1. NAME OF THE MEDICINAL PRODUCT

Malarone tablets for adults
Malarone paediatric tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Each Malarone paediatric tablets contains 62.5 mg atovaquone and 25 mg proguanil hydrochloride.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablet.

Malarone tablets for adults – Round, biconvex, pink tablets engraved 'GX CM3' on one side.
Malarone paediatric tablets – Round, biconvex, pink tablets engraved 'GX CG7' on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prevention of Malaria
Malarone is indicated for the prophylaxis of *Plasmodium falciparum* malaria, including in areas where chloroquine resistance has been reported.

Treatment of Malaria
Malarone is indicated for the treatment of acute, uncomplicated *P. falciparum* malaria. Malarone has been shown to be effective in regions where the drugs chloroquine, halofantrine, mefloquine, and amodiaquine may have unacceptable failure rates, presumably due to drug resistance.

4.2 Posology and method of administration

The daily dose should be taken at the same time each day with food or a milky drink. In the event of vomiting within 1 hour after dosing, a repeat dose should be taken.

Malarone Paediatric Tablets:
Malarone may be crushed and mixed with condensed milk just prior to administration to patients who may have difficulty swallowing tablets.

Malarone Tablets for adults:
There is no data regarding crush/divide/chew

Prevention of Malaria

Start prophylactic treatment with Malarone 1 or 2 days before entering a malaria-endemic area and continue daily during the stay and for 7 days after return.

Adults: One tablet of Malarone Tablets For Adults (250 mg atovaquone/100 mg proguanil hydrochloride) per day.

Paediatric Patients: The dosage for prevention of malaria in paediatric patients is based upon body weight (Table 1).

Table 1. Dosage for Prevention of Malaria in Paediatric Patients

Weight (kg)	**Atovaquone/ Proguanil HCl Total Daily Dose**	**Dosage Regimen**
11-20	62.5 mg/25 mg	1 Malarone Paediatric Tablet daily
21-30	125 mg/50 mg	2 Malarone Paediatric Tablets as a single daily dose
31-40	187.5 mg/75 mg	3 Malarone Paediatric Tablets as a single daily dose
>40	250 mg/100 mg	1 Malarone Tablets For Adults as a single daily dose

Treatment of Acute Malaria

Adults: Four Malarone Tablets For Adults (total daily dose 1 g atovaquone/400 mg proguanil hydrochloride) as a single daily dose for 3 consecutive days.

Paediatric Patients: The dosage for treatment of acute malaria in paediatric patients is based upon body weight (Table 2).

Table 2. Dosage for Treatment of Acute Malaria in Paediatric Patients

Weight (kg)	**Atovaquone/ Proguanil HCl Total Daily Dose**	**Dosage Regimen**
5-8	125 mg/50 mg	2 Malarone Paediatric Tablets daily for 3 consecutive days.
9-10	187.5 mg/75 mg	3 Malarone Paediatric Tablets daily for 3 consecutive days.
11-20	250 mg/100 mg	1 Malarone Tablet For Adults daily for 3 consecutive days
21-30	500 mg/200 mg	2 Malarone Tablets For Adults as a single daily dose for 3 consecutive days
31-40	750 mg/300 mg	3 Malarone Tablets For Adults as a single daily dose for 3 consecutive days
>40	1 g/400 mg	4 Malarone Tablets For Adults as a single daily dose for 3 consecutive days

Renal Impairment

Do not use Malarone for malaria prophylaxis in patients with severe renal impairment (creatinine clearance <30 mL/min) *[see Contraindications (4.2)]*. Use with caution for the treatment of malaria in patients with severe renal impairment, only if the benefits of the 3-day treatment regimen outweigh the potential risks associated with increased drug exposure. No dosage adjustments are needed in patients with mild (creatinine clearance 50 to 80 mL/min) or moderate (creatinine clearance 30 to 50 mL/min) renal impairment. *[See Clinical Pharmacology (12.3).]*

Hepatic Impairment

No dosage adjustments are needed in patients with mild or moderate hepatic impairment. No trials have been conducted in patients with severe hepatic impairment.

Paediatric Use

Prophylaxis of Malaria
Malarone is not indicated for the prophylaxis of malaria in paediatric patients who weigh less than 11 kg.
Safety and effectiveness have not been established in paediatric patients who weigh less than 11 kg.
The efficacy and safety of Malarone have been established for the prophylaxis of malaria in controlled trials involving paediatric patients weighing 11 kg or more.

Treatment of Malaria
Malarone is not indicated for the Treatment of Malaria in paediatric patients who weigh less than 5 kg.
Safety and effectiveness have not been established in paediatric patients who weigh less than 5 kg. The efficacy and safety of Malarone for the treatment of malaria have been established in controlled trials involving paediatric patients weighing 5 kg or more.

Geriatric Use
Clinical trials of Malarone did not include sufficient numbers of subjects aged 65 years and older to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, the higher systemic exposure to cycloguanil, and the greater frequency of concomitant disease or other drug therapy.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

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

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 with malaria prevention measures by complying 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 and the patient's clinical condition should be closely monitored.

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.

Occasionally, severe allergic reactions (including anaphylaxis) have been reported in patients taking Malarone. If patients experience an allergic reaction (see section 4.8) Malarone should be discontinued promptly and appropriate treatment initiated.

Malarone has been shown to have no efficacy against hypnozoites of Plasmodium vivax as 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 recrudescent infections due to *P. falciparum* after treatment with Malarone, or failure of chemoprophylaxis with Malarone, patients should be treated with a different blood schizonticide as such events can reflect a resistance of the parasite.

Parasitaemia should be closely monitored in patients receiving concurrent tetracycline (see section 4.5).

The concomitant administration of Malarone and efavirenz or boosted protease-inhibitors should be avoided whenever possible (see section 4.5).

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

Concurrent use of metoclopramide is not recommended. Another antiemetic treatment should be given (see section 4.5).

Caution is advised when initiating or withdrawing malaria prophylaxis or treatment with Malarone in patients on continuous treatment with warfarin and other coumarin based anticoagulants (see section 4.5).

Atovaquone can increase the levels of etoposide and its metabolite (see section 4.5).

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 sections 4.2, 4.3 and 5.2).

Malarone Tablets for adults
The safety and effectiveness of Malarone tablets for adults (atovaquone 250mg/proguanil hydrochloride 100mg tablets) has not been established for prophylaxis of malaria in patients who weigh less than 40kg, or in the treatment of malaria in paediatric patients who weigh less than 11kg.

Malarone Paediatric Tablets
The safety and effectiveness of Malarone paediatric tablets for the prophylaxis of malaria in children who weigh less than 11 kg and the treatment of malaria in children who weigh less than 5 kg have not been established.

Malarone paediatric tablets are not indicated for the treatment of acute uncomplicated *P. falciparum* malaria in individuals weighing 11-40 kg. Malarone tablets for adults (atovaquone 250mg/proguanil hydrochloride 100mg tablets) should be used in these individuals (see section 4.2).

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium free'.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant administration of rifampicin or rifabutin is not recommended as it is known to reduce plasma concentrations of atovaquone levels by approximately 50% and 34%, respectively (see section 4.4).

Concomitant treatment with metoclopramide has been associated with a significant decrease (about 50 %) in plasma concentrations of atovaquone (see section 4.4). Another antiemetic treatment should be given.

Although some children have received concomitant Malarone and metoclopramide in clinical trials without any evidence of decreased protection against malaria, the possibility of a clinically significant drug interaction cannot be ruled out.

When given with efavirenz or boosted protease-inhibitors, atovaquone concentrations have been observed to decrease as much as 75%. This combination should be avoided whenever possible (see section 4.4)

Proguanil may potentiate the anticoagulant effect of warfarin and other coumarin based anticoagulants which may lead to an increase in the risk of haemorrhage. 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 oral anticoagulants. The dose of the oral anticoagulant may need to be adjusted during Malarone treatment or after its withdrawal, based on INR results.

Concomitant treatment with tetracycline has been associated with decreases in plasma concentrations of atovaquone.

The co-administration of atovaquone at doses of 45mg/kg/day in children (n=9) with acute lymphoblastic leukaemia for prophylaxis of PCP was found to increase the plasma concentrations (AUC) of etoposide and its metabolite etoposide catechol by a median of 8.6% (P=0.055) and 28.4% (P=0.031) (respectively compared to the co-administration of etoposide and sulfamethoxazole-trimethoprim). Caution should be advised in patients receiving concomitant therapy with etoposide (see section 4.4).

Proguanil is primarily metabolised by CYP2C19. However, potential pharmacokinetic interactions with other substrates, inhibitors (e.g. moclobemide, fluvoxamine) or inducers (e.g. artemisinin, carbamazepine) of CYP2C19 are unknown (see section 5.2).

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 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.

Breast-feeding
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

Dizziness has been reported. Patients should be warned that if affected they should not drive, operate machinery or take part in activities where this may put themselves or others at risk.

4.8 Undesirable effects

Malarone Paediatric Tablets
In clinical trials of Malarone paediatric tablets for prophylaxis of malaria, 357 children or adolescents 11 to ≤40 kg body weight received Malarone paediatric tablets. Most of these were residents of endemic areas and took Malarone paediatric tablets for about 12 weeks. The rest were travelling to endemic areas, and most took Malarone paediatric tablets for 2-4 weeks.

Open label clinical studies investigating the treatment of children weighing between ≥5 kg and <11 kg have indicated that the safety profile is similar to that in children weighing between 11 kg and 40 kg, and adults.

There are limited long term safety data in children. In particular, the long-term effects of Malarone on growth, puberty and general development have not been studied.

Malarone Tablets for Adults
In clinical trials of Malarone in the treatment of malaria the most commonly reported adverse reactions were abdominal pain, headache, anorexia, nausea, vomiting, diarrhoea and coughing. In clinical trials of Malarone for prophylaxis of malaria, the most commonly reported adverse reactions were headache, abdominal pain and diarrhoea.

Malarone Tablets for Adults and Malarone Paediatric Tablets
The following table provides a summary of adverse reactions that have been reported to have a suspected (at least possible) causal relationship to treatment with atovaquone-proguanil in clinical trials and spontaneous post-marketing reports. The following convention is used for the classification of frequency: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); not known (cannot be estimated from the available data).

There are limited long term safety data in children. In particular, the long-term effects of Malarone on growth, puberty and general development have not been studied.

System Organ Class	**Very Common**	**Common**	**Uncommon**	**Rare**	**Not known[2]**
Blood and lymphatic disorders		Anaemia Neutropenia [1]			Pancytopenia
Immune system disorders		Allergic reactions			Angioedema[3] Anaphylaxis (see section 4.4) Vasculitis[3]
Metabolism and nutrition disorders		Hyponatraemia[1] Anorexia	Elevated amylase levels[1]		
Psychiatric disorders		Abnormal dreams Depression	Anxiety	Hallucinations	Panic attack Crying Nightmares Psychotic disorder

Nervous system disorders	Headache	Insomnia Dizziness			Seizure
Cardiac disorders			Palpitations		Tachycardia
Gastrointestinal disorders	Nausea[1] Vomiting Diarrhoea Abdominal pain		Stomatitis		Gastric intolerance[3] Oral ulceration[3]
Hepatobiliary disorders		Elevated liver enzymes[1]			Hepatitis Cholestasis[3]
Skin and subcutaneous tissue disorders		Pruritus Rash	Hair loss Urticaria		Stevens-Johnson Syndrome Erythema multiforme Blister Skin exfoliation Photosensitivity reactions
General disorders and administration site conditions		Fever			
Respiratory, thoracic and mediastinal disorders		Cough			

1. 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. These events may have been seen at a lower frequency or not at all in clinical trials with atovaquone-proguanil.
2. Observed from post-marketing spontaneous reports and the frequency is therefore unknown
3. Observed with proguanil.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

Additionally, you should also report to GSK Israel (il.safety@gsk.com).

4.9 Overdose

There is insufficient experience to predict the consequences or suggest specific management of Malarone overdose. However, in the reported cases of atovaquone overdose, the observed effects were consistent with known undesirable effects of the drug. If overdose occurs, the patient should be monitored and standard supportive treatment applied.

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 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* IC_{50} against *P. falciparum* 0.23-1.43 ng/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* 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 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 in both immune and non-immune patients.

Clinical Efficacy- Malarone paediatric tablets

<u>Prophylaxis</u>

The efficacy in non-immune paediatric travellers has not been directly established, but may be assumed through extrapolation by the results on safety and efficacy in studies of up to 12 weeks in paediatric residents (semi-immune) of endemic areas, and from results of safety and efficacy in both semi-immune and non-immune adults.

Data in the paediatric population are available from two trials that primarily evaluated the safety of Malarone paediatric tablets in (non-immune) travellers to endemic areas. In these trials, a total of 93 travellers weighing <40 kg were given Malarone and 93 received another prophylactic antimalarial regimen (81 chloroquine/proguanil and 12 mefloquine). The majority of travellers went to Africa and the mean duration of stay was between 2-3 weeks. There were no cases of malaria recorded in any subjects who took part in these studies.

<u>Treatment</u>

An open-label, randomised, parallel-group trial was undertaken in Gabon in 200 children weighing ≥5 kg and <11 kg with confirmed, uncomplicated *P. falciparum* malaria. Treatment was with Malarone paediatric tablets or amodiaquine suspension. In the intent-to-treat population, the 28-day cure rate was 87% in the Malarone group (87/100 subjects). In the per-protocol population, the 28-day cure rate was 95% in the Malarone group (87/92 subjects). The parasitological cure rates for the Malarone group were 88% and 95% for the ITT and PP populations, respectively.

5.2 Pharmacokinetic properties

There are no pharmacokinetic interactions between atovaquone and proguanil at the recommended dose. In clinical trials, where children have received Malarone dosed by bodyweight, trough levels of atovaquone, proguanil and cycloguanil in children are generally within the range observed in adults.

In prophylaxis clinical trials where children have received Malarone dosed by bodyweight, trough levels of atovaquone, proguanil and cycloguanil in children are generally within the range observed in adults (see following table).

Trough Plasma Concentrations [Mean ± SD, (range)] of Atovaquone, Proguanil and Cycloguanil during Prophylaxis with Malarone in Children* and Adults

Atovaquone:Proguanil HCl Daily Dose [Weight Category]	62.5 mg:25 mg [11-20 kg]	125 mg:50 mg [21-30 kg]	187.5 mg:75 mg [31-40 kg]	250mg:100 mg Adult (>40 kg)
Atovaquone (μg/mL)	2.2 ± 1.1 (0.2-5.8)	3.2 ± 1.8 (0.2-10.9)	4.1 ± 1.8 (0.7-8.8)	2.1 + 1.2 (0.1-5.7)
No. Subjects	*n=87*	*n=88*	*n=76*	*n=100*
Proguanil (ng/mL)	12.3 ± 14.4 (<5.0-14.3)	18.8 ± 11.2 (<5.0-87.0)	26.8 ± 17.1 (5.1-55.9)	26.8 + 14.0 (5.2-73.2)
No. Subjects	*n=72*	*n=83*	*n=75*	*n=95*
Cycloguanil (ng/mL)	7.7 ± 7.2 (<5.0-43.5)	8.1 ± 6.3 (<5.0-44.1)	8.7 ± 7.3 (6.4-17.0)	10.9 + 5.6 (5.0-37.8)
No. Subjects	*n=58*	*n=69*	*n=66*	*n=95*

* Pooled data from two studies

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

Apparent volume of distribution of atovaquone and proguanil is a function of bodyweight.

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 and children ranged from 20 to 42 L/kg.

In human plasma the binding of atovaquone and proguanil was 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 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 elimination half lives of proguanil and cycloguanil are about 12-15 hours in both adults and children.

Malarone Paediatric Tablets
Oral clearance for atovaquone and proguanil increases with increased body weight and is about 70% higher in a 40 kg subject relative to a 20 kg subject. The mean oral clearance in paediatric and adult patients weighing 5 to 40 kg ranged from 0.5 to 6.3 L/h for atovaquone and from 8.7 to 64 L/h for proguanil.

Malarone Tablets for Adults
Oral clearance for atovaquone and proguanil increases with increased bodyweight and is about 70% higher in an 80 kg subject relative to a 40 kg subject. The mean oral clearance in paediatric and adult patients weighing 10 to 80 kg ranged from 0.8 to 10.8 L/h for atovaquone and from 15 to 106 L/h for proguanil.

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 clinically significant change in its elimination half life (see section 4.2).

Pharmacokinetics in renal impairment

There are no studies in children with renal impairment.
In adult 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 adult patients with severe renal impairment (<30 mL/min/1.73 m^2).
In adult patients with severe renal impairment, the elimination half lives for proguanil ($t_{½}$ 39 h) and cycloguanil ($t_{½}$ 37 h) are prolonged, resulting in the potential for drug accumulation with repeated dosing (see sections 4.2 and 4.4).

Pharmacokinetics in hepatic impairment

There are no studies in children with hepatic impairment.

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

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.

Carcinogencity:

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.

Oncogenicity studies on proguanil in combination with atovaquone have not been performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core

Low-substituted Hydroxypropyl Cellulose
Microcrystalline Cellulose
Povidone K30
Sodium Starch Glycollate (Type A)
Magnesium Stearate
Poloxamer 188

Coating
Pink colour concentrate OY-SR-24972 (Hypromellose, Titanium Dioxide E171, Macrogol 400, Iron Oxide)
Macrogol 400
Polyethylene Glycol 8000

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 30˚C.

6.5 Nature and contents of container

PVC-aluminium/paper child-resistant foil blister pack/s containing either 12 or 24 tablets.
Not all pack size shall be marketed

6.6 Special precautions for disposal

No special requirements.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. LICENSE HOLDER AND IMPORTER

GlaxoSmithKline (Israel) Ltd., 25 Basel St., Petach Tikva.

8. LICENSE NUMBER

Malarone Tablets For Adults : 128-46-30733
Malarone Paediatric Tablets: 128-45-30732

9. MANUFACTURER

Glaxo Wellcome S.A., Burgos, Spain.

Revised in July 2021 according to MoHs guideline

Mal DR v7