SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Atovaquone/Proguanil Hydrochloride 62.5 mg/25 mg film-coated tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Atovaquone/Proguanil Hydrochloride tablet contains 62.5 mg atovaquone and 25 mg proguanil hydrochloride.

Excipients with known effect:

Each Atovaquone/Proguanil Hydrochloride tablet contains less than 1 mmol sodium, that is so to say essentially ‘sodium-free’.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Pink, round, biconvex film coated tablets debossed with 'I' on one side and '11' on the other side. They are 7.20 – 7.60mm in diameter.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Prophylaxis of Plasmodium falciparum malaria in adults and children weighing 11-40 kg.

Treatment of acute, uncomplicated Plasmodium falciparum malaria in adults and in children weighing ≥5 kg and <11 kg.

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

The dosage for the prophylaxis and treatment of acute, uncomplicated *P. falciparum* malaria in children is based on body weight.

Prophylaxis

Dosage in individuals weighing 11-40 kg

	Dosage/ day		
Body Weight Range (kg)	**Atovaquone (mg)**	**Proguanil (mg)**	**No of Tablets**
11-20	62.5	25	One Atovaquone/Proguanil Hydrochloride paediatric tablet
21-30	125	50	Two Atovaquone/Proguanil Hydrochloride paediatric tablets
31-40	187.5	75	Three Atovaquone/Proguanil Hydrochloride paediatric tablet
>40	250	100	Subjects of >40 kg should receive ONE Atovaquone/Proguanil Hydrochloride 250/100 mg tablet daily

The safety and effectiveness of atovaquone/proguanil 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
- continue for 7 days after leaving the area.

The safety and effectiveness of atovaquone/proguanil paediatric tablets have been established in studies of up to 12 weeks in residents (semi-immune) of endemic areas. (see section 5.1).

In non-immune subjects, the average duration of exposure in clinical studies was 27 days.

Treatment

Dosage in individuals weighing 5-11 kg

	Dosage /day		
Body Weight Range (kg	**Atovaquone (mg)**	**Proguanil (mg)**	**No of Tablets**
5-8	125	50	Two Atovaquone/Proguanil Hydrochloride paediatric tablets daily for 3 consecutive days
9-10	187.5	75	Three Atovaquone/Proguanil Hydrochloride paediatric tablets daily for 3 consecutive days.
≥11	Refer to Atovaquone/Proguanil Hydrochloride 250/100 mg tablets SmPC		

The safety and effectiveness of atovaquone/proguanil paediatric tablets for the treatment of malaria in children who weigh less than 5 kg has not been established.

For individuals whom weight 11 kg or more, the first choice for the treatment of acute, uncomplicated *P. falciparum* malaria is Atovaquone/Proguanil Hydrochloride tablets (250/100 mg). Please consult the Atovaquone/Proguanil Hydrochloride tablets SmPC for the recommended dosage for this weight range. Atovaquone/Proguanil Hydrochloride tablets are four-times the strength of Atovaquone/Proguanil Hydrochloride paediatric tablets.

In circumstances when sufficient Atovaquone/Proguanil Hydrochloride tablets are not available, then Atovaquone/Proguanil Hydrochloride paediatric tablets may be used.

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).

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, Atovaquone/Proguanil Hydrochloride is contraindicated for the prophylaxis of malaria in adults and children with severe renal impairment (creatinine clearance <30 mL/min; see sections 4.3 and 5.2).

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 Atovaquone/Proguanil Hydrochloride 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.

Atovaquone/Proguanil Hydrochloride paediatric tablets should preferably be swallowed whole. If difficulties are encountered when dosing young children, the tablets may be crushed and mixed with food or a milky drink just prior to administration.

4.3 Contraindications

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

Atovaquone/Proguanil Hydrochloride 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 precautions for use

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

Persons taking Atovaquone/Proguanil Hydrochloride paediatric tablets for prophylaxis or treatment of malaria should take a repeat dose if they vomit within 1hour 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

atovaquone/proguanil for malaria prophylaxis. However, as with other antimalarial agents, subjects with diarrhoea or vomiting should be advised to continue with malaria prevention measures by complying with personal protection measures (repellants, bednets).

In patients with acute malaria who present with diarrhoea or vomiting, alternative therapy should be considered. If Atovaquone/Proguanil Hydrochloride is used to treat malaria in these patients, parasitaemia and the patient's clinical condition should be closely monitored.

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

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

Atovaquone/proguanil has been shown to have no efficacy against hypnozoites of Plasmodium vivax as parasite relapse occurred commonly when *P. vivax* malaria was treated with atovaquone/proguanil 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 Atovaquone/Proguanil Hydrochloride, or failure of chemoprophylaxis with Atovaquone/Proguanil Hydrochloride paediatric tablets, patients should be treated with a different blood schizonticide as such events can reflect a resistance of the parasite.

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

The concomitant administration of Atovaquone/Proguanil Hydrochloride and efavirenz or boosted protease-inhibitors should be avoided whenever possible (see section 4.5)

The concomitant administration of Atovaquone/Proguanil Hydrochloride and rifampicin or rifabutin is not recommended (see section 4.5).

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

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

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

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

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

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

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

Proguanil may potentiate the anticoagulant effect of warfarin and other coumarin based anticoagulants which may lead to an increase in the risk of haemorrhage. The mechanism of this potential drug interaction has not been established. Caution is advised when initiating or withdrawing malaria prophylaxis or treatment with atovaquone-proguanil in patients on continuous treatment with oral anticoagulants. The dose of the oral anticoagulant may need to be adjusted during atovaquone-proguanil treatment or after its withdrawal, based on INR results.

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

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

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

4.6 Fertility, Pregnancy and lactation

Pregnancy

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

Animal studies showed no evidence for teratogenicity of the combination.

The individual components have shown no effects on parturition or pre- and post-natal development.

In rabbits treated with atovaquone during pregnancy, embryotoxicity was observed only in the presence of maternal toxicity. (see section 5.3)

The use of Atovaquone/Proguanil Hydrochloride 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 Atovaquone/Proguanil Hydrochloride paediatric tablets.

Breast-feeding

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

Proguanil is excreted in human milk in small quantities.

Atovaquone/Proguanil Hydrochloride paediatric tablets should not be taken by breast-feeding women.

Fertility

Proguanil hydrochloride did not cause effects on fertility in rats at exposures below the human therapeutic exposure. Otherwise, there are no data regarding potential effects of atovaquone and proguanil hydrochloride on fertility.

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

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

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

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

In clinical trials of atovaquone/proguanil for treatment of malaria, the most commonly reported adverse reactions were abdominal pain, headache, anorexia, nausea, vomiting, diarrhoea and coughing.

In clinical trials of atovaquone/proguanil for prophylaxis of malaria, the most commonly reported adverse reactions were headache, abdominal pain and diarrhoea.

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

System Organ Class	**Very Common**	**Common**	**Uncommon**	**Rare**	**Not known[2]**
Blood and lymphatic disorders		Anaemia Neutropenia[1]			Pancytopenia
Immune system disorders		Allergic reactions			Angioedema[3] Anaphylaxis (see section 4.4) Vasculitis[3]
Metabolism and nutrition disorders		Hyponatraemia[1] Anorexia	Elevated amylase levels[1]		
Psychiatric disorders		Abnormal dreams Depression	Anxiety	Hallucinations	Panic attack Crying Nightmares Psychotic disorder
Nervous system disorders	Headache	Insomnia Dizziness			Seizure
Cardiac disorders			Palpitations		Tachycardia
Gastrointestinal disorders	Nausea[1] Vomiting Diarrhoea Abdominal pain		Stomatitis		Gastric intolerance[3] Oral ulceration[3]
Hepatobiliary disorders		Elevated liver enzymes[1]			Hepatitis Cholestasis[3]
Skin and subcutaneous tissue disorders		Pruritus Rash	Hair loss Urticaria		Stevens-Johnson syndrome Erythema multiforme Blister Skin exfoliation Photosensitivity reactions
General disorders and administration site conditions		Fever			
Respiratory,		Cough			

thoracic and mediastinal disorders					

1. Frequency taken from atovaquone label. Patients participating in clinical trials with atovaquone have received higher doses and have often had complications of advanced Human Immunodeficiency Virus (HIV) disease. These events may have been seen at a lower frequency or not at all in clinical trials with atovaquone-proguanil.

2. Observed from post-marketing spontaneous reports and the frequency is therefore unknown

3. Observed with proguanil.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimalarials

ATC code: P01B B51

Mode of Action

Atovaquone/Proguanil Hydrochloride 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.

The constituents of Atovaquone/Proguanil Hydrochloride 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 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. 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* IC_{50} against *P. falciparum* 0.23-1.43 ng/mL).

Resistance

Atovaquone is not cross-resistant with any other antimalarial drugs in current use. Isolated cases of treatment failures associated with mutations in codon 268 of cytochrome b have been reported after treatment with atovaquone-proguanil.

The IC_{50} of the primary metabolite of proguanil-cycloguanil against various *P. falciparum* strains was 4-20 ng/mL; some activity of proguanil and another metabolite, 4-chlorophenylbiguanide, is seen *in vitro* at 600-3000 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.

Clinical Efficacy

<u>Prophylaxis</u>

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

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

<u>Treatment</u>

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

5.2 Pharmacokinetic properties

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

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

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

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

* Pooled data from two studies

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_{max} 5 times over fasting. Patients are recommended to take Atovaquone/Proguanil Hydrochloride paediatric 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 and proguanil is approximately 8.8 L/kg.

Proguanil is 75% protein bound. Following oral administration, the volume of distribution of proguanil in adults and children (>5 kg) ranged from 20 to 79 L/kg.

In human plasma the binding of atovaquone and proguanil was unaffected by the presence of the other.

Biotransformation:

There is no evidence that atovaquone is metabolised, and there is negligible excretion of atovaquone in urine with the parent drug being predominantly (->-90%) eliminated unchanged in faeces.

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

During administration of Atovaquone/Proguanil Hydrochloride 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.

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

Oral clearance for atovaquone and proguanil increases with increased body weight and is about 70% higher in a 40 kg subject relative to a 20 kg subject. The mean oral

clearance in paediatric and adult patients weighing 5 to 40 kg ranged from 0.5 to 6.3 L/h for atovaquone and from 8.7 to 64 L/h for proguanil.

Pharmacokinetics in children:

In clinical trials, where children have received atovaquone/proguanil dosed by bodyweight, trough levels of atovaquone, proguanil and cycloguanil in children were generally within the range observed in adults.

Pharmacokinetics in renal impairment

There are no studies in children with renal impairment.

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

Atovaquone C_{max} and AUC are reduced by 64% and 54%, respectively, in adult patients with severe renal impairment (<30 mL/min/1.73 m^2).

In adult patients with severe renal impairment, the elimination half lives for proguanil ($t_{½}$ 39 hours) and cycloguanil ($t_{½}$ 37 hours) are prolonged, resulting in the potential for drug accumulation with repeated dosing (see sections 4.2 and 4.4).

Pharmacokinetics in hepatic impairment

There are no studies in children with hepatic impairment.

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

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

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

5.3 Preclinical safety data

Repeat dose toxicity:

Findings in repeat dose toxicity studies with atovaquone/proguanil hydrochloride combination were entirely proguanil related and were observed at doses providing no

significant margin of exposure in comparison with the expected clinical exposure. As proguanil has been used extensively and safely in the treatment and prophylaxis of malaria at doses similar to those used in the combination, these findings are considered of little relevance to the clinical situation.

Reproductive toxicity studies:

In rats and rabbits there was no evidence of teratogenicity for the combination. No data are available regarding the effects of the combination on fertility or pre- and post-natal development, but studies on the individual components of Atovaquone/Proguanil Hydrochloride paediatric tablets have shown no effects on these parameters. In rabbits treated with atovaquone during pregnancy, a decreased foetal body weight and increased early resorptions were observed at maternally toxic doses. Systemic exposure was similar to that observed in humans following clinical use. In rats and rabbits treated with the combination at exposures around or below the human therapeutic exposure, no teratogenicity or embryotoxicity were observed.

Mutagenicity:

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

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

Cycloguanil, the active metabolite of proguanil, was also negative in the Ames test, but was positive in the Mouse Lymphoma assay and the Mouse Micronucleus assay. These positive effects with cycloguanil (a dihydrofolate antagonist) were significantly reduced or abolished with folinic acid supplementation.

Carcinogencity:

Oncogenicity studies of atovaquone alone in mice showed an increased incidence of hepatocellular adenomas and carcinomas. No such findings were observed in rats and mutagenicity tests were negative. These findings appear to be due to the inherent susceptibility of mice to atovaquone and are considered of no relevance in the clinical situation.

Oncogenicity studies on proguanil alone showed no evidence of carcinogenicity in rats and mice.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Poloxamer188

Microcrystalline Cellulose (E460)

Low-substituted Hydroxypropyl Cellulose (E463)

Povidone K30 (E2101)

Sodium Starch Glycolate (Type A)

Magnesium Stearate (E572)

Silica colloidal anhydrous (E551)

Coating

Hypromellose (E464)

Titanium dioxide (E171)

Macrogol 400 (E1521)

Macrogol 8000 (E1521)

Iron Oxide Red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Clear Alu-PVC blister, Aluminium/Aluminium blister and HDPE containers

Pack size:

Alu-Alu Blister: 1, 12, 21, 24, 28, 36 film-coated tablets

Alu-PVC Blister: 1, 12, 21, 24, 28, 36 film-coated tablets

HDPE containers: 30, 100 film-coated tablets

Not all pack sizes may be marketed

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Amarox Limited

Congress House, 14 Lyon Road

Harrow, Middlesex HA1 2EN

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 49445/0016

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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