SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Maloff Protect 250 mg/100 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Maloff Protect tablet contains 250 mg atovaquone and 100 mg proguanil hydrochloride.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets (tablets).
Pinkish brown to brown coloured, circular, biconvex bevelled edge film-coated tablets with '404' debossed on one side and 'G' debossed on the other side

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Maloff 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 in adults and in children weighing more than 40 kg.Treatment of acute, uncomplicated *Plasmodium falciparum* malaria in adults and in children weighing 11 kg or more.

Because Maloff 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

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.
The tablets should preferably not be crushed.

If patients are unable to tolerate food, Maloff Protect should be administered, but systemic exposure of atovaquone will be reduced. In the event of vomiting within one hour of dosing a repeat dose should be taken.

Posology
Chemoprophylaxis
Chemoprophylaxis should:
- commence one to two days prior to entering a malaria-endemic area, continue during the period of the stay,
- continue for seven days after leaving the area.

In residents (semi-immune subjects) of endemic areas, the safety and effectiveness of Maloff Protect 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 Maloff Protect tablet daily.
Maloff Protect tablets are not recommended for malaria chemoprophylaxis in persons under 40 kg bodyweight.

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

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1
- Patients with diagnosed renal impairment of any severity
- Patients with diagnosed hepatic impairment of any severity.
- Maloff Protect is contraindicated for use in children and adolescents

4.4 Special warnings and precautions for use

Persons taking Maloff Protect for chemoprophylaxis of malaria should be advised to take a repeat dose if they vomit within one 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 Maloff Protect for malaria chemoprophylaxis. 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, bed nets).

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

Maloff Protect should not be used unless advised by a doctor or other qualified prescriber:
- In patients who are taking etoposide. (see section 4.5)
- In patients who are taking rifampicin or rifabutin (see section 4.5)
- In patients taking metoclopramide (see section 4.5)
- In patients taking warfarin or other oral anticoagulant (see section 4.5)

- In patients who are taking tetracycline (see section 4.5)
- In patients who are taking indinavir, efavirenz, zidovudine or boosted protease inhibitors (see section 4.5)
- In patients with a history of depression or seizures
- In patients with tuberculosis
- Patients who are pregnant, planning to become pregnant or breastfeeding. Pregnant women have an increased risk of developing severe malaria and a higher risk of fatality compared to non-pregnant women.

The safety and effectiveness of Maloff Protect has not been established for chemoprophylaxis of malaria in patients who weigh less than 40 kg.

Travellers should be reminded the need of receiving a full travel consultation if they have not already done so to undertake an overall risk assessment-based package of travel health advice. Malaria prophylaxis is only one of the aspects of pre-travel advice.

The maximum duration of travel for which Maloff Protect can be supplied without prescription is 12 weeks (93 tablets). For longer durations of travel, advice should be sought from a doctor or other qualified prescriber.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant administration of rifampicin or rifabutin with Maloff Protect 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.

When given with efavirenz or boosted protease-inhibitors, atovaquone concentrations have been observed to decrease by 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 risk of haemorrhage. The mechanism of this potential drug interaction has not been established. Caution is advised when initiating or withdrawing malaria prophylaxis with atovaquone proguanil in patients on continuous treatment with oralanticoagulants. The dose of oral anticoagulant may need to be adjusted during Maloff Protect use or after its withdrawal, based on INR results. Concomitant treatment with warfarin, other coumarin-based anticoagulants, or NOACs such as dabigatran etexilate, rivaroxaban, and apixaban should be undertaken with caution. (see section 4.4) Apixaban and rivaroxaban are substrates of CYP3A4 and p-glycoprotein, whilst dabigatran is a substrate of p-glycoprotein. Atovaquone may produce minor inhibition of CYP3A4, but the effect of proguanil on this enzyme is unknown. Neither atovaquone nor proguanil inhibits p-glycoprotein.

Concomitant treatment with tetracycline has been associated with decreases in plasma concentrations (AUC) of atovaquone. (see section 4.4)

Concomitant administration of atovaquone and indinavir results in a decrease in the minimum concentration after dosing (C_{min}) of indinavir (23% decrease; 90% CI 8-35%). (see section 4.4)

The co-administration of atovaquone at doses of 45 mg/kg/day in children (n=9) with acute lymphoblastic leukaemia for chemoprophylaxis of pneumocystis pneumonia (PCP) was found to increase the 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).

Pharmacokinetic data have shown that atovaquone appears to decrease the rate of metabolism of zidovudine to its glucuronide metabolite (steady state AUC of zidovudine was increased by 33% and peak plasma concentration of the glucuronide was decreased by 19%). At zidovudine dosages of 500 or 600 mg/day it would seem unlikely that a concomitant course of Maloff Protect would result in an increased incidence of adverse reactions attributable to higher plasma concentrations of zidovudine.

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).
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 Fertility, pregnancy and lactation

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

Animal studies showed no evidence for teratogenicity of the combination. The individual components have shown no effects on parturition or pre- and post-natal development. Maternal toxicity was seen in pregnant rabbits during a teratogenicity study (see section 5.3). The use of Maloff in pregnancy should only be considered if the expected benefit to the mother outweighs any potential risk to the foetus.

The proguanil component of Maloff 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 Maloff.

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.

Maloff 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

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 Maloff on growth, puberty and general development have not been studied.

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

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

1. Frequency taken from atovaquone label. Patients participating in clinical trials with atovaquone have received higher doses and have often had complications of advance Human Immunodeficiency Virus (HIV) disease. These events may have been seen at a lower frequency or not at all in clinical trials with atovaquone-proguanil.
2. Observed from post-marketing spontaneous reports and the frequency is therefore unknown
3. Observed with proguanil.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in 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 Maloff Protect 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:**

Pharmacotherapeutic group: ANTIMALARIALS, ATC Code: P01BB51

Maloff 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*.

Mode of Action
The constituents of Maloff, 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* IC50 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).

Atovaquone-proguanil acts as a blood schizonticide and also as activity against hepatic schizonts of *P. falciparum* that are resistant to other antimalarials, e.g. chloroquine, halofantrine, mefloquine, amidiaquine, and chloroquine + pyrimethamide/sulfadoxine.

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 Maloff dosed by bodyweight, 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. The pharmacokinetics of atovaquone is similar for healthy subjects and HIV-infected patients. There is no bioavailability data for healthy subjects. 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 Maloff 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 that 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 Maloff 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 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 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 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 chemoprophylaxis 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 Maloff Protect 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

Poloxamer 188

Microcrystalline Cellulose

Low-substituted Hydroxypropyl Cellulose

Povidone K30

Sodium Starch Glycolate Type A

Silica colloidal anhydrous

Magnesium Stearate

Coating

Hypromellose

Titanium Dioxide E171

Iron Oxide Red E172

Macrogol 400

Macrogol 8000

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

PVC/PVDC (clear) and hard tempered PVC/PVDC-Aluminium foil blisters containing 12 tablets.
Pack size: 24 or 36 tablets

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Glenmark Pharmaceuticals Europe Limited

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8 MARKETING AUTHORISATION NUMBER(S)

PL 25258/0166

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24/02/2015

10 DATE OF REVISION OF THE TEXT

15/01/2016