SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Atovaquone/Proguanil hydrochloride 250 mg/100 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 250 mg atovaquone and 100 mg proguanil hydrochloride.

Excipient with known effect:

Each film-coated tablet also contains 3.82 mg of lactose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Buff coloured, round, biconvex, film-coated tablets debossed with ‘A-P’ over ‘2’ on one side and ‘M’ on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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*. It is indicated for:

Prophylaxis of *Plasmodium falciparum* malaria.

Treatment of acute, uncomplicated Plasmodium falciparum malaria.

Because atovaquone/proguanil hydrochloride 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 medicinal products should be taken into consideration. Official guidelines will normally include WHO and public health authorities' guidelines.

4.2 Posology and method of administration

Posology

Prophylaxis

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.

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

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

Dosage in Adults

One tablet daily.

Atovaquone/Proguanil hydrochloride is not recommended for malaria prophylaxis in persons under 40 kg bodyweight. Other pharmaceutical strengths may be more appropriate for malaria prophylaxis in persons weighing under 40 kg.

Treatment

Adults

Four tablets as a single dose for three consecutive days.

Children

	Dosage/day
Body weight range (kg)	**No. of tablets**
11-20	One tablet daily for three consecutive days
21-30	Two tablets as a single dose for three consecutive days
31-40	Three tablets as a single dose for three consecutive days
>40	Dose as for adults

Elderly

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

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).

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 (creatine clearance <30 mL/min) alternatives to atovaquone/proguanil hydrochloride 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 several renal impairments see Section 4.3.

Method of administration

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

If patients are unable to tolerate food, atovaquone/proguanil hydrochloride 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.

4.3 Contraindications

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

Atovaquone/Proguanil hydrochloride is contraindicated for prophylaxis of *P. falciparum* malaria in patients with severe renal impairment (creatinine clearance <30 mL/min).

4.4 Special warnings and precautions for use

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

Persons taking atovaquone/proguanil hydrochloride 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 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 (repellents, impregnated 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, 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 and efavirenz or boosted protease-inhibitors should be avoided whenever possible (see section 4.5)

The concomitant administration of atovaquone/proguanil 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 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 for treatment of acute *P. falciparum* malaria should be recommended whenever possible (see sections 4.2, 4.3 and 5.2).

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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.

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 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 45 mg/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 (in rat and rabbit) showed no evidence for teratogenicity of the combination (see section 5.3).

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 atovaquone/proguanil hydrochloride in pregnancy should only be considered if the expected benefit to the mother outweighs any potential risk to the foetus.

The proguanil component of atovaquone-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.

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 should not be taken by breast-feeding women.

Fertility

No data are available regarding the effects of the combination on fertility, but in animal studies the individual components atovaquone and proguanil have shown no effects on fertility (see section 5.3).

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 in the treatment of malaria, the most commonly reported adverse reactions were abdominal pain, headache, anorexia, nausea, vomiting, diarrhoea and coughing.

In clinical trials of 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); rare (≥1/10,000 to <1/1,000); not known (cannot be estimated from the available data).

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

System Organ Class	**Very Common**	**Common**	**Uncommon**	**Rare**	**Not known[2]**
Blood and lymphatic system 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
Respiratory, thoracic and mediastinal disorders		Cough			
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			

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 Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard.

4.9 Overdose

There is insufficient experience to predict the consequences or suggest specific management of atovaquone/proguanil 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: Anitprotozoals, antimalarials, biguanides

ATC code: P01B B51

Mechanism of Action

The constituents of atovaquone/proguanil hydrochloride, 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).

Resistance

Atovaquone is not cross-resistant with any other antimalarial drugs in current use. In *in-vitro* studies with more than 30 *P. falciparum* isolates, resistance had been detected against chloroquine (41% of isolates), quinine (32% of isolates), mefloquine (29% of isolates), and halofantrine (48% of isolates) and not against 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.

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 atovaquone/proguanil hydrochloride with food or a milky drink (see section 4.2).

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

Distribution

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

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

Following oral administration, the volume of distribution of atovaquone in adults and children is approximately 8.8 L/kg.

Proguanil is 75% protein bound. Following oral administration, the volume of distribution of proguanil in adults and children ranged from 20 to 42 L/kg.

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

Biotransformation

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

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

During administration of atovaquone/proguanil 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 bodyweight and is about 70% higher in an 80 kg subject relative to a 40 kg subject. The mean oral clearance in paediatric and adult patients weighing 10 to 80 kg ranged from 0.8 to 10.8 L/h for atovaquone and from 15 to 106 L/h for proguanil.

Pharmacokinetics in 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 the elderly

There is no clinically significant change in the average rate or extent of absorption of atovaquone or proguanil between elderly and young patients. Systemic availability of cycloguanil is higher in the elderly compared to the young patients (AUC is increased by 140% and C_{max} is increased by 80%), but there is no clinically significant change in its elimination half life (see section 4.2).

Pharmacokinetics in renal impairment

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

Atovaquone C_{max} and AUC are reduced by 64% and 54%, respectively, in patients with severe renal impairment.

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

Pharmacokinetics in hepatic impairment

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

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

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

5.3 Preclinical safety data

Repeat dose toxicity

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

Reproductive toxicity studies

In rats and rabbits there was no evidence of teratogenicity for the combination. No data are available regarding the effects of the combination on fertility or pre- and

post-natal development, but studies on the individual components of atovaquone/proguanil tablets have shown no effects on these parameters. In a rabbit teratogenicity study using the combination, unexplained maternal toxicity was found at a systemic exposure similar to that observed in humans following clinical use.

Mutagenicity

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

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

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.

Carcinogenicity

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

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core

Cellulose, microcrystalline

Povidone (K-30)

Crospovidone Type A

Poloxamer 188

Magnesium stearate

Film-coating

Titanium dioxide (E171)

Lactose monohydrate

Macrogol 4000

Hypromellose 15cP (E464)

Hypromellose 50cP (E464)

Hypromellose 3cP (E464)

Iron oxide red (E172)

Iron oxide black (E172)

Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

PVC-Aluminium foil blister: 2 years.
OPA/Aluminium/PVC – Aluminium foil blister: 2 years.
PVC/PVdC – Aluminium foil blister: 3 years.

6.4 Special precautions for storage

Store in the original package in order to protect from moisture.

PVC-Aluminium foil blister only: Do not store above 25°C.

6.5 Nature and contents of container

PVC-Aluminium foil blister

OPA/Aluminium/PVC – Aluminium foil blister

PVC/PVdC – Aluminium foil blister

Pack sizes: 12, 24, 30, 36, 48 tablets or 12 x 1, 24 x 1, 30 x 1, 36 x 1, 48 x 1 tablets in perforated unit dose blisters.

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

Generics UK t/a Mylan

Station Close,

Potters Bar,

Herfordshire

EN6 1TL

8 MARKETING AUTHORISATION NUMBER(S)

PL 04569/1271

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

08/08/2017

10 DATE OF REVISION OF THE TEXT

06/09/2016