

Malarone Tablets™

1. TRADE NAME OF THE MEDICINAL PRODUCT

Malarone Tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

3. PHARMACEUTICAL FORM

Film-coated tablets.

Round, biconvex, pink tablets.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

Malarone is a fixed dose combination of atovaquone and proguanil hydrochloride which acts as a blood schizonticide. It is indicated for:

- Prophylaxis of *Plasmodium falciparum* malaria.
- Treatment of *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 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. Posology 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.

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 (250 mg atovaquone/100 mg proguanil) daily.

Dosage in Children:

Greater than 40 kg body-weight - One Malarone tablet daily.

TREATMENT:**Dosage in Adults:**

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

Dosage in Children:

11-20 kg bodyweight - One Malarone tablet daily for three consecutive days.

21-30 kg bodyweight - Two Malarone tablets as a single dose for three consecutive days.

31-40 kg bodyweight - Three Malarone tablets as a single dose for three consecutive days.

>40 kg bodyweight - Four Malarone tablets as a single dose for three consecutive days.

Dosage in the Elderly (Prophylaxis and Treatment):

Pharmacokinetic studies indicate that no dosage adjustments are needed in the elderly (see 5.2 Pharmacokinetic Properties).

Dosage in Hepatic Impairment (Prophylaxis and Treatment):

There are no studies in children with hepatic impairment. However, a pharmacokinetic study in adults 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 5.2 Pharmacokinetic Properties).

Dosage in Renal Impairment (Prophylaxis and Treatment):

There are no studies in children with renal impairment. However, pharmacokinetic studies in adults 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 4.4 Special Warnings and Special Precautions for Use and 5.2 Pharmacokinetic Properties). For prophylaxis of *P. falciparum* malaria in patients with severe renal impairment see 4.3 Contra-indications.

4.3. Contra-indications

Malarone is contra-indicated 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 Special 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 effectiveness of Malarone for the treatment of malaria in paediatric patients who weigh less than 11 kg 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 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.

Parasitaemia should be closely monitored in patients receiving concurrent metoclopramide or tetracycline (see 4.5 Interaction with Other Medicinal Products and Other Forms of Interaction).

The concomitant administration of Malarone and rifampicin or rifabutin is not recommended (see 4.5 Interaction with Other Medicinal Products 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 4.2 Posology and Method of Administration, 4.3 Contra-indications and 5.2 Pharmacokinetic Properties).

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 tetracycline, metoclopramide, rifampicin and rifabutin have been associated with significant decreases in plasma concentrations of atovaquone (see 4.4 Special Warnings and Special 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 drugs in vitro, indicating significant drug interactions arising from displacement are unlikely.

4.6. Use During 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.

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.

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 drugs.

4.8. Undesirable Effects

Adverse reactions 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, very rare <1/10,000. Very common, common and uncommon frequencies were determined from clinical trial data. Rare and very rare frequencies were generally derived from spontaneous data. The frequency classification "Not known" has been applied to those reactions where a frequency could not be estimated from the available data.

Malarone contains atovaquone and proguanil hydrochloride, therefore, the adverse events 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 & Lymphatic system disorders

Common: Anaemia¹, neutropenia²

Not Known: Pancytopenia in patients with severe renal impairment⁴

Immune system disorders

Not Known: Angioedema⁴, anaphylaxis³, vasculitis⁴

Metabolism and nutritional disorders

Common: Hyponatraemia², anorexia¹

Uncommon: Elevated amylase levels²

Psychiatric disorders

Rare: Hallucinations¹

Nervous system disorders

Very common: Headache¹

Common: Insomnia¹, dizziness¹

Gastrointestinal disorders

Very common: Abdominal pain¹, nausea², vomiting¹, diarrhoea¹

Uncommon: Stomatitis¹

Not Known: Gastric intolerance⁴, oral ulceration⁴

Hepatobiliary disorders

Common: Elevated liver enzyme levels²

Not Known: Hepatitis³, cholestasis⁴

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

Skin and subcutaneous tissue disorders

Common: Rash¹

Uncommon: Hair loss¹, urticaria¹

Not Known: Stevens- Johnson Syndrome³, erythema multiforme³

General disorders and administration site conditions

Common: Fever¹

Respiratory, thoracic and mediastinal disorders

Common: Cough¹

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, diarrhea and coughing, and were generally reported in a similar proportion of patients receiving Malarone or a comparator antimalarial drug.

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.

4.9. Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic Group: Antimalarials

ATC Code: P01B B51

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* 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 4-20 ng/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 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.

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 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 4.2. Posology 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 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 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.

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 drug 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.

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

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 2.2 to 1.0 L/h/Kg in children weighing 11 to 40 kg.

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 4.2. Posology 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 4.2. Posology and Method of Administration and Special Warnings and 4.4. Special 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 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_{max} and AUC for cycloguanil.

No data are available in patients with severe hepatic impairment (see 4.2. Posology and Method of Administration).

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 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.

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.

Macrogol 400.

Polyethylene Glycol 8000.

6.2. Incompatibilities

None known.

6.3. Shelf Life

The expiry date is indicated on the packaging.

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.

6.6. Instructions for Use/Handling

None.

Manufactured by GlaxoSmithKline Inc., Mississauga, Canada

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