

SOUHRN ÚDAJŮ O PŘÍPRAVKU

1. NAME OF THE MEDICINAL PRODUCT

Malarone ® Tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Malarone tablet contains:

Atovaquone 250mg

Proguanil hydrochloride 100mg

For excipients, see Section 6.1

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 and also has activity against hepatic schizonts of *Plasmodium falciparum*. It is indicated for:

Prophylaxis of *Plasmodium falciparum* malaria.

Treatment of acute, uncomplicated *Plasmodium falciparum* malaria.

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

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

4.2 Posology and method of administration

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

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

PROPHYLAXIS :

Prophylaxis should

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

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

Dosage in Adults

One Malarone tablet daily.

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

TREATMENT

Dosage in Adults

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

Dosage in Children

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

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

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

> 40kg bodyweight. Dose as for adults.

Dosage in the Elderly

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

Dosage in Hepatic Impairment

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

Dosage in Renal Impairment

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

4.3 Contraindications

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 < 30mL/min).

4.4 Special warnings and precautions for use

Safety and effectiveness of Malarone for prophylaxis of malaria in patients who weigh less than 40kg has not been established.

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

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

Safety and effectiveness of Malarone for treatment of malaria in paediatric patients who weigh less than 11kg has not been established.

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

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

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

Parasitaemia should be closely monitored in patients receiving concurrent metoclopramide or tetracycline (See Section 4.5).

The concomitant administration of Malarone and rifampicin or rifabutin is not recommended (See Section 4.5).

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

4.5 Interaction with other medicinal products and other forms of Interaction

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

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

Concomitant administration of rifampicin or rifabutin is known to reduce atovaquone levels by approximately 50% and 34%, respectively.

(See Section 4.4).

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

4.6 Pregnancy and lactation

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

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

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

Lactation

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

Proguanil is excreted in human milk in small quantities.

Malarone should not be taken by breast-feeding women.

4.7 Effects on ability to drive and use machines

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

As Malarone contains atovaquone and proguanil hydrochloride 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: Anaemia, neutropenia, Pancytopenia in patients with severe renal impairment

Endocrine & Metabolic: Anorexia, hyponatraemia

Gastrointestinal: Abdominal pain, nausea, vomiting, diarrhoea, gastric intolerance, oral ulceration, stomatitis

Hepatobiliary Tract & Pancreas: Elevated liver enzyme levels, elevated amylase levels

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

Lower Respiratory: Cough

Neurology: Headache, insomnia

Non-Site Specific: Fever, angioedema

Skin: Rash (including urticaria), hair loss

In clinical trials 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 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 drug.

4.9 Overdose

There have been no reports of overdosage with Malarone. 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* 0.23-1.43ng/mL).

Atovaquone is not cross-resistant with any other antimalarial drugs in current use.

Among more than 30 *P. falciparum* isolates, *in vitro* resistance was detected against chloroquine (41% of isolates), quinine (32% of isolates), mefloquine (29% of isolates), and halofantrine (48% of isolates) but not atovaquone (0% of isolates).

The antimalarial activity of proguanil is exerted via the primary metabolite cycloguanil (*in vitro* 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- 3000ng/mL).

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

5.2 Pharmacokinetic properties

There are no pharmacokinetic interactions between atovaquone and proguanil at the recommended dose.

Absorption

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

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

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

Distribution

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.

The volume of distribution of atovaquone is 0.62± 0.19L/Kg.

Proguanil is 75% protein bound.

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, primarily by the polymorphic cytochrome P450 isoenzyme 2C19, with less than 40% being excreted unchanged in the urine. Its metabolites cycloguanil and 4-chlorophenylbiguanide are also excreted in the urine.

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

Elimination

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

The clearance of atovaquone is 0.15 ± 0.09 ml/min/Kg.

The elimination half lives of proguanil and cycloguanil are 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 (AUC is increased by 140% and C_{max} is increased by 80%), but there is no change in its elimination half-life (see Section 4.2).

Pharmacokinetics in renal impairment

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

Atovaquone C_{max} and AUC are reduced by 64% and 54%, respectively, in patients with severe renal impairment. In patients with severe renal impairment, the elimination half lives for proguanil (t_{1/2} 39h) and cycloguanil (t_{1/2} 37h) are prolonged, resulting in the potential for drug accumulation with repeated dosing (see Section 4.2 and 4.4).

Pharmacokinetics in hepatic impairment

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

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

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

5.3 Preclinical safety data

Repeat dose toxicity:

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

Reproductive toxicity studies:

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

Mutagenicity:

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

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

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 or in combination with atovaquone have not been undertaken.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipient(s)

Core

Poloxamer 188 BP

Microcrystalline Cellulose Ph.Eur

Low-substituted Hydroxypropyl Cellulose USNF

Povidone K30 Ph.Eur

Sodium Starch Glycollate Ph.Eur

Magnesium Stearate Ph.Eur

Coating

Methylhydroxypropyl cellulose Ph.Eur

Titanium Dioxide Ph.Eur

Iron Oxide Red E172

Macrogol 400 Ph.Eur

Polyethylene Glycol 8000 USNF

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

5 years.

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

PVC aluminium foil blister pack/s containing 12 tablets.

6.6 Instructions for use and handling

No special requirements.

Administrative Data

7. MARKETING AUTHORISATION HOLDER

<http://emc.medicines.org.uk/emc/assets/c/html/displaydoc.asp?documentid=756>

Glaxo Wellcome UK Ltd, trading as GlaxoSmithKline UK.

Stockley Park West

Uxbridge

Middlesex

UB11 1BT

8. MARKETING AUTHORISATION NUMBER(S)

PL 10949/0258

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21 October 1996

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31st July 2002