Public Assessment Report

Mutual Recognition Procedure

Malarone Tablets

UK/H/0170/001/E02

GlaxoWellcome (trading as GlaxoSmithKline UK)

Malarone Tablets

LAY SUMMARY

Czech Republic, Finland, Hungary, Iceland, Ireland, Latvia, Lithuania, Poland, Portugal, Slovak Republic and Slovenia today granted GlaxoWellcome (trading as GlaxoSmithKline UK) Marketing Authorisations (licences) for the medicinal products Malarone Tablets (PL 10949/0258). These are prescription only medicines (POM) for the prevention and treatment of malaria caused by an infection of the blood with the parasite *Plasmodium falciparum*.

Malarone Tablets contain the active ingredients atovaquone and proguanil hydrochloride, which work by killing malarial parasites in the blood to treat or prevent the malaria infection.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Malarone Tablets outweigh the risks, hence Marketing Authorisations have been granted.

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Module 1

Product Name	Malarone Tablets
Type of Application	Article 10.1(b)
Active Substance	Atovaquone, Proguanil hydrochloride
Form	Film-coated tablet
Strength	Atovaquone 250mg, Proguanil Hydrochloride 100mg
MA Holder	GlaxoWellcome (trading as GlaxoSmithKline UK), Stockley Park West, Uxbridge, Middlesex, UB11 1BT
RMS	UK
CMS	Czech Republic, Finland, Hungary, Iceland, Ireland, Latvia, Lithuania, Poland, Portugal, Slovak Republic and Slovenia
Procedure Number	UK/H/0170/001
Timetable	Day 90 – 28th November 2005

Module 2

Summary of Product Characteristics

European Summary of Product Characteristics

1. Trade Name of the Medicinal Product
Malarone ® Tablets.

2. Qualitative and Quantitative Composition
Each Malarone tablet contains:
Atovaquone 250 mg
Proguanil hydrochloride 100 mg

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 40 kg bodyweight.

TREATMENT
Dosage in Adults
Four Malarone tablets as a single dose for three consecutive days.

Dosage in Children

11-20 kg bodyweight.	One tablet daily for three consecutive days.
21-30 kg bodyweight.	Two tablets as a single dose for three consecutive days.
31-40 kg bodyweight.	Three tablets as a single dose for three consecutive days.
> 40 kg 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 < 30 mL/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 < 30 mL/min).

4.4 Special warnings and special precautions for use
Safety and effectiveness of Malarone for prophylaxis of malaria in patients who weigh less than 40 kg 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 11 kg 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 *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 *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_{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

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

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, dizziness
Non-Site Specific:	Fever
Skin/hypersensitivity:	Allergic reactions: including rash, urticaria, angioedema and isolated reports of anaphylaxis. 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 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.

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 body weight, trough levels of atovaquone, proguanil and cycloguanil in children are generally within the range observed in adults.

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

Oral clearance for atovaquone and proguanil increases with increased body weight 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 Cmax is increased by 80%), but there is no clinically significant 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 ($t_{½}$ 39h) and cycloguanil ($t_{½}$ 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.

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.

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 and handling (and disposal)
No special requirements.

Administrative Data

7. Marketing Authorisation Holder
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 Authorisation**
21 October 1996

10. **Date of (Partial) Revision of Text**
21 March 2005

11. **Legal Status**
POM

Module 3

Product Information Leaflet

LE328703

GlaxoSmithKline

Malarone® tablets

Patient Information Leaflet

Please read this information carefully before taking your medication. If you have any questions ask your doctor or pharmacist.

What is Malarone?

The name of your medicine is Malarone.

Malarone tablets are round, pink film-coated tablets. Each tablet contains the active ingredients atovaquone 250mg and proguanil hydrochloride 100mg.

There are also some inactive ingredients in Malarone tablets. These are: poloxamer 188, microcrystalline cellulose, hydroxypropyl cellulose, povidone K30, sodium starch glycollate, magnesium stearate, methylhydroxypropyl cellulose, titanium dioxide (E171), iron oxide red (E172), macrogol 400 and polyethylene glycol 8000.

Malarone comes in blister packs of 12 tablets.

Who makes Malarone?

Glaxo Wellcome Operations, Greenford, Middlesex UB6 0NN makes Malarone and GlaxoSmithKline UK, Stockley Park West, Uxbridge, Middlesex UB11 1BT is licensed to sell it in the UK.

What is Malarone used for?

Malarone belongs to a group of medicines called antimalarials. It is used as a form of protection (prophylaxis) against malaria and to treat malaria caused by an infection of the blood with the parasite *Plasmodium falciparum*. Malarone contains two active ingredients which work by killing the malarial parasites in your body to treat or prevent the malaria infection.

What should I check before taking Malarone?

This medicine suits most people but there are a few people who should not take it. Ask yourself these questions to check whether Malarone is right for you:

- Have you ever had an allergic reaction to atovaquone, proguanil hydrochloride or to any of the other ingredients in Malarone listed above?
- Have you been told that your malaria infection is severe and is affecting your lungs, kidneys and/or brain?
- Have you had malaria before?
- Are you pregnant, trying to become pregnant, or breast-feeding?
- Are you currently suffering from diarrhoea and/or vomiting?
- Do you have kidney disease?
- Is the medicine to be taken for the treatment of malaria by a child who weighs less than 11kg?
- Is the medicine to be taken for the prevention of malaria and you or the patient weigh less than 40kg?
- Are you expecting to stay in an area where there is malaria for more than 28 days?

If the answer is "YES" to any of these questions, tell your doctor.

What if I am taking other medicines?

Always tell your doctor about any other medicines you are taking, including those you can buy yourself.

Some medicines can stop Malarone working properly, these are:

- Metoclopramide - used to treat sickness (vomiting) and feelings of sickness (nausea).
- Tetracycline, rifampicin or rifabutin - antibiotics.
- Indinavir

How do I take Malarone?

It is important to take your medicine at the right times, and in the way your doctor has told you to. The label on your pack will tell you how many tablets to take and how often. If the label doesn't say, or if you are not sure, ask your doctor or pharmacist.

Malarone can be taken for two reasons:

- To prevent malaria infection (prophylaxis)
- To treat malaria infection

The following important information applies whether you are taking your Malarone tablets **for prevention or treatment of malaria**

- If possible take Malarone tablets with food or a milky drink, so that the medicine is absorbed better and works properly.
- It is also important to take your tablets at the same time each day and complete the full course.
- If you are sick (vomit) within one hour of taking your tablets, take another dose and then go on as before. If you do this you should contact your doctor for more Malarone tablets to replace those you brought up. If you have diarrhoea, continue taking these tablets as normal.
- If you feel ill again, particularly if you develop a fever at any time up to a month after finishing your tablets see your doctor immediately.
- There are no special doses for elderly patients.

To prevent malaria infection

If you are expecting to stay in an area with malaria for more than 28 days check before travelling, with a pharmacist or doctor, whether Malarone tablets are appropriate for you.

- The usual dose in adults is one tablet daily.
- Start the course of tablets 1 to 2 days before arriving in an area which has malaria
- Continue taking these tablets every day during your stay
- Continue taking these tablets for a further 7 days after your return to a malaria free area.

This may be different to how other medicines are used to prevent malaria, however, it is important to follow these instructions unless your doctor has told you otherwise.

If you weigh less than 40 kilograms (Kg), it is recommended that you do NOT take Malarone to prevent malaria infection. There is other very important information on how, in addition to taking Malarone, you can protect yourself against malaria infection at the end of this leaflet.

To treat malaria infection

The usual dose in adults is four tablets once a day for 3 days.

The dose for children depends upon their bodyweight, as follows:

11-20kg:	ONE tablet daily for 3 days
21-30kg:	TWO tablets daily for 3 days
31-40kg:	THREE tablets daily for 3 days
Over 40kg:	Dose as for adults.

If you are taking Malarone to treat an attack of malaria and you have diarrhoea or are sick (vomit), tell your doctor. Your doctor may want to check how well these tablets are working and if necessary may decide to change your treatment. A few days after finishing your treatment course you should visit your doctor to check that your malaria has been fully treated.

What to do if you take too many tablets

It is important to stick to the dose on the label of your medicine. If you take too much Malarone, or if someone else takes your medicine by mistake, tell your doctor at once.

What to do if you miss a dose

If you forget to take a dose, don't worry. Just take one as soon as you remember and then take the next dose at the right time.

Does Malarone have side effects?

Although most people find taking Malarone causes no problems, like all medicines Malarone can have side effects, however some of these can be symptoms of malaria. The following side effects have been reported in persons taking Malarone, most of these have been mild and have not lasted very long:

- Tiredness, weakness, giddiness or breathlessness, these symptoms may mean that you are suffering from a reduction in red blood cell count (anaemia)
- A reduction in white blood cells (neutropenia)
- Disturbance of the salt balance of the body (hyponatraemia)
- Feeling sick (nausea) and/or being sick (vomiting), stomach pain, diarrhoea
- Loss of appetite
- Inflammation of the mouth (stomatitis) and mouth ulcers
- Headache
- Difficulty in sleeping (insomnia)
- Cough
- Fever
- Allergic reactions, including rash, itching and swelling
- Hairloss

Temporary increases of some enzymes produced by your liver and pancreas have been reported in some patients. You may not notice any symptoms if this happens. These substances can be measured in your blood and therefore, if you have any blood tests, remind your doctor that you are taking Malarone.

Tell your pharmacist or doctor if you get these or any other side effects from your medicine which are not mentioned here.

Looking after your Malarone tablets

Keep your Malarone tablets in a safe place where children cannot see or reach them.

Do not take Malarone tablets after the expiry date shown on the label.

If your doctor stops your treatment, do not keep any leftover tablets unless your doctor tells you to. Return any unused tablets to your pharmacist for safe disposal.

REMEMBER: This medicine is for you. Never give it to any one else. It may harm them even if they have the same symptoms as you.

More about Malaria

What is Malaria?

Malaria is a serious but preventable disease spread by the bite of an infected mosquito. Anyone, of any age, can get malaria. To protect yourself against malaria, it is important to know the risks, avoid being bitten, take preventative treatment where appropriate and seek early diagnosis and treatment if necessary.

Know the risks

It is important for all people to seek advice before travelling to an area where malaria is prevalent.

Avoid being bitten

- Wear light coloured clothing that covers most of the body especially after sunset. In particular do not forget to cover your arms and legs.
- Use insect repellant on exposed areas of the skin.
- Sleep in a screened room or under a mosquito net impregnated with insecticide. If windows and doors are not screened – close them at sunset.
- Consider the use of an insecticide (mats, spray, plug-ins) to clear a room of insects before going to bed or to deter mosquitoes from entering the room.

Your pharmacist will be able to offer advice on the appropriate products to use.

Prevention (why take a prophylactic medication?)

Antimalarial prophylactic medication can protect you against contracting malaria.
It is essential to seek medical advice on which antimalarial prevention (prophylactic) medicine to take, as Malarone may not provide adequate protection in some countries. It is important to take your tablets correctly (see "How do I take Malarone?").

Prompt treatment

A few people may still get malaria despite taking the necessary precautions.
The initial signs may be mild and often appear flu-like (fever with or without weakness, shivering, pain in the joints, headaches, diarrhoea, vomiting). **Should you develop any illness within 1 year and particularly within 3 months of returning from an area where malaria is prevalent, you must contact your doctor immediately.**

Finding out more

- You may be able to find out more from public libraries.
- **If you have any other questions** about malaria or are not sure about anything, ask your doctor or pharmacist, who will be able to advise you.

You may need to read this leaflet again. Please keep it until you have finished your medicine.

This leaflet does not tell you everything about your medicine. If you have any questions or are not sure about anything, then ask your doctor or pharmacist.

The information provided applies only to Malarone tablets.

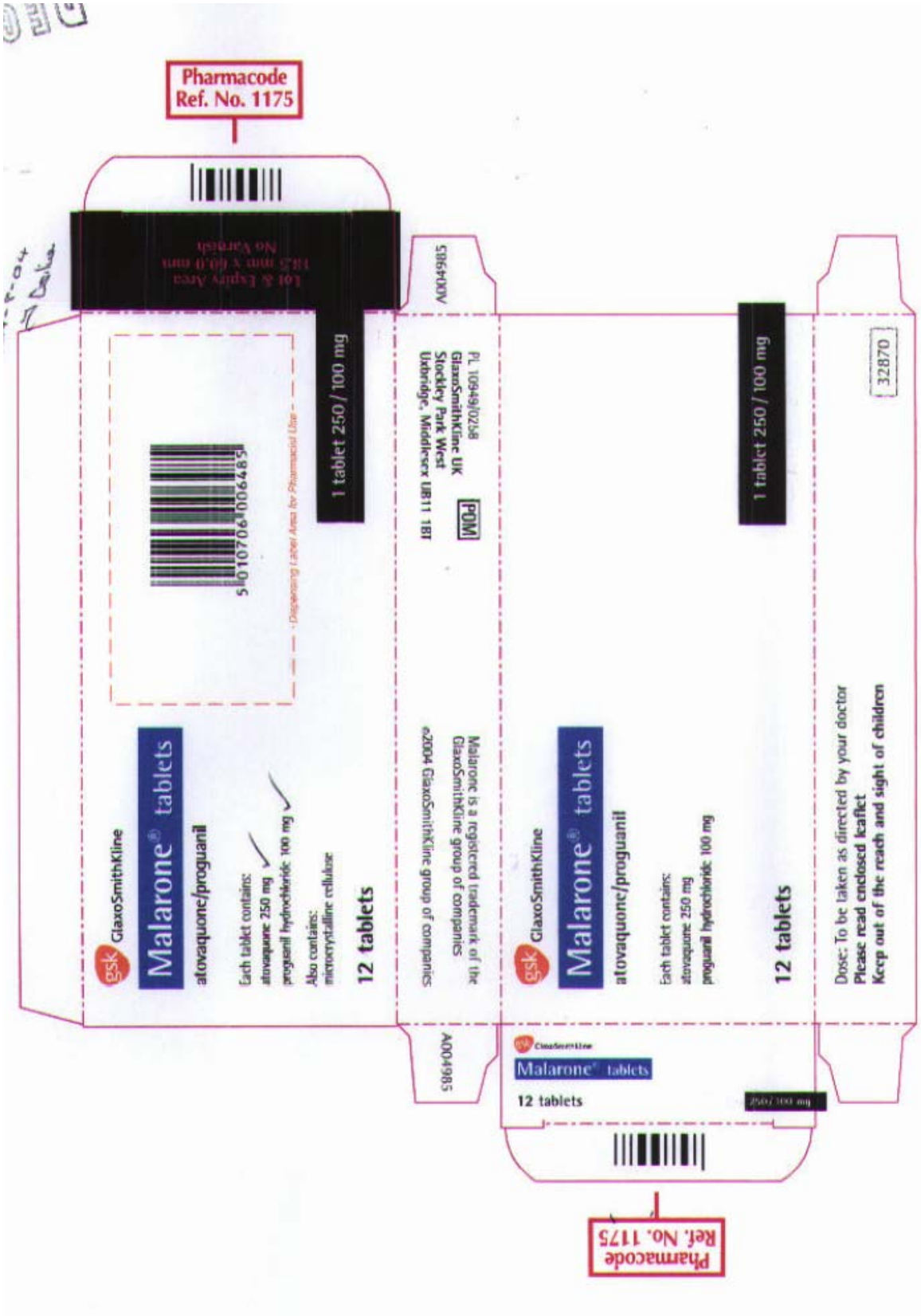
Leaflet revised April 2002.

GlaxoSmithKline

LE328703

Module 4

Labelling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Ref. No. 1175
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18.5 mm x 60.0 mm
No Varnish
A004985
1 tablet 250 / 100 mg
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Dispensing Label Area for Pharmacist Use
GlaxoSmithKline
Malarone® tablets
atovaquone/proguanil
Each tablet contains:
atovaquone 250 mg
proguanil hydrochloride 100 mg
Also contains:
microcrystalline cellulose
12 tablets
PL 10949/0248
GlaxoSmithKline UK
Stockley Park West
Uxbridge, Middlesex UB11 1BT
POM
Malarone is a registered trademark of the GlaxoSmithKline group of companies
©2004 GlaxoSmithKline group of companies
A004985
1 tablet 250 / 100 mg
32870
Dose: To be taken as directed by your doctor
Please read enclosed leaflet
Keep out of the reach and sight of children
GlaxoSmithKline
Malarone® tablets
atovaquone/proguanil
Each tablet contains:
atovaquone 250 mg
proguanil hydrochloride 100 mg
12 tablets
GlaxoSmithKline
Malarone® tablets
12 tablets
250/100 mg
Pharmacode
Ref. No. 1175

Module 5

Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA has granted a marketing authorisation for Malarone Tablets, from GlaxoWellcome (trading as GlaxoSmithKline UK) for the prophylaxis and treatment of *Plasmodium falciparum* malaria.

This is an application made under Article 10.1(b), first paragraph of Directive 2001/83 EC for Malarone Tablets. Malarone Tablets comprise a fixed dose combination of two established active ingredients: each tablet contains 250 mg atovaquone and 100 mg proguanil hydrochloride.

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.

Preclinical studies were carried out in accordance with Good Laboratory Practice (GLP), and in accordance with recognized guidelines. No new toxicological problems for this product were found. Clinical studies on the combination of atavaquone and proguanil hydrochloride were carried out in accordance with Good Clinical Practice (GCP). The clinical programme showed that Malarone provides satisfactory clinical benefits.

The product was granted a marketed authorisation in the UK on 21st October 1996. A first-wave mutual recognition procedure determined on 30th April 1997 led to the grant of marketing authorisation in Austria, Belgium, Germany, Italy, Luxembourg, Portugal and Sweden. A second-wave mutual recognition procedure, determined on 7th August 2000, led to the grant of a marketing authorisation in Greece, Spain, The Netherlands and Norway. A third-wave mutual recognition procedure, determined on 28th November 2005, led to the grant of a marketing authorisation in Czech Republic, Finland, Hungary, Iceland, Ireland, Latvia, Lithuania, Poland, Portugal, Slovak Republic and Slovenia.

The UK acting as reference member state (RMS) has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product prior to granting its national authorisation. For manufacturing sites within the community, the RMS has accepted copies of

current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

Malarone Tablets are available on prescription.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Malarone Tablets
Name(s) of the active substance(s) (INN)	Atovaquone 250mg, Proguanil Hydrochloride 100mg
Pharmacotherapeutic classification (ATC code)	Antimalarials P01B B51
Pharmaceutical form and strength(s)	Film-coated tablet, Atovaquone 250 mg Proguanil Hydrochloride 100 mg
Reference numbers for the Mutual Recognition Procedure	UK/H/0170/01/E02
Reference Member State	United Kingdom
Member States concerned	Czech Republic, Finland, Hungary, Iceland, Ireland, Latvia, Lithuania, Poland, Portugal, Slovak Republic and Slovenia.
Name and address of manufacturer responsible for batch release in the EEA	1. Glaxo Wellcome GmbH and Co, Industriestrasse 32-36, 23843 Bad Oldesloe, Germany 2. Glaxo Wellcome Operations, Temple Hill, Dartford, Kent DA1 5AH, UK
Date of first authorisation	21st October 1996
Marketing Authorisation Number(s)	PL 10949/0258
Date of assessment report	26/01/2006
Name and address of the authorisation holder	GlaxoWellcome (Trading as GlaxoSmithKline UK), Stockley Park West, Uxbridge, Middlesex, UB11 1BT, UK

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

ACTIVE SUBSTANCES

Atovaquone

Atovaquone is a yellow powder and is identical to the atovaquone drug substance used in the currently licensed Wellvone Tablets. European Community competent Authorities have already approved data on atovaquone. There are no proposed changes to the synthesis or control of this active substance in this application.

Proguanil Hydrochloride

Proguanil hydrochloride is a white crystalline powder that is manufactured by a well established synthetic route and is covered by a monograph in the British and European Pharmacopoeias. The applicant considers that the monograph is inappropriate to control the quality of the drug substance and additional controls are applied to limit named related substances

The HPLC assay method has been satisfactorily validated and system suitability has been demonstrated.

There are no proposed changes to the synthesis or control of proguanil hydrochloride with this application.

Since the Marketing Authorisation was originally granted in the RMS, a variation has been approved to allow the detector wavelength used in the assay and impurity method of proguanil hydrochloride to be changed. The robustness of the method in terms of variations in wavelength and bandwidth settings is greatly enhanced.

Stability

Stability data have not been provided for atovaquone as the drug substance is identical to that used in the currently licensed product, Wellvone.

A comprehensive stability testing programme was performed on proguanil hydrochloride. In addition, three production-scale batches of proguanil hydrochloride will be placed on stability, stored at 25°C/60%RH and tested annually for appearance, acidity or alkalinity, 4-chloroaniline, related substances, loss on drying and assay.

A shelf-life of 5 years is proposed, with re-test periods of 3 and 5 years.

FINISHED PRODUCT

Formulation and Manufacture

Malarone Tablets contain atovaquone and proguanil hydrochloride as actives, together with low substituted hydroxypropyl cellulose (disintegrating agent), microcrystalline cellulose (compression aid), povidone K30 (binding agent), sodium starch glycollate (disintegrating agent), magnesium stearate (lubricant). Poloxamer 188 (surfactant), purified water (granulating solvent) and ethanol 96% (granulating solvent) as excipients. The film coat is composed of Pink Colour Concentrate (film-coating agent), macrogol 400 (plasticiser) and purified water (film coating solvent). All excipients, except for Pink Colour Concentrate, are pharmacopoeial, complying with

the Ph Eur, BP or USNF. A satisfactory in-house specification has been applied to the colour concentrate. A Certificate of Analysis has been provided for each excipient. Sufficient identity tests to confirm the authenticity of the material are carried out by the company.

The tablets are packed in blister packs prepared from unplasticised PVC and aluminium foil.

The formulation has been developed from that of the currently licensed Atovaquone Tablets to include proguanil hydrochloride. The inclusion of this second active has necessitated other changes to the formulation.

The surfactant was included to aid the rapid collapse of the powder during the wet granulation stage. Batches were prepared that incorporated sodium lauryl sulphate, poloxamer and polysorbate. Both sodium lauryl sulphate and poloxamer produced acceptable granule and tablet characteristics, but poloxamer was selected as it is already used in Atovaquone Suspension. The suitability of poloxamer was confirmed using a development-scale batch.

Compatibility of the actives with the excipients was demonstrated using differential scanning calorimetry and by accelerated stability testing for 4 weeks at 70°C and 40°C/75%RH.

Satisfactory studies were carried out to optimize the levels of excipients. Stages in the development of the film coat are fully described.

The method of manufacture utilizes a standard wet granulation process with an ethanol/water mix as granulating fluid. The granules are dried, sifted and blended with magnesium stearate and compressed into tablets that are film coated and polished. The manufacturing process has been satisfactorily validated.

Pre-compression checks are carried out on all final granule blends for loss on drying, bulk density and sieve analysis. The compressed tablet cores are examined visually, tested for weight, hardness and thickness, friability, disintegration and dimensions. The coated tablets are examined visually for uniformity of coating. The final product then undergoes complete QE testing for compliance with the specification.

Finished Product Specification
The finished product and shelf life specifications for Malarone Tablets tests and limits are suitable for a preparation of this type.

Assay
All test and assay methods have been satisfactorily validated. HPLC assay methods have been shown to be stability indicating with respect to the impurities listed in the finished product specification.

Impurities
Impurities are adequately controlled in the drug substances. Therefore, in line with current ICH guidelines, release limits for these impurities are not included in the finished product specification.

Other Aspects

Dissolution testing for the atovaquone component is carried out using the flow through apparatus of the Ph Eur (Apparatus 4 of the USP). The rationale behind the selection of the dissolution method is discussed, the use of a two stage process justified and dissolution profiles provided.

Proguanil hydrochloride is water soluble (1 in 110) and dissolution testing was not considered relevant, release being tested by means of a disintegration test.

Stability of the Finished Product

Up to 60 months stability data have been generated for batches of Malarone Tablets stored at 30°C and as real time data. Samples were tested according to appropriate, stability-indicating finished product specifications.

Results were generally satisfactory. No significant changes in assay or impurity levels were detected for product when stored under any of the conditions used for the stability studies. The data presented were sufficient to support the proposed shelf-life of 5 years with no specific storage instructions imposed.

BIOEQUIVALENCE

An open 3-way crossover study was carried out in 26 healthy volunteers. The first two periods followed a randomized, balanced, 2-period crossover design in which all volunteers received combination tablets or separate tablets of atovaquone and proguanil given concomitantly. The third period was a repeat of the second in order to assess any treatment carry over effect. The washout period was at least 3 weeks.

Plasma levels of atovaquone were measured using RIA and levels of proguanil hydrochloride measured using HPLC with UV detection. Both analytical methods have been fully validated. Dissolution data have been provided for the single constituent tablets used in the biostudy. C_{max}, T_{max} and $AUC_{0-\infty}$ were calculated and results were as follows:

Parameter	**Separate Tablet Entities (mean)**	**Combination Tablets (Mean)**	**90% Confidence Interval**
Atovaquone			
C_{max}(µg/ml)	4.32 ± 2.22	4.25 ± 2.15	88-116
T_{max} (h)	30.9 ± 38.1	25.5 ± 19.6	
$AUC_{0-\infty}$(µgh/ml)	630 ± 406	585 ± 349	86-111
Proguanil			
C_{max}(µg/ml)	433 ± 133	429 ± 126	95-105
T_{max} (h)	3.2 ± 0.9	3.3 ± 0.9	
$AUC_{0-\infty}$(µgh/ml)	6130 ± 2392	5809 ± 1990	92-99

Treatments can be considered to be bioequivalent as the confidence intervals for the ratios of $AUC_{0-\infty}$ and C_{max} between treatments are in the range 80-125%.

PART I - ADMINISTRATIVE PARTICULARS

Completed European Application Forms are provided.

GMP statement

There are no GMP issues. The manufacturing sites are in the UK and Ontario, Canada. Both sites are satisfactory for this type of product.

Product labelling & leaflets

Contain satisfactory pharmaceutical details.

Summary of Product Characteristics

Satisfactory pharmaceutical details.

EXPERT REPORT

The Pharmaceutical Expert Report is satisfactory and represents an adequate critical summary of the data.

COMPLIANCE WITH GUIDELINES

The application complied with the guidelines available at the time of initial assessment by the UK Licensing Authority.

CONCLUSION ON QUALITY

The pharmaceutical assessor concluded that marketing authorisations may be granted for these products.

III.2 PRE-CLINICAL ASPECTS

PHARMACODYNAMICS [III F] (A) PRIMARY ACTIVITY AS AN ANTI-MALARIAL

The mode of action of cycloguanil (a major metabolite of proguanil) as an inhibitor of dihydrofolate reductase (DHFR) has been established previously. It is possible that, at high concentration, proguanil might have anti-parasitic activity via a separate mechanism. However, such concentrations are very unlikely to be achieved systemically in the dose regimen proposed for human treatment.

Atovaquone is an inhibitor of some cytochromic electron transport and, consequently, particularly in *Plasmodium spp*, an inhibitor of pyrimidine synthesis, which is essential for the parasites but not for mammals, which can salvage pyrimidines from other sources. Thus, the test for a combination's effectiveness would be its ability to return the sensitivity, of any *Plasmodium* strain resistant to either compound alone, to its historical baseline value or to that of non-resistant strains.

This test was not applied to Malarone, although it was possible to isolate atovaquone-resistant malaria parasite strains in the laboratory and *Plasmodium* strains resistant to pro (cyclo) guanil are known.

The only preclinical model used was *Plasmodium yoelii* in the mouse, in which it was shown that Malarone activity was additive with respect to its two components. All other efficacy data come from human studies.

Secondary pharmacology

One experiment in beagle dogs on a combination of atovaquone and proguanil at a ratio of 20 : 8 mg/kg, respectively, compared the cardiovascular, respiratory and behavioural pharmacology with that of either compound alone in a 3-way crossover study. Plasma concentrations were monitored to obtain a systemic exposure for the basis of interpretation.

From 0 to 24 hours after dosing, there were no significant cardiovascular changes in any dog, despite widely varying maximum and total (AUC) exposure to atovaquone. The Expert Report suggests biphasic plasma exposure curves with C_{max} averages of 4.8 and 7.4 µg/ml, whereas examination of the individual exposures at 24 hours postdose shows two dogs without pharmacological response when plasma concentrations were 10.8 and 12 µg/ml and another dog achieving a similar exposure level during the first 6-hour BP/ECG monitoring period. Since these higher maximum concentrations were found in patients receiving the recommended dose of atovaquone, it is reassuring to observe the absence of cardiovascular pharmacology in the dog model.

No behavioural changes associated with the treatments were observed during the whole course of the study (3 x 21 days). The only pharmacology of note was the effect on blood gases and pH when atovaquone was administered alone. This had not occurred in previous studies at the same oral dose, nor did it occur when proguanil was added and it was an early change – not correlated with times of higher plasma concentration.

Blood chemistry and haematology were not affected by the treatments and, overall, the secondary pharmacology at therapeutic dose level was acceptable for the indication.

The secondary pharmacology of proguanil (cycloguanil) is reviewed in the written summary. It raises no new safety issues for the combination.

PHARMACOKINETICS AND BIOTRANSORMATION [III G]

Atovaquone and proguanil, plus its metabolites, were assayed by HPLC/UV methods. For the combination studies, a check was conducted to ensure that there was no interference between the assay methods. The kinetics of proguanil (cycloguanil) alone are available from the published literature and are summarized in this application. For atovaquone alone, the data are available from previously submitted applications and are also only summarized for this submission.

When administered orally as a combination, atovaquone and proguanil generally retain the characteristics established by dosing each separately, namely
Atovaquone is absorbed slowly but relatively well in the rat at 20 mg/kg orally, but in the dog shows erratic and sometimes poor absorption .
Proguanil is absorbed to a limited extent in rats (only 10-15% of an oral dose is excreted in urine), whereas dog urine accounts for 50 - 60% of a radiolabelled oral dose.

In rats, tissue distribution of **[**^{14}C**]**-proguanil and its metabolites was apparently more restricted in the presence of atovaquone. In particular, no radioactivity reached the

fetuses and less escaped the intestine and liver than was reported in the literature for proguanil administered alone. In pregnant rats, radioactivity was found in bone.

Toxicokinetics

Because of the above differences in absorption characteristics after oral dosing for rats and dogs, there is an apparently reassuring safety margin based on systemic exposure for atovaquone when comparing rat and man but not between dog and man. The reverse holds true for proguanil when the highest dose in the repeat-dose toxicity study is compared with the C_{max} and AUC from humans receiving the recommended daily dose. Both ratios of safety margin are approximately 4 (Expert Report Table 7/8).

For both compounds, where absorption was poor, there is evidence that higher oral doses would not have generated significantly greater systemic exposure in the majority of test animals (Expert Report Tables 2-5). Other routes of administration to generate 'worstcase' exposure would not have been appropriate for such poorly soluble compounds.

Within the limits of the variability, it was concluded that bioavailability of the chosen doses was unaffected by concomitant administration of the other compound.

The extent of the possible variation in absorption of atovaquone in dogs is illustrated by comparing Tables 1 and 4 in the Expert Report. AUC values were 457 on one occasion and 31 or 131 µg/ml/hr at the start and end of the 4-week study, respectively.

The conclusion from these results is that any sign/symptoms of toxicity in individual animals need to be related to the relevant systemic exposure for interpretation rather than relying on average concentration or area values.

In vitro biotransformation studies with human CYP isozymes indicated the possibility of atovaquone inhibiting the metabolism (via CYP 2C enzymes) of proguanil but the concentration required suggests that this is unlikely to be significant during therapy for malaria.

TOXICOLGY

General toxicity – repeated dose *(III A)*

Taking into account that single- and repeated-dose toxicity of atovaquone and proguanil as single agents is known (summarized in Expert Report), the Applicant has submitted 30-day studies of repeated daily administration of the combination in rat and dog.

In general, proguanil is the more toxic of the two active substances and this is reflected in the dose ratio selected (2.5 : 1; atovaquone : proguanil). When the dose of proguanil reached 40 mg/kg in rats, some signs of adverse effects were seen, despite the low oral bioavailability (AUC, 0.94 µg/ml/hr). This indicates that this species is more sensitive to proguanil or its metabolites than dogs in which AUC values of 12 (proguanil) or 2.5 (cycloguanil) µg/ml/hr, following administration of 20 mg proguanil/kg, were considered to be a No Effect level of exposure.

Thus, the expected toxicity from the combination would be predominantly that of proguanil. This is confirmed by the results of the 30-day studies.

Toxicity to reproduction (III B/C)
The effect of proguanil on mouse fertility, reported from a published work of 1962, is considered by its author to be mediated *via* the females whose corpora lutea were increased in number. The 5 weeks of pre-mating administration to male mice was considered sufficient to have uncovered any effect on spermatogenesis or performance.

At dose levels (20 mg/kg) toxic to pregnant rats, proguanil was not teratogenic. Atovaquone (50 mg/kg) in combination with proguanil did not provoke further reproductive toxicity.

There is no evidence that combining these two anti-malarial compounds will pose a hazard to pregnant women, but the wording of the SmPC (Section 4.6) is suitably cautious considering treatment of resistant *P. falciparum* malaria is usually imperative.

Genotoxic potential (III D)
The assay of any combination of proguanil and atovaquone for genotoxicity was not attempted *in vitro* because of the differential cellular toxicity and incompatible solubility characteristics of the two compounds. Tested separately in conventional assays (Ames, mouse lymphoma and human lymphocyte~~s~~ for atovaquone; Ames, mouse lymphoma and mouse micronucleus for proguanil), neither compound showed any genotoxic potential. The atovaquone results have been reported previously and are re-stated in, this application.

The Part III dossier gives no indication as to whether the rat liver S9 metabolizing fraction is capable of mimicking *in vivo* biotransormations of proguanil; this is of less interest for atovaquone which is mostly eliminated unchanged.

Carcinogenic potential (III E)
No carcinogenicity studies have been conducted with a combination of atovaquone and proguanil. Carcinogenicity studies on proguanil alone showed no evidence of carcinogenicity in the rat and mouse. Rat and mouse carcinogenicity assays have been performed with atovaquone. In the rat, the results indicate no increase in tumour burden at doses that achieve significant systemic exposure.

In the mouse, an increase in the incidence of hepatocellular tumours was seen. A possible mechanism is suggested based on induction of a CYP 450 isozyme (2B1) in mouse liver and not in the rat liver, and the equivalent isoenzyme in humans (2B6) is expressed at very low levels in normal human liver. It is argued that this metabolic path is responsible for a liver carcinogenesis that is irrelevant to man.

Local tolerance(III H)
Local (site of administration) reactions were sought in the repeat-dose studies which included GI tract examination and histopathology. Nothing of significance was found.

Other studies (III Q)
There are no other studies for the combination of atovaquone and proguanil.

Environmental Risk Assessment
Not applicable.

EXPERT REPORT
The applicant has supplied a Pharmaco-toxicological Expert Report, which is satisfactory.

SUMMARY OF PRODUCT CHARACTERISTICS
This is acceptable from a toxicological perspective.

DISCUSSION
There is little information from animal or *in vitro* models of malarial infection on whether Malarone is likely to be effective in combating resistant *Plasmodium* strains. This is not important if the human trial data provide sufficient assurance on benefit. The general toxicity testing is supported by systemic exposure data in rat and dog, which indicate that, even in those animals with the highest circulating concentrations of atovaquone, toxicity remains linked to the exposure to proguanil or its metabolites. Adverse reactions for the combination are not worse than for proguanil alone.

Effects on reproduction are not exacerbated by combining the two compounds. Genotoxicity is absent from either component assayed separately. The increased incidence of mouse liver tumours is attributable to a species-specific biotransformation.

There are no other preclinical issues.

CONCLUSION
There are no preclinical objections to the grant of a Marketing Authorisation for Malarone.

III.3 CLINICAL ASPECTS

III.3.1 Clinical Pharmacology

Pharmacodynamics
There are no significant pharmacodynamic effects in man with either atovaquone or proguanil. Anti-protozoal activity is the important feature for both active substances.

Atovaquone and proguanil hydrochloride, interfere with two different pathways involved in the biosynthesis of pyrimidines required for nucleic acid replication. Atovaquone is a selective and potent inhibitor of parasite mitochondrial electron transport. Proguanil hydrochloride primarily exerts its effect by means of the metabolite cycloguanil, a dihydrofolate reductase inhibitor. Inhibition of dihydrofolate reductase in the malaria parasite disrupts deoxythymidylate synthesis. These two mechanisms are believed to be the prime explanation of the synergy seen when used in combination.

Microbiology:
Atovaquone has potent activity against *Plasmodium spp* (*in vitro* IC_{50} against *P. falciparum* 0.23-1.43ng/ml).

The antimalarial activity of proguanil is exerted via the primary metabolite cycloguanil (*in vitro* IC_{50} 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.

Pharmacokinetics
As these are well-established products and full information is given in the Clinical Expert Report, only a summary is given here.

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

Absorption
Atovaquone is a highly lipophilic compound with low aqueous solubility. The bioavailability of atovaquone shows considerable inter-individual variability. 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**.**

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 metabolized and there is negligible excretion of atovaquone in urine with the parent drug being predominantly (> 90%) eliminated unchanged in faeces.

Proguanil hydrochloride is partially metabolized with less than 40% being excreted unchanged in the urine. Its metabolites cycloguanil and 4-chlorophenylbiguanide are also excreted in the urine.

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

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.

Bioequivalence of the combined atovaquone/proguanil tablet
In almost all of the clinical trials, atovaquone and proguanil were given as separate tablets concomitantly. Thus it was essential to demonstrate that the new combined tablet is bioequivalent with the individual drugs.

Study Number BLVS/95/0018
This was an open three-period crossover study in 26 healthy volunteers. The first two periods were randomized, balanced, two-period crossover design in which all volunteers received combination tablets or separate tablets of atovaquone and proguanil given concomitantly.

On the third occasion, subjects repeated the treatment of the second occasion, irrespective of whether they had taken the combination tablet or separate tablets, in order to assess any treatment carry-over effect.

For atovaquone assay, blood was sampled for 14 days and, for proguanil assay, blood was sampled for 7 days. Between occasions, there was a washout period of at least 3 weeks.

The main pharmacokinetic parameters were $AUC_{0-\infty}$ and C_{max}. The $AUC_{0-\infty}$ and C_{max} ratios for the comparison of a combination tablet and the separate tablets were estimated along with the 90% confidence intervals. Treatments were considered to be bioequivalent if the 90% confidence intervals for the ratios of $AUC_{0-\infty}$ and C_{max} between treatments were within the range 80-125%.

Several assay methods were developed throughout the clinical study programme but all were validated.

Drug interactions
Atovaquone and Proguanil
Study number BLVS/96/0002 compared, in normal volunteers, atovaquone or proguanil alone with combined doses of the two drugs. The results of this study showed that the pharmacokinetics of atovaquone and proguanil and its metabolite cycloguanil were not modified when atovaquone and proguanil were given alone or in combination.

Other Drug Interactions
A. Metoclopramide and rifampicin reduce steady state concentrations of atovaquone.
B. There might be reduced plasma levels of atovaquone when co-administered with tetracycline. This does not appear to be of clinical importance.

Plasma concentrations/effect relationship
In clinical trials, atovaquone, proguanil and cycloguanil plasma concentrations showed wide inter individual availability. Because not many plasma samples were obtained during clinical trials, and there were few recrudescences of malaria, it is not possible to determine the relationship between blood concentrations and antimalarial response.

Significance of $t_{½}$ of atovaquone
As the $t_{½}$ of atovaquone is longer than that of proguanil, there will be times when atovaquone is in the plasma without proguanil. This causes a potential risk of resistance developing to atovaquone.

Gender effect
There appears to be no clinical difference for males and females.

Races
With other antimalarial drugs, race can be an important factor but, as yet, there is insufficient evidence for Malarone.

Children
No pharmacokinetic studies have been performed but it is considered that the bodyweight formula should be used.

Elderly
Very few elderly patients have been treated but it is considered that they should be able to take the usual adult dose.

Renal Failure
No studies have been performed. Atovaquone is not excreted in urine. Accumulation of proguanil and cycloguanil is unlikely over the short period of treatment.

Liver impairment
No studies have been performed. The applicant considers that the short duration of treatment should not present a problem.

Efficacy
The applicant has presented 12 clinical trials; four of which are uncontrolled and eight of which are controlled. Summaries of all studies are in the applicant's Appendix.
Uncontrolled Studies
1. BQRT/92/0003 (15 patients)
Details of this study were submitted when the company sought a Marketing Authorisation for Wellvone tablets. It was a pilot study of atovaquone alone and although there were good clinical and parasitological responses there was an unacceptable recrudescence rate within 3 months.

2. BQRT/95/0001 (314 patients)
This is important because cohorts of patients received different doses of atovaquone and proguanil for various times. It was shown that neither atovaquone nor proguanil alone was effective therapy. The ideal treatment appeared to be atovaquone 1000mg

once daily with proguanil 400mg once daily for three consecutive days. This was the dose that was used in the controlled clinical trials. It should be noted that treatment was given as 4 x 250mg atovaquone and 4 x 100mg proguanil daily. A combination tablet was not used in these clinical trials.

3. BQRT/95/0008 (31 patients)
This was a study of atovaquone alone.

4. BQR/95/0005 (32 patients)
This was a pilot study in children who weighed less than 40kg.

Controlled Studies
Clinical trials were performed at single centres in Thailand, Zambia, Kenya, Gabon, Brazil, Peru and The Philippines. Studies were focused on *P. falciparum* malaria because it is the commonest, most severe form of malaria and for which drug resistance is an increasing problem.

Primary Efficacy End-Point
This was the proportion of patients cured of malarial infection. Cure is eradication of parasites from blood within 7 days and no recrudescences within 28 days (WHO criteria used).

An intent-to-treat analysis is inappropriate for malaria treatment because the definition of cure required follow-up for 28 days.

Secondary end-points
A. Parasite clearance time (PCT)
B. Fever clearance time (FCT)

Power of Statistical Analysis
All eight controlled clinical trials were adequately powered to detect a clinically important difference in treatment. Results of the eight controlled clinical trials are tabled overleaf.

Conclusions from Controlled Clinical Trials
These eight studies have shown atovaquone and proguanil hydrochloride to be effective treatment for acute falciparum malaria.

Table 8. Efficacy Evaluation of Controlled Clinical Trials of Atovaquone and Proguanil Hydrochloride for Treatment of Malaria.

Study	Group	Treatment[a]	Number of Patients								Cure rate	Parasite clearance time (hr)	Fever clearance time (hr)
			Enrolled	Lost to follow-up	Withdrawn	Sensitive S	Resistant RI	Resistant RII	Resistant RIII	Total evaluable			
BQRT/95/0002	1	1000 mg ATQ q24h x 3 400 mg PRG q24h x 3	82	0	2	80	0	0	0	80	100%	72	23
	2	75 mg PYR x 1 1500 mg SDX x 1	81	1	0	79	1	0	0	80	99%	48	48
BQRT/95/0003	1	1000 mg ATQ q24h x 3 400 mg PRG q24h x 3	91	11	1	79	0	0	0	79	100%	66	54
	2	1250 mg MFQ (750 & 500 mg at 0 & 6h)	91	11	1	68	11	0	0	79	86%	65	50
BQRT/95/0006	1[b]	20 mg/kg ATQ q24h x 3 8 mg/kg PRG q24h x 3	84	0	3	76	5	0	0	81	94%	64	30
	2[c]	8 mg/kg HLF q6h x 3	84	0	1	75	8	0	0	83	90%	50	35
BQRT/95/0004[d]	1	1000 mg ATQ q24h x 3 400 mg PRG q24h x 3	70	5	2	62	1	0	0	63	98%	83	12
	2	2000 mg ADQ (800, 800 & 400 mg at 0, 24 & 48h)	71	7	1	51	12	0	0	63	81%	60	12
BQRT/95/0017	1	1000 mg ATQ q24h x 3 400 mg PRG q24h x 3	55	0	1	54	0	0	0	54	100%	49	36
	2	1500 mg CQ (600,300,300 & 300 mg at 0,6,24&48h)	23	0	0	7	11	3	2	23	30%	52	48
	3	1500 mg CQ as above 75 mg PYR x 1 1500 mg SDX x 1	32	0	0	28	4	0	0	32	88%	42	34
GM1997/00067	1	1000 mg ATQ q24h x 3 400 mg PRG q24h x 3	87	0	13	73	1	0	0	74	99%	58	23
	2	650 mg QN q8h x 24 250 mg TCN q6h x 28	88	0	12	76	0	0	0	76	100%	68	26

Study	Group	Treatment[a]	Number of Patients								Cure rate	Parasite clearance time (hr)	Fever clearance time (hr)
			Enrolled	Lost to follow-up	Withdrawn	Sensitive S	Resistant RI	Resistant RII	Resistant RIII	Total evaluable			
GM1997/00068	1	1000 mg ATQ q24h x 3 400 mg PRG q24h x 3	15	0	1	14	0	0	0	14	100%	57	46
	2	1500 mg CQ (600,300,300 & 300 mg at 0,6,24&48h)	14	0	1	1	7	5	0	13	8%	48	48
	3	1000 mg ATQ q24h x 3 400 mg PRG q24h x 3	5	0	0	5	0	0	0	5	100%	42	40
	4	75 mg PYR x 1 1500 mg SDX x 1	9	0	2	7	0	0	0	7	100%	42	44
GM1997/00098	1	1000 mg ATQ q24h x 3 400 mg PRG q24h x 3	25	1	3	21	0	0	0	21	100%	60	62
	2	(500 mg HLF q6h x 3) x2	23	3	2	18	0	0	0	18	100%	48	57

[a] ATQ = atovaquone, PRG = proguanil hydrochloride, PYR = pyrimethamine, SDX = sulphadoxine, MFQ = mefloquine hydrochloride, HLF = halofantrine, ADQ = amodiaquine hydrochloride, CQ = chloroquine, QN = quinine, TCN = tetracycline.

[b] Three patients in group 1 were treated twice, for initial parasitaemia and for re-treatment of recrudescent parasitaemia. Two had a sensitive response and one had an RII response after re-treatment. The responses to re-treatment are not tabulated here.

[c] Four patients in group 2 were treated twice, for initial parasitaemia and for re-treatment of recrudescent parasitaemia. All had a sensitive response after re-treatment. The responses to re-treatment are not tabulated here.

[d] An additional 7 patients in study BQRT/95/0004 with non-falciparum malaria are described in Table 7.

Treatment of Non-Falciparum Malaria

P. vivax infections respond promptly to Malarone but, within 2 weeks, relapses occur probably because of persistent hepatic infection with the organism, although recrudescences of erythrocytic infection cannot be excluded. It is likely that concurrent therapy with primaquine is required to eradicate persistent hepatic infection. Information is too limited with *P. ovale* and *P. malariae* to draw any conclusions.

Treatment Failures

Thirteen patients who were treated with atovaquone and proguanil hydrochloride for an initial episode of malaria were not cured. In all 13 patients, parasitaemia cleared within 7 days after the initial therapy but recurrent parasitaemia developed 19-28 days after starting treatment.

Seven of these patients were in the dose ranging study BQRT/95/0001 and might have received sub-optimal therapy. The other six patients were observed in hospital for 7 days or less and were followed up as outpatients. Therefore, it is, possible that they had reinfection rather than recrudescence.

Re-treatment with Atovaquone with or without Proguanil Hydrochloride

Three of five patients in study BQRT/95/0006 had recurrent parasitaemia after initial treatment of atovaquone and proguanil hydrochloride and were re-treated with these drugs. One of the patients had an RII response to re-treatment. It is likely that this patient had a recrudescent infection with drug-resistant parasites.

The clinical expert comments that treatment with an alternative anti-malarial drug is recommended for patients who have recurrent or persistent parasitaemia after treatment with Malarone.

Comparative Studies

In the comparative studies, atovaquone and proguanil hydrochloride have been shown to be better than amodiaquine, chloroquine, mefloquine and pyrimethamine together with sulphadioxide in some studies and, in three others, to have a similar cure rate to halafantrine and quinine plus tetracycline.

Summary of Efficacy

It was shown that the overall cure rate with 1000mg atovaquone and 400mg proguanil hydrochloride for adults, and an equivalent dose based on bodyweight for children, once daily for 3 days was 99% effective in 464 of 471 evaluable patients with *P. falciparum* malaria. Results were similar for adults and children, males and females.

SAFETY

Safety data are available for 1427 patients in all of the efficacy trials of whom 466 received the recommended dose of Malarone.

Adults

Four hundred and thirty-six patients in seven controlled studies had the recommended dose of Malarone. The most common adverse experiences were abdominal pain (25%), headache (22%), vomiting (17%), diarrhoea (14%) and nausea (5%).

There were also 56 less common adverse events, such as insomnia, palpitations and asthenia, but these often occurred more commonly with comparators.

Children

One hundred and sixteen children received the recommended dose in two clinical trials. The most common adverse drug effects were coughing (21%), headache (19%), vomiting (17%), abdominal pain (14%) and anorexia (13%).

Abdominal pain occurred more frequently in patients treated with halofantrine ($p = 0.004$) but the other adverse experiences were similar with Malarone and the comparators.

Treatment-Limiting Adverse Effects, Serious Adverse Effects and Deaths

Nine patients were withdrawn from atovaquone and/or proguanil treatment [five vomiting, one headache, one viral gastroenteritis, one seizure, one anaphylactic reaction (vomiting, urticaria and hypotension)]. The latter two were considered to be serious. Two patients on atovaquone alone had psychiatric symptoms and one on atovaquone and proguanil had seizures but did not stop treatment. Patients with seizures had a past history of the condition.

A 23-year-old Zambian man died whilst receiving atovaquone alone. He had long-standing psychiatric illness. Cause of death is unknown.

Laboratory Evaluations

As is to be expected with malaria, mean data showed patients to have evidence of anaemia, reduced platelet counts and mild abnormalities in laboratory tests of hepatic and renal function. Overall, there appeared to be no super-imposed adverse trends that could be attributed to treatment with atovaquone, proguanil or a combination of the drugs.

During a study in Thailand (BQRT/95/0003), there were marked elevations in ALT or AST in 21% of patients who received atovaquone and proguanil. The incidence was 9% of patients who received mefloquine ($p < 0.05\%$). There were also elevations in bilirubin but no patient was clinically jaundiced. Such abnormal laboratory tests returned to normal within 28 days. It was considered that laboratory abnormalities were no more significant with atovaquone and proguanil together, than with the individual drugs.

POST-MARKETING EXPERIENCE

Malarone Tablets (each containing 250 mg atovaquone and 100 mg proguanil hydrochloride) are approved for treatment of acute, uncomplicated *Plasmodium falciparum* malaria in both adults and children in over 40 countries. They are also approved for prophylaxis of *P. falciparum* malaria.

Malarone Tablets have been marketed for over 5 years and no safety issues have arisen during this time.

Atovaquone has been available since 1992 for the treatment of Pneumocystis carinii pneumonia. The dose is 700mg 3 times daily for 28 days, which is much in excess of what is required with Malarone.

Of 160 000 treatment courses for AIDS-related infections, there have been 122 adverse drug events from 53 spontaneous reports. One fatality due to respiratory failure was not considered to be drug related.

Proguanil has been in clinical use for more than 50 years and is considered to have a reasonable safety profile even when used long-term as a prophylactic agent.

RISK/BENEFIT ASSESSMENT
Malaria is a very common life-threatening condition. Well-conducted clinical trials have shown that Malarone (or at least atovaquone plus proguanil) is an effective, acceptably safe medication for *P. falciparum* malaria.

CLINICAL EXPERT REPORT
The report deals fully with the world-wide malaria problem, reviews current therapy and stresses the problem of multiple-drug resistance. It is made clear that proguanil hydrochloride is becoming a less valuable treatment and that atovaquone alone is unsatisfactory.

By laboratory testing, but particularly by clinical trials, it was shown that a fixed dose of atovaquone and proguanil is effective in the treatment of *P. falciparum* malaria. The expert does not state that evidence for treating other forms of malaria with Malarone is inadequate. When the term 'multi-drug resistant falciparum malaria' is used, it is not stated whether clinical trials were performed in areas where drug resistance is known to exist or whether patients who received Malarone were infected by resistant plasmodia.

Otherwise, it is a comprehensive review of Malarone.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)
The Summary of Product Characteristics is satisfactory.

PATIENT INFORMATION LEAFLET (PIL)
The Patient Information Leaflet is satisfactory.

LABELLING
The labels are satisfactory.

PART I - ADMINISTRATIVE PARTICULARS
Completed European Application Forms are provided.

DISCUSSION
Proguanil hydrochloride is a well-established antimalarial drug against which plasmodial resistance is developing. Atovaquone is a weak schizonticide which has a mode of action similar to that of proguanil. Well-conducted, controlled clinical trials of the two drugs given together have shown them to be effective in the treatment of *P. falciparum* malaria even in countries where drug resistance is recognized. It is possible that the combination of the two drugs might be of some value in treating the three other types of malaria but adequate clinical data have not been supplied. Although atovaquone and proguanil hydrochloride were given as separate drugs concomitantly, a bioequivalence study has shown that the combined

Malarone tablet should be equally effective in clinical use. Because Malarone will be used only for 3-day periods the risk of resistance developing is probably small.

The clinical expert has made a fair appraisal of the data derived from the clinical studies. His overall conclusions, including the benefit/risk assessment and the comments on the Summary of Product Characteristics appeared to be well judged. There are no major public health concerns and the data presented here are sufficient to establish the efficacy and safety of Malarone for the treatment of acute, uncomplicated *Plasmodium falciparum* malaria.

RECOMMENDATIONS

The efficacy and safety of Malarone from Glaxo Wellcome UK Ltd are satisfactory for the grant of a Marketing Authorisation.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

This is an application for a fixed combination, made under Article 10.1(b). The applicant has submitted suitable pharmacological data.

It is accepted that bioequivalence has been demonstrated between the fixed combination tablets and doses of each active given as separate tablet entities.

It is accepted that risk:benefit ratio is favourable.

The product literature has been amended in-line with the current guidelines. The SmPC includes all relevant warnings.

There are no pre-clinical concerns with these applications or with the clinical use of either atovaquone or proguanil hydrochloride.

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