At a meeting of the Advisory Committee on Malaria Prevention in UK Travellers (ACMP) held on 19th November 2002 it was agreed that it was necessary to update the Guidelines for malaria prevention in travellers from the United Kingdom (http://www.phls.org.uk/publications/cdph/issues/CDPHvol4/No2/malaria_guidelinesp.pdf) that were published in 2001.

This update was prompted by an amendment to the licence for Malarone (atovaquone 250 mg/proguanil 100 mg) Tablets so as to recommend use for prophylaxis against falciparum malaria in adults. Also, by the approval of Malarone Paediatric (62.5/25 mg) Tablets for prophylaxis against falciparum malaria in children of 11-40 kg body weight.

In addition the Advisory Committee also felt that it was necessary to provide some guidance on Stand-by Emergency Medication (SEM). This term refers to drugs that may be prescribed for use by travellers at risk of developing malaria who may be unable to obtain medical treatment immediately. SEM may also be prescribed for use by those who have access to medical advice but are in areas where suitable drugs are not available. SEM may also be appropriate for travellers to high-risk areas who are taking a sub-optimal chemoprophylactic regimen because the optimal choice(s) is/are contraindicated for some reason(s). This section includes prescribing information on Riamet (20 mg artemether and 120 mg lumefantrine per tablet), which has been licensed in the UK for the treatment of acute uncomplicated falciparum malaria.

Links are provided below either directly to the Summary of Product Characteristics (SPC), where we have been able to gain permission to publish them on this website, or to the manufacturers’ website. In the case of Riamet you will be required to register your details prior to accessing the SPC.

- SPC for Malarone (http://uk.gsk.com/products/assets/uk_malarone.pdf)
- SPC for Malarone Paediatric
- SPC for Riamet (http://www.malariaandhealth.com/professional/index.htm)

**Adverse Drug Reactions**

Please note that Malarone, Malarone Paediatric and Riamet are newly-introduced drugs and have therefore been assigned a ‘black triangle’ (➔) (http://www.mca.gov.uk/ourwork/monitorsafequalmed/yellowcard/submityc/newdrugs.htm) in the British National Formulary listings, indicating that the Committee on Safety of Medicines (CSM)/Medicines Control Agency (MCA) are intensively monitoring these products. This mark is to remind prescribers that they should report ALL possible adverse reactions to these drugs, using the 'Yellow Card' system (https://www.mca.gov.uk/ourwork/monitorsafequalmed/yellowcard/yellowcardscheme.htm). These reports should include reports of malaria occurring while on prophylactic treatment with the Malarone products, and of failure of treatment courses for all three products and should clearly indicate if the person reported on is a child. Doctors, Pharmacists, Nurses, Midwives (https://www.mca.gov.uk/ourwork/monitorsafequalmed/yellowcard/nurses.htm) and Coroners are encouraged to use the Yellow Card systems.

Submit a yellow card (https://www.mca.gov.uk/ourwork/monitorsafequalmed/yellowcard/submityc/ycreporter.htm)
Summary of Product Characteristics

1. **Trade Name of the Medicinal Product**

   MALARONE™ Paediatric Tablets.

2. **Qualitative and Quantitative Composition**

   Each MALARONE Paediatric Tablet contains:
   - Atovaquone 62.5mg
   - Proguanil hydrochloride 25mg

   For excipients, see Section 6.1

3. **Pharmaceutical Form**

   Film coated tablets.
   Round, biconvex, pink tablets engraved ‘GX CG7’ on one side.

**Clinical Particulars**

4.1 **Therapeutic Indications**

   MALARONE Paediatric Tablets contain a fixed dose combination of atovaquone and proguanil hydrochloride, which acts as a blood schizontocide and also has activity against hepatic schizonts of *Plasmodium falciparum*. They are indicated for:

   Prophylaxis of *P. falciparum* malaria in individuals weighing 11-40kg.

   (For treatment of acute, uncomplicated *P. falciparum* malaria in individuals weighing 11-40kg please refer to the Summary of Product Characteristics for MALARONE tablets).

   MALARONE may be active against *P. falciparum* that are resistant to one or more other antimalarial agents. Therefore, MALARONE may be particularly suitable for prophylaxis against *P. falciparum* infections in areas where this species is known to be commonly resistant to one or more other antimalarial agents.

   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**

   **Posology**
Dosage in individuals weighing 11–40kg

<table>
<thead>
<tr>
<th>Body Weight Range (kg)</th>
<th>Atovaquone (mg)</th>
<th>Proguanil (mg)</th>
<th>No of Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>11–20</td>
<td>62.5</td>
<td>25</td>
<td>One MALARONE Paediatric Tablet</td>
</tr>
<tr>
<td>21–30</td>
<td>125</td>
<td>50</td>
<td>Two MALARONE Paediatric Tablets</td>
</tr>
<tr>
<td>31–40</td>
<td>187.5</td>
<td>75</td>
<td>Three MALARONE Paediatric Tablet</td>
</tr>
<tr>
<td>&gt;40</td>
<td>250</td>
<td>100</td>
<td>Subjects of &gt;40 kg should receive ONE MALARONE 250/100mg Tablet daily</td>
</tr>
</tbody>
</table>

The safety and effectiveness of MALARONE Paediatric Tablets for prophylaxis of malaria in children who weigh less than 11 kg has not been established.

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.

The safety and effectiveness of MALARONE Paediatric Tablets have been established in studies of up to 12 weeks in residents (semi-immune residents) of endemic areas.

**Dosage in Hepatic Impairment**

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. Although no studies have been conducted in patients with severe hepatic impairment, no special precautions or dosage adjustment are anticipated (See Section 5.2 Pharmacokinetics).

**Dosage in Renal Impairment**

There are no studies in children with renal impairment. However, pharmacokinetic studies in adults indicate that no dosage adjustments are needed in those with mild to moderate renal impairment. Due to the lack of information regarding appropriate dosing, MALARONE is contraindicated for the prophylaxis of malaria in adults and children with severe renal impairment (creatinine clearance < 30mL/min; see Section 4.3 Contraindications and Section 5.2 Pharmacokinetics).

**Method of Administration**

The daily dose should be taken once daily with food or a milky drink (to ensure maximum absorption) at the same time each day.
If patients are unable to tolerate food, MALARONE Paediatric Tablets 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.

MALARONE Paediatric Tablets should preferably be swallowed whole. If difficulties are encountered when dosing young children, the tablets may be crushed and administered with food.

4.3 Contra-indications
MALARONE Paediatric Tablets are contra-indicated in individuals with known hypersensitivity to atovaquone or proguanil hydrochloride or any component of the formulation.

MALARONE Paediatric Tablets are contra-indicated for prophylaxis of *P. falciparum* malaria in patients with severe renal impairment (creatinine clearance < 30mL/min).

4.4 Special Warnings and Special Precautions for Use
Individuals taking MALARONE Paediatric Tablets for prophylaxis 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 individuals with diarrhoea or vomiting, but diarrhoea or vomiting was not associated with reduced efficacy in clinical trials of MALARONE for malaria prophylaxis in adults. However, as with other antimalarial agents, individuals with diarrhoea or vomiting should be advised to continue to comply with personal protection measures (repellants, bednets).

Safety and effectiveness of MALARONE Paediatric Tablets for prophylaxis of malaria in children who weigh less than 11kg has not been established.

MALARONE Paediatric Tablets are not suitable for the treatment of acute uncomplicated *P. falciparum* malaria in individuals weighing 11-40 kg. MALARONE Tablets (250/100mg) should be used in these individuals.

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 failure of chemoprophylaxis with MALARONE Paediatric Tablets, individuals should be treated with a different blood schizonticide.

4.5 Interaction with Other Medicaments and Other Forms of Interaction
Metoclopramide and tetracycline have been associated with significant decreases in plasma concentrations of atovaquone when administered concomitantly. 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.

Concomitant administration of atovaquone and indinavir results in a decrease in the $C_{\text{min}}$ 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 MALARONE with rifampicin or rifabutin should be avoided due to the reduction in plasma levels of atovaquone by approximately 50% and 34%, respectively.

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 Paediatric Tablets in pregnancy should only be considered if the expected benefit to the mother outweighs any potential risk to the foetus.

Proguanil 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 Paediatric Tablets.

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 Paediatric Tablets 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 Paediatric Tablets 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

In clinical trials of MALARONE Paediatric Tablets for prophylaxis of malaria, 357 children or adolescents ≤ 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.

In clinical trials, commonly reported (greater than 1/100) adverse events included abdominal pain, diarrhoea, fever, nausea, vomiting and headache. However, in placebo controlled trials all these events occurred at similar rates in the MALARONE and placebo groups.
A summary of other adverse events associated with the use of MALARONE or MALARONE Paediatric Tablets, atovaquone or proguanil hydrochloride is provided below:

*Non-Site Specific:* Fever, angioedema

*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 Tablets indicated that abnormalities in liver function tests were reversible and not associated with untoward clinical events

*Lower Respiratory:* Cough

*Neurology:* Headache, insomnia, dizziness

*Skin:* Rash, urticaria, pruritus, hair loss

4.9 **Overdose**

There have been no reports of overdosage with MALARONE or MALARONE Paediatric Tablets. In cases of suspected overdosage, symptomatic and supportive therapy should be given as appropriate.

**Pharmacological Properties**

5.1 **Pharmacodynamic Properties**

**Pharmacotherapeutic Group:** Antimalarials  
**ATC Code:** P01B B51

**Mode of Action**

The constituents of MALARONE Paediatric Tablets, 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. Proguanil, but not cycloguanil, is able to potentiate the ability of atovaquone to collapse mitochondrial membrane potential in malaria parasites. This latter mechanism may contribute to the antimalarial synergy seen when atovaquone and proguanil are used in combination.
Microbiology

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

Cross-resistance between atovaquone and antimalarial agents of other drug classes was not detected among more than 30 *P. falciparum* isolates that demonstrated resistance *in vitro* to one or more of chloroquine (41% of isolates), quinine (32% of isolates), mefloquine (29% of isolates), and halofantrine (48% of isolates).

The IC₅₀ of the primarily metabolite of proguanil-cycloguanil - against various *P. falciparum* strains was 4-20 ng/mL;

The combination of atovaquone and proguanil was shown to be synergistic against *P. falciparum in vitro*. The combination was more effective than either drug alone in clinical studies of the treatment of malaria in both immune and non-immune patients.

5.2 Pharmacokinetic Properties

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

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 dose for body weight (see following table).

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

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

* Pooled data from two studies

NOTE: Effective trough concentrations in adults : 0.1-5.7 µg/mL, 5.2-73.2 ng/mL, and 5.0-37.8 ng/mL for atovaquone, proguanil and cycloguanil, respectively

Absorption
Atovaquone is a highly lipophilic compound with low aqueous solubility. 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_{\text{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 vivo*, indicating significant drug interactions arising from displacement are unlikely.

Following oral administration, the volume of distribution of atovaquone in adults and children is approximately 7 to 8L/kg.

Proguanil is 75% protein bound. Following oral administration, the volume of distribution of proguanil in adults is 25L/kg. In children (weighing 11-40kg), the volume of distribution is approximately 27 to 30L/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, 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 1-2 days in children.

Following oral administration, the clearance of atovaquone in adults and children (weighing > 40kg) is approximately 0.04 to 0.05 L/h/kg. In children (weighing 11 - 40 kg), the clearance is approximately 0.12 L/h/kg (for 11kg child) to 0.05 L/h/kg (for 40 kg child).
Following oral administration, the clearance of proguanil in adults is 1.3 L/h/kg. In children (weighing 11-40 kg), the clearance is approximately 1.5 to 1.9 L/h/kg.

The elimination half lives of proguanil and cycloguanil are each about 12-15 hours in children.

**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 Cmax and AUC are reduced by 64% and 54%, respectively, in adult patients with severe renal impairment (< 30 mL/min/1.73 m²). In adult patients with severe renal impairment, the elimination half lives for proguanil (t½ 39h) and cycloguanil (t½ 37h) are prolonged, resulting in the potential for drug accumulation with repeated dosing (see Section 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 Cmax 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. However, 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 Paediatric Tablets 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.

**Pharmaceutical Particulars**

6.1 List of Excipients

**Core**
- Poloxamer 188 BP
- Microcrystalline Cellulose Ph.Eur
- Low-substituted Hydroxypropyl Cellulose USNF
- Povidone K30 Ph.Eur
- Sodium Starch Glycollate (Type A) Ph.Eur
- Magnesium Stearate Ph.Eur

**Coating**
- Hycromellose 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

Do not store above 30 °C.

6.5 Nature and Contents of Container

PVC aluminium foil blister pack containing 12 tablets.

6.6 Instructions for Use/Handling

No special requirements.
Guidelines: Standby Emergency Medication

*(The term ‘standby emergency medication’ is preferred to ‘standby emergency treatment’ to convey the concept that it should not be regarded as total treatment without the need for follow-up).*

Standby Emergency Medication (SEM)
This term refers to drugs that may be prescribed for use by those travellers at risk of developing malaria and who may be unable to obtain medical treatment immediately. SEM may also be prescribed for use by those who have access to medical advice but are in areas where suitable drugs are not available. SEM may also be appropriate for travellers to high-risk areas who are taking a sub-optimal chemoprophylactic regimen because the optimal choice(s) is/are contraindicated for some reason(s).

Medical advisers prescribing drugs for self-administration by travellers, should take into consideration the following factors:

- None of the antimalarials recommended for stand-by emergency medication in table 2 below is licensed for this mode of use.
- SEM can be perceived as a way of avoiding a large number of tablets with possible toxic effects, but it should not, as a rule, be used as an alternative to chemoprophylaxis. Each case must be considered on its merits.
- Despite instructions, travellers do not always recognise the symptoms of malaria and therefore may either fail to take the medication when required or take it when it is inappropriate. In the latter case, if the symptoms are not due to malaria, the illness may progress because of inappropriate treatment.
- In two particular studies only 1 in 6 or 1 in 9 (approximately) travellers using SEM had confirmed falciparum malaria.\(^{(i, ii)}\)
- All drugs, but quinine in particular, can have side effects that may be sufficient to result in a failure to complete the course of medication.

For these reasons, it is recommended that SEM be prescribed cautiously and within the following parameters:

- Stand-by emergency medication should not be prescribed for trips of less than one week because the development of symptoms after infection requires at least this period of time.
- All those who start SEM should subsequently seek medical advice as soon as possible.
- Criteria for using standby drugs should be clear and supplemented with written instructions. All travellers prescribed SEM should be advised to seek medical advice immediately if they develop a fever of 38°C or more, measured with a thermometer, seven days or more after arriving in a malarious area. If medical help cannot be obtained that day, or the condition is deteriorating, self-treatment is indicated.

Indications for SEM (table 1)
These must be individually assessed, and SEM should not, as a rule, be recommended in preference to prophylaxis. However, there may be a place for its use in frequent short-term travellers to low risk areas in whom the balance of quantity of medication taken against the risk of contracting malaria is in favour of SEM. SEM is indicated when it has been necessary to use a sub-optimal chemoprophylactic regimen in a high risk area and it may be indicated for a lower risk area where reliable treatment is not available within 24 hours.
Table 1: Indications

<table>
<thead>
<tr>
<th>Indication</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Using sub-optimal regime in high-risk situation.</td>
<td>Chloroquine and Proguanil used in Sub Saharan Africa or Brazilian Amazon</td>
</tr>
<tr>
<td>Frequent short-term travel aircrew/business trips</td>
<td>Low risk areas</td>
</tr>
<tr>
<td>Travel to any remote area away from medical treatment having visited a malaria area in previous 3 months</td>
<td>Himalayas, Sahara desert, across Pacific Ocean by yacht, rural W. China</td>
</tr>
<tr>
<td>Residence in low risk areas, for selected persons</td>
<td>Java, Philippines</td>
</tr>
<tr>
<td>Using (optimal) prophylaxis, but where no treatment will be available</td>
<td>Remote or certain developing areas</td>
</tr>
</tbody>
</table>

Recommended standby regimens (table 2)

**Chloroquine**
Chloroquine is only suitable as a stand-by drug in areas where chloroquine resistance to falciparum malaria does not exist and vivax malaria is present, and if the traveller is either not taking prophylaxis, or taking proguanil alone.

**Atovaquone/proguanil (Malarone) or co-artemether (Riamet)**
These drugs are appropriate in areas where chloroquine or multi-drug resistance exists, although, strictly speaking, they are licensed only for the treatment of falciparum malaria.

**Quinine**
This is widely available in most malarious regions and is useful in areas of multi-drug resistant malaria. Travellers should be made aware that there is a significant risk of nausea or tinnitus when using the drug. Non-pregnant travellers would usually be advised to use an alternative drug.

**Special cases – pregnant women and children**
Whenever possible, pregnant women should avoid situations in which SEM may be needed. The only recognised drug for treatment of malaria in pregnancy is a quinine salt. The risk of the complications outlined above should also be emphasised.

Whenever possible, children should avoid situations where SEM is necessary. When there is no alternative, atovaquone/proguanil or mefloquine may be prescribed at weight-adjusted doses. All children should be taken to medical help as a matter of urgency. A second full dose should be taken if vomiting occurs within one hour in both children and adults.
Table 2: Regimens for standby emergency medication

<table>
<thead>
<tr>
<th>Drug resistance</th>
<th>Standby treatment regimen</th>
<th>Usual amount per tablet</th>
<th>Adult Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>For multi-drug resistance</td>
<td>Atovaquone-Proguanil</td>
<td>250 mg plus 100 mg</td>
<td>4 tablets as a single dose on each of three consecutive days</td>
</tr>
<tr>
<td></td>
<td>(Malarone)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>PoM (Glaxo Wellcome)</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>For multi-drug resistance</td>
<td>Co-artemether</td>
<td>20 mg artemether plus 120 mg</td>
<td>Six doses of 4 tablets over a period of 60 hours</td>
</tr>
<tr>
<td></td>
<td>(Riamet)</td>
<td>lumefantrine</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>PoM (Novartis)</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>For no chloroquine resistance</td>
<td>Chloroquine</td>
<td>150 mg chloroquine base</td>
<td>4 tablets on days 1 &amp; 2, 2 tablets on day 3</td>
</tr>
<tr>
<td></td>
<td>(Nivaquine / Avloclor)</td>
<td>or 155 chloroquine mg base</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Nivaquine)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>or Avloclor</td>
<td></td>
</tr>
<tr>
<td>For multi-drug resistance and pregnancy</td>
<td>Quinine</td>
<td>300 mg Quinine</td>
<td>Quinine 2 tablets 3 times a day for 5-7 days</td>
</tr>
<tr>
<td></td>
<td><em>Quinine - PoM (Non-proprietary)</em></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Exclusion of Fansidar and Halofantrine from these recommendations

**Fansidar**
There is increasing evidence of resistance and there is a significant risk of skin, liver and bone marrow toxicity when compared with the new combination drugs.

**Halofantrine**
There is a risk of potentially fatal cardiac arrhythmias due to the prolongation of the QT interval that this drug causes especially when used following mefloquine

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SUMMARY OF PRODUCT CHARACTERISTICS

Product Summary

1. **Trade 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.

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 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 < 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 recrudescent infections due to \textit{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 $< 30$ mL/min) alternatives to Malarone for treatment of acute \textit{P. falciparum} malaria should be recommended whenever possible (See Sections 4.2, 4.3 and 5.2).

### 4.5 Interaction with other Medicaments 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 $C_{\text{min}}$ 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 \textit{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.

### 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 Cₘₐₓ 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 Cmax 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 Cmax 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 Cmax 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 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.

**Carcinogeneity:**
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.

**Pharmaceutical Particulars**

6.1 **List of Excipients**

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/Handling

No special requirements.

Administrative Data

7. Marketing Authorization Holder

Glaxo Wellcome UK Ltd.
Stockley Park West
Uxbridge
Middlesex
UB11 1BT

8. Marketing Authorization Number(s)

PL 10949/0258

9. Date of First Authorization/Renewal of Authorization

21 October 1996

10. Date of (Partial) Revision of Text

September 2001

11. Legal Status

POM