NEW ZEALAND DATA SHEET

1. PRODUCT NAME

MALARONE 250 mg/100 mg film coated tablets.

MALARONE JUNIOR 62.5 mg/25 mg film coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Each MALARONE JUNIOR tablet contains atovaquone 62.5 mg and proguanil hydrochloride 25 mg.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTCIAL FORM

Film coated tablets.

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

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

4. CLINCAL 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 the hepatic forms of *Plasmodium falciparum (P. 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.

4.2 Dose and method of administration

Dose

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.

Adults

Dosage in Adults

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

Paediatric population

Dosage in Children

11 to 20 kg bodyweight One MALARONE JUNIOR tablet (paediatric strength 62.5 mg atovaquone/25 mg proguanil) daily.

21 to 30 kg bodyweight Two MALARONE JUNIOR tablets as a single dose daily.

31 to 40 kg bodyweight Three MALARONE JUNIOR tablets as a single dose daily.

>40 kg bodyweight One MALARONE tablet (adult strength) daily.

Treatment

Adults

Dosage in Adults

Four MALARONE tablets (adult strength; total daily dose 1,000 mg atovaquone/ 400 mg proguanil hydrochloride) as a single dose for three consecutive days.

Paediatric population

Dosage in Children

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

21 to 30 kg bodyweight Two MALARONE tablets (adult strength) as a single dose for three consecutive days.

31 to 40 kg bodyweight Three MALARONE tablets (adult strength) as a single dose for three consecutive days.

>40 kg bodyweight Four MALARONE tablets (adult strength) as a single dose for three consecutive days.

Special populations

Elderly population

A pharmacokinetic study indicates that no dosage adjustments are needed in the elderly (See Section 5.2 Pharmacokinetic properties - Pharmacokinetics in the elderly).

Hepatic impairment

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 - Pharmacokinetics in hepatic impairment).

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 should be recommended for treatment of acute P. falciparum malaria whenever possible (See Section 4.4 Special warnings and precautions for use and Section 5.2 Pharmacokinetic properties - Pharmacokinetics in renal impairment). For prophylaxis of *P. falciparum* malaria in patients with severe renal impairment see Section 4.3 Contraindications.

Method of Administration

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.

4.3 Contraindications

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 <30 mL/min).

4.4 Special warnings and precautions for use

Severe Cutaneous Adverse Reactions

Cases of severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), drug reaction with eosinophilia and systemic symptoms (DRESS) and erythema multiforme (EM) have been reported in patients treated with MALARONE.

As SCARs can be life-threatening or fatal, if signs and symptoms suggestive of SCARs appear, treatment with MALARONE must be discontinued immediately, and alternative treatment should be given. Patients who have developed SCARs with the use of MALARONE must not receive MALARONE (see Section 4.3 Contraindications and Section 4.8 Undesirable Effects).

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 5 kg, and prophylaxis of malaria in paediatric patients who weigh less than 11 kg has 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 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 (repellents, 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 Section 4.5 Interactions with other medicines and other forms of interaction).

The concomitant administration of MALARONE and rifampicin or rifabutin is not recommended (See Section 4.5 Interactions with other medicines and other forms of interaction).

In patients with severe renal impairment (creatinine clearance <30 mL/min) alternatives to MALARONE should be recommended for treatment of acute *P. falciparum* malaria whenever possible (See Section 4.2 Dose and method of administration, Section 4.3 Contraindications and Section 5.2 Pharmacokinetic properties - Pharmacokinetics in renal impairment).

4.5 Interactions with other medicines 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 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 Section 4.4 Special warnings and precautions for use).

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.

4.6 Fertility, 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 50:20 mg/kg/day in the rat or 100:40 mg/kg/day in the rabbit. In rabbits given atovaquone alone at dosages up to 1200 mg/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.

Breastfeeding

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.

Fertility

No information.

4.7 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.

4.8 Undesirable effects

Summary of adverse events

Adverse events are listed below by MedDRA system organ class and by frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <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

Common: Anaemia[a], neutropenia[b]

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

Immune system disorders

Not known: Angioedema[d], anaphylaxis[c], vasculitis[d]

Metabolism and nutritional disorders

Common: Hyponatraemia[b], anorexia[a]

Uncommon: Elevated amylase levels[b]

Psychiatric disorders

Rare: Hallucinations[a]

Very rare: Psychiatric disorders including abnormal dreams, depression, anxiety, panic attacks, crying, nightmares, psychotic disorders

Nervous system disorders

Very common: Headache[a]

Common: Insomnia[a], dizziness[a]

Gastrointestinal disorders

Very common: Abdominal pain[a], nausea[b], vomiting[a], diarrhoea[a]

Uncommon: Stomatitis[a]

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

Hepatobiliary disorders

Common: Elevated liver enzyme levels[b]

Not known: Hepatitis[c], Cholestasis[d]

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[a]

Uncommon: Hair loss[a], urticaria[a]

Very rare: Drug reaction with eosinophilia and systemic symptoms (see Section 4.4 Special Warnings and Precautions for Use)

Not known Stevens-Johnson syndrome[c], erythema multiforme[c] (see Section 4.4 Special Warnings and Precautions for Use)

General disorders and administration site conditions

Common: Fever[a]

Respiratory, thoracic and mediastinal disorders

Common: Cough[a]

a. Frequency calculated from atovaquone-proguanil clinical trials.

b. 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 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.

c. Observed from post-marketing spontaneous reports and the frequency is therefore not known.

d. 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected reactions via: https://pophealth.my.site.com/carmreportnz/s.

4.9 Overdose

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

For risk assessment and advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimalarials, ATC code: P01B B51

Mechanism 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 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.

Microbiology

Atovaquone has potent activity against *Plasmodium spp* (*in vitro* IC50 against *P. falciparum* 0.23-1.43 ng/mL).

The antimalarial activity of proguanil is exerted via the primary metabolite cycloguanil (*in vitro* IC50 against various *P. falciparum* strains of 4-20ng/mL; some activity of proguanil and another metabolite, 4-chlorophenylbiguanide, is seen *in vitro* at 600-3000 ng/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.

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 5 to 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.

The pharmacokinetics of atovaquone are comparable between healthy subjects and HIV-infected patients. Although there are no atovaquone bioavabilability 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, 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 Dose and method of 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 8.8 L/kg.

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

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

Biotransformation

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 80 kg is approximately 0.16 to 0.05 L/h/kg. The clearance is approximately 0.21 to 0.06 L/h/kg in children weighing 11 to 40 kg, respectively and 0.25 to 0.21 L/h/kg in children weighing 5 to 10 kg.

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

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 Section 4.2 Dose and method of 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 Cmax and AUC for cycloguanil.

No data are available in patients with severe hepatic impairment (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 Cmax and AUC are reduced in patients with severe renal impairment. The elimination half-life 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 and Section 4.4. Special warnings and precautions for use).

5.3 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 folinic 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.

6. PHARMACEUTICAL PARTICULARS

6.1 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

6.2 Incompatibilities

None known.

6.3 Shelf Life

5 years.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

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

6.6 Special precautions for disposal

None.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

GlaxoSmithKline NZ Limited

Private Bag 1006600

Downtown

Auckland

New Zealand

Phone (09) 367 2900

Fax: (09) 367 2910

9. DATE OF FIRST APPROVAL

MALARONE

Date of publication in the New Zealand Gazette of consent to distribute the medicine: 21 September 2000

MALARONE JUNIOR

Date of publication in the New Zealand Gazette of consent to distribute the medicine: 7 November 2002

10. DATE OF REVISION OF THE TEXT

04 March 2026

Summary table of changes:

Section changed	Summary of new information
4.8	Addition of new adverse event: Psychiatric disorders including abnormal dreams, depression, anxiety, panic attacks, crying, nightmares, psychotic disorders
4.1; 4.2; 4.3; 4.4; 4.5; 4.8; 5.2	Editorial changes

Version: 8.0