1.3 Product Information

1.3.1 Summary of product characteristics (SmPC)

1.3.1.1 Name of the drug product: LEMAL (ATOVAQUONE & PROGUANIL HYDROCHLORIDE TABLETS)

1.3. 1.2 Qualitative and quantitative composition:

Each Film coated tab contains
Atovaquone USP.....250mg
Proguanil Hydrochloride BP.....100mg
Excipients.....q.s.
Colour: Red oxide of Iron & Titanium dioxide BP

Sr. No.	Ingredients	Specifi-cation	Label Claim / Tablet (In mg)	Over-ages added (In %)	Qty. / Tablet (in mg)	Reason for Function
a)	**Dry Mixing**					
1.	Atovaquone	USP	250.0	NA	251.6	Active
2.	Microcrystalline Cellulose	BP	NA	NA	96.5	Binder
3.	Maize Starch	BP	NA	NA	58.0	Binder
b)	**Binder Preparation**					
4.	Ethyl cellulose	BP	NA	NA	3.0	Binder
5.	Purified Water	BP	NA	NA	-	Diluent
c)	**Lubrication**					
6.	Proguanil Hydrochloride	BP	NA	NA	0.04	Lubricant
7.	Sodium Starch Glycolate (Potato)	BP	NA	NA	0.16	Glidant
8.	Colloidal Silicon Dioxide (Aerosil) Light	BP	NA	NA	*00.70	Active
9.	Magnesium Stearate	BP	NA	NA	7.0	Lubricant
10.	Laffcol -6000 (PEG 6000)	BP	NA	NA	5.0	Lubricant
11.0	Sodium Lauryl Sulphate	BP	NA	NA	7.0	Lubricant
12.0	Flocel 102 IP RQ V MCCP	BP	NA	NA	8.0	Lubricant
	Average Weight of Uncoated Tablet (in mg)				**581.80 mg**	
13.0	Elegance Coat EL-OR-1268 Brown (Film Coat Organic Iron Oxide)	IH	NA	NA	16.2	Colourant
14.0	Isopropyl Alcohol**	BP	NA	NA	-	Solvent
15.0	Methylene Dichloride**	BP	NA	NA	--	Solvent
	Average Weight of Uncoated Tablet (in mg)				**598.0 mg**	

1.3.1.3 Pharmaceutical form: Uncoated tablet

1.3.1.4 Clinical Particulars

1.3.1.4.1 Therapeutic indications:

LEMAL 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 LEMAL 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..

1.3.1.4.2 Posology and method of administration

Route: Oral

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, LEMAL 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.

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 LEMAL 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 LEMAL tablet daily.
LEMAL tablets are not recommended for malaria prophylaxis in persons under 40 kg bodyweight.
LEMAL paediatric tablets are recommended for malaria prophylaxis in persons weighing <40 kg

Treatment

Dosage in Adults

Four LEMAL 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 (creatine clearance <30 mL/min) alternatives to LEMAL 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.

1.3.1.4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
LEMAL is contraindicated for prophylaxis of *P. falciparum* malaria in patients with severe renal impairment (creatinine clearance <30 mL/min).

1.3.1.4.4 Special warnings and precautions for use

Persons taking LEMAL 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 LEMAL 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 LEMAL is used to treat malaria in these patients, parasitaemia and the patient's clinical condition should be closely monitored.
LEMAL 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 LEMAL . If patients experience an allergic reaction (see section 4.8) LEMAL should be discontinued promptly and appropriate treatment initiated.
LEMAL has been shown to have no efficacy against hypnozoites of Plasmodium vivax as parasite relapse occurred commonly when *P. vivax* malaria was treated with LEMAL 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 LEMAL , or failure of chemoprophylaxis with LEMAL , 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 LEMAL and efavirenz or boosted protease-inhibitors should be avoided whenever possible (see section 4.5).
The concomitant administration of LEMAL 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 LEMAL 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 LEMAL for treatment of acute *P. falciparum* malaria should be recommended whenever possible (see sections 4.2, 4.3 and 5.2).
The safety and effectiveness of LEMAL (atovaquone 250mg/proguanil hydrochloride 100mg tablets) has not been established for prophylaxis of malaria in patients who weigh less than 40kg, or in the treatment of malaria in paediatric patients who weigh less than 11kg.

1.3.1.4.5 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 theeffect 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 LEMAL 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).

1.3.1.4.6 Pregnancies 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 LEMAL in pregnancy should only be considered if the expected benefit to the mother outweighs any potential risk to the foetus.
The proguanil component of LEMAL 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 LEMAL .
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.
LEMAL should not be taken by breast-feeding women.

1.3.1.4.7 Effects on the ability to drive and use machines

1.3.1.4.8 Side effects

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.

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			

A
L 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 LEMAL 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 LEMAL on growth, puberty and general development have not been studied.

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.

1.3.1.4.9 Overdoses

There is insufficient experience to predict the consequences or suggest specific management of LEMAL 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.

1.3.1.5 Pharmacological properties

1.3.1.5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimalarials, ATC Code: P01B B51
Mode of Action
The constituents of LEMAL , 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.

1.3.1.5.2 Pharmacokinetic

There are no pharmacokinetic interactions between atovaquone and proguanil at the recommended dose. In clinical trials, where children have received LEMAL 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. 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 LEMAL 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 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 LEMAL 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 ($t_{½}$ 39 h) 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).

1.3.1.5.3 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 LEMAL 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.

1.3.1.6 Pharmaceutical particulars

1.3.1.6.1 List of excipients

Atovaquone

Microcrystalline Cellulose

Maize Starch

Ethyl cellulose

Proguanil Hydrochloride

Sodium Starch Glycolate (Potato)

Colloidal Silicon Dioxide (Aerosil) Light

Magnesium Stearate

Laffcol -6000 (PEG 6000)

Sodium Lauryl Sulphate

Flocel 102 IP RQ V MCCP

Elegance Coat EL-OR-1268 Brown

1.3.1.6.2 Incompatibilities
Not applicable

1.3.1.6.3 Shelf life
36 months

1.3.1.6.4 Special precautions for storage

No special requirements.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements

1.3.1.6.5 Nature and contents of container

Primary packing: 12 T PVC -ALU blister.

Secondary packing: 12T PVC –ALU Blister packed in carton with literature.

1.3.1.6.6 Special precautions for disposal and other handling

None.

1.3.1.7 Applicant / Manufacturer

Applicant

Applicant name and address	Devon Pharmaceuticals Co. Ltd. 15 Oke-Afa Road, Ilupeju,Magboro, Ogun State, Nigeria.
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Manufacturer

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