

Embryofoetal development studies in animals with the combination of atovaquone and proguanil did not indicate any teratogenic potential in rats at doses up to 50:20 mg/kg/day (approximately 5 times the human exposure to atovaquone and 0.3 times human exposure to proguanil, based on treatment AUCs), nor in rabbits at doses up to 100:40 mg/kg/day (approximately 1 times the human exposure to atovaquone and 0.5 times the exposure to proguanil, based on treatment AUCs). In rabbits given atovaquone alone at 1200 mg/kg/day (approximately 1.4 times the estimated human exposure during treatment of malaria), an increased incidence of resorptions and decreased length and weight of foetuses was noted. These effects were observed only in the presence of maternal toxicity.

In a peri-postnatal study in rats dosed with proguanil alone up to 16 mg/kg/day (0.03 times the human exposure, based on treatment AUC), no treatment-related effects were seen in reproductive or other parameters in the F0, F1 and F2 generations.

However, as animal studies are not always predictive of human response, the use of atovaquone-proguanil in pregnancy should only be considered if the expected benefit to the mother outweighs the risk to the foetus.

Use in lactation

It is not known whether atovaquone is excreted into human milk. In a rat study, the atovaquone concentrations in milk were 30% of the concurrent atovaquone concentrations in maternal plasma. Proguanil is excreted in human milk in small quantities. Breast feeding is not recommended during treatment with MALARONE.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

There have been no studies to investigate the effect of atovaquone and proguanil hydrochloride on driving performance or the ability to operate machinery. Detrimental effect on such activities is not predicted from the pharmacology of the component drugs.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

As MALARONE contains atovaquone and proguanil hydrochloride, the type and severity of adverse reactions associated with each of the compounds may be expected. However, at the doses employed for both treatment and prophylaxis of malaria, adverse reactions are generally mild and of limited duration. There is no evidence of added toxicity following concurrent administration of the two compounds.

Prophylaxis:

Individuals > 40 kg:

The nature and frequency of adverse reactions reported in clinical trials of MALARONE (atovaquone and proguanil hydrochloride) for the prophylaxis of malaria in individuals weighing > 40 kg were similar to those reported with placebo or the active comparator drug (mefloquine or chloroquine/proguanil). However, patients receiving MALARONE had fewer

neuropsychiatric and gastrointestinal adverse reactions than patients receiving mefloquine and chloroquine/proguanil respectively. Overall, MALARONE has a better safety profile than mefloquine or chloroquine/proguanil (see Tables 1 and 2).

Table 1: Drug-Related Adverse Reactions, Occurring in ≥1% of Patients Taking MALARONE TABLETS (250/100) in Placebo Controlled Studies.

Adverse Event	MALARONE (n=232)	Placebo (n=241)
Gastrointestinal		
Diarrhoea	2% (4)	4% (9)
Dyspepsia	2% (4)	4% (9)
Gastritis	3% (6)	2% (5)
Vomiting	1% (3)	<1% (1)
Abdominal Pain	7% (16)	9% (21)
Cutaneous		
Pruritus	1% (3)	<1% (2)
Nervous/psychiatric		
Headache	6% (13)	9% (22)

Table 2: Drug-Related Adverse Reactions*, Occurring in ≥1% of Patients Taking MALARONE TABLETS (250/100) in Active-Controlled Studies.

	MALB30010		MALB30011	
Adverse Event	**MALARONE (n = 482)**	**MFQ (n =471)**	**MALARONE (n=511)**	**C + P (n = 511)**
Gastrointestinal				
Diarrhoea	7% (36)	7% (35)	5% (24)	7% (37)
Nausea	3% (15)	9% (42)	2% (9)	7% (34)
Vomiting	1% (7)	2% (9)	0	2% (11)
Abdominal Pain	5% (26)	5% (23)	3% (15)	6% (30)
Oral Ulceration	6% (28)	4% (17)	4% (18)	5% (25)
Cutaneous				
Pruritus	1% (7)	2% (11)	1% (6)	<1% (5)
Hair Loss	1% (5)	0	<1% (4)	1% (6)
Nervous/psychiatric				
Headache	4% (19)	7% (34)	4% (21)	4% (19)
Dreams	7% (32)	14% (66)	4% (19)	3% (14)
Insomnia	3% (15)	14% (65)	2% (8)	2% (12)
Dizziness	2% (10)	9% (43)	3% (17)	4% (19)
Visual difficulties	2% (8)	3% (16)	2% (10)	2% (10)

MFQ = mefloquine, C = chloroquine, P = proguanil hydrochloride

* The duration of dosing for MALARONE (1-2 days before until 7 days after travel) is shorter than for mefloquine (2-3 weeks before until 4 weeks after travel) or chloroquine (1 week before until 4 weeks after travel). Adverse reaction data is therefore presented for only the period the patient was receiving active treatment.

Individuals 11-40 kg:

The incidence of adverse reactions reported in clinical trials using MALARONE JUNIOR TABLETS (62.5/25) for the prophylaxis of malaria in individuals weighing 11-40 kg were

similar to those reported with placebo (MALB3003 & MAL30015). In studies MAL30010 and MAL30012, the incidence of drug-related adverse events was higher in the chloroquine/proguanil group (15% vs 11% for MALARONE) during active treatment. Due to the low number of patients in study MAL30010 (n=12), no drug-related adverse events were reported by the mefloquine recipients. Tables 3 & 4 list the common drug-related adverse reactions reported during chemoprophylaxis by treatment group.

Table 3: Drug-Related Adverse Reactions, Occurring in ≥1% of Patients Taking MALARONE JUNIOR TABLETS (62.5/25) in Placebo Controlled Studies.

Adverse Event	MALARONE n=264	Placebo n=270
Body as a Whole		
Abdominal pain	12% (32)	11% (30)
Headache	4% (10)	4% (11)
Gastrointestinal		
Vomiting	3% (7)	3% (8)

Table 4: Drug-Related Adverse Reactions*, Occurring in ≥1% of Patients Taking MALARONE JUNIOR TABLETS (62.5/25) in Active-Controlled Studies.

Adverse Event	MALARONE n=93	C + P n=81
Gastrointestinal		
Diarrhoea	4% (4)	4% (3)
Abdominal pain	0	9% (7)
Oral ulceration	2% (2)	2% (2)
Vomiting	1% (1)	6% (5)
Nausea	0	9% (7)
Decreased appetite	1% (1)	0
Nervous		
Dreams	3% (3)	0
Dizziness	1% (1)	1% (1)
Body as a Whole		
Lethargy	2% (2)	0
Fever	1% (1)	1% (1)
Skin and Appendages		
Pruritus	2% (2)	1% (1)
Special Senses		
Visual impairment	0	2% (2)
Respiratory		
Cough	1% (1)	0

C = chloroquine, P = proguanil hydrochloride

* Adverse reaction data is presented for only the period the patient was receiving active treatment.

Treatment:

The nature and frequency of adverse experiences reported in controlled clinical trials of atovaquone and proguanil hydrochloride for the treatment of malaria were generally similar in patients treated with the combination or with a comparator antimalarial drug. This suggests that the adverse experiences are largely due to the disease rather than to study drugs (see Table 5).

Table 5: Adverse Events Considered by Investigators to be Attributable to Study Medication, Occurring in ≥1% of Adults with Malaria in Completed Phase III Studies

Adverse Event	MALARONE (n = 304)	PYR + S (n = 81)	MFQ (n = 91)	ADQ (n = 71)	C±PYR+S* (n = 55)
Gastrointestinal					
Abdominal Pain	15% (45)	21% (17)	0%	8% (6)	0%
Vomiting	12% (35)	15% (12)	0%	25% (18)	2% (1)
Nausea	11% (32)	14% (11)	2% (2)	21% (15)	2% (1)
Diarrhoea	8% (25)	11% (9)	0%	7% (5)	2% (1)
Anorexia	5% (15)	5% (4)	1% (1)	13% (9)	2% (1)
Hepatomegaly	2% (6)	6% (5)	0%	0%	0%
Constipation	1% (2)	0%	0%	0%	0%
Dyspepsia	1% (2)	0%	0%	0%	0%
Nervous/Psychiatric					
Headache	8% (25)	31% (25)	1% (1)	7% (5)	0%
Dizziness	3% (8)	11% (9)	0%	11% (8)	2% (1)
Insomnia	1% (3)	4% (3)	0%	25% (18)	0%
Body as a Whole					
Asthenia	7% (20)	16% (13)	0%	3% (2)	0%
Back **Pain**	1% (2)	4% (3)	0%	0%	0%
Abnormal liver function tests					
ALT	6% (18)	6% (5)	7% (6)	0%	0%
AST	5% (16)	5% (4)	7% (6)	0%	0%
Bilirubin	2% (7)	0%	1% (1)	0%	0%
Cardiovascular					
Hypotension, postural	2% (6)	17% (14)	0%	0%	0%
Palpitations	2% (5)	0%	0%	6% (4)	0%
Cutaneous					
Pruritus	2% (6)	2% (2)	0%	46% (33)	0%
Rash	1% (2)	0%	0%	0%	0%
Musculoskeletal					
Myalgia	3% (8)	6% (5)	0%	4% (3)	0%
Erythropoietic					
Splenomegaly	1% (4)	2% (2)	0%	0%	0%
Respiratory					
Coughing	1% (3)	0%	0%	2% (2)	0%

PYR = pyrimethamine, S = sulfadoxine, MFQ = mefloquine, ADQ = amodiaquine, C = chloroquine,
* Data for both comparator groups of chloroquine alone plus pyrimethamine and sulfadoxine.

A similar profile of clinical adverse events was reported in children with malaria treated with atovaquone and proguanil hydrochloride in phase III trials as occurred in the adult studies. Regardless of attributability, the following were also commonly reported (> 2%) in children: dehydration, tinnitus and anorexia.

Of the seven severe or treatment limiting adverse experiences reported in clinical trials with atovaquone and proguanil hydrochloride, three were considered to be treatment related; two were reports of nausea and/or vomiting and one report of an anaphylactic reaction. During clinical trials, two subjects receiving atovaquone monotherapy experienced psychiatric symptoms. One subject had a history of psychiatric illness and the other a history of drug

and alcohol abuse. Two subjects receiving atovaquone/proguanil hydrochloride had seizures; in one of these cases the patient successfully continued treatment. Both subjects had a prior history of seizures and the investigators did not consider the events attributable to the MALARONE treatment.

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1000 and <1/100), rare (≥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.

A summary of adverse events identified during world-wide post-approval use of MALARONE or its components, atovaquone and proguanil hydrochloride is provided below.

Blood and Lymphatic system disorders

Common: Anaemia[1], neutropenia[2]

Not known: Pancytopenia in patients with severe renal impairment[4]

Immune system disorders

Not known: Angioedema[4], anaphylaxis[3], vasculitis

Metabolism and nutritional disorders

Common: Anorexia[1], Hyponatraemia[2]

Uncommon: Elevated amylase levels[2] occurred in patients treated with atovaquone

Psychiatric disorders

Rare: Hallucinations[1]

Nervous system disorders

Very common: Headache[1]

Common: Insomnia[1], dizziness[1]

Gastrointestinal disorders

Very common: Abdominal pain[1], nausea[2], vomiting[1], diarrhoea[1]

Uncommon: Stomatitis[1]

Not known: Gastric intolerance[4], oral ulceration[4]

Hepatobiliary disorders

Common: Elevated liver enzyme levels[2]

Not known:	Hepatitis[3], Cholestasis
	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[1]
Uncommon:	Hair loss[1], urticaria[1]
Not Known:	Stevens-Johnson syndrome[3], erythema multiforme[3]

General disorders and administration site conditions

Common:	Fever[1]

Respiratory, thoracic and mediastinal disorders

Common:	Cough[1]

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 advance Human Immunodefficiency Virus (HIV) disease. Therefore, the casual 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. Oberserved from post-marketing spontaneous reports and the frequency is therefore Not known.
4. Observed with proguanil and the frequency is therefore not known.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

The constituents of MALARONE, atovaquone and proguanil hydrochloride, interfere with two different pathways 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_1 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, as in MALARONE.

Microbiology

Atovaquone is active against *Plasmodium spp* (*in vitro* IC_{50} against *P. falciparum* 0.23-1.43 ng/mL).

The antimalarial activity of proguanil is exerted via the primary metabolite cycloguanil (*in vitro* IC_{50} against various *P. falciparum* strains of 4-20 ng/mL). Some activity of proguanil and another metabolite, 4-chlorophenylbiguanide, is seen *in vitro* at 0.6-3.0 µg/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.

Clinical trials

The safety and effectiveness of MALARONE TABLETS (250/100) and MALARONE JUNIOR TABLETS (62.5/25) have been established in studies of up to 12 weeks in adult and paediatric subjects.

Prophylaxis of Malaria (individuals > 40 kg): The safety and efficacy of MALARONE TABLETS (250/100) in the prophylaxis of *P. falciparum* malaria was demonstrated in five randomised, double-blind clinical studies. Three placebo-controlled parallel group studies were conducted in residents of malaria-endemic areas (MALB2001, MALB3001 and MALB3003), and two active-controlled studies were conducted in non-immune travellers (MALB30010 and MALB30011).

There were 473 patients in placebo-controlled studies, 232 of whom received one MALARONE TABLETS (250/100) daily for 10-12 weeks of chemoprophylaxis, and 241 received placebo. Prevention of parasitaemia was the primary endpoint in the studies. MALARONE had an overall efficacy of 97% (range 95-100%) for prevention of *P. falciparum* parasitaemia and an adverse event profile similar to placebo.

MALB3003 included 204 children (weighing 11-40 kg) who received a lower dose of MALARONE or placebo based on body weight (see Prophylaxis of Malaria (individuals 11-40 kg)

There were 1975 patients in active controlled studies, 993 of whom received one MALARONE TABLETS (250/100) daily at the recommended dose (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION), 471 received mefloquine weekly (1 to 3 weeks

before until 4 weeks after travel) and 511 patients received chloroquine weekly (1 week before until 4 weeks after travel) plus daily proguanil (1-2 days before until 4 weeks after travel). Frequency of adverse events was the primary endpoint and development of confirmed falciparum malaria within 60 days after leaving the malaria-endemic area was the secondary endpoint in the studies. No patients receiving MALARONE or mefloquine contracted malaria (efficacy 100%), and 3 patients receiving chloroquine/proguanil contracted malaria (efficacy at least 70%). Patients receiving MALARONE experienced fewer neuropsychiatric and gastrointestinal adverse reactions than patients receiving mefloquine and chloroquine/proguanil respectively.

Prophylaxis of Malaria (individuals 11-40 kg): The efficacy and safety MALARONE JUNIOR TABLETS (62.5/25) in the prophylaxis of *P. falciparum* malaria in patients weighing 11-40 kg was demonstrated in two randomised, placebo-controlled, double blind studies of 12 week duration conducted in residents of malaria endemic areas. A total of 534 patients (11-40 kg) were enrolled in the studies, of which 264 received the recommended dose of MALARONE JUNIOR TABLETS (62.5/25) based on body weight; 11-20 kg - 1 Junior tablet containing 62.5 mg atovaquone + 25 mg proguanil hydrochloride; 21-30 kg - 2 Junior tablets; 31-40 kg - 3 Junior tablets (MALB3003 and MAL30015).

In the combined data from the two studies (per-protocol population), only one of 238 patients (0.4%) in the MALARONE group developed *P. falciparum* parasitaemia during chemoprophylaxis over 12 weeks, compared with 50 of 245 (20.4%) patients in the placebo group. The protective efficacy of MALARONE was calculated to be 97.9% in this population. The safety findings with regard to adverse events during chemosuppression showed no differences between MALARONE and placebo.

The safety profile of MALARONE was assessed in two active controlled studies in travelers to malaria endemic areas (Studies MAL30010 - mefloquine and MAL30012 - chloroquine/ proguanil) (See Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). With respect to efficacy, in combined data from the two active-controlled studies (n=186; 93 in the MALARONE group), there was no confirmed cases of *P. falciparum* during chemoprophylaxis or in follow-up to Day 60.

Treatment of Malaria: Eight clinical studies (5 controlled and 3 uncontrolled) were conducted in 1115 patients of atovaquone and/or proguanil hydrochloride administered for the treatment of falciparum malaria. Studies in children were conducted at doses of atovaquone and proguanil hydrochloride based on body weight; 466 patients (adults and children) received concurrent atovaquone and proguanil hydrochloride at the recommended dose (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

The primary efficacy endpoint was the proportion of evaluable patients cured of acute malaria. Cure was defined by clearance of asexual parasitaemia within 7 days of initiation of treatment, without subsequent recrudescence during the 28 day follow-up period.

In the controlled clinical trials, the study population included only patients with uncomplicated falciparum malaria. The comparator was standard antimalarial therapy within the country in which the study was conducted. Treatment with combination of atovaquone and proguanil hydrochloride was curative in 98% of evaluable patients (combined result). The concurrent administration of atovaquone and proguanil hydrochloride was more efficacious in three

studies and of equivalent efficacy in two trials as the respective comparator antimalarial regimen (Table 6).

Table 6. Summary of Controlled Clinical Studies

			Evaluable Patients		Cure Rate (%)	
Country	Age Range (years)	Comparator	ATOV and PROG	Comparator	ATOV and PROG	Comparator
Zambia	14-54	Pyrimethamine and Sulphadoxine	80	80	100	99
Thailand	15-63	Mefloquine Hydrochloride	79	79	100***	86
Gabon	15-80	Amodiaquine Hydrochloride	63	63	98**	81
Philippines	12-64	Chloroquine[+], Pyrimethamine and Sulphadoxine	54	32	100*	88
Kenya	3-12	Halofantrine	81	83	94	90

ATOV - Atovaquone; PROG - Proguanil hydrochloride.
* p<0.05, **p<0.005, ***p<0.002 versus comparator.
[+] Initially as monotherapy, followed by combination therapy.

In uncontrolled studies conducted in Thailand using the recommended dose of atovaquone and proguanil hydrochloride, the cure rate of malaria was 100% in adults (n=24, *P. falciparum*) and 100% in children (n=26, *P. falciparum*).

5.2 PHARMACOKINETIC PROPERTIES

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 11-40 kg) are within the effective range observed in adults after adjusting for bodyweight.

Absorption

Atovaquone is a highly lipophilic compound with low aqueous solubility and poor oral bioavailability that varies with dose and diet.

Although there are no atovaquone bioavailability data in healthy subjects, in HIV-infected patients the absolute bioavailability of a 750 mg 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. When taken with a standard breakfast containing 23 g of fat, AUC was increased 2-3 times and C_{max} 5 times compared with fasting. Patients are recommended to take MALARONE TABLETS with food or a milky drink (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Proguanil hydrochloride is rapidly and extensively absorbed regardless of food intake. Peak plasma concentrations occur between 2-4 hours after a single 200 mg dose. The absolute bioavailability is not known.

In a comparative bioavailability study in healthy adult volunteers, MALARONE administered as a single dose was bioequivalent to separate tablets of atovaquone 250 mg and proguanil hydrochloride 100 mg given concomitantly. In healthy adult subjects treated for 3 days, the pharmacokinetics of atovaquone, and proguanil and its metabolite cycloguanil, were not modified when atovaquone and proguanil were given alone or in combination as MALARONE.

Distribution

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 7 to 8 L/Kg.

Proguanil is 75% protein bound. Following oral administration, the volume of distribution of proguanil in adults is 25 L/Kg. In children (weighing 11 - 40 kg), the volume of distribution is approximately 27 to 30 L/Kg.

In human plasma, the protein binding of atovaquone or proguanil was unaffected by the presence of the other drug.

Metabolism

There is no evidence that atovaquone is metabolised. Greater than 90% of atovaquone is eliminated unchanged in the faeces with negligible excretion in urine.

Proguanil hydrochloride is partially metabolised to cycloguanil and 4-chlorophenyl biguanide with less than 40% being excreted unchanged in urine. These metabolites are also excreted in the urine. Conversion of proguanil to cycloguanil is mediated in the liver by cytochrome P450 3A4 and 2C19. Conversion of proguanil to cycloguanil may be reduced in some individuals, due to genetic polymorphism of the metabolising enzyme. During administration with MALARONE, at the recommended doses, proguanil metabolism status appears to have no implications for treatment or prophylaxis of malaria.

Excretion

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

Following oral administration, the clearance of atovaquone in adults and children (weighing 40 kg) is approximately 0.04 to 0.05 L/h/Kg. In children (weighing 11 - 40 kg), the clearance is approximately 0.12 to 0.05 L/h/Kg, respectively.

Following oral administration, the clearance of proguanil in adults is 1.3 L/h/Kg. In children (11-40 kg body-weight) after adjusting for differences in body-weight, clearance is higher in an 11 kg child (0.12 L/h/kg) and decreases with increasing weight to 0.05 L/h/kg in a 40 kg child.

In both adults and children, the elimination half life for proguanil or cycloguanil is about 12-15 hours.

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 cyloguanil is higher in the elderly compared with young patients, but there is no clinically significant change in its elimination half-life (see Section 4.2 DOSE AND METHOD OF 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_{max} 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 Section 4.2 DOSE AND METHOD OF ADMINISTRATION, Section 4.3 CONTRAINDICATIONS and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Pharmacokinetics in hepatic impairment

In patients with mild to moderate hepatic impairment, there is no clinically significant change in exposure to atovaquone compared with 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_{max} and AUC for cycloguanil. No data are available in patients with severe hepatic impairment. (See Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

There was no evidence that either atovaquone or proguanil alone were mutagenic in bacterial and mammalian cell gene mutation assays *in vitro*, and in mouse bone marrow micronucleus assays for chromosome damage *in vivo*. Cycloguanil, an active metabolite of proguanil, was negative in a bacterial mutagenicity assay but positive in both a mammalian cell mutagenicity assay and a mouse micronucleus test. As the genotoxicity of cycloguanil is prevented or moderated by the co-administration of folinic acid, it appears to be related to the inhibition of mammalian dihydrofolate reductase, causing a reduction in the nucleotide pool and a consequent perturbation of DNA synthesis rather than a direct interaction with DNA. Neither proguanil nor cycloguanil is likely to present a genotoxic risk at clinical exposure levels. Mutagenicity studies have not been performed with atovaquone in combination with proguanil.

Carcinogenicity

Oncogenicity studies of atovaquone alone in mice showed an increased incidence of hepatocellular adenomas and carcinomas at all dose levels tested, yielding exposures

approximately 5 to 8 times the average steady-state plasma concentrations in humans during prophylaxis of malaria. The pattern of associated histological findings observed in the liver, is consistent with a species specific, non genotoxic, neoplastic response. Studies in rats at oral dose levels of up to 500 mg/kg/day were negative. Atovaquone is unlikely to present a carcinogenic risk to humans at therapeutic doses.

Oncogenicity studies on proguanil alone showed no evidence of carcinogenicity in rats and mice at doses resulting in exposures approximately equal to those obtained in humans during prophylaxis of malaria but considerably below exposures obtained during treatment of malaria. Carcinogenicity studies have not been conducted with atovaquone in combination with proguanil.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The tablets also contain: hyprolose, magnesium stearate, microcrystalline cellulose, poloxamer, povidone and sodium starch glycollate.

The film coating on the tablets also contains: hypromellose, iron oxide red, macrogol 400, macrogol 8000 and titanium dioxide.

6.2 INCOMPATIBILITIES

See Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store tablets below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Each tablet strength is provided in PVC aluminium foil blister packs or PVC-aluminium/paper child resistant foil blister packs* in the following pack sizes:

MALARONE TABLETS (250/100): 12 and 24 tablets

MALARONE JUNIOR TABLETS (62.5/25): 12, 24 and 60 tablets

*complies with European Standard *EN 14375:2003 Child-resistant Non-reclosable Packaging for Pharmaceutical Products - Requirements And Testing.*

Not all strengths and/or pack sizes may be distributed in Australia.

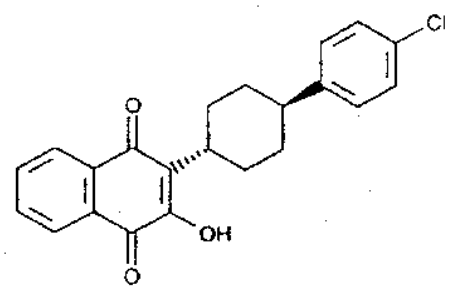
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

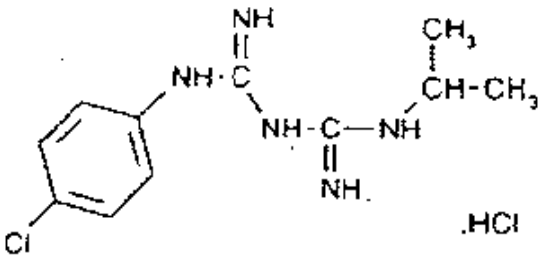
Chemical structure

The chemical name of atovaquone is trans-2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone. The molecular formula of atovaquone is $C_{22}H_{19}Cl0_3$ and it has a molecular weight of 366.84. Atovaquone is virtually insoluble in water (less than 2 x 10^{-4} mg/mL) and slightly soluble (1.7 mg/mL) in 0.1 M sodium hydroxide. The structural formula is shown below:



Atovaquone

The chemical name of proguanil hydrochloride is 1-(4-chlorophenyl)-5-isopropyl-biguanide hydrochloride. The molecular formula of proguanil hydrochloride is $C_{11}H_{16}ClN_5$.HCl and it has a molecular weight of 290.20. Proguanil hydrochloride is slightly soluble at 1 part in 110 parts of water and is sparingly soluble in alcohol (1 part in 40 parts of alcohol). The structural formula is shown below:



Proguanil hydrochloride

CAS number

Atovaquone: 95233-18-4

Proguanil hydrochloride: 637-32-1

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

GlaxoSmithKline Australia Pty Ltd

Level 4, 436 Johnston Street,

Abbotsford, Victoria, 3067

9 DATE OF FIRST APPROVAL

04 May 1998

10 DATE OF REVISION

30 April 2025

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
6.1	Update to excipient names to remove reference to the Opadry proprietary ingredient and instead list the composition of the film coating.

Version 10.0