PACKAGE INSERT

SCHEDULING STATUS:

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PROPRIETARY NAME AND DOSAGE FORM:

MALANIL® Tablets

COMPOSITION:

Each tablet contains 250 mg atovaquone and 100 mg proguanil hydrochloride

PHARMACOLOGICAL CLASSIFICATION:

A 20.2.6 Medicines against protozoa

PHARMACOLOGICAL ACTION:

Pharmacodynamics:

Mode of action:

The constituents of MALANIL, 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.

Microbiology:

Atovaquone has activity against *Plasmodium spp.* (*in vitro* IC_{50} against *P. falciparum* 0,23-1,43 ng/ml).

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 600-3 000 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.

Pharmacokinetics:

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

Absorption:

Atovaquone is a highly lipophilic compound with low aqueous solubility.

The pharmacokinetics of atovaquone are comparable between healthy subjects and HIV-infected patients. 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 MALANIL tablets with food or milk (see DOSAGE AND DIRECTIONS FOR USE).

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

Distribution:

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

Following oral administration, the apparent volume of distribution of atovaquone in adults and children is approximately 8,8 l/kg.

Proguanil is 75 % protein bound.

Following oral administration, the apparent volume of distribution of proguanil in adults weighing 41 to 80 kg is 42 to 27 l/kg.

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

Metabolism:

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

Proguanil hydrochloride is partially metabolised, 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 MALANIL at recommended doses, proguanil metabolism status appears to have no implications for prophylaxis of malaria.

Elimination:

The elimination half-life of atovaquone is about 2-3 days in adults and 1-2 days in children.

Following oral administration, the clearance of atovaquone in adults and children weighing 41 to 80 kg is approximately 0,16 to 0,05 l/h/kg.

The elimination half-life of proguanil and cycloguanil is about 12-15 hours in both adults and children.

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 young patients, but there is no change in its elimination half-life (see DOSAGE AND DIRECTIONS FOR USE).

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 increase in proguanil AUC with no change in its elimination half-life and there is a decrease in C_{max} and AUC for cycloguanil.

No data are available in patients with severe hepatic impairment (see DOSAGE AND DIRECTIONS FOR USE).

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 in patients with severe renal impairment.

The elimination half-lives for proguanil and cycloguanil are prolonged in patients with severe renal impairment with corresponding increases in AUC, resulting in the potential of drug accumulation with repeated dosing (see DOSAGE AND DIRECTIONS FOR USE and WARNINGS AND SPECIAL PRECAUTIONS).

INDICATIONS:

MALANIL is indicated for the prophylaxis of drug sensitive and drug resistant *Plasmodium falciparum* malaria.

Official guidelines and local information on the prevalence of resistance to antimalarial drugs should be taken into consideration.

CONTRA-INDICATIONS:

MALANIL is contra-indicated in individuals with known hypersensitivity to atovaquone or proguanil hydrochloride or any component of the formulation.

MALANIL is contra-indicated for prophylaxis of *P. falciparum* malaria in patients with severe renal impairment (creatinine clearance < 30 ml/min).

WARNINGS AND SPECIAL PRECAUTIONS:

Safety and effectiveness of MALANIL for the prophylaxis of malaria in patients who weigh less than 40 kg has not been established.

In the event of recrudescent infections due to *P. falciparum* or failure of chemoprophylaxis, patients should be treated with a different blood schizonticide.

Persons taking MALANIL for prophylaxis 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 MALANIL for malaria prophylaxis. However, patients with diarrhoea or vomiting should be advised to continue to comply with personal protection measures (repellents, bednets).

The concomitant administration of MALANIL and rifampicin or rifabutin is not recommended (see INTERACTIONS).

It is not recommended that mothers receiving MALANIL breastfeed their babies.

MALANIL should be used with caution in patients with a history of epilepsy (see SIDE EFFECTS).

Skin rashes ranging from photosensitivity rashes and urticaria to Stevens-Johnson syndrome have been reported. MALANIL must be stopped immediately at the first sign of a serious skin rash or where there is blistering or mucosal involvement.

There have been no studies to investigate the effect of MALANIL on driving performance or the ability to operate machinery, but a detrimental effect on such activities is not predicted from the pharmacology of the component drugs.

INTERACTIONS:

Proguanil may potentiate the anticoagulant effect of warfarin and other coumarin based anticoagulants. The mechanism of this potential drug interaction has not been

established. Caution is advised when initiating or withdrawing malaria prophylaxis with MALANIL in patients on continuous treatment with anticoagulants.

Concomitant use of tetracycline, metoclopramide, rifampicin and rifabutin have been associated with significant decreases in plasma concentrations of atovaquone (see WARNINGS AND SPECIAL PRECAUTIONS).

Concomitant administration of atovaquone and indinavir results in a decrease in the C_{min} of indinavir (23 % decrease; 90 % CI 8-35 %). Caution should be exercised in prescribing atovaquone with indinavir due to the decrease in trough levels of indinavir.

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.

PREGNANCY AND LACTATION:

The safety of atovaquone and proguanil hydrochloride when administered concurrently in human pregnancy and lactation have not been established.

The proguanil component of MALANIL 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 may be continued while taking MALANIL.

DOSAGE AND DIRECTIONS FOR USE:

The daily dose should be taken with food or milk at the same time each day. In the event of vomiting within 1 hour of dosing, a repeat dose should be taken.

Prophylaxis:

Prophylaxis should start 1 to 2 days before entering a malaria-endemic area, and be continued daily until 7 days after leaving the area.

Dosage in adults:

One MALANIL tablet daily.

Dosage in the elderly:

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

Dosage in hepatic impairment:

A pharmacokinetic study indicates that no dosage adjustments are needed in patients with mild to moderate hepatic impairment. No studies have been conducted in patients with severe hepatic impairment (see Pharmacokinetics in hepatic impairment).

Dosage in renal impairment:

Pharmacokinetic studies indicate that no dosage adjustments are needed in patients with mild to moderate renal impairment.

For prophylaxis of *P. falciparum* malaria in patients with severe renal impairment (see CONTRA-INDICATIONS).

SIDE EFFECTS:

Adverse reactions are listed below by system organ class and frequency. Frequencies are defined as: very common > 1/10, common > 1/100 and < 1/10, uncommon > 1/1 000 and < 1/100, rare > 1/10 000 and < 1/1 000, very rare < 1/10 000. Very common, common and uncommon frequencies were determined from clinical trial data. Rare and very rare frequencies were generally derived from spontaneous data. The frequency classification "Not known" has been applied to those reactions where a frequency could not be estimated from the available data.

MALANIL contains atovaquone and proguanil hydrochloride, therefore, the adverse events associated with each of these compounds may be expected with MALANIL. At the doses employed for prophylaxis of malaria, adverse events are generally mild and of limited duration. There is no evidence of added toxicity following concurrent

administration of atovaquone and proguanil. A summary of adverse events associated with the use of MALANIL, atovaquone or proguanil hydrochloride is provided below.

Blood & Lymphatic system disorders:

Common:	anaemia, neutropenia
Not Known:	pancytopenia in patients with severe renal impairment.

Immune system disorders:

Common:	rash
Uncommon:	urticaria
Not Known:	angioedema, anaphylaxis, vasculitis, photosensitivity reactions, Stevens-Johnson syndrome

Metabolism and nutritional disorders:

Common:	hyponatraemia, anorexia
Uncommon:	elevated amylase levels

Nervous system disorders:

Very common:	headache
Common:	insomnia, dizziness
Not Known:	Cases of convulsions have been reported (see WARNINGS AND SPECIAL PRECAUTIONS)

Psychiatric disorders:

Not Known:	depression, anxiety, mood disorders, and psychotic reactions including paranoid reactions and hallucinations have been reported.

Gastrointestinal disorders:

Very common:	abdominal pain, nausea, vomiting, diarrhoea
Uncommon:	stomatitis

Not Known:	gastric intolerance**,** oral ulceration

Hepatobiliary disorders:

Common:	elevated liver enzyme levels
Not Known:	hepatitis, cholestasis
	Clinical trial data for MALANIL indicated that abnormalities in liver function tests were reversible and not associated with untoward clinical events.

Skin and subcutaneous tissue disorders:

Uncommon:	hair loss

General disorders and administration site conditions:

Common:	fever

Respiratory, thoracic and mediastinal disorders:

Common:	cough.

In clinical trials of MALANIL for prophylaxis of malaria, the most commonly reported adverse events, independent of attributability, were headache, abdominal pain and diarrhoea, and were reported in a similar proportion of subjects receiving MALANIL or placebo.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

In case of suspected overdosage, symptomatic and supportive therapy should be given as appropriate.

IDENTIFICATION:

MALANIL Tablets: Round, biconvex, pink, film-coated tablet with a yellow core. Branded 'GX CM3'.

PRESENTATION:

MALANIL Tablets will be packed into PVC/aluminium foil blisters containing 12 tablets.

STORAGE INSTRUCTIONS:

Store below 30 °C.

Keep out of reach of children.

REGISTRATION NUMBER:

37/20.2.6/0075

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

LITHA PHARMA (PTY) LTD

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DATE OF PUBLICATION OF THIS PACKAGE INSERT:

05 March 2009