1.3.1

Summary of Product Characteristics (SmPC)

1. NAME OF THE MEDICINAL PRODUCT

MALDOX DISPERSIBLE TABLET

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains pyrimethamine 12.5 mg and sulfadoxine 250

mg Each tablet also contains 20 mg of lactose monohydrate.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White round tablets, debossed with "SP" on both sides and a scoreline on one side.

The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

Therapeutic indications

MALDOX is indicated for intermittent preventive treatment of malaria in first or second pregnancy as part of antenatal care, in areas of moderate-to-high malaria transmission in Africa.

MALDOX is also indicated for intermittent preventive treatment of malaria in infants aged less than 12 months at the time of the second and third rounds of vaccination against diphteria, tetanus and pertussis and vaccination against measles, in areas of moderate-to-high malaria transmission of Africa (annual entomological inoculation rate ≥ 10), where the combination of sulfadoxine and pyrimethamine is still effective(prevalence of the Pfdhps 540 mutation of ≤ 50%).

The most recent official guidelines on the use of antimalarial agents and local information (including resistance patterns) should be considered.

Official guidance will normally include those from WHO and public health authorities' guidelines.

Posology and method of administration

Intermittent preventive treatment of malaria in pregnancy

MALDOX should ideally be administered as directly observed therapy (DOT) of three tablets giving the total required dosage of 75 mg/1500mg pyrimethamine/sulfadoxine.

Doses should be given at each scheduled antenatal care (ANC) visit, from the beginning of the second trimester until delivery, provided that the doses of MALDOX are given at least one month apart. WHO recommends a schedule of at least four antenatal care visits during pregnancy. The objective is to ensure that at least three doses of MALDOX are received during pregnancy.

Method of administration

Tablets for oral administation.

MALDOX can be given either on an empty stomach or with food.

Missing a dose reduces protection but does not prevent receiving the next dose.

Contraindications

Maldox is contraindicated in patients with:

- hypersensitivity to any of the active ingredients, to sulfonamide drugs or to any of the excipients (see section 6.1)
- documented megaloblastic anaemia due to folate deficiency.

Special warnings and precautions for use

If skin eruptions, cytopenia or a bacterial or fungal super-infection occurs, use of MALDOX should be discontinued. Caution is advised in repeated administration of MALDOX to patients with blood dyscrasias and those with renal hepatic failure, in whom the drugs accumulate.

Folic acid

A dose of 0.4 mg daily of folic acid may be safely used in conjunction with MALDOX. Folic acid at a daily dose equal or above 5 mg should not be given together with MALDOX as this counteracts its efficacy as an antimalarial.

Acute illness

Maldox should not be given if the child has an acute illness. If the child has malaria, specific treatment should be given according to recent official guidelines.

Increased adverse effects

To avoid excessive effects, MALDOX should not be given if the patient:

- has received pyrimethamine/sulfadoxine in the past 30 days
- is HIV-positive and is receiving sulfamethoxazole/trimethoprim prophylaxis

Hypersensitivity reactions

Because of a rare risk of severe hypersensitivity reactions (see section 4.3), treatment with MALDOX should be stopped if one develops a rash or urticarial reaction.

Excipients

MALDOX contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption may experience symptoms of intolerance.

It is important to consider the contribution of excipients from all the medicines that the patient is taking.

Interaction with other medicinal products and other forms of interaction

Concomitant use of MALDOX with trimethoprim, or sulfamethoxazole /trimethoprim, or another sulfonamide can increase haematological side effects and the risk of severe cutaneous reactions. Concomitant use should therefore be avoided.

The risk of hepatic and haematological adverse effects may increase if MALDOX is given with other drugs with hepatic or haematological toxicity.

Fertility, pregnancy and breast-feeding

Pregnancy

Pyrimethamine/sulfadoxine showed reproductive toxicity in animal studies (see section 5.3).

Pyrimethamine/sulfadoxine should not be used during the first trimester of pregnancy unless the benefit is considered to outweigh the risks and alternative drugs are not available.

During 2nd or 3rd trimesters of pregnancy, MALDOX may be used for intermittent preventive treatment in pregnancy.

Breast-feeding

Pyrimethamine is excreted in human milk. Some sulfonamides are excreted in human milk.

Sulfonamides are avoided in premature infants and in infants with hyperbilirubinemia or glucose-6-phosphate dehydrogenase deficiency. Except for the preceding conditions, sulfonamides are compatible with breastfeeding.

MALDOX can be used during breast-feeding.

Fertility

No human data on the effect of MALDOX on fertility are available. Animal data showed that pyrimethamine impaired fertility (see section 5.3).

Effects on ability to drive and use machines

Side effects are not expected to affect attention or reduce co-ordination but undesirable effects such as dizziness may occur, in which case patients should not drive or use machines.

Undesirable effects

Mild adverse events associated with pyrimethamine/sulfadoxine involve the skin and mucous membranes. Serious cutaneous toxicity (Steven–Johnson syndrome) and hepatotoxicity may occur rarely.

The adverse events listed below are not based on adequately sized studies, but on literature data generally published after approval and for the use of each of these antimalarials in adults. Frequency estimates are highly variable across the studies.

Gastrointestinal reactions

glossitis, stomatitis, nausea, emesis, abdominal pain, diarrhoea, feeling of fullness

Skin and subcutaneous tissue disorders

photosensensitivity, urticaria, pruritus, exfoliative dermatitis, slight hair loss, Lyell's syndrome, erythema multiforme, Stevens-Johnson syndrome, generalised skin eruptions, toxic epidermal necrolysis

General disorders

fever, chills, periarteritis nodosa and lupus erythematosus phenomenon

Nervous system disorders

headache, peripheral neuritis, convulsions, ataxia, hallucinations, insomnia, fatigue, muscle weakness, polyneuritis

Psychiatric disorders

depression, nervousness, apathy

Blood and lymphatic disorders

agranulocytosis, aplastic anaemia, megaloblastic anaemia, thrombocytopenia, leucopoenia, haemolytic anaemia, purpura, hypoprothrombinaemia, methaemoglobinaemia, and eosinophilia

Cardiac disorders

allergic myocarditis/pericarditis

Ear and labyrinth disorders

tinnitus, vertigo

Endocrine disorders

Sulfadoxine, a sulphonamide is similar to some diuretics (acetazolamide and the thiazides), and sulfonylurea hypoglycaemics. Diuresis and hypoglycaemia have occurred rarely in patients receiving sulphonamide.

Eye disorders

periorbital oedema, conjunctival and scleral injection

Hepatobiliary disorders

hepatitis, hepatocellular necrosis, pancreatitis, transient rise of liver enzymes

Immune system disorders

hypersensitivity reactions, serum sickness, anaphylactoid reactions.

Musculoskeletal and connective tissue disorders

arthralgia

Renal and urinary disorders

renal failure, interstitial nephritis, blood-urea nitrogen and serum creatinine elevation, toxic nephrosis with oliguria and anuria, crystalluria

Respiratory disorders

pulmonary infiltrates resembling eosinophilic or allergic alveolitis

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. Health care professionals are asked to report any suspected adverse reactions to the marketing authorisation holder, or, if available, via the national reporting system.

Overdose

Symptoms: headache, anorexia, nausea, vomiting, agitation, convulsions, haematologic changes (megaloblastic anaemia, leucopoenia, thrombocytopenia), glossitis, crystalluria.

Treatment: the patient should be urgently transferred to a specialised unit for close monitoring and supportive therapy including, where appropriate, activated charcoal and fluid administration; a parenteral benzodiazepine, phenytoin or a barbiturate can be given for convulsions. Liver and renal function should be monitored and blood counts checked repeatedly for up to four weeks after the overdose. Should blood dyscrasia occur, folinic acid (leucovorin) may be used.

5. PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Antimalarial

Pyrimethamine combinations. ATC code P01BD51

Pyrimethamine is a diaminopyrimidine. It exerts its antimalarial activity by inhibiting plasmodial dihydrofolate reductase thus indirectly blocking the synthesis of nucleic acids in the malaria parasite. It is a slow-acting blood schizontocide and is also possibly active against pre-erythrocytic forms of the malaria parasite and inhibits sporozoite development in the mosquito vector. It has in vitro activity against the four long-established human malaria parasites. There has been rapid emergence of clinical resistance.

Sulfadoxine is a sulfonamide. Sulfonamides are competitive antagonists of p-aminobenzoic acid. They are competitive inhibitors of dihydropteroate synthase, the enzyme in *P. falciparum*, which is responsible for the incorporation of p-aminobenzoic acid in the synthesis of folic acid. Therefore, by acting at a different step in folate synthesis, sulfadoxine increases the effect of pyrimethamine.

P. falciparum can become resistant to the effects of pyrimethamine/sulfadoxine.

Clinical efficacy

Intermittent preventive treatment of malaria in pregnancy
Seven trials enrolling 2190 participants showed that three or more monthly doses of pyrimethamine/sulfadoxime, in comparison with two doses, increased the mean birth weight by about 56 g (95% CI, 29-83), reduced the number of low-birth-weight infants by about 20% (RR 0.80, 95% CI 0.69-0.94) and maternal parasitaemia by about 33% (RR 0.68, 95% CI 0.52-0.89). Six trials based on 1436 participants showed that three or more monthly doses compared to two doses reduced placental parasitaemia by about 50% (RR 0.51, CI 95%, 0.38-0.68)

Intermittent preventive treatment of malaria in infants

A pooled analysis of six randomised placebo controlled studies, conducted in areas of moderate to high transmission of malaria, showed that the use of pyrimethamine/sulfadoxime in intermittent preventive treatment of malaria in infants delivered through EPI provides an overall protection in the first year of life against clinical malaria (30.3%, CI 19.8%-39.4%), anaemia (21.3%, 95% CI 8.3%-32.5%), hospital admissions associated with malaria parasitaemia (38.1%, 95% CI 12.5%-56.2%) and all-cause hospital admissions (22.9%, 95% CI 10%-34%). Pyrimethamine/sulfadoxine in intermittent preventive treatment of malaria in infants offers a personal protection against clinical malaria for a period of approximately 35 days following the administration of each dose.

Pharmacokinetic properties

Absorption of MALDOX

The absorption characteristics of MALDOX have been determined after administration of three (3) tablets in healthy volunteers in the fasting state as follows:

Pharmacokinetic variable	Mean value (± standard deviation)	
	Pyrimethamine	**Sulfadoxine**
Maximum concentration (C_{max})	0.55 (0.07) µg/mL	183 (18) µg/mL
Area under the curve ($AUC_{0–72h}$), a measure of the extent of absorption	29.8(3.4) µg.h/mL	11037(1142) µg.h/mL
Time to attain maximum concentration (t_{max})#	5.5 (1.0 – 10.0) h	5.5 (4.0 – 48.0) h

#Median (range)

Absorption

After oral administration both sulfadoxine and pyrimethamine are well absorbed (bioavailability of >90%) in healthy adults.

Distribution

The volume of distribution for pyrimethamine and sulfadoxine is 2.3 l/kg and 0.14 l/kg, respectively. Plasma protein binding is about 90% for both pyrimethamine and sulfadoxine. Both cross the placental barrier and pass into breast milk.

Metabolism

Pyrimethamine is transformed to several unidentified metabolites. About 5% of sulfadoxine appears in the plasma as acetylated metabolite, about 2 to 3% as the glucuronide.

Elimination

The elimination half-lives are about 100 hours for pyrimethamine and about 200 hours for sulfadoxine. Both are eliminated mainly through the kidneys.

Preclinical safety data

General toxicity

Non-clinical data reveal no special hazard for humans not already covered in other sections of SmPC based on conventional studies of safety pharmacology and repeated dose toxicity.

Genotoxicity

Pyrimethamine was not found mutagenic in the Ames test. Pyrimethamine was found to be mutagenic in laboratory animals and also in human bone marrow following 3 or 4 consecutive daily doses totalling 200–300 mg.

Carcinogenesis

Pyrimethamine was not found carcinogenic in female mice or in male and female rats.

Reproductive toxicity

Sperm motility and count were significantly decreased in pyrimethamine-treated male mice, and their fertility rate fell to zero. These adverse effects were reversible when pyrimethamine was discontinued. Testicular changes have been observed in rats treated with pyrimethamine/sulfadoxine. The pregnancy rate of female rats was not affected following treatment with 10.5 mg/kg daily, but was significantly reduced at doses of 31.5 mg/kg daily or higher. Pyrimethamine/sulfadoxine was teratogenic in rats when given in weekly doses about 12 times the normal human dose.

6. PHARMACEUTICAL PARTICULARS

List of Excipients

Lactose monohydrate, hyprolose, sodium starch glycolate, microcrystalline cellulose, sodium lauryl sulfate, magnesium stearate, corn starch and hypromellose

Incompatibilities

Not applicable.

Shelf life

36 months

Special precautions for storage

Do not store above 30°C. Store the tablets in blisters in the provided box or carton.

Nature and contents of container

3 tablets are packed in a PVC/Alu blister card.

Pack sizes:
1x3 and 50x3 tablets

7. SUPPLIER

Emzor Pharmaceutical Industries Limited
Flowergate Mixed Development Scheme. Km 1 Sagamu/Benin Expressway, Sagamu, Ogun State

8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

N/A

9. DATE OF PREQUALIFICATION

N/A

10. DATE OF REVISION OF THE TEXT

N/A